9000 **Oral Abstract Session**

First-line nivolumab (NIVO) plus ipilimumab (IPI) plus two cycles of chemotherapy (chemo) versus chemo alone (4 cycles) in patients with advanced non-small cell lung cancer (NSCLC): Two-year update from CheckMate 9LA.

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Background: In the randomized phase 3 CheckMate 9LA trial (NCT03215706), first-line NIVO + IPI combined with 2 cycles of chemo significantly improved overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) vs chemo alone (4 cycles). Clinical benefit was observed regardless of programmed death ligand 1 (PD-L1) expression level and histology. Here we report data with 2 years' minimum follow-up from this study. **Methods:** Adult patients (pts) with stage IV / recurrent NSCLC, ECOG performance status ≤ 1, and no known sensitizing *EGFR/ALK* alterations were stratified by PD-L1 ($< 1\%$ vs $\geq 1\%$), sex, and histology (squamous vs non-squamous) and were randomized 1:1 to NIVO 360 mg Q3W + IPI 1 mg/kg Q6W + chemo (2 cycles; n = 361) or chemo alone (4 cycles; n = 358). Pts with non-squamous NSCLC in the chemo-alone arm could receive pemetrexed maintenance. The primary endpoint was OS. Secondary endpoints included PFS and ORR by blinded independent central review, and efficacy by different PD-L1 levels. Safety was exploratory. **Results:** At a minimum follow-up of 24.4 months for OS (database lock: Feb 18, 2021), pts treated with NIVO + IPI + chemo continued to derive OS benefit vs chemo, with a median OS of 15.8 months vs 11.0 months, respectively (HR, 0.72 [95% CI, 0.61–0.86]); 2-year OS rates were 38% vs 26%. Median PFS with NIVO + IPI + chemo vs chemo was 6.7 months vs 5.3 months (HR, 0.67 [95% CI, 0.56–0.79]); 8% and 37% of pts who had disease progression received subsequent immunotherapy, respectively. ORR was 38% with NIVO + IPI + chemo vs 25% with chemo. Similar clinical benefit with NIVO + IPI + chemo vs chemo was observed in all randomized pts and across the majority of subgroups, including by PD-L1 expression level (Table) or histology. Any grade and grade 3–4 treatment-related adverse events were reported in 92% and 48% of pts in the NIVO + IPI + chemo arm vs 88% and 38% in the chemo arm, respectively. **Conclusion:** With 2 years' minimum follow-up, first-line NIVO + IPI + chemo demonstrated durable survival and benefit versus chemo in pts with advanced NSCLC; no new safety signals were identified. Clinical trial information: NCT03215706. Research Sponsor: Bristol Myers Squibb.

9001 **Oral Abstract Session**

Outcomes of anti-PD-(L1) therapy in combination with chemotherapy versus immunotherapy (IO) alone for first-line (1L) treatment of advanced non-small cell lung cancer (NSCLC) with PD-L1 score 1-49%: FDA pooled analysis.

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Background: IO + chemotherapy ± anti-angiogenics comprise FDA-approved 1L regimens for metastatic NSCLC, with IO-only therapy approved only for PD-L1-positive NSCLC. Patients with PD-L1 scores 1-49% have many therapeutic options, and little is known about how subgroups of patients experience benefit across treatment regimens. **Methods:** Data was pooled from 8 randomized controlled trials investigating anti-PD-(L)1 therapy as IO-only or in chemo-IO regimens for the 1L treatment of patients with advanced NSCLC. PD-L1 score was defined as the proportion of tumor cells stained by the assay, and analysis was conducted for patients whose tumors had PD-L1 score 1-49%. Tumor-infiltrating immune cell staining was not considered. OS and PFS were compared between chemo-IO and IO alone via a pooled analysis. Median survival times were estimated using Kaplan-Meier methods. Hazard ratios were estimated using Cox proportional hazards models stratified by trial and adjusted for age, sex, race, ECOG, histology and smoking status. **Results:** A total of 2108 patients with NSCLC and PD-L1 score 1-49% were identified for this analysis. Baseline characteristics were: 37% aged 65-74 years and 12% aged ≥75; 67% male; 79% white; 65% ECOG ≥ 1; and 85% smokers. Median follow-up was 12.1 months. This pooled analysis showed that patients receiving chemo-IO (N=639) had longer PFS and OS compared to patients treated with IO alone (N=529), with median PFS 7.7 vs 4.2 months (HR 0.60; 95% CI 0.48, 0.76) and median OS 21.4 vs 14.5 months (HR 0.68; 95% CI 0.52, 0.90). All results presented are considered exploratory and hypothesis generating. **Conclusions:** This exploratory pooled analysis suggests that chemo-IO may improve efficacy outcomes over IO alone in most subgroups of patients with advanced NSCLC with PD-L1 score 1-49%. Patients 75 and over experienced similar outcomes across therapeutic options. Research Sponsor: None.

Efficacy outcomes of Chemo-IO vs. IO alone by subgroup.

	Subgroup	N[1]	Median OS in months	OS HR[2] (95% CI)	Median PFS in months	PFS HR[2] (95% CI)
Age	<65	580	23.7 vs 16.1	0.63 (0.43, 0.92)	7.1 vs 4.0	0.55 (0.40, 0.76)
	65-74	443	22.5 vs 14.8	0.61 (0.38, 0.97)	9.5 vs 4.5	0.60 (0.40, 0.88)
	≥75	132	13.9 vs 10.3	0.95 (0.42, 2.14)	6.4 vs 4.9	0.85 (0.42, 1.71)
ECOG	0	415	25.2 vs 20.0	0.65 (0.38, 1.10)	9.6 vs 5.8	0.57 (0.38, 0.86)
	1+	751	16.8 vs 11.0	0.68 (0.50, 0.94)	7.0 vs 4.0	0.65 (0.49, 0.86)
Smoking	Never	160	28.2 vs 18.0	0.57 (0.22, 1.46)	8.1 vs 4.1	0.44 (0.21, 0.92)
	Ever	1005	20.8 vs 13.5	0.68 (0.51, 0.91)	7.6 vs 4.2	0.62 (0.49, 0.80)

[1]Number of patients in the chemo-IO and IO-only arms of all trials [2]Comparisons utilized chemotherapy as the control arm.

9002 **Oral Abstract Session**

Pooled analyses of immune-related adverse events (irAEs) and efficacy from the phase 3 trials IMpower130, IMpower132, and IMpower150.

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Background: PD-L1/PD-1 inhibitors have transformed the treatment (tx) of advanced NSCLC. Evidence suggests that the occurrence of irAEs with these agents may predict improved outcomes in cancers such as NSCLC. Atezolizumab (atezo; anti–PD-L1) has shown efficacy and tolerability in NSCLC and is currently approved in the 1L and 2L+ settings. The Ph 3 IMpower130, IMpower132 and IMpower150 trials evaluated atezo + chemo ± bevacizumab (bev) as 1L tx of NSCLC. We explore the association between irAEs and efficacy in these trials. **Methods:** Each trial enrolled tx-naive patients (pts) with nonsquamous stage IV NSCLC. Pts were randomized to: carboplatin (carbo) + *nab*-paclitaxel alone or with atezo in IMpower130; carbo or cisplatin alone or with atezo in IMpower132; atezo (A) + bev (B) + carbo + paclitaxel (CP), ACP or BCP in IMpower150. Data were pooled (data cutoffs: Mar 15 2018 [IMpower130]; May 22 2018 [IMpower132]; Sep 13 2019 [IMpower150]) and analyzed by tx (atezo-containing vs control) and irAE status. A time-dependent Cox model and landmark analyses at 1, 3, 6 and 12 mo were used to control for immortal bias. Study protocols required atezo tx interruption/discontinuation for grade (Gr) ≥3 irAEs. **Results:** 2503 pts were included in the analysis (atezo, n = 1577; control, n = 926). In both arms, baseline characteristics were generally balanced between pts with irAEs (atezo, n = 753; control, n = 289) and without irAEs (atezo, n = 824; control, n = 637). Any-Gr irAEs occurred in 48% (atezo) and 32% (control) of pts; Gr 3-5 irAEs occurred in 11% (atezo) and 5% (control). The most common irAEs (atezo vs control) were rash (28% vs 18%), hepatitis (lab abnormalities; 15% vs 10%) and hypothyroidism (12% vs 4%). Median time to onset of first irAE was 1.7 (atezo) vs 1.4 mo (control). OS HRs (95% CI) from the time-dependent Cox model between pts with vs without irAEs were 0.69 (0.60, 0.78) in the atezo arm and 0.82 (0.68, 0.99) in the control arm; after excluding rash (perceived as the least specific irAE), OS HRs (95% CI) were 0.75 (0.65, 0.87) and 0.90 (0.71, 1.12), respectively. OS landmark data are in the Table. **Conclusions:** In this exploratory pooled analysis, pts with irAEs had longer OS vs pts without irAEs in the atezo-containing and control arms per the time-dependent Cox model and landmark analyses; this trend remained for the atezo arm after excluding rash. Landmark analyses suggest that in the atezo arm, pts with Gr 1/2 irAEs had the longest OS and pts with Gr ≥3 irAEs had the shortest OS, potentially due to tx interruption/discontinuation. Clinical trial information: NCT02367781; NCT02657434; NCT02366143. Research Sponsor: F. Hoffmann-La Roche, Ltd.

Landmark	Atezo with irAE	Atezo with Gr 1/2 irAE	Atezo with Gr 3-5 irAE	Atezo without irAE	Control with irAE	Control without irAE
	n mOS, mo	n mOS, mo	n mOS, mo	n mOS, mo	n mOS, mo	n mOS, mo
1 mo	305	247	58	1210	116	764
	22.2	23.8	11.3	18.9	19.3	14.3
3 mo	451	370	81	963	180	625
	23.1	24.8	16.6	19.6	19.1	16.0
6 mo	532	431	101	736	197	498
	25.6	26.6	21.5	22.4	21.8	19.3
12 mo	519	428	91	455	175	329
	32.7	33.4	29.9	27.5	31.8	25.5

9003 **Oral Abstract Session**

Overall survival and exploratory subgroup analyses from the phase 2 CodeBreaK 100 trial evaluating sotorasib in pretreated *KRAS* p.G12C mutated non-small cell lung cancer.

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Background: In the registrational phase 2 CodeBreaK 100 trial, sotorasib demonstrated an objective response rate (ORR) of 37.1% (95% CI: 28.6, 46.2) and a median progression-free survival (PFS) of 6.8 months (95% CI: 5.1, 8.2) in patients with pretreated *KRAS* p.G12C mutated non-small cell lung cancer (NSCLC). Tumor response was observed in patients bearing co-mutations in *STK11*, a driver of poor clinical outcomes with standard of care. Here, we report efficacy across an extended set of patient subgroups by key baseline characteristics and biomarkers. **Methods:** Sotorasib was given orally at 960 mg once daily to eligible patients who had advanced NSCLC harboring *KRAS* p.G12C and received prior standard therapies. Primary endpoint was ORR assessed by central review. Key secondary endpoints included PFS, overall survival, and safety. *KRAS* p.G12C mutant allele frequency (MAF) and tumor mutational burden (TMB) were analyzed by next-generation sequencing (NGS) using tissue samples. Mutational status of individual genes was determined by NGS using tissue and/or plasma samples. Correlations between response and *KRAS* p.G12C MAF, TMB, or co-mutations were analyzed in subsets of patients who had available respective results. Association between MAF and response was reported by odds ratio (95% CI), from a logistic regression with dependent variable of log odds of being a responder and an independent variable of MAF in a unit of 10%. **Results:** ORR across subgroups is presented in the Table. Response was independent of *KRAS* p.G12C MAF in the study population (odds ratio [95% CI]: 1.11 [0.88, 1.39]). OS remained immature. **Conclusions:** In the exploratory analyses of the phase 2 CodeBreaK 100 trial, the clinical benefit of sotorasib was observed across patient subgroups. Overall survival and updated exploratory analyses will be presented. Clinical trial information: NCT03600883. Research Sponsor: Amgen Inc.

Subgroups (n)	ORR % (95% CI)
Total patients evaluable (N = 124)	37.1 (28.6, 46.2)
Age	
< 65 years (65)	30.8 (19.9, 43.4)
≥ 65 years (59)	44.1 (31.2, 57.6)
ECOG PS status	
0 (37)	43.2 (27.1, 60.5)
1 (87)	34.5 (24.6, 45.4)
Metastatic disease	
Yes (120)	36.7 (28.1, 45.9)
No (4)	50.0 (6.8, 93.2)
Prior lines of therapy	
1 (53)	39.6 (26.5, 54.0)
≥2 (71)	35.2 (24.2, 47.5)
Prior anti-PD-1 or PD-L1	
Yes (113)	36.3 (27.4, 45.9)
No (11)	45.5 (16.7, 76.6)
***TP53* co-mutation**	
Wild-type (20)	40.0 (19.1, 63.9)
Mutant (84)	39.3 (28.8, 50.5)
***STK11* co-mutation**	
Wild-type (69)	39.1 (27.6, 51.6)
Mutant (35)	40.0 (23.9, 57.9)
***KEAP1* co-mutation**	
Wild-type (84)	44.0 (33.2, 55.3)
Mutant (20)	20.0 (5.7, 43.7)
TMB level	
Low, < 10 Mut/Mb (69)	42.0 (30.2, 54.5)
High, ≥ 10 Mut/Mb (15)	40.0 (16.3, 67.7)

9004 Oral Abstract Session

Biomarker tissue journey among patients (pts) with untreated metastatic non-small cell lung cancer (mNSCLC) in the U.S. Oncology Network community practices.

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Background: Given the importance of molecular testing and targeted therapy for mNSCLC, the MYLUNG (Molecularly Informed Lung Cancer Treatment in a Community Cancer Network) consortium pragmatic study assessed real-world biomarker testing rates and turnaround times (TAT) within The US Oncology Network of over 1,000 providers across the United States. **Methods:** This was a retrospective observational chart review study of pts with mNSCLC initiating first-line (1L) systemic therapy between 04/01/2018 and 03/31/2020. iKnowMed electronic health records were used to examine timing of biomarker testing: before 1L therapy (cohort 1), after 1L therapy (cohort 2) or no testing (cohort 3). We assessed testing rates for ALK, BRAF, EGFR, ROS1, and PD-L1; use of full next-generation sequencing panel (NGS); time from mNSCLC diagnosis (dx) to 1L therapy; TAT from biomarker orders to results; and time from mNSCLC dx to test results. **Results:** We identified 3474 adults. Median age was 69 years (range 23-90), 51% female, 74% with adenocarcinoma and 76% with a documented ECOG performance status of 0 or 1. Testing rates are shown in table: 90% of pts had at least one biomarker test and 46% received all 5 biomarker tests. Changes in testing rates from 2018 to 2020 were 51% to 59% for BRAF, 71% to 71% for EGFR, 71% to 70% for ALK, 69% to 67% for ROS1, 82% to 84% for PD-L1, and 42% to 49% for pts tested for all 5 biomarkers. NGS testing increased from 33% to 44% ($p<0.0001$). The median (interquartile range [IQR]) time from mNSCLC dx to 1L therapy for all pts was 35 (22, 55) days. Median (IQR) TAT from biomarker testing orders to results ranged from 10 (6, 17) to 15 (10, 22) days for the individual biomarkers; and time from mNSCLC dx to biomarker results ranged from 14 (7, 26) to 21 (12, 36) days by biomarker. **Conclusions:** This real-world study showed that most pts received at least one biomarker test prior to 1L, but <50% received all 5 tests. NGS testing occurred in <50% of pts but increased over the periods examined. Median time from dx to 1L therapy was about 5 weeks and TAT from orders to results about 2 weeks. Analyses by histology and other trends will be reported. These data will be compared to the next phase of the MYLUNG study, which will evaluate contemporary ordering practices and TATs prospectively Research Sponsor: Amgen Inc.; Mirati Therapeutics, Inc.; Eli Lilly and Company.

	Total Patients	Cohort 1 biomarker test result received prior to 1L	Cohort 2 biomarker test result received during/after 1L	Cohort 3 no biomarker test
Overall n (%)[a]	3474	2752 (79)	371 (11)	351 (10)
Any biomarker test[b]	3123	2752 (88)	371 (12)	NA
All 5 biomarker tests[b]	1602	1230 (77)	372 (23)	NA
Biomarker testing, n (%)[a]				
ALK	2446	1986 (57)	460 (13)	1028 (30)
BRAF	1912	1489 (43)	423 (12)	1562 (45)
EGFR	2443	1979 (57)	464 (13)	1031 (30)
PD-L1	2882	2526 (73)	356 (10)	592 (17)
ROS1	2348	1897 (55)	451 (13)	1126 (32)

[a]Row percentage denominator: 3474 [b]Row percentage denominator: total patients with test.

9005 **Oral Abstract Session**

Racial disparities in biomarker testing and clinical trial enrollment in non-small cell lung cancer (NSCLC).

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Background: Cancer racial disparities may exist at many levels in the health care system, from screening to timely diagnosis and treatments received, as well as clinical trial enrollment. This study investigated differences in black versus white race among patients with NSCLC undergoing biomarker testing and clinical trial enrollment in the US. **Methods:** This retrospective observational study utilized the Flatiron Health database, which includes longitudinal data of patients with advanced/metastatic NSCLC. Patients were eligible if they had evidence of systemic therapy in the database from 1/1/2017 through 10/30/2020. Descriptive analyses summarized differences by race in biomarker testing and trial enrollment. Multivariable regression examined the relationship between these factors. **Results:** A total of 14,768 patients were eligible: 9,793 (66.3%) were white and 1,288 (8.7%) were black. 76.4% of white patients and 73.6% of black patients underwent at least one single molecular test or comprehensive genomic analysis ($p = 0.03$). Next-generation sequencing (NGS) was performed among 50.1% of white patients and 39.8% of black patients ($p < 0.0001$. Trial participation was observed among 3.9% of white and 1.9% of black patients ($p = 0.0002$). There was a statistically significant association between race (white vs black) and both biomarker testing (ever vs never) and trial participation (yes vs no) (both $p < 0.001$, unadjusted chi square). Differences in NGS testing, baseline biomarker testing, and race were retained as statistically significant ($p < 0.01$) in adjusted regression analyses. The receipt of first-line targeted therapy was comparable between white and black patients (10.2% and 9.2%, respectively, $p = 0.24$); however, this summary did not consider biomarker test results. First line use of pembrolizumab+carboplatin+pemetrexed was observed among 19.8% of white and 22.6% of black patients; carboplatin+paclitaxel was observed among 16.5% and 18.6%, and single-agent pembrolizumab was observed among 14.8% and 11.5%, respectively. **Conclusions:** The use of NGS-based testing, which is recommended by the National Comprehensive Cancer Network Clinical Guidelines in Oncology for patients with advanced/metastatic NSCLC, is the most notable disparity among black patients, with more than a 10 percentage-point difference in receipt of this testing versus white counterparts. This may in part contribute to the more than double the rate of participation in clinical trials observed among white patients, as many second line and beyond trials utilize molecular targets as inclusion criteria. While multiple factors are known to impact health care disparities, access to and receipt of appropriate biomarker testing may be an attenable goal in order to ensure equal access to quality care. Research Sponsor: None.

9006 **Oral Abstract Session**

Amivantamab in combination with lazertinib for the treatment of osimertinib-relapsed, chemotherapy-naïve EGFR mutant (EGFRm) non-small cell lung cancer (NSCLC) and potential biomarkers for response.

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Background: Preliminary efficacy was observed with the combination of amivantamab, an EGFR-MET bispecific antibody, and lazertinib, a 3rd-generation tyrosine kinase inhibitor, in both treatment-naïve and osimertinib (osi)-relapsed patients (pts) with EGFRm NSCLC (Cho *Ann Oncol* 2020;31:S813). We present updated results of the combination in osi-relapsed pts, including an analysis of potential biomarkers of response. **Methods:** Pts with EGFR exon 19 deletion or L858R mutation NSCLC, who had progressed on osi without intervening chemotherapy, were enrolled in the combination cohort of the ongoing CHRYSALIS study (NCT02609776). With pre-treatment tumor biopsies and ctDNA collected prospectively, pts received the combination dose of 1050/1400 mg amivantamab + 240 mg lazertinib to assess safety and efficacy in the osi-relapsed population. Response was assessed by investigator per RECIST v1.1. Osi-resistance mutations or amplifications in EGFR/MET identified by next-generation sequencing (NGS) in either ctDNA or tumor biopsy (biomarker-positive [pos]), were evaluated for enriching response. Immunohistochemistry (IHC) staining for EGFR and MET expression was also explored as a potential biomarker for response. **Results:** Of the 45 osi-relapsed pts, 36% (95% CI, 22–51) had a confirmed response (1 complete response and 15 partial responses [PR]). At a median follow-up of 8.2 mo (1.0–11.8), 20/45 pts (44%) remain on treatment. With 11/16 pts (69%) continuing in response (2.6–9.6+ mo), median duration of response has not been reached (NR). The median progression-free survival (mPFS) was 4.9 mo (95% CI, 3.7–8.3). In total, 44/45 pts were evaluable by ctDNA and 29/45 by tumor NGS. Genetic testing identified 17 biomarker-pos pts, of whom 8 (47%) responded. Of the remaining 28 pts, 8 (29%) responded. Among these 28 pts, 18 had unknown mechanisms of osi-resistance (8 PR) and 10 had non-EGFR/MET mechanisms of resistance identified (none responded). The mPFS (95% CI) for biomarker-pos and remaining pts was 6.7 mo (3.4–NR) and 4.1 mo (1.4–9.5), respectively. Adequate tissue was available for 20 pts to perform IHC testing for EGFR and MET–9/10 (90%) IHC high (combined EGFR+MET H score>400) pts responded to treatment, while 1/10 IHC low pts responded to treatment. **Conclusions:** Treatment with the combination of amivantamab and lazertinib yielded responses in 36% of chemotherapy-naïve pts who progressed on osi. Among these pts, genetic EGFR and MET-based biomarkers of resistance identified a subgroup of pts more likely to respond to amivantamab and lazertinib, although additional pts lacking identified resistance markers also responded. An IHC-based approach may identify pts most likely to benefit from the combination regimen, but further investigation is warranted. Clinical trial information: NCT02609776. Research Sponsor: Janssen R&D, LLC.

9007 **Oral Abstract Session**

Efficacy and safety of patritumab deruxtecan (HER3-DXd) in EGFR inhibitor-resistant, *EGFR*-mutated (*EGFR*m) non-small cell lung cancer (NSCLC).

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Background: Patients (pts) with advanced *EGFR*m NSCLC have limited treatment options after failure of EGFR TKI and platinum-based chemotherapy (PBC). HER3-DXd is an antibody drug conjugate consisting of a fully human monoclonal antibody to HER3 attached to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker. We previously presented efficacy/safety data (median follow-up, 5.4 mo) from an ongoing study of HER3-DXd in *EGFR*m NSCLC after failure of EGFR TKI therapy. We now present extended follow-up of pts receiving the recommended dose for expansion (5.6 mg/kg IV Q3W). **Methods**: This Ph 1 dose-escalation/expansion study included pts with locally advanced or metastatic *EGFR*m NSCLC with prior EGFR TKI therapy (NCT03260491). Pts with stable brain metastases (BM) were allowed. The primary endpoint was confirmed ORR by blinded independent central review (BICR) per RECIST v1.1; secondary endpoints included DOR, PFS and safety. **Results**: At data cutoff (Sept 24, 2020), 57 pts were treated with HER3-DXd 5.6 mg/kg IV Q3W; median follow-up, 10.2 mo (range, 5.2-19.9 mo). Median number of prior anticancer regimens was 4 (range, 1-10). 100% had prior EGFR TKI (86% prior osimertinib [OSI]) and 91% had prior PBC. 47% had a history of BM. Median treatment duration was 5.5 mo (range, 0.7-18.6 mo); treatment was ongoing in 18 pts (32%). Confirmed ORR by BICR was 39% (22/57; 95% CI, 26.0%-52.4%; 1 CR, 21 PR, 19 SD) with 14/22 responses occurring within 3 mo of starting HER3-DXd. DCR was 72% (95% CI, 58.5%-83.0%). Median DOR was 6.9 mo (95% CI, 3.1 mo-NE), and median PFS was 8.2 mo (95% CI, 4.4-8.3 mo). Antitumor activity was observed across diverse mechanisms of EGFR TKI resistance, including those not directly related to HER3 (*EGFR* C797S, MET or HER2 amp, and BRAF fusion). Among pts with prior PBC, ORR was 37% (19/52; 95% CI, 23.6%-51.0%); in pts with prior OSI and PBC, ORR was 39% (17/44; 95% CI, 24.4%-54.5%). Among 43 pts evaluable for HER3 expression, nearly all expressed HER3; median membrane H-score by IHC was 180 (range, 2-280). Median H-score (range; N) was 195 (92-268; 15) in pts with CR/PR, 180 (4-280; 15) with SD, 126.5 (2-251; 6) with PD, and 180 (36-180; 7) in pts unevaluable for best overall response. The most common grade ≥3 adverse events (AEs) were thrombocytopenia (30%), neutropenia (19%), and fatigue (14%). Drug-related interstitial lung disease by central adjudication occurred in 4 pts (7%; 1 grade ≥3 [2%]; no grade 5). 6/57 pts (11%) had AEs associated with treatment discontinuation (none were due to thrombocytopenia). **Conclusions**: HER3-DXd 5.6 mg/kg IV Q3W demonstrated antitumor activity across various EGFR TKI resistance mechanisms in heavily pretreated metastatic/locally advanced *EGFR*m NSCLC. The safety profile was consistent with previous reports. A Ph 2 study of HER3-DXd in pts with *EGFR*m NSCLC after failure of EGFR TKI and PBC has been initiated (NCT04619004). Clinical trial information: NCT03260491. Research Sponsor: Daiichi Sankyo, Inc.

9008 **Oral Abstract Session**

Preliminary safety and efficacy results from phase 1 studies of DZD9008 in NSCLC patients with EGFR Exon20 insertion mutations.

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Background: There are no approved targeted therapies for EGFR exon20 insertion (exon20ins) mutant NSCLC. DZD9008 is a rationally designed selective, irreversible EGFR exon20ins inhibitor being studied in two ongoing phase 1/2 studies (NCT03974022 and CTR20192097). **Methods:** The objectives of the studies are to assess the safety, tolerability, pharmacokinetics, and preliminary anti-tumor efficacy of DZD9008 in NSCLC with EGFR or HER2 mutations. Both studies include dose escalation and expansion cohorts. Pooled analysis is applied to define recommended phase 2 dose (RP2D). **Results:** Between July 9, 2019 and February 5, 2021, 97 NSCLC patients with EGFR or HER2 mutations were dosed with DZD9008 (dose range: 50 mg to 400 mg, once daily). M/F: 44/53; 59 with EGFR exon 20. DZD9008 was well tolerated up to 400 mg (MTD) once daily. The DLTs were diarrhea and cardiac arrhythmia. The most common TEAEs were diarrhea (grade 3, 5.2%) and skin rash (grade 3, 1%). DZD9008 showed approximately dose-proportional PK, with a half-life of around 50 hours. Fifty-six patients with $>$ 16 different EGFR exon20ins mutations had $>$ 1 post-treatment efficacy assessment. Prior therapies: median 2 (range 1 - 10), prior chemotherapy 92.9% (52/); prior TKI 44.6% (25/56) including 1 patient had poziotinib treatment; 42.9% (24/56) with brain metastasis. Partial response was observed at $\geq$ 100 mg dose levels. At the RP2D dose of 300 mg once daily, the objective response rate was 48.4% (15/31), and disease control rate (DCR) was 90.3% (28/31). Responses were observed in 2 patients with prior JNJ-61186372 treatment. Anti-tumor activity was observed across different EGFR exon20ins mutation subtypes. By data cut-off, the median treatment duration was 100 days (range 1 – 422). The longest duration of response was over 6 months, and 18 out of 22 responders are still responding. **Conclusions:** DZD9008 showed a favorable safety profile and promising anti-tumor efficacy in pre-treated NSCLC with EGFR exon20ins mutations. The updated data will be presented at the meeting. DZD9008 is currently in phase II clinical development (NCT03974022). Clinical trial information: NCT03974022. Research Sponsor: Dizal pharma.

9009 **Clinical Science Symposium**

Overall survival with circulating tumor DNA-guided therapy in advanced non-small cell lung cancer.

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Background: The effectiveness of circulating tumor DNA (ctDNA) at matching patients to life prolonging therapy has been studied mostly in small cohorts with limited follow up. The prognostic value of ctDNA alterations, particularly those absent on tissue, is also unclear. To address these questions, we studied survival outcomes in a prospective cohort of patients (N = 1002) with non-small cell lung cancer (NSCLC). **Methods:** Adults with metastatic or recurrent NSCLC were eligible if they had no known driver mutation or a known driver with progression following targeted therapy. Patients were enrolled at Memorial Sloan Kettering Cancer Center (New York, NY) starting October 21, 2016; analysis here is from a snapshot November 1, 2020. All patients had ctDNA sequenced via the Resolution ctDx Lung platform. To reduce inclusion of incidental germline mutations, we excluded non-functionally significant mutations with an allele frequency 35-65% that were present in gnomAD. Patients could also receive, at their provider's discretion, tissue sequencing with MSK-IMPACT, which filters germline and clonal hematopoietic (CH) mutations with matched white blood cell sequencing. We performed survival analyses using Cox proportional hazards models from time of diagnosis of advanced disease to death, left truncating at time of study entry. **Results:** Of 1002 patients, 348 (35%) were treated with targeted therapy; in 181 of these (52%) the targetable alteration was detected in ctDNA. Patients treated with targeted therapy had prolonged survival whether matched by tissue-based methods (HR 0.39, 95%CI 0.30-0.51) or ctDNA (HR 0.47, 95%CI 0.37-0.61). These benefits persisted across multiple subgroups. ctDNA alterations themselves were associated with worse survival (HR 2.2, 95%CI 1.8-2.8), in a manner that scaled with allele fraction and burden. Of 401 patients with time-matched tissue sampling, 62 (15%) had ctDNA alterations that were absent on IMPACT ("unique" ctDNA alterations). Three such patients had unique ctDNA EGFR T790M mutations leading to changes in therapy. However, unique ctDNA alterations were generally associated with worse survival than no ctDNA alterations (HR 2.5, 95%CI 1.7-3.7) and even tissue-matched ctDNA alterations (HR 1.7, 95%CI 1.1-2.4). Of 98 unique ctDNA mutations, 48 (49%) were detectable in tissue at subthreshold levels, 12 (12%) were filtered by IMPACT as CH or germline, and 38 mutations (39%) were absent even at subthreshold levels. ctDNA alteration burden correlated with radiographic disease extent. In multivariate models with radiographic disease extent and other clinical variables, ctDNA alterations were the strongest independent predictor of worse survival. **Conclusions:** Our results show that ctDNA may match patients to life-prolonging targeted therapy and have prognostic importance. ctDNA may provide data about a patient's cancer missed by spatially restricted tissue sequencing. Clinical trial information: NCT01775072. Research Sponsor: U.S. National Institutes of Health.

9010 **Poster Session**

Concordance of tissue- and plasma-derived genomic profiling in CheckMate 9LA, using the FoundationOne CDx and GuardantOMNI assays.

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Background: Blood-based profiling of genomic features including tumor mutational burden (TMB) has generally demonstrated positive correlations with tissue-derived assessments from paired tumor samples. However, both technical and biological factors contributing to discordance between these measurements and underlying sequence alterations need further investigation for the successful adoption of noninvasive tumor profiling. We explored the genomic landscape, including the association between tissue TMB (tTMB) and blood TMB (bTMB), in samples from patients with stage IV non-small cell lung cancer (NSCLC) enrolled in CheckMate 9LA (NCT03215706), a phase 3, randomized clinical trial of nivolumab + ipilimumab in combination with 2 cycles of chemotherapy (chemo) vs 4 cycles of chemo as first-line treatment for NSCLC. **Methods:** Tissue- (FoundationOne CDx [F1CDx]) and blood-based (GuardantOMNI [OMNI]) genomic data obtained from both treatment arms were utilized for our retrospective analysis of genomic variants and complex biomarkers, including tTMB and bTMB. In total, 692 tissue and 646 plasma samples were analyzed. **Results:** Following the established criteria for the validated F1CDx and OMNI platforms, 464 tissue and 537 plasma samples passed quality control, resulting in ascertainment levels of 67% for tTMB and 83% for bTMB. Across 344 paired tissue and plasma samples, tTMB and bTMB scores were found to be moderately correlated (Spearman's $r = 0.56$; $P < 0.001$); median tTMB score was 7.7 mutations per megabase (mut/Mb) and median bTMB score was 13.5 mut/Mb. For the prespecified cutoffs of 10 mut/Mb for tTMB and 16 mut/Mb for bTMB, the positive, negative, and overall percentage agreements between assays were 65%, 79%, and 73%, respectively. Interestingly, 2 discordant sample pairs had considerably higher bTMB than tTMB (76.1 vs 3.8 and 172.6 vs 5.0 mut/Mb for bTMB and tTMB, respectively) and both had high microsatellite instability from blood-based assessments. OMNI and F1CDx data from 477 patients were evaluable for the analysis of short sequence variants (single nucleotide variations and indels). OMNI detected 4557 variants, F1CDx detected 4620, and 2903 (46% of total reported variants) were detected by both assays. **Conclusions:** In CheckMate 9LA, data from paired samples revealed the complementary nature of TMB assessments from tissue and blood and suggest that both approaches may have the potential to identify genomic alterations that may be useful in the management of patients with NSCLC. Further interrogation of the biological and analytical factors affecting tumor- and blood-derived genomic profiling is warranted to support their implementation in clinical settings. Clinical trial information: NCT03215706. Research Sponsor: Bristol Myers Squibb.

9011 **Clinical Science Symposium**

Early circulating tumor (ct) DNA dynamics and efficacy of lorlatinib: Analysis from the CROWN study.

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Background: Lorlatinib, a third-generation ALK tyrosine kinase inhibitor, significantly improved progression-free survival (PFS) and overall/intracranial responses vs crizotinib in patients (pts) with previously untreated *ALK*-positive advanced non-small cell lung cancer (NSCLC) in the ongoing randomized Phase 3 CROWN study (NCT03052608). To identify whether additional molecular biomarker analysis correlated with efficacy, we evaluated early ctDNA dynamics compared with clinical outcomes. **Methods:** Plasma samples were prospectively collected at screening (SC), week 4 (cycle 2, day 1 [C2D1]), week 24 (C7D1), and end of treatment for ctDNA analysis. ctDNA was analyzed using Guardant360CDx (Guardant Health, Inc., Redwood City, CA, USA). Mean variant allele fraction (VAF) of *ALK* alterations (fusions and/or mutations) and overall detected alterations at each time point and longitudinal mean change (dVAF) as (VAF_{C2D1}) – (VAF_{SC}) were calculated; dVAF <0 indicated decreased ctDNA at week 4. Objective tumor response and PFS were evaluated according to dVAF. These analyses were repeated vs ctDNA results at week 24. Additional correlation analyses between depth of molecular response and/or ctDNA clearance and clinical outcomes are ongoing. **Results:** Paired samples were available at SC and week 4 from 232 of 255 pts included in the ctDNA analysis: 118/130 (90.8%) in the lorlatinib arm and 114/125 (91.2%) in the crizotinib arm. *ALK* alterations were detected in 122/232 (52.6%) pts at SC (62/118 [52.5%] from the lorlatinib arm) but only 19/232 (8.2%) at week 4 (8/118 [6.8%] from the lorlatinib arm). Mean VAF of *ALK* alterations at week 4 was significantly decreased compared with SC in both treatment arms (lorlatinib -1.54, crizotinib -1.25; both $P<0.0001$; $P=0.4239$ between arms). In the lorlatinib arm, mean VAF at week 4 was significantly decreased compared with SC in pts with a complete or partial response (dVAF -1.53; n=47; $P<0.0001$), or stable disease (dVAF -1.37; n=12; $P=0.0304$). Similar results were observed in the crizotinib arm. In pts with dVAF <0 for *ALK* alterations, mean percent change from screening in tumor size was -40.8% with lorlatinib (n=59) and -38.7% with crizotinib (n=58). Only 2 pts had dVAF ≥ 0, both from the crizotinib arm. Median PFS for pts with dVAF <0 for *ALK* alterations was not reached in the lorlatinib arm (n=62), and was 7.4 months (95% CI, 7.2–9.3) in the crizotinib arm (n=58). Similar response and PFS data were observed in the analysis of dVAF for *ALK* alterations at week 24. **Conclusions:** Early ctDNA dynamics may predict lorlatinib efficacy in pts with previously untreated *ALK*-positive NSCLC. The magnitude of reduction in ctDNA at 4 weeks may be associated with better responses and potentially longer PFS. These findings further support the utility of dynamic ctDNA monitoring in *ALK*-positive NSCLC. Reference: Shaw AT, et al. N Engl J Med. 2020;383:2018-2029. Clinical trial information: NCT03052608. Research Sponsor: Pfizer Inc.

*MET*ex14 ctDNA dynamics & resistance mechanisms detected in liquid biopsy (LBx) from patients (pts) with *MET*ex14 skipping NSCLC treated with tepotinib.

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Background: In the VISION study, tepotinib in *MET*ex14 skipping NSCLC pts (Cohort A) had robust and durable clinical activity. Serial LBx samples were collected for biomarker analyses, presented herein. **Methods:** LBx samples taken at baseline (BL), Week 6, 12, & end of treatment (EOT) were analyzed using Guardant360® CDx (73 genes). Investigator (INV)-assessed clinical outcome was evaluated per BL biomarker profiles and by molecular response (MR; defined as $>$ 75% depletion from BL in *MET*ex14 variant allele frequency [VAF] ctDNA confirmed in 2 consecutive samples) or molecular progression (MP; defined as VAF increase $>$ 0 from BL). Acquired resistance was investigated in EOT samples, following progression per INV. **Results:** LBx pts (n = 99) had a median age of 72 yrs (range 49–88), 53% were male, 44% never smokers, 85% had adenocarcinoma. INV ORR was 53% (95% CI 42, 63); ORR in 1L (n = 44) was 59% (43, 74) & $\geq$2L (n = 55) was 47% (33, 61). 94 pts had BL biomarker profiles; these were similar in 1L and $\geq$2L pts, except *EGFR* amp: 1/43 1L [2%] vs 8/51 $\geq$2L [16%]. Outcomes were not impacted by location/type of *MET*ex14 alteration. 1 pt with concomitant *MET* M1250T mutation had a PFS of 17.3 months. A trend towards better efficacy was seen in pts with concomitant *MET* amp (6 responses in 8 pts). Response to tepotinib occurred both in pts with wt or mutant *TP53*; however, there was a trend for longer mDOR in pts with wt *TP53* (18.3 [95% CI 9.7, ne] vs 7.1 [4.7, 10.9] months) and mPFS (9.5 [6.7, 19.7] vs 5.1 [2.8, 6.9] months). Concomitant oncogenic mutations were rare, with no responses in 3 pts with *KRAS*, *NRAS* alterations and 3 responses in 5 pts with *PI3K/AKT* alterations. 65 pts had 2 consecutive on-treatment samples: 46 (71%) had confirmed MR, 5 (8%) had confirmed MP, 14 (22%) had no change in VAF or lacked confirmation. MR was associated with clinical response and MP was associated with no response/short PFS (Table). 52 pts with progression had EOT LBx samples. Emerging *MET* resistance mutations (Y1230H/C & D1228H/N) occurred in 7 (13%) pts, all responders and 5/7 had PFS $>$ 10 months. Analyses on non-MET-driven resistance mechanisms will be presented. **Conclusions:** LBx biomarker analysis from the largest on-treatment data set for a MET inhibitor in *MET*ex14 skipping NSCLC, showed that ctDNA depletion in *MET*ex14 VAF is associated with improved clinical response in pts treated with tepotinib. This suggests serial LBx could help us to monitor response/non-response, understand resistance, and guide trials that test escalation/de-escalation strategies to improve outcomes and maximize QOL. Clinical trial information: NCT02864992. Research Sponsor: Merck KGaA, Darmstadt, Germany.

	All		1L		≥2L	
N	65		30		35	
Confirmed molecular status	MR	MP	MR	MP	MR	MP
n (%)	46 (71)	5 (8)	20 (67)	4 (11)	26 (74)	1 (3)
ORR, n (%)	35 (76)	0	18 (90)	0	15 (58)	0
mDOR, months (95% CI)	14 (9.8, ne)	0	18 (7.23, ne)	0	14 (9.69, ne)	0
DCR, n (%)	42 (91)	3 (60)	18 (90)	2 (50)	24 (92)	1
mPFS, months (95% CI)	11.0 (8.6, 17.7)	5.5 (2.8, ne)	19.7 (9.67, ne)	4.8 (2.8, ne)	9.9 (6.9, 13.8)	5.8

9013 **Poster Discussion Session**

Randomized phase III trial of aumolertinib (HS-10296, Au) versus gefitinib (G) as first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) and EGFR exon 19 del or L858R mutations (EGFRm).

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Background: Au is a novel, irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) with favorable pharmacologic properties that selectively inhibits both EGFR sensitizing and resistance mutations. Au has been approved in China for treatment of patients (pts) with EGFR mutant NSCLC with EGFR T790M upon progression of disease on previous EGFR TKIs (Proc. AACR 2020, Abstract CT190). This Phase III trial assessed the efficacy and safety of Au versus G as initial treatment of patients with advanced NSCLC with EGFRm. **Methods:** Pts with previously untreated metastatic or locally advanced NSCLC and EGFR exon 19 deletion or L858R were randomly assigned in a 1:1 ratio to receive either Au (110 mg once daily) or G (250 mg once daily). The primary endpoint was progression-free survival (PFS) by RECIST v1.1 per investigator assessment. At 262 PFS events, the study had 90% power to detect a PFS HR = 0.67. Secondary endpoints included overall survival (OS), objective response rate (ORR), duration of response (DoR) and safety. **Results:** Between Nov 30, 2018 and Sept 6, 2019, 429 patients across 53 sites in China were enrolled and randomized. Pt. characteristics were well-balanced. At the planned final event-driven PFS analysis, Au significantly prolonged PFS (median 19.3 vs 9.9 months, HR 0.46, p-value <0.0001). DoR was also significantly prolonged with Au. Median OS has not been reached. Efficacy and relevant safety results are summarized in Table. Despite a significantly longer duration of treatment (median 463 vs 254 days), Au was associated with a lower incidence of rash, diarrhea, AST/ALT increase, and treatment related serious adverse events (SAEs) (4.2% vs 11.2%). Au was associated with more frequent events of CPK increased, platelet count decreased, and neutrophil count decreased, which were predominantly low grade. **Conclusions:** Au significantly prolonged PFS and DoR compared to G as first-line therapy in pts with advanced NSCLC with EGFRm. Au demonstrated a favorable safety profile, especially regarding toxicities mediated by wild-type EGFR. These results establish Au as a promising option for advanced NSCLC with EGFRm. Clinical trial information: NCT03849768. Research Sponsor: Hansoh Pharma.

	Au (N=214)	G (N=215)	Hazard ratio (95% CI)	P-value
Efficacy				
Median PFS (95% CI), mo	19.3 (17.8, 20.8)	9.9 (8.3, 12.6)	0.46 (0.36, 0.60)	<0.0001
Median DoR (95% CI), mo	18.1 (15.2, NA)	8.3 (6.9, 11.1)	0.38 (0.28, 0.51)	<0.0001
Selected AEs, n (%)				
Alanine aminotransferase increased	63 (29.4)	120 (55.8)		
Aspartate aminotransferase increased	64 (29.9)	116 (54.0)		
Rash	50 (23.4)	89 (41.4)		
Diarrhea	35 (16.4)	77 (35.8)		
Creatine phosphokinase increased	76 (35.5)	20 (9.3)		

Mobocertinib (TAK-788) in *EGFR* exon 20 insertion (ex20ins)+ metastatic NSCLC (mNSCLC): Additional results from platinum-pretreated patients (pts) and EXCLAIM cohort of phase 1/2 study.

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Background: No approved targeted therapies are available for *EGFR* ex20ins+ mNSCLC. Mobocertinib, a first-in-class, potent, oral TKI targeting *EGFR* ex20ins mutations, has Breakthrough Therapy Designation in the US and China for post-platinum-based chemotherapy pts with *EGFR* ex20ins+ mNSCLC. **Methods:** This 3-part, open-label, multicenter study (NCT02716116) has dose-escalation/expansion and extension (EXCLAIM) cohorts. Pts with *EGFR* ex20ins+ mNSCLC, ECOG status 0–1, and ≥1 prior line of therapy for locally advanced/metastatic disease received mobocertinib 160 mg QD. Primary endpoint was confirmed objective response rate (ORR; RECIST v1.1) assessed by independent review committee (IRC). We present additional efficacy and safety data for 114 platinum-pretreated pts (PPP) and 96 pts from EXCLAIM safety cohort. **Results:** Results are from Nov 1, 2020, data cutoff. Among PPP pts (n=114; median age 60 y [27–84 y]), 66% were female, 60% were Asian, and 59% had ≥2 prior systemic anticancer lines. Confirmed ORR per IRC was 28%, including 1 complete response (CR); disease control rate (DCR) was 78% [95% CI: 69–85]; median duration of response (DOR) was 17.5 mo (Table). In EXCLAIM (n=96; median age 59 y [27–80 y]), 65% were female, 69% were Asian, and 49% had ≥2 prior lines. Confirmed ORR per IRC was 25%, with 1 CR; DCR was 76% [95% CI: 66–84]; median DOR was not reached (Table). In EXCLAIM, baseline brain metastases were present in 33/96 pts (34%); the first site of disease progression by IRC was the brain in 40% of all pts and 73% of pts with baseline brain metastases. Confirmed responses were seen in all prespecified subgroups in PPP and EXCLAIM. Efficacy by *EGFR* ex20ins mutation variant will be presented. Treatment-related adverse events (TRAEs; >20%) in PPP were diarrhea (91%), rash (45%), paronychia (38%), decreased appetite (35%), nausea (34%), dry skin (31%), vomiting (30%), increased blood creatinine (25%), stomatitis (24%), and pruritus (21%); the only grade ≥3 TRAE in ≥5% was diarrhea (22%). AEs leading to discontinuation in >2% were diarrhea (4%) and nausea (4%). A similar safety profile was observed in EXCLAIM. **Conclusions:** Mobocertinib demonstrated clinically meaningful benefit for pts with *EGFR* ex20ins+ mNSCLC in PPP and EXCLAIM cohorts, with a manageable safety profile.Clinical trial information: NCT02716116. Research Sponsor: Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

	PPP(n=114)	EXCLAIM(n=96)
Median follow-up, mo	14.2	13.0
Confirmed ORR, n (%) [95% CI] Per IRC	32 (28) [20–37]	24 (25) [17–35]
Per investigator	40 (35) [26–45]	31 (32) [23–43]
Median DOR, mo [95% CI] Per IRC	17.5 [7.4–20.3]	NE [5.6–NE]
Per investigator	11.2 [5.6–NE]	11.2 [7.0–NE]
Median progression-free survival, mo [95% CI] Per IRC*	7.3 [5.5–9.2]	7.3 [5.5–9.1]
Median OS, mo [95% CI]	24.0 [14.6, 28.8]	NE [13.1, NE]
6 mo OS rate, %	87%	87%
12 mo OS rate, %	70%	69%

*Investigator-assessed median PFS was similar in both cohorts.

9015 **Poster Discussion Session**

Combination of trastuzumab, pertuzumab and docetaxel in patients with advanced non-small cell lung cancer (NSCLC) harboring HER2 mutation: Final results from the IFCT-1703 R2D2 trial.

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Background: Human epidermal growth factor receptor 2 (*HER2)* exon 20 insertions and mutations are oncogenic drivers found in 1-2% of NSCLC. However, there are no approved therapies for these patients. Many studies suggest that the use of HER2 inhibitors developed for breast cancer patients might be of interest in this setting. The aim of this trial was to prospectively evaluate the interest of a combination of two antibodies against HER2 (trastuzumab and pertuzumab) with docetaxel. **Methods:** IFCT-1703 R2D2 trial is a multicenter, non-randomized phase 2 study with a two-stage design, a power of 90% and an alpha risk at 5% (one-sided). *HER2* mutational status was assessed locally in certified molecular genetic centers. Main other inclusion criteria were advanced NSCLC, progression after $\geq$ 1 platinum-based chemotherapy, asymptomatic brain metastases, left ventricular ejection fraction (LVEF) $\geq$ 50%, and PS 0-2. Patients were treated every 3 weeks with pertuzumab at a loading dose of 840 mg, and 420 mg thereafter; plus trastuzumab at a loading dose of 8 mg/kg and 6 mg/kg thereafter; and docetaxel at 75 mg/m^2. Treatment was given until toxicity or disease progression. The primary outcome was overall response rate (ORR). Other endpoints included duration of response, progression-free survival and safety. NCT number: NCT03845270. **Results:** From May 2019 to October 2020, 45 patients were enrolled in 17 centers and received study treatment. Median age was 64.5 years (range 31–84), 72% females, 35% smokers, 100% non-squamous histology and 15% with ECOG PS 2. 31.1% patients had brain metastases. PD-L1 was expressed $\geq$ 1% and $\geq$ 50% in 36% and 7% of the patients, respectively. No other oncogene driver was found associated with HER2 exon 20 mutation. With a median follow-up of 12 months, 44 (98%) patients were evaluable for the primary endpoint. Overall response rate was 29% (n = 13), stable disease 56% (n = 26). Median PFS was 6.8 months (95% CI[4.0-8.5]). Median duration of treatment in patients with confirmed response (n = 13) was 10 months (95% CI[2.7-14.9]). At the time of data cut-off, 15 patients (33%) were still under treatment. Grade 3/4 treatment-related adverse events (AEs) were observed in 64% of patients. No patient experienced treatment discontinuation because of toxicity. One sudden death was possibly related to treatment. Most frequent grade $\geq$ 3 AEs were neutropenia (33%), diarrhea (13%) and anaemia (9%). Grade 1/2 dyspnea was observed in 3 (6.7%) patients. No ILD were reported. Variation LVEF was -1.72% on average (min: -18 %; max: 10 %). **Conclusions:** The triplet trastuzumab, pertuzumab and docetaxel is feasible and active in *HER2* pretreated advanced NSCLC. These results confirm the activity of *HER2* antibodies-based strategy which should be considered in these patients. Clinical trial information: NCT03845270. Research Sponsor: Intergroupe Francophone de Cancerologie Thoracique, Pharmaceutical/Biotech Company.

Nivolumab (NIVO) plus ipilimumab (IPI) versus chemotherapy (chemo) as first-line (1L) treatment for advanced non-small cell lung cancer (NSCLC): 4-year update from CheckMate 227.

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Background: 1L NIVO + IPI was shown to provide durable long-term overall survival (OS) benefit vs chemo regardless of tumor programmed death ligand 1 (PD-L1) expression in patients (pts) with advanced NSCLC in CheckMate 227 Part 1 (NCT02477826); 3-year OS rates were 33% vs 22% in pts with PD-L1 $\geq$ 1% (HR, 0.79 [95% CI, 0.67–0.93]) and 34% vs 15% in pts with PD-L1 $<$ 1% (HR, 0.64 [95% CI, 0.51–0.81]). Here we report updated results from the study with 4 years' minimum follow-up. **Methods:** Adults with previously untreated stage IV / recurrent NSCLC, no known *EGFR*/*ALK* alterations, and ECOG performance status $\leq$ 1 were enrolled; pts were stratified by squamous (SQ) and non-squamous (NSQ) histology. Pts with PD-L1 $\geq$ 1% (n = 1189) were randomized 1:1:1 to receive NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), NIVO alone (240 mg Q2W), or chemo. Pts with PD-L1 $<$ 1% (n = 550) were randomized 1:1:1 to receive NIVO + IPI, NIVO (360 mg Q3W) + chemo, or chemo. OS with NIVO + IPI vs chemo in pts with PD-L1 $\geq$ 1% was the primary endpoint. **Results:** With minimum follow-up of 49.4 months (database lock, Feb 18, 2021), pts were at least 2 years beyond the protocol-specified end of immunotherapy treatment. Pts with PD-L1 $\geq$ 1% continued to show durable benefit with NIVO + IPI vs chemo (HR, 0.76 [95% CI, 0.65–0.90]); 4-year OS rates were 29% (NIVO + IPI), 21% (NIVO), and 18% (chemo). At 4 years, 14% (NIVO + IPI), 10% (NIVO), and 4% (chemo) remained progression free. Among responders, 34%, 30%, and 7% remained in response, respectively. In an exploratory analysis in pts with PD-L1 $\geq$ 50%, 4-year OS rates were 37% (NIVO + IPI), 26% (NIVO), and 20% (chemo). In pts with PD-L1 $<$ 1%, OS HR for NIVO + IPI vs chemo was 0.64 (95% CI, 0.51–0.81); 4-year OS rates were 24% (NIVO + IPI), 13% (NIVO + chemo) and 10% (chemo). At 4 years, 12% (NIVO + IPI), 7% (NIVO + chemo), and 0% (chemo) remained progression free. Among responders, 31%, 13%, and 0% remained in response, respectively. Among pts who progressed on NIVO + IPI vs chemo, 7% vs 40% (PD-L1 $\geq$ 1%), and 9% vs 33% (PD-L1 $<$ 1%), received subsequent immunotherapy. Benefit with NIVO + IPI vs chemo was observed for both SQ and NSQ histology (Table). With long-term follow-up, no new safety signals were identified. **Conclusions:** With 4 years' minimum follow-up, 1L NIVO + IPI continued to provide durable, long-term OS benefit vs chemo in pts with advanced NSCLC regardless of PD-L1 expression or histology. Clinical trial information: NCT02477826. Research Sponsor: Bristol Myers Squibb and Ono Pharmaceutical.

OS with NIVO + IPI vs chemo by PD-L1 expression and histology.

PD-L1	≥ 1%	≥ 1%	< 1%	< 1%
Histology	NSQ	SQ	NSQ	SQ
	NIVO + IPI (n = 278) vs chemo (n = 279)	NIVO + IPI (n = 118) vs chemo (n = 118)	NIVO + IPI (n = 141) vs chemo (n = 140)	NIVO + IPI (n = 46) vs chemo (n = 46)
Median OS, months	19.4 vs 17.2	14.8 vs 9.2	17.5 vs 13.1	15.9 vs 8.5
HR (95% CI)	0.81 (0.67–0.99)	0.68 (0.51–0.89)	0.69 (0.53–0.89)	0.53 (0.34–0.84)
4-year OS rate, %	32 vs 23	20 vs 6	25 vs 12	22 vs 7

9017 **Poster Discussion Session**

Effect of antibiotic therapy on immunotherapy outcomes for non-small cell lung cancer: Analysis from the Veterans Health Administration Database.

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Background: Dysregulation of the gut microbiota induced by antibiotic therapy (Abx) may alter the anticancer immune response. Multiple small studies have associated Abx use with inferior immune checkpoint inhibitor (ICI) efficacy in patients with non-small cell lung cancer (NSCLC). We aimed to study the impact of Abx in a larger population of NSCLC patients treated with ICI within the Veterans Health Administration. **Methods:** We conducted a nested cohort study of Veterans who were diagnosed with NSCLC between 2010 & 2018 and treated with ICI. Two exposures to Abx were specified and separately analyzed: prior Abx (pAbx) was defined as receipt of an Abx prescription within 30 days prior to initiation of ICI, and concurrent Abx (cAbx) was defined as receipt of an Abx prescription within 60 days following ICI initiation. A landmark analysis of 2 months from ICI start was applied to the cAbx analysis to exclude any Veterans with an OS event before that time point. OS was measured from start of ICI using Cox proportional hazard multivariate analyses (MVA). **Results:** 3,634 Veterans received ICI, mostly nivolumab (59.3%) or pembrolizumab (35.1%). Their median age was 69, and a plurality had male gender (97.0%), white race (73.0%), comorbidity count $\geq$1 (60.4%), adenocarcinoma (47.8%), and stage IV disease at diagnosis (40.9%). Of the 762 (21.0%) Veterans prescribed pAbx, beta-lactams, quinolones, and macrolides were the most common classes. These patients had shorter OS than those without pAbx (median 7 versus 10 months). Receipt of pAbx was also associated with lower OS on MVA (HR 1.31, $p<0.01$). In the propensity-matched cohort analysis, Veterans receiving pAbx had lower OS (HR 1.27, $p<0.01$) (Table top). For the cAbx analysis, 3,223 Veterans survived to the 2-month landmark, of whom 970 (30.1%) received cAbx. These Veterans had shorter OS than those without cAbx (median 7 versus 10 months). Lower OS with cAbx was also observed both on Cox MVA (HR 1.33, $p<0.01$) and in the matched cohort (HR 1.32, $p<0.01$) (Table bottom). **Conclusions:** In the largest analysis to date of Abx use in NSCLC patients receiving ICI, receipt of Abx within either 30 days before or 60 days after start of ICI was associated with lower OS. These findings suggest Abx therapy may have a detrimental effect on immunotherapy outcomes. Research Sponsor: Morningside Center for Innovative and Affordable Medicine, Emory Woodruff Health Sciences Center, Other Government Agency.

	No. of Pts	Median OS	Cox MVA HR	Cox MVA 95%CI	Matched No. of Pts	Matched median OS	Matched UVA HR	Matched UVA 95%CI
pAbx								
no	2,872	10 m	-	-	760	9 m	-	-
yes	762	7 m	1.31	1.20-1.44	760	7 m	1.27	1.14-1.41
cAbx								
no	2,253	10 m	-	-	968	10 m	-	-
yes	970	7 m	1.33	1.21-1.45	968	7 m	1.32	1.19-1.46

Association of a very high tumor mutational load with increased CD8+ and PD-1+ T-cell infiltration and improved clinical outcomes to PD-(L)1 blockade across different PD-L1 expression levels in non-small cell lung cancer.

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Background: Although high TMB correlates with improved outcomes to immune checkpoint inhibitors (ICI) in patients (pts) with non-small cell lung cancer (NSCLC), an optimal TMB cutoff to discriminate cancers most likely to respond to ICI has not been identified. Whether TMB impacts outcomes to ICI in different PD-L1 levels subgroups is also unclear. **Methods:** Unbiased recursive partitioning (URP) was used to identify an optimal TMB cutoff for objective response rate (ORR) in two independent cohorts of pts with NSCLC treated with ICI at DFCI and MSKCC. TCGA was interrogated to find differences in tumor immune cell subsets according to the TMB cutoff identified. Multiplexed immunofluorescence (IF) for CD8, PD-1, PD-L1, Foxp3, and CK7 was also performed on NSCLC samples at the DFCI. **Results:** In the DFCI (N=686) and MSKCC (N=672) cohorts, URP found an optimal TMB cutoff for ORR at 19 mutations/megabase (mut/Mb), corresponding to the ~90th percentile in each cohort. Median progression-free (PFS) and overall survival (OS) were significantly longer in NSCLCs with TMB ≥19 mut/Mb vs <19 mut/Mb, in both cohorts (Table). After harmonizing TMB between DFCI OncoPanel and MSK-IMPACT NGS platforms, URP confirmed an optimal TMB cutoff for ORR at the 90th percentile in the combined cohort, which also associated with longer PFS/OS to ICI (Table). A TMB ≥90th percentile correlated with longer PFS/OS to ICI among NSCLCs with PD-L1 levels ≥50% and 1-49%, and longer PFS among those with PD-L1 <1% (Table). Cell subset transcriptome analysis from the TCGA showed higher proportions of CD8+ T cells (P=0.02) and M1 macrophages (P<0.01) among NSCLCs with a TMB ≥ vs <90th percentile. IF confirmed increased CD8+, CD8+ PD1+ T-cell infiltration (P<0.01), and increased CD8+/Foxp3+ ratio in NSCLC with very high TMB. **Conclusions:** A very high TMB is associated with better outcomes to ICI and a distinct immunophenotype in NSCLC. Rational integration of TMB and PD-L1 expression may identify NSCLCs most likely to respond to ICI. Research Sponsor: None.

Cohort	PD-L1 expression	PFS TMB ≥ vs <90th percentile HR [95%CI], P	OS TMB ≥ vs <90th percentile HR [95%CI], P
DFCI N=686	0-100	0.48 [0.36-0.65], P<0.01	0.57 [0.41-0.78], P<0.01
MSKCC N=672	0-100	0.38 [0.28-0.52], P<0.01	0.46 [0.33-0.65], P<0.01
DFCI+MSKCC	0-100	0.44 [0.35-0.54], P<0.01	0.50 [0.39-0.64], P<0.01
DFCI+MSKCC	≥50%	0.52 [0.34-0.81], P<0.01	0.54 [0.32-0.94], P=0.03
	1-49%	0.33 [0.19-0.57], P<0.01	0.36 [0.19-0.69], P<0.01
	<1%	0.40 [0.25-0.65], P<0.01	0.72 [0.34-1.18], P=0.19

9019 **Poster Discussion Session**

Intestinal *Akkermansia muciniphila* predicts overall survival in advanced non-small cell lung cancer patients treated with anti-PD-1 antibodies: Results a phase II study.

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Background: The gut microbiome, most specifically centered on one of the most prevalent anaerobic bacterium *Akkermansia muciniphila (Akk),* has emerged as a potential hallmark of clinical benefit to ICI. The goal of this study was to validate the prognostic significance of *Akk* in advanced NSCLC patients amenable to ICI. **Methods:** The multicentric prospective observational study enrolled patients with advanced NSCLC amenable to single agent ICI in first and second line. Stool sample was collected at study entry. Primary end-point was investigator-assessed objective response rate (ORR). We considered that a meaningful clinical difference would correlate to a 10% ORR increase in the Akk-Pos group compared to the Akk-Neg group. At least 292 patients equally divided each in each group would be required for a power at 80% and a two-sided alpha level of 5%. **Results:** From Dec 2015 to Nov 2019, a total of 409 patients were screened and 311 patients enrolled across 12 academic centers in France and Canada. Median age was 64yr, 32% were female, 77% had non-squamous NSCLC and PD-L1 was $\geq$1% in 70% of the 213 assessable samples. *Akk* was detectable in 158 (51%) and absent in 153 (49%) patients. Baseline characteristics were well balanced between the two groups. When considering Akk-Pos *vs* Akk-Neg groups the primary endpoint ORR was 27% and 17% respectively ($p = 0.04$). Rates of partial response, stable disease and progressive disease (PD) were 62%, 50% and 46% respectively in the Akk-Pos group compared to 38%, 50% and 54% in the Akk-Neg group ($p = 0.04$). Moreover, 57% of patients were still alive after 12 months in the Akk-Pos group *vs* 43% in the Akk-Neg group ($p = 0.04$). Microbiome profiling demonstrated that Akk-Pos group was associated with increase bacterial diversity and enrichment of *Ruminococcus, Alistipes* and *Eubacterium.* When considering the variations of the relative abundance of *Akk* within the Akk-Pos group, we obtained a large interval ranging from 0.0022% up to 64.78% with a 75th percentile at 4.42%. The relative abundance of *Akk* within $>$ 0% to $<$ 4.42% range in stools at diagnosis was associated with increased ORR, overall survival (OS) in multivariate analysis, independent of PD-L1 expression and ECOG. This sub-group was associated with more inflamed tumors with upregulation of CD3e, *Ifng*TH1 and Vcam-1. Conversely, patients with over-representation of *Akk* $>$ 4.42% experienced more PD and shorter OS. Antibiotic use was associated with a shift in favor of Gammaproteobacteria, enrichment of *Akk* ($>$ 4.42%) and shorter OS. **Conclusions:** We validated the prognostic role of *Akk* in patients with NSCLC. Stratification based on *Akk* relative abundance represents a more accurate independent predictor than the binary modality. Our study provides the rationale to develop microbiome-based approach to study gut dysbiosis in routine clinical oncology care. Clinical trial information: NCT04567446. Research Sponsor: Torino Lumiere.

Capmatinib in *MET* exon 14-mutated, advanced NSCLC: Updated results from the GEOMETRY mono-1 study.

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Background: Capmatinib, a selective MET inhibitor, is approved in the USA and Japan for the treatment of patients (pts) with *MET* exon 14 skipping mutation (*MET*ex14) advanced non-small-cell lung cancer (NSCLC) based on the multi-cohort phase II GEOMETRY mono-1 study. This is the first report on expansion Cohort 7 in first line (1L) *MET*ex14 NSCLC pts, with updates to previously reported results (Wolf et al, *NEJM* 2020) for *MET*ex14 pts. **Methods:** In GEOMETRY mono-1, pts were assigned to cohorts based on previous lines of therapy and *MET* status (*MET*ex14 or *MET* amplification). This efficacy analysis includes patients with *MET*ex14 NSCLC who were treatment-naive (Cohort 5b and 7) and those who had previously received 1L or 2L of therapy (expansion Cohort 6 and Cohort 4) for their advanced disease (data cutoff: Sep 18, 2020). Evaluated outcomes included overall response rate (ORR), duration of response (DOR), and progression-free survival (PFS), all by BIRC; and overall survival (OS). The safety analysis includes all patients enrolled. **Results:** In total, 160 pts with *MET*ex14 who received capmatinib 400 mg BID were analyzed. ORR of 65.6% (95% CI 46.8-81.4) for the treatment-naive expansion Cohort 7 was in line with that previously reported for Cohort 5b (Table). Though Cohort 7 data are still immature, median PFS was 10.8 mo (95% CI 6.87-not estimable [NE]). Mature median OS was 20.8 mo (95% CI 12.4-NE) in Cohort 5b and 13.6 mo (95% CI 8.6-22.2) in Cohort 4. Median OS for Cohorts 6 and 7 and DOR for Cohort 7 are not yet reached. The safety profile remained unchanged across all study cohorts (N = 373): 98.4% of pts reported AEs (68.6% Grade [G] 3/4) regardless of causality and 16.1% reported AEs leading to discontinuation (10.5% G3/4). The most common AEs (≥20% all G) were peripheral edema (54.2%), nausea (45.0%), vomiting (28.2%), increased blood creatinine (26.5%), dyspnea (23.3%), fatigue (22.3%), and decreased appetite (21.2%). **Conclusions:** Results of Cohort 7 confirm those previously reported for Cohort 5b showing higher efficacy of capmatinib when used as 1L in *MET*ex14 NSCLC pts. A clinically meaningful median OS of 20.8 mo in 1L (Cohort 5b) and of 13.6 mo in relapse (Cohort 4) was also observed and, together with the continued manageable toxicity profile, the data support capmatinib as a valuable targeted treatment option for *MET*ex14 NSCLC pts. Clinical trial information: NCT02414139. Research Sponsor: Novartis Pharmaceuticals.

	Treatment-naive N = 60		Previously treated N = 100	
	Cohort 5b N = 28	Expansion cohort 7 N = 32	Cohort 4 (2/3L) N = 69	Expansion cohort 6 (2L) N = 31
ORR by BIRC* % (95% CI)	67.9 (47.6-84.1)	65.6 (46.8-81.4)	40.6 (28.9-53.1)	51.6 (33.1-69.8)
Median DOR by BIRC† mo (95% CI)	12.6 (5.6-NE)	NE‡ (5.5-NE)	9.7 (5.6-13.0)	8.4 (4.2-NE)
Median PFS by BIRC mo (95% CI)	12.4 (8.2-23.4)	10.8‡ (6.9-NE)	5.4 (4.2-7.0)	6.9 (4.2-13.3)
Median OS mo (95% CI)	20.8 (12.4-NE)	NE‡ (10.6-NE)	13.6 (8.6-22.2)	NE‡ (13.5-NE)

Data cutoff: Sep 18, 2020; *Primary endpoint; †Key secondary endpoint; ‡Not yet mature.

9021 **Poster Discussion Session**

Tepotinib in patients (pts) with advanced non-small cell lung cancer (NSCLC) with *MET* amplification (*MET*amp).

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Background: *MET*amp is an oncogenic driver occurring in 1–5% of NSCLCs that confers a poor prognosis and lacks approved targeted therapies. Tepotinib, a highly selective MET inhibitor, provided durable response in NSCLC with *MET* exon 14 (*MET*ex14) skipping in Cohort A of the Phase II VISION trial (NCT02864992). VISION Cohort B evaluated tepotinib in pts with advanced NSCLC and *MET*amp, as detected by a convenient and minimally invasive liquid biopsy assay, in the absence of *MET*ex14 skipping. **Methods:** Pts with locally advanced or metastatic NSCLC, Eastern Cooperative Oncology Group performance status (ECOG PS) 0–1, 0–2 prior lines of therapy, *EGFR*/*ALK* wild-type status, no *MET*ex14 skipping, and *MET*amp by liquid biopsy (Guardant360®; *MET* gene copy number ≥2.5) received oral tepotinib 500 mg QD (450 mg active moiety). The primary endpoint was objective response (RECIST v1.1) by independent review committee (IRC). Secondary endpoints included duration of response (DOR), progression-free survival (PFS) and safety. The data cut-off was July 1, 2020. **Results:** Among 24 enrolled pts, median age was 63.4 years (range: 38–73), 21 pts (88%) were male, 21 (88%) had ECOG PS 1 and 21 (88%) were smokers. Tepotinib was given to 7 pts (29%) in first line (1L), 10 pts (42%) in second line (2L) and 7 pts (29%) in third line (3L). As of November 2020, treatment was ongoing for > 1 year in 5 pts (1L, n = 2; 2L, n = 2; 3L, n = 1). Objective response rate (ORR) by IRC was 42% (10/24 pts) overall, 71% (5/7 pts) in 1L, 30% (3/10 pts) in 2L and 29% (2/7 pts) in 3L (Table). Median DOR by IRC was not estimable (NE; 95% confidence interval [CI]: 2.8 months–NE). Investigator-assessed outcomes were similar. Five pts (20.8%) discontinued due to adverse events (AEs), which were considered unrelated to tepotinib. Treatment-related AEs were reported in 16 pts (67%; Grade 3/4, 7 pts [29%]) and included peripheral edema (9 pts [38%]; Grade 3/4, 2 pts [8%]), generalized edema (4 pts [17%]; Grade 3/4, 2 pts [8%]) and constipation (4 pts [17%]; Grade 3/4, 0 pts). **Conclusions:** In the first study of a MET inhibitor in NSCLC with *MET*amp prospectively detected by liquid biopsy, tepotinib showed high and clinically meaningful activity, especially in 1L, and was generally well tolerated. Tepotinib warrants further evaluation in NSCLC with *MET*amp. Clinical trial information: NCT02864992. Research Sponsor: Merck KGaA, Darmstadt, Germany.

Endpoints by IRC		Overall (n = 24)	1L (n = 7)	2L (n = 10)	3L (n = 7)
Best overall response, n (%)	Partial response	10 (42)	5 (71)	3 (30)	2 (29)
	Stable disease	1 (4)	0	1 (10)	0
	Progressive disease	5 (21)	1 (14)	2 (20)	2 (29)
	Not evaluable	8 (33)	1 (14)	4 (40)	3 (43)
ORR	n, % [95 CI]	10 (42) [22–63]	5 (71) [29–96]	3 (30) [7–65]	2 (29) [4–71]
DOR	9-month event-free rate, % (95% CI)	67 (28–88)	60 (13–88)	100 (NE–NE)	NE (NE–NE)
	Median, months (95% CI)	NE (2.8–NE)	NE (2.8–NE)	NE (NE–NE)	NE (3.2–NE)
PFS	9-month event-free rate, % (95% CI)	40 (19–61)	51 (12–81)	58 (18–84)	NE (NE–NE)
	Median, months (95% CI)	4.2 (1.4–NE)	NE (1.4–NE)	NE (1.0–NE)	1.4 (0.6–4.5)

9022 **Poster Discussion Session**

Final OS analysis from the phase III j-alex study of alectinib (ALC) versus crizotinib (CRZ) in Japanese ALK-inhibitor naïve *ALK*-positive non-small cell lung cancer (*ALK*+ NSCLC).

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Background: The primary analysis of the J-ALEX (JapicCTI-132316) study for the ALK-inhibitor naïve *ALK*+ NSCLC demonstrated superior progression-free survival (PFS) in Japanese patients randomized to the ALC, compared with those assigned in the CRZ (HR 0.34, 99.7% CI 0.17–0.71, stratified log-rank p<0·0001) by the Independent Review Facility (IRF) (Hida et al., Lancet 2017). The final PFS and 2nd overall survival (OS) interim analysis (IA) data were subsequently reported (Nakagawa et al., Lung cancer 2020). Here, we report the final OS data. **Methods:** *ALK*+ NSCLC (by IHC and FISH or RT-PCR) patients were randomized 1:1 either to receive ALC (Japanese approved dose 300 mg BID, n = 103) or CRZ (250 mg BID, n = 104). Stratification factors included ECOG PS, treatment line, and clinical stage. The primary endpoint was PFS according to the blinded IRF. Secondary endpoints included OS, objective response rate, and safety. **Results:** After a median follow-up of 68.6 months in the ALC arm and 68.0 months in the CRZ arm, death events occurred in 40.8% and 39.4% in the ALC and the CRZ arms, respectively. Five-year survival rates for patients in the ALC and CRZ arm were 60.85% and 64.11%, respectively. The final OS HR was 1.03 (95%CI 0.67-1.58), however, median OS was not reached in either arm. Of note, patients in the CRZ arm tended to have their treatment switched earlier than those in the ALC arm (median time to treatment-switch: 12.3 months vs. NE). Most of the patients (78.8%) in the CRZ arm received ALC as a 1st subsequent therapy, whereas only 10.7% of patients in the ALC arm received CRZ. **Conclusions:** In this final J-ALEX OS analysis, prolongation of OS in the ALC arm was not observed compared to the CRZ arm. However, OS result may be substantially confounded since 78.8% of the patients in the CRZ arm received ALC as initial, subsequent therapy. Clinical trial information: 132316. Research Sponsor: Chugai pharmaceutical.

9023 **Poster Discussion Session**

Clinicogenomic real-world data analysis of patients (pts) with *KRAS G12C*-mutant advanced non-small cell lung cancer (aNSCLC) from the natural history cohort of the Blood First Assay Screening Trial (BFAST).

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Background: BFAST (NCT03178552) is a global, multicohort trial of targeted therapies or cancer immunotherapy (CIT) in treatment (tx)-naive aNSCLC. Pts are screened for the study using comprehensive blood-based next-generation sequencing (NGS). In the BFAST natural history cohort, data were collected for pts who received tx or care outside the study's interventional cohorts. Here, we analyzed the subset of pts whose tumors have *KRAS G12C* mutations (mut). **Methods:** Pts eligible for blood-based NGS screening had unresectable aNSCLC, ECOG PS 0-2 and no prior systemic tx for aNSCLC. Pts without tissue samples were eligible. Key genomic and molecular features, including bTMB, PD-L1 and ctDNA concentration; cancer tx; tx response and survival data were collected and analyzed in an exploratory analysis. **Results:** In the full BFAST screening population through December 2020 (N = 5917), 23% of pts had tumors with any *KRAS* mut; 9% were *KRASG12C*. Pts were enrolled in the natural history cohort from October 2018 to October 2020 (n = 1017); 63 pts had tumors with *KRAS G12C* mut. Median age was 68 y, 59% were male, 86% had ECOG PS 0-1 and 84% had non-squamous histology. Co-mut in *TP53* (60%) and *STK11* and/or *KEAP1* (25%) were detected; 8% of pts had bTMB ≥16. High PD-L1 expression per local testing was reported in 32% of pts; 38% were not tested. Among pts with 1L tx (n = 50), 50%, 28% and 20% received chemo, CIT or CIT + chemo, respectively, with real-world response rates (CR/PR per physician assessment) of 20%, 29% and 30%, respectively. Of the 13 pts (21%) without documented 1L tx, 7 died ≤3 mo from enrollment. Median OS was 14 mo overall, with differences found between key genomic subsets (Table). **Conclusions:** BFAST is the first study to identify *KRAS G12C* mut using blood-based NGS and describe the natural history, clinical characteristics and genomic landscape of this pt subset. Up to 21% of pts may not receive 1L tx. Pts with *TP53* co-mut appear to have favorable outcomes, while those with *STK11* and/or *KEAP1* co-mut appear to have inferior outcomes vs pts without these mut. The lack of PD-L1 testing in many pts indicates a lack of tissue for comprehensive tissue testing, highlighting a potential benefit of blood-based detection of biomarkers, including *KRASG12C*. Clinical trial information: NCT03178552. Research Sponsor: F. Hoffmann-La Roche, Ltd.

Pt subset bymut status[a]	n	mOS (from aNSCLC diagnosis), 95% CI, mo	n	mOS (from 1L tx start), 95% CI, mo	n	1L CIT[b] mOS (from 1L tx start), 95% CI, mo
All pts	63	14.0 9.8, 41.6	49	16.8 10.3, NE	24	17.9 13.1, NE
***TP53* mut−**	27	9.8 8.0, NE	22	7.9 6.0, NE	9	9.6 4.1, NE
***TP53* mut+**	36	19.6^ 12.7, NE	27	17.9** 16.8, NE	15	17.9* NE, NE
***STK11* and *KEAP1* mut−**	47	19.6 14.0, NE	38	19.1 13.1, NE	–	–
***STK11* and/or *KEAP1* mut+**	16	5.2** 3.5, 11.4	11	6.0** 3.0, NE	–	–

NE, not estimable [a] Known/likely function per Foundation Medicine [b] Monotherapy or combination therapy * $P < 0.05$; ** $P < 0.001$; ^ $P < 0.1$ (comparing pts with mut+ tumors vs those with mut− tumors).

9024 **Poster Discussion Session**

A phase II study of rucaparib in patients with high genomic LOH and/or BRCA 1/2 mutated stage IV non-small cell lung cancer (Lung-MAP Sub-Study, S1900A).

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Background: While prior studies have shown robust efficacy leading to FDA approval of PARP inhibitors (PARPi) in BRCA-associated cancers, data in NSCLC are much less clear. S1900A, a LUNG-MAP substudy, evaluated the PARPi rucaparib in advanced stage NSCLC harboring BRCA1/2 mutations or genomic loss of heterozygosity (LOH) as a phenotypic marker of homologous recombination deficiency (HRD). **Methods:** Eligible patients (pts) were required to have a deleterious mutation in BRCA1/BRCA2 and/or high (≥21%) genomic LOH. Key eligibility criteria: advanced NSCLC patients (pts) with progression on or after platinum based chemotherapy and/or PD-(L)1 antibody and progressed on most recent line of systemic therapy, a Zubrod performance status of 0-1, adequate organ function, no ≥ grade 3 hypercholesterolemia, no previous PARPi exposure and no systemic therapy within 21 days of registration. Pts stratified by histology into two cohorts (squamous [sq] and non-squamous/mixed histology [nsq]). With 40 eligible pts per cohort, the design had 91% power to rule out an ORR of 15% if the true ORR was at least 35% at the 1-sided 5% level. A planned interim analysis on the first 20 pts evaluable for response per cohort required ≥ 3 responses to proceed to full enrollment. **Results:** 64 pts enrolled (27 sq cohort; 37 nsq cohort) of whom 59 are eligible. Median age 65.7 yrs; M/F 33/26 (56/44%); 98% of the pts received at least 1 prior line of treatment for stage IV disease. Biomarker selection included 36 pts (61%) LOH only, 4 pts (7%) BRCA1 only, 11 pts (19%) BRCA2 only, 4 pts (7%) BRCA1 + LOH high and 4 pts (7%) BRCA2 + LOH high. Both cohorts were closed for futility with insufficient responses in the interim analysis populations. In the full study, 4 responses (3 nsq/1 sq) were reported. ORR was 7% (95% CI: 0-13) (9% nsq/4% sq) and DCR was 62% (95% CI: 50-75) (62% nsq/64% sq); 3 of the 4 responders harbored BRCA1/2 mutations and 1 of 4 high LOH; ORR in BRCA1/2+ pts 3/23 (13%). Median PFS was 3.2 months (95% CI: 1.6-4.6) in nsq cohort and 2.9 months (95% CI 1.6-6.2) in sq cohort. Median OS was 7.8 months in nsq cohort and 7.9 months in sq cohort. The most frequent grade ≥3 adverse events were anemia (22%), lymphopenia (8%), fatigue (8%) and transaminitis (5%). **Conclusions:** S1900A failed to show the requisite level of efficacy for rucaparib in advanced NSCLC pts with high genomic LOH and/or a BRCA1/2 mutation. There were no new safety signals and hematologic toxicities were the most frequent adverse events. Genomic LOH as a phenotypic marker of HRD does not predict sufficient activity of rucaparib in NSCLC. These results stand in contrast to the high level of efficacy of PARPi in patients with BRCA-associated or high LOH cancers of other tumor types. Underlying biologic differences in the genomic characteristics of these cancers vs. NSCLC may be responsible. Studies examining this premise are ongoing. (NCT03845296). Clinical trial information: NCT03845296. Research Sponsor: U.S. National Institutes of Health.

9025 **Poster Session**

Anti PD-(L)1 in KRAS mutant advanced nsclcs: A meta-analysis of randomized controlled trials.

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Background: KRAS comprise the most frequently found oncogene driver mutation in non-small cell lung cancer (NSCLC), accounting for 20-25% of these patients. Single-agent Anti PD-(L)1 clinical efficacy against KRAS mutant NSCLC is a topic of debate. **Methods:** This meta-analysis examined randomized-trial data comparing first-or second line Anti PD-(L)1 +/- chemotherapy (CT) vs CT alone for KRAS mutant advanced NSCLCs. Outcome measures included overall survival (OS) and progression-free survival (PFS). Analyses were computed using the Cochrane method of collaboration for meta-analyses, with Review Manager software (RevMan version 5.3; Oxford, UK). **Results:** We analyzed 3 trials in first line (IMPOWER-150, KEYNOTE-189 and KEYNOTE-042), as well as 3 trials in second line (OAK, POPLAR and CHECKMATE-057) including 1313 NSCLCs (386 KRAS mutant and 927 KRAS wild-type tumor). Anti PD-(L)1 +/- CT was significantly associated (hazard ratio [95% confidence interval]) with prolonged OS (0.59 [0.49-0.72]; $p < 0.00001$) and PFS (0.58 [0.43-0.78]; $p = 0.0003$) compared to CT alone in KRAS mutant NSCLCs. Survival benefits occured in both first and second line. Survival benefits observed in KRAS wild-type NSCLCs were (0.87 [0.76-0.99]; $p = 0.03$) and (0.79 [0.56-1.11]; $p = 0.17$) respectively. OS benefit in KRAS mutant was significantly superior compared to OS benefit in KRAS wild-type ($p = 0,001$). **Conclusions:** Anti PD-(L)1 (+/- CT) appears superior to CT alone both for mutant and wild-type KRAS in advanced NSCLCs for OS and PFS with higher magnitude of benefit in KRAS mutated group for OS. Research Sponsor: None.

9026 **Poster Session**

Clinical performance of artificial intelligence-powered annotation of tumor cell PD-L1 expression for treatment of immune-checkpoint inhibitor (ICI) in advanced non-small cell lung cancer (NSCLC).

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Background: Programmed death ligand 1 (PD-L1) expression is the standard biomarker for first line ICI in advanced NSCLC. However, manual evaluation of tumor proportion score (TPS) by pathologists has practical limitations including intra/inter-observer bias, variation in subjectivity on area of interest and intensive labor. We developed an artificial intelligence (AI)-powered TPS analyzer, namely Lunit SCOPE PD-L1, for objective annotation of tumor cell PD-L1 expression for prediction of ICI response in advanced NSCLC. **Methods**: Lunit SCOPE PD-L1 was developed by a total of 393,565 tumor cells annotated by board-certified pathologists for PD-L1 expression in 802 whole-slide images (WSI) stained by 22C3 pharmDx immunohistochemistry. A After excluding the in-house control tissue regions, the WSI were divided into patches, from which a deep learning-based model detected the location and PD-L1 positivity of tumor cells. The patch-level cell predictions were aggregated for TPS estimation. Clinical performance of the model was validated in an external cohort of 430 NSCLC tumor slides from patients treated with $\geq$ ICI at Seoul National University Bundang Hospital and Samsung Medical Center. Independent control TPS annotation of this external validation cohort was performed by three pathologists, and their consensus TPS was calculated by mean value of such. **Results**: AI-model (Lunit SCOPE PD-L1) predicts PD-L1-positive tumor cell with the area under the curves of 0.889 and PD-L1-negative tumor cells with that of 0.809 at cell-level analysis. At WSI-level, significant positive correlation was observed between TPS by AI model and control TPS by pathologists (Spearman coefficient = 0.9247, $P < 0.001$). Concordance rate between AI-model and control TPS by pathologists according to expression level of PD-L1 $\geq$ 50%, 1-49%, and $<$ 1% status was 85.7%, 89.3%, and 52.4%, respectively. Median progression-free survival (mPFS) according to TPS by AI model $\geq$ 1% vs. $<$ 1% were 2.8 vs. 1.7 months (hazard ratio, HR, 0.52, 95% confidence interval, CI, 0.38-0.71, $P < 0.001$). In contrast, mPFS according to control TPS was 2.8 vs. 2.1 months (HR 0.70, 95% CI 0.55-0.91, $P < 0.001$). Forty out of 84 patients (47.6%) annotated as control TPS $<$ 1% by pathologists were considered as TPS $\geq$ 1% by AI-model and mPFS of this subgroup was 2.7 months. **Conclusions**: PD-L1 expression by AI-model correlates with PD-L1 expression by pathologists. Clinical performance of AI-model in WSI-level is comparable with assessment by pathologists. The AI-model can accurately predict tumor response and progression-free survival of ICI in advanced NSCLC. Research Sponsor: Lunit Inc.

9027 **Poster Session**

Clinical outcomes for plasma-based comprehensive genomic profiling versus tissue testing in advanced lung adenocarcinoma.

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Background: Somatic genomic testing is recommended by numerous expert guidelines to inform targeted therapy treatment for patients with advanced lung adenocarcinoma (aLUAD). The NILE study was a prospective observational study that demonstrated non-inferiority of cell-free circulating tumor DNA (cfDNA)-based tumor genotyping compared to tissue-based genotyping to find targetable genomic alterations in patients with newly diagnosed aLUAD. As the cohort has matured, clinical outcomes data can now be reported. **Methods:** This prospective, multicenter North American study (NCT03615443) enrolled patients with previously untreated aLUAD who had standard of care (SOC) tissue genotyping performed and concurrent comprehensive cfDNA analysis using the commercially available Guardant360 assay (Guardant Health, Redwood City, CA). After 12 months of study enrollment, objective response rates, disease control rate, and time to treatment data were collected for patients with targetable genomic alterations, as defined by NCCN guidelines, who were treated with physician's choice of therapy. **Results:** Among 282 patients on the study, 89 (31.6%) had an actionable biomarker detected by tissue (21.3%) and/or cfDNA (27.3%) analysis. Sixty-one (68.5%) of these patients were treated with an FDA-approved targeted therapy guided by somatic genotyping results (*EGFR*, *ALK*, *ROS1*). Thirty-three patients were eligible for clinical response evaluation and demonstrated an objective response rate of 58% and disease control rate of 94%. Twenty-five (76%) achieved a durable response $>$ 6 months; 17 (52%) achieved a durable response $>$ 12 months. Patients responded to targeted therapy regardless of the variant allele frequency of the target alteration. The time to treatment (TtT) was significantly faster for cfDNA-informed biomarker detection as compared to tissue genotyping (median 18 vs 31 days, respectively; $p = 0.0008$). **Conclusions:** This is the first prospective community-based study to find that cfDNA detects guideline-recommended biomarkers at a rate similar to tissue genotyping, and therapeutic outcomes based on plasma-based comprehensive genomic profiling are comparable to published tissue-based targeted therapy clinical outcomes. The NILE study complements and confirms findings in the prospective FLAURA and SLLIP studies, which exclusively enrolled at academic sites. Clinical trial information: NCT03615443. Research Sponsor: Guardant Health.

9029 **Poster Session**

Changes in PD-L1 tumor proportion score are associated with *CD274* gene (encoding PD-L1) copy number variation in non-small cell lung cancer.

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Background: PD-L1 tumor proportion score (TPS) is often used to determine eligibility for first line therapy with immune checkpoint inhibitors (ICIs) in advanced non-small cell lung cancer (NSCLC). However, PD-L1 expression can vary over time and between tumor sites, potentially leading to inaccurate patient stratification. Therefore, it is critical to understand the clinicopathologic and genomic factors that are associated with PD-L1 changes in NSCLC. **Methods:** Clinicopathologic and genomic data were collected from patients with NSCLC and quantitative PD-L1 immunohistochemistry (IHC) on at least two different biopsies. NSCLC biopsies were categorized as PD-L1 negative, low, and high if they had a PD-L1 TPS $<$ 1%, 1-49%, and $\geq$50%, respectively. Intrapatient changes in PD-L1 TPS between samples (DPD-L1) were defined as follows: major decrease (decrease in PD-L1 TPS from $\geq$50% to $<$ 50% or from $\geq$1% to $<$ 1%), major increase (increase in PD-L1 TPS from $<$ 1% to $\geq$1% or $<$ 50% to $\geq$50%), and non-major change (all other cases). Next-generation sequencing (NGS) was used to evaluate copy number (CN) variations at the *CD274* locus, which encodes PD-L1. Wilcoxon and Kruskal-Wallis rank sum tests were used to analyze continuous variables and Fisher's exact test was used to analyze categorical variables. **Results:** Among 250 patients with NSCLC with PD-L1 IHC assays performed on at least two distinct tissue samples, PD-L1 TPS of the first biopsy was $<$ 1% in 104 (41.6%), 1-49% in 80 (32.0%), and $\geq$50% in 66 (26.4%) samples, for a median PD-L1 TPS of 2% (range: 0% to 100%). When intrapatient DPD-L1 was examined, there were major decreases and major increases in PD-L1 TPS in 49 (19.6%) and 65 (26.0%) cases, respectively, and non-major changes were observed in the remaining 136 samples (54.4%), with a median DPD-L1 of 0% (range: -90% to +90%). Baseline PD-L1 TPS and DPD-L1 were not significantly affected by histology, smoking status, sex, or treatment. Among 219 NSCLC samples that underwent tissue NGS and had full CN data available, the median PD-L1 TPS differed significantly based on *CD274* CN: PD-L1 TPS 1% with single copy deletion vs. 5% with copy neutral vs. 42.5% with low amplification vs. 97.5% with high amplification ($p < 0.01$). Among 56 patients with paired PD-L1 TPS and NGS on both samples, there was a significant difference in median DPD-L1 according to *CD274* CN change: DPD-L1 TPS -49% with acquired *CD274* CN loss vs. 0% with no major change in *CD274* CN vs. +1.75% with acquired *CD274* CN gain ($p = 0.01$). **Conclusions:** PD-L1 TPS varies within the same patient in almost half of NSCLC cases, with few clinicopathologic correlates of change in expression. Variation in PD-L1 TPS correlates with changes in *CD274* CN across biopsies. These findings suggest a genomic correlate to predict PD-L1 TPS across samples, as well as a potential complementary method in determining in ICI initiation. Research Sponsor: None.

9030 **Poster Session**

The combination of EGFR-TKIs and anlotinib as a first-line therapy for *EGFR*-mutant advanced non-small cell lung cancer: A multicenter, single-arm, phase II clinical trial.

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Background: Currently,EGFR-TKIs are widely accepted as the standard treatment for EGFR-*mutant* advanced non-small-cell lung cancer (NSCLC); however, acquired resistance is inevitable. Combination therapy is considered as a strategy to overcome the resistance to EGFR-TKIs. Anlotinib, a novel multi-targeting, small-molecule TKI, has shown active to suppress tumor angiogenesis and growth. However, there is still a lack of evidence supporting the use of EGFR-TKIs in combination with anlotinib for the treatment of NSCLC until now. A multi-center, single-arm, phase II clinical trial was therefore designed to examine the efficacy and safety of EGFR-TKIs combined with anlotinib for treatment-naïve, advanced NSCLC patients, and unravel the possible mechanisms. **Methods:** This study was conducted in 14 research centers in Fujian, China. The main eligibility criteria were stage IV or relapsed nonsquamous NSCLC with EGFR mutations (exon 19 deletion, and L858R), ECOG score 0-2,and age 20 to 75 years and no previous systemic treatment. Patients with asymptomatic brain metastases were admitted.Eligible patients were given gefitinib (250 mg QD) or icotinib (125 mg TID) in combination with anlotinib (10 mg per day, on days 1–14; 21 days per cycle) until disease progression. The primary endpoint is progression-free survival (PFS) and safety, and the secondary endpoint is overall survival (OS), objective response rate (ORR) and disease control rate (DCR).Peripheral blood was sampled pre-treatment, once every two months during treatment and after disease progression, and *T790M* mutation was detected in plasma ctDNA using a droplet digital PCR (ddPCR) assay. **Results:** Of 60 patients enrolled (August 2, 2018 to May 28, 2020). As of February 1, 2021, 37 patients (61.7%) experienced PFS events and 10 (16.7%) died. The ORR was 78.3%, and the DCR was100%.Median PFS was 13.0 months (95%CI,10.7-15.3).The 5 most common treatment-related adverse events included rash (63.3%), fatigue (55.0%), hypertension (48.3%), diarrhea (33.3%) and hand-foot syndrome (30.0%), and grade 3 adverse events included hypertension (5.0%), rash (1.67%), hypertriglyceridemia (1.67%), vomiting (1.67%) and elevated ALT (1.67%); no grade 4 adverse events or drug-related deaths were observed. Peripheral blood samples were collected from 36 patients pre-treatment, and 30.6% were identified with low-frequency *de novo T790M* mutations, with the mutation-allele frequency (MAF) ranging from 0.01% to 0.28%. **Conclusions:** The combination of the first-generation EGFR-TKIs and anlotinib shows impressive ORR and DCR, and acceptable toxicity in treatment-naïve advanced NSCLC patients with activating *EGFR* mutations, and we observed a high proportion of patients harboring *de novo EGFR T790M* mutations in this study. Clinical trial information: NCT03720873. Research Sponsor: None.

9031 **Poster Session**

A randomized phase III study comparing carboplatin with nab-paclitaxel versus docetaxel for elderly patients with squamous-cell lung cancer: Capital study.

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Background: Cytotoxic monotherapy is one of the standard treatments for elderly patients with advanced non-small cell lung cancer (NSCLC). Carboplatin plus nab-paclitaxel demonstrated significantly higher objective response rate (ORR) than carboplatin plus paclitaxel in patients with squamous histology and could improve overall survival (OS) in patients aged ≥70 years. Here, we compared carboplatin plus nab-paclitaxel with docetaxel in elderly patients with squamous NSCLC. **Methods:** The CAPITAL study is a multicenter, open-label, phase 3, randomized trial at 92 institutions in Japan. Eligible patients had advanced squamous NSCLC with no prior systemic chemotherapy, aged ≥70 years, and had an ECOG performance status of 0 or 1. Patients were randomized 1:1 to docetaxel 60 mg/m^2 (D arm) or carboplatin AUC 6 mg/mL/min plus nab-paclitaxel 100 mg/m^2 weekly (nab-PC arm) for each 21-day cycle. The primary endpoint was OS. This trial is registered with the UMIN Clinical Trials Registry (UMIN000019843) and the Japan Registry of Clinical Trials (jRCTs041180110). **Results:** Between December 2015 and August 2020, 196 patients were randomly assigned to the two treatment arms (D arm, n=98; nab-PC arm, n=98). The median follow-up and age were 11.5 months and 76 years (range: 70–88 years), respectively, and 87% of the patients were male. After the planned interim analysis, the independent data monitoring committee confirmed that the study met the primary endpoint of improved OS in August 2020, and this report represents the final analysis. The nab-PC arm showed significant superiority in OS versus the D arm (hazard ratio [HR], 0.52; 90% CI, 0.38-0.70; median, 16.9 vs. 10.9 months; $p<0.001$). There were also significant improvements in progression-free survival (median, 5.8 vs. 4.0 months; HR, 0.42; 95% CI, 0.30-0.58; $p<0.001$) and objective response rate (66.3 vs. 28.0 %; $p<0.001$) in the nab-PC arm versus the D arm. The most common grade 3 or 4 adverse events were leukopenia (46.3 %), neutropenia (63.2 %), and anemia (38.9 %) in the nab-PC arm, and leukopenia (56.7 %), neutropenia (77.3 %), and febrile neutropenia (17.5 %) in the D arm. As notable adverse events, grade ≥2 sensory peripheral neuropathy was observed in 15 (15.8%) and 1 (1.0%) patient in the nab-PC and D arms, respectively. Moreover, serious treatment-related adverse events and treatment-related deaths occurred in 14 (14.7%) and 12 (12.4%) patients and in two and one patient in the nab-PC and D arms, respectively. **Conclusions:** The nab-PC arm had a significantly improved OS than the D arm among elderly patients with squamous NSCLC. Carboplatin plus nab-paclitaxel became a new standard treatment for these patients. Clinical trial information: UMIN000019843. Research Sponsor: Taiho Pharmaceutical.

9032 **Poster Session**

Response to selpercatinib versus prior systemic therapy in patients (pts) with *RET* fusion+ non-small-cell lung cancer (NSCLC).

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Background: Selpercatinib, a first-in-class highly selective, potent, CNS-active RET kinase inhibitor, is approved in multiple countries for treatment of *RET* fusion+ lung or thyroid cancers. Selpercatinib demonstrated durable antitumor activity in previously treated pts with *RET* fusion+ NSCLC in an ongoing Phase 1/2 trial, LIBRETTO-001 (Besse et al., ASCO 2021). **Methods:** Pts with *RET* fusion+ NSCLC enrolled in the global, multicenter, LIBRETTO-001 trial (NCT03157128; 16 countries, 89 sites). Primary endpoint was objective response rate (ORR). Secondary endpoints included progression-free survival, duration of response, and safety. This post-hoc intrapatient analysis was based on a 30 March 2020 data cutoff date. Historical physician-reported best overall response (BOR) from last systemic therapy received prior to enrollment was compared with selpercatinib BOR by independent review committee per RECIST v1.1, with each patient serving as his/her own control. **Results:** In efficacy-evaluable pts (N = 218) who previously received platinum-based chemotherapy (chemo), median pt age was 61 years, the majority with ECOG of 0/1 (37%/61%), with a median of 2 (range: 1-15) prior systemic therapies. Overall, 57% of patients responded to selpercatinib while 16% responded to the immediate prior therapy. ORR improvements with selpercatinib were observed regardless of prior therapy: chemotherapy + immune checkpoint inhibitor (ICI) (57% vs 14%), single-agent ICI (48% vs 3%), or chemotherapy (58% vs 15%). A total of 108 patients (49%) did not respond to immediate prior therapy but responded to selpercatinib. Fewer patients had progressive disease as their BOR with selpercatinib (2%) compared to the immediate prior therapy (28%). The median duration of therapy for selpercatinib was notably extended compared with that of the immediate prior therapy (11.8 vs. 3.4 months, respectively). **Conclusions:** In pts with *RET* fusion+ NSCLC treated on LIBRETTO-001, systemic therapies administered prior to enrollment achieved less meaningful clinical benefit than selpercatinib. Selpercatinib demonstrated consistent efficacy regardless of the type of prior therapy. Clinical trial information: NCT03157128. Research Sponsor: Eli Lilly and Company.

9033 **Poster Session**

Second-line nintedanib plus docetaxel for patients with lung adenocarcinoma after failure on first-line immune checkpoint inhibitor combination therapy: Initial efficacy and safety results from VARGADO Cohort C.

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Background: The treatment landscape in advanced non-small cell lung cancer (NSCLC) has undergone significant changes, with immune checkpoint inhibitor (ICI) +/- chemotherapy now the preferred first-line (1L) regimen for metastatic, non-mutated NSCLC. However, only limited clinical data are available to guide subsequent treatment selection. Nintedanib (Vargatef), an oral triple angiokinase inhibitor targeting the vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR) pathways, is approved in the EU and other countries in combination with docetaxel for the treatment of advanced adenocarcinoma NSCLC after failure on 1L chemotherapy. **Methods:** This analysis is part of the ongoing, prospective, non-interventional VARGADO study (NCT02392455) of nintedanib + docetaxel. Here, we present initial efficacy and safety results from 100 patients (pts) with adenocarcinoma NSCLC in Cohort C, who received second-line (2L) nintedanib + docetaxel after failure on prior 1L ICI in combination with chemotherapy. **Results:** In Cohort C, the median age was 63 years (range: 43–84); 58 pts (58.0%) were men, and 71 pts (71.0%) had ECOG PS 0/1. Ninety-five pts (95.0%) had received prior 1L pembrolizumab-based combination therapy. Thirty-nine pts (39.0%) had progressed within 6 months after the start of 1L therapy, and 66 pts (66.0%) had progressed within 9 months. Objective response rate with 2L nintedanib + docetaxel was 37.3% (22/59 pts), disease control rate was 67.8% (40/59 pts), and median progression-free survival (PFS) was 4.4 months (95% confidence interval [CI]: 2.6–6.6). Among pts who had experienced disease progression $<$ 9 months after the start of 1L therapy (n = 66), median PFS from the start of 2L nintedanib + docetaxel was 4.1 months (95% CI: 2.5–6.6). Among pts with disease progression $\geq$9 months after the start of 1L therapy (n = 34), median PFS from the start of 2L nintedanib + docetaxel was 8.5 months (95% CI: 2.4–not estimable). Grade $\geq$3 treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs leading to treatment discontinuation were observed in 47 pts (47.0%), 37 pts (37.0%) and 28 pts (28.0%), respectively. **Conclusions:** Initial data from VARGADO Cohort C provide the first evidence that 2L nintedanib + docetaxel has encouraging and clinically meaningful efficacy, and a manageable safety profile in pts with advanced adenocarcinoma NSCLC following progression on 1L ICI in combination with chemotherapy. Clinical trial information: NCT02392455. Research Sponsor: Boehringer Ingelheim Pharma GmbH & Co. KG.

9034 **Poster Session**

Phase II trial of atezolizumab (A) + carboplatin (C) + pemetrexed (P) + bevacizumab (B) in pts with stage IV non-squamous non-small cell lung cancer (NSq-NSCLC): Big Ten Cancer Research Consortium Study LUN 17-139.

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Background: The addition of A to C+ Paclitaxel (Pac) + plus B improved progression free survival (PFS) and overall survival (OS) compared with C + Pac + B alone in pts with metastatic NS-NSCLC. However, C + Pem is more commonly used for this patient population with a shorter infusion time and favorable toxicity profile compared with Pac. **Methods:** Multicenter single arm phase II clinical trial of chemo and immunotherapy-naïve pts with stage IV NSq-NSCLC. All pts received A (1200 mg, D1) + C (AUC 5, D1) + P (500 mg/m2, D1) + B (15mg/kg D1) q3 week x4. If non-PD, pts could receive maintenance APB until PD or intolerable side effects. The primary endpoint was 1 yr. PFS. Sample size of 42 planned with 87% power and two-sided type I error of 0.05 for 1 yr PFS. Secondary endpoints included ORR, disease control rate (DCR) [defined by CR + PR + SD], and toxicity. **Results:** 30 pts were enrolled from 11/15/2018 to 10/5/2020. The study was closed early due to 3 patient deaths, possibly related to treatment (VTE, Febrile neutropenia, colonic perforation). Median age 64 (range 38-83); M/F 20/10; mutations in EGFR/ALK/KRAS/BRAF (5/1/4/2); PD-L1 TPS $<$ 1%/1-49%/ $>$ 50% (9/14/6) and one pt did not have PDL-1 status. Median f/u was11.6 mos (range 1-20). ORR 35.71% (95% CI: 18.64%-55.95%), DCR 92.85% (95% CI: 83%-100%). 1yr PFS and OS were 55.27% and 82.90% respectively. The most common G III and G II toxicity were HTN (20%) and fatigue (33.3%).3 pts had G IV toxicity (Anemia, Febrile neutropenia and colonic perforation) and 2 pts had Grade (G) V toxicity (VTE, Hypoxia/Sepsis). **Conclusions:** Atezolizumab + Carboplatin + Pemetrexed + Bevacizumab was associated with longer DCR, PFS, and OS than historical controls. 3 on-treatment deaths, possibly related to therapy (more likely bevacizumab), prompted early closure. A phase 3 study evaluating this regimen is ongoing by another group NCT03786692. Clinical trial information: NCT03713944. Research Sponsor: Genentech.

9035 **Poster Session**

Efficacy and safety of pan-ErbB inhibitor pyrotinib combined with antiangiogenic agent apatinib for HER2-mutant or amplified metastatic NSCLC: A phase II clinical study.

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Background: Tumor angiogenesis could be induced by activation of HER2 receptor, and currently, there is lack of clinical evidence of anti-HER2 tyrosine kinase inhibitors (TKIs) combined with antiangiogenic therapy for HER2-mutant or amplified non-small cell lung cancer (NSCLC). We conducted a study to explore the efficacy and safety of a pan-ErbB inhibitor pyrotinib combined with apatinib for metastatic NSCLC patients harboring HER2 amplification or activating mutations. **Methods:** This was a single-center, single-arm phase II study with Simon's optimal two-stage design. Metastatic NSCLC patients with ECOG scores of 0-1 and harboring primary HER2 amplification, exon 20 insertion or activating missense mutations who had failed to prior chemotherapies or anti-HER2 TKIs were eligible to be enrolled. All patients received oral pyrotinib (400mg once daily) combined with apatinib (250mg once daily) therapy. The primary endpoint was objective response rate (ORR), and second endpoints included progression-free survival (PFS), duration of response (DoR), disease control rate (DCR), overall survival (OS) and safety. **Results:** Between March 5, 2019, and December 1, 2020, 33 metastatic NSCLC patients with HER2 alterations were enrolled, including exon 20 insertions (A775_G776insYVMA, 20/33; P780_Y781insGSP, 6/33; other variants, 2/33), missense mutations (3/33), and primary HER2 amplification (2/33). Seventeen patients (51.5%) were pretreated with first-line platinum-based chemotherapies or anti-HER2 TKIs, and the remaining had received at least 2 lines of prior therapies (range, 2-6). At the last follow-up time January 23, 2021, the overall ORR and DCR were 45.5% (15/33) and 93.9% (31/33), respectively. The median PFS was 6.8 (95%CI: 5.4-8.2) months. The median DoR and OS were 5.3 (95%CI: 0-11.8) and 12.9 (95%CI: 8.6-17.2) months, respectively. The mPFS was significantly longer in patients who received second-line pyrotinib combined with apatinib therapy than those in third- or above-line settings (9.8 *vs.* 5.3 months, $P = 0.018$, HR = 0.281 [95%CI: 0.098-0.807]). Although pyrotinib combined with apatinib therapy showed similar ORRs in patients with presence (46.2%, 6/13) or absence (45.0%, 9/20) of brain metastases, and those in second-line (47.1%, 8/17) or above-line settings (43.8%, 7/16). Common treatment-related adverse events (AEs) were grade 1-2, mainly including diarrhea (90.9%), hypertension (72.7%), asthenia (63.6%), anorexia (54.5%) and nausea (51.5%). Grade 3 AEs were diarrhea (3.0%) and hypertension (9.1%). No grade 4 or 5 AE or treatment-related deaths were reported. **Conclusions:** Pyrotinib combined with apatinib showed potent anti-tumor activity and acceptable safety profile in metastatic NSCLC with HER2 amplification or activating mutations. Clinical trial information: ChiCTR1900021684. Research Sponsor: None.

9036 **Poster Session**

Treatment outcome and functional characterization of uncommon EGFR mutations in the German National Network Genomic Medicine Lung Cancer (nNGM).

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Background: The nNGM centralizes molecular diagnostics, treatment recommendations and follow-up reporting in NSCLC in Germany. Uncommon EGFR mutations pose a clinical challenge because they comprise a heterogenous group and analyses of treatment outcome are still scarce. Here, we analyzed follow-up data of patients with rare EGFR mutations and performed functional characterization of recurrent mutations with unknown function. **Methods:** This multicenter, retrospective analysis of uncommon EGFR mutations (excluding L858R-, T790M mutations and exon 19 deletions) includes stage IV patients with NSCLC from 12 nNGM centers. We categorized EGFR-mutations into 3 groups: uncommon EGFR mutations with known driver function, for instance E709X, G719X, S768I and L861Q (group 1), exon 20 insertions (group 2) and all other very rare mutations (group 3). Functional characterization of unknown mutations was performed by insertion mutagenesis in Ba/F3 cells and monitoring of growth factor-independent proliferation. **Results:** In total, 834 cases with uncommon EGFR mutations were reported. Follow-up data after EGFR-TKI (Erlotinib, Gefitinib, Afatinib and Osimertinib), chemotherapy and/or mono-PD(L)1 blockade was available for 252 patients. Mean progression free survival (mPFS) on EGFR-TKIs vs. chemotherapy was 6.6 months vs. 5.0 months (HR 0.54, 95%CI 0.35 to 0.81, P=.003) in group 1 (n = 84), and 6.7 months vs. 3.4 months (HR 0.66, 95%CI 0.47 to 0.92, P=.015) in group 3 (n = 104). Mono-anti-PD(L1) blockade was not superior to chemotherapy (group 1, mPFS 3.0 months, HR 1.32, 95% 0.55 – 3.15, P=.535 and group3, mPFS 4.3 months, HR 1.02, 95% CI 0.64 – 1.62, P= 0.951). Exon 20 insertions (group 2, n = 63) did not benefit from EGFR-TKIs or anti-PD(L1) blockade vs. chemotherapy. Overall survival (OS) analysis (n = 218) following chemotherapy (56%) or EGFR-TKI treatment (44%) showed median OS (mOS) of 18.0 months vs. 13.9 months in patients treated with EGFR-TKI and chemotherapy, respectively in group 1 (HR 0.97, 95%CI 0.54 to 1.75, P =.929). In group 3 patients treated with EGFR-TKI and chemotherapy had a mOS of 35.4 months vs. 12.0 months, respectively (HR 0.59, 95%CI 0.35 to 1.01, P =.056). In the Ba/F3 system we could identify 8 recurrent driver and 12 non-driver mutations with a clinically applicable assay turnaround time of 4 weeks to inform clinical decision-making in the future. **Conclusions:** This real-world dataset confirms that patients with group 1(uncommon) EGFR mutations benefit from EGFR-TKIs and indicates that mono-anti PD(L)1 blockade is not superior to chemotherapy. Furthermore, patients with very rare EGFR mutations (group 3) also experienced a PFS benefit from EGFR-TKI compared to chemotherapy while immune therapy was not beneficial. Research Sponsor: Deutsche Krebshilfe, Hector Stiftung, Margarete Clemens Stiftung.

9037 **Poster Session**

A randomized phase II study comparing nivolumab (NIVO) with carboplatin-pemetrexed (CbPEM) for patients (pts) with EGFR mutation-positive non-small cell lung cancer (NSCLC) who acquire resistance to tyrosine kinase inhibitors (TKIs) not due to a secondary T790M mutation (WJOG8515L).

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Background: Although the efficacy of antibodies to programmed cell death–1 (PD-1) appears to be less pronounced in patients with NSCLC harboring epidermal growth factor receptor gene (*EGFR*) mutations, patients who develop disease progression (PD) to TKIs due to mechanisms other than secondary T790M mutation of *EGFR* might be more likely to benefit from NIVO. Here, we report the results of first randomized phase II trial to compare NIVO with the CbPEM in those population. **Methods:** Pts with advanced *EGFR* mt NSCLC who experienced PD after EGFR-TKIs were randomized 1:1 to NIVO or CbPEM. Eligibility criteria included the treatment history with TKIs as follow; no evidence of T790M after PD on 1st/2nd generation (gen) TKIs (A) after PD on 3rd gen TKIs as a 2nd line for T790M positive tumor (B) or 3rd gen TKIs as a front-line (C). The primary end point is progression-free survival (PFS) and biomarker analysis were included for exploratory analysis. **Results:** A total of 102 patients was randomized. Median PFS and overall survival (OS) were 1.7 and 20.7 months (mo), respectively, for NIVO arm (n = 52) versus 5.6 and 19.9 months for CbPEM (n = 50) (Hazard ratio [HR] = 1.92 and 0.88, respectively). Overall response rate and duration of response were 9.6% and 5.3 months for NIVO and 36.0% and 5.5 months for CbPEM. PD-L1 expression on tumor cells and tumor mutation burden (TMB) were evaluated in 77 (TPS 0%. 1-49%, > 50%, n = 46, 20, and 11) and 50 (Median TMB 6.2mt/mb). Immune-related gene expression profiling was under evaluation and the results will be demonstrated in the meeting. The efficacy of NIVO in PD-L1 strong positive (>50%, n = 8) and no evidence of T790M after PD on 1st/2nd gen TKIs (n = 29) was tended to be better than their counterparts. There was no significant correlation between TMB and the efficacy of NIVO. Pneumonitis was observed in one patient (1.0%) for NIVO arm and no new safety signals were noted. **Conclusions:** NIVO was not associated with longer PFS than CbPEM in selected pts with advanced *EGFR* mt NSCLC. OS was similar between groups. Baseline PD-L1 status and genetic alteration features may be relevant predictive markers to select pts who would benefit from NIVO. Clinical trial information: jRCTs051180133. Research Sponsor: Ono Pharmaceutical Co. Ltd.

	PFS for entire population	OS for entire population	PFS by PD-L1 (0%, 1-49%, 50%)	OS by PD-L1 (0%, 1-49%, 50%)	PFS by TMB (Low, High cutoff 6.2mt/mb)	OS by TMB (High, Low cutoff 6.2mt/mb)	PFS by resistance mechanisms (A, B, C)	OS by resistance mechanisms (A, B, C)
NIVO (Median, months)	1.7	20.7	1.4/2.2/4.6	17.9/18.0/NR	2.1/1.7	19.1/15.3	2.7/1.3/NR	19.9/22.7/NR
CbPEM (Median, months)	5.6	19.9	3.6/5.3/5.6	20.7/19.9/NR	2.9/2.5	12.2/9.5	5.8/4.9/3.2	19.0/17.9/13.3
Hazard ratio (NIVO vs CbPEM)	1.92	0.88	1.67/2.10/1.49	0.90/2.50/0.72	1.06/1.22	0.59/0.32	1.62/13.3/0.43	0.99/0.79/0.29

9038 **Poster Session**

Health-related quality of life for pembrolizumab (pembro) plus ipilimumab (ipi) versus pembro plus placebo in patients with metastatic NSCLC with PD-L1 tumor proportion score ≥ 50%: KEYNOTE-598.

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Background: In the phase 3 KEYNOTE-598 study (NCT03302234), OS (HR, 1.08; 95% CI, 0.85–1.37; $P = 0.74$) and PFS (1.06; 95% CI, 0.86–1.30; $P = 0.72$) were not improved for pembro + ipi vs pembro + placebo in patients (pts) with previously untreated metastatic NSCLC with PD-L1 tumor proportion score (TPS) ≥50% and without *EGFR/ALK* genomic alterations. Incidence of treatment-related grade 3–5 AEs, fatal AEs, and AEs leading to discontinuation was higher with pembro + ipi vs pembro + placebo. We present prespecified patient-reported outcome (PRO) analyses from KEYNOTE-598. **Methods:** Pts (n = 568) with previously untreated stage IV NSCLC with PD-L1 TPS ≥50% were randomized 1:1 to pembro 200 mg Q3W for up to 35 cycles + ipi 1 mg/kg or placebo Q6W for up to 18 cycles. The EORTC QLQ-C30, QLQ-LC13, EQ-5D-5L, and NSCLC-SAQ were administered at cycles 1–7, then every 3 cycles through cycle 19, and every 4 cycles until PD or a maximum of 35 cycles. Change from baseline in global health status (GHS)/quality of life (QoL) score from the QLQ-C30 and the time to true deterioration (TTD) in the composite endpoint of cough (LC13), chest pain (LC13), or dyspnea (C30) were secondary objectives in KEYNOTE-598. Change from baseline in GHS/QoL was analyzed using a constrained longitudinal data analysis model with missing at random assumption. Difference in TTD was evaluated using a Cox proportional hazards model and stratified log-rank test. PROs were analyzed in all pts who completed ≥1 PRO assessment and received ≥1 dose of study treatment. *P* values are two-sided and nominal. **Results:** As of data cutoff (Sept 1, 2020), PRO analyses included 280 pts in the pembro + ipi group and 280 pts in the pembro + placebo group. QLQ-C30 completion rates were 95.7% in the pembro + ipi group vs 96.1% in the pembro + placebo group at baseline and 63.6% vs 70.0% at week 18. QLQ-LC13 completion rates were 95.4% vs 96.4% at baseline and 63.6% vs 69.6% at week 18. Mean QLQ-C30 GHS/QoL scores at baseline were 62.8 in the pembro + ipi group and 64.2 in the pembro + placebo group and were similar between the groups across the follow-up period. Least squares (LS) mean (95% CI) change from baseline to week 18 in GHS/QoL scores was improved in both groups (pembro + ipi: 3.7 [0.9–6.5]; pembro + placebo: 4.1 [1.4–6.9]), with no significant difference between groups (LS mean difference −0.4 [−4.0 to 3.1], $P = 0.82$). Median TTD in composite of cough, chest pain, or dyspnea was not reached (NR; 95% CI, 13.0 mo–NR) in the pembro + ipi group vs 20.0 (95% CI, 12.7–NR) mo in the pembro + placebo group (hazard ratio, 0.98 [95% CI, 0.74–1.30]; $P = 0.91$). **Conclusions:** There was no difference in health-related QoL or TTD in lung cancer symptoms between pembro + ipi and pembro + placebo in pts with previously untreated metastatic NSCLC with PD-L1 TPS ≥50%. Clinical trial information: NCT03302234. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

9039 **Poster Session**

Whole-exome sequencing in advanced-stage sensitizing *EGFR* mutation non-small cell lung cancer: Explore resistance biomarkers to EGFR TKI treatment.

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Background: Despite the development of predictive biomarkers to shape treatment paradigms and outcomes, 10-20% of *de novo* EGFR TKI resistance advanced non-small cell lung cancer (NSCLC) in the presence of *EGFR* mutation remains the issue of concern. **Methods:** We explored clinical factors in 332 advanced NSCLC who received EGFR TKI and molecular characteristics through 65 whole exome sequencing of various EGFR TKI responses including; *de novo* (progression within 3 months), intermediate response (IRs) and long-term response (LTRs) (durability $>$ 2 year). **Results:** Uncommon *EGFR* mutation subtype was a significant variable in *de novo* resistance vs. IRs and LTRs with odd ratios of 6.83 ([95% CI 2.36 – 19.80], *p*-value $<$ 0.001) and 16.84 ([95%CI 1.66 – 171.45, *p*-value 0.02), respectively. The remaining sensitizing *EGFR* mutation subtype (exon 19 del and L858R) accounted for 75% of *de novo* resistance. Genomic landscape analysis was conducted, focusing in 10 frequent oncogenic signaling pathways with functional contributions; cell cycle, Hippo, Myc, Notch, Nrf2, PI-3-Kinase/Akt, RTK-RAS, TGF-β, p53 and β-catenin/Wnt signaling. Cell cycle pathway was the only significant alteration pathway among groups with the FDR *p*-value of 6×10^{-4}. We found only significant *q*-values of $<$ 0.05 in 7 gene alterations; *CDK6*, *CCNE1, CDK4, CCND3, MET, FGFR4* and *HRAS* which enrich in *de novo* resistance [range 36-73%] compared to IRs/LTRs [range 4-22%]. Amplification of *CDK4*/6 was significant in *de novo* resistance, contrary to IRs and LTRs (91%, 27.9% and 0%, respectively). The presence of co-occurrence *CDK4/6* amplification correlated with poor disease outcome with HR of progression-free survival of 3.63 [95% CI 1.80-7.31, *p*-value $<$ 0.001]. **Conclusions:** The presence of *CDK4/6* amplification in pretreatment specimen serve as a predictive biomarker for *de novo* resistance in sensitizing *EGFR* mutation. Research Sponsor: Chulalongkorn Academic Advancement into Its 2nd Century (CUAASC) Project.

9040 **Poster Session**

Phase II study of brigatinib in ROS1 positive non-small cell lung cancer (NSCLC) patients previously treated with crizotinib: Barossa cohort 2.

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Background: Brigatinib is a next-generation tyrosine kinase inhibitor targeting ALK and ROS1. Crizotinib is the first drug approved for the treatment of ROS1 fusion-positive NSCLC. Standard treatment for crizotinib-resistant ROS1 positive NSCLC is not established. Barossa is a multicenter, phase II basket, study of brigatinib in patients with ROS1 positive solid tumors. This study is composed of three cohorts. ROS1 inhibitor-naïve ROS1 positive NSCLC patients were enrolled in the cohort 1, and ROS1 positive NSCLC patients previously treated with crizotinib were enrolled in the cohort 2. Patients with ROS 1 positive solid tumors other than NSCLC were enrolled in the cohort 3. This time we report the cohort 2 results. **Methods:** Patients with advanced, previously treated with crizotinib, ROS1 positive NSCLC received brigatinib at a dose of 180 mg once daily with a 7-day lead-in period at 90 mg. The primary end point was objective response rate (ORR; RECIST 1.1) by independent review. Key secondary endpoint was PFS, OS, and safety. The sample size was set at 19 patients, with a one-sided alpha of 0.05, beta of 0.2, and threshold and expected values for primary endpoint of 20% and 50%, respectively. **Results:** From July 2019 and Jan 2020, 19 patients were enrolled from 9 institutions. Baseline characteristics as follows: median age (range): 60 (31-75) years; women, n = 10 (53%); ECOG PS of 0 to 1, n = 18 (95%); never smoker, n = 11 (58%); tumor histopathological type: adenocarcinoma, n = 18 (95%). Five and 6 patients achieved PR and SD, respectively at data cutoff date of 30 Oct 2020. The ORR was 26.3% (90%CI, 11.0-47.6), and the disease control rate was 57.9% (95%CI, 33.5-79.7). The median duration of follow-up for PFS was 12.0 months. The median PFS was 7.3 months (95% CI, 1.3-9.3), and the 1-year PFS rate was 26.9% (95%CI, 9.2-48.6). Grade ≥3 TRAEs were CPK increased (21.1%), infection (5.3%), AST and/or ALT increased (5.3%), hypercalcemia (5.3%), anorexia (5.3%), hypoxia (5.3%), erythema (5.3%), hypertension (5.3%). Pneumonitis was observed in one patient (5.3%, Grade 2). No treatment-related death was observed. **Conclusions:** Brigatinib has modest activity for ROS1 positive NSCLC patients previously treated with crizotinib. The safety profile of brigatinib was consistent with previous studies. Enrollment of the cohort 1 for ROS1 inhibitor-naïve NSCLC patients is ongoing, and the data will be presented at a future congress. Clinical trial information: JapicCTI-194851. Research Sponsor: AMED.

9041 **Poster Session**

Determination of clinical benefit among patients with radiological stable disease to immune checkpoint inhibitors.

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Background: SD is a common but ambiguous outcome in patients receiving immune checkpoint inhibitors (ICIs) and likely represents a heterogenous mix of responders and non-responders. This study aimed to characterize SD and identify the subset of patients with SD who are benefiting from treatment. The ability to distinguish whom among patients with SD is actually benefiting from treatment would facilitate drug development and improve precision in correlative research. **Methods:** A systematic review was performed to characterize SD in ICI trials. SD and objective response was compared to proliferation index using TCGA gene expression data. To identify a subgroup of SD with outcomes mirroring responders, we examined a discovery cohort of NSCLC treated with ICIs and had RECIST assessment. In patients with best overall response (BOR) of SD, serial cutpoints of two variables, % BOR and PFS, were tested to define a subgroup with similar survival as PR-minor (patients with partial response [PR] and % shrinkage $<$ median among responders). Results were then tested in two external validation cohorts (n = 326, n = 381). **Results:** Among trials of ICIs (59 studies, 14,280 patients), SD ranged from 16-42% in different tumor types and was associated with disease-specific proliferation index (Spearman rho = -0.75, p = 0.03), a proxy of tumor kinetics, rather than relative response to ICIs. In a discovery cohort of 1220 patients with NSCLC who were treated with ICIs, 26% had SD, 19% had PR/CR, and 55% had PD. Outcomes among those with SD ranged widely (OS range 0.5-76 months, PFS range 0.2-49 months). The subset of SD with PFS $>$ 6 months and no tumor growth mirrored PR-minor (OS HR 1.0) and was proposed as the definition of "SD-responder". SD-responders (n = 87) represented 7% (95% CI 6-9%) of the overall population and 28% (95% CI 23-33%) of the SD population. This definition was confirmed in two validation cohorts from trials of NSCLC treated with durvalumab. **Conclusions:** RECIST-defined SD to immunotherapy is common, heterogenous, and may largely reflect tumor growth rate rather than ICI response. In patients with NSCLC and SD to ICIs, PFS $>$ 6 months and no tumor growth (~1/3 of SD) may be considered "SD responders." This definition may improve the efficiency of and insight derivable from clinical and translational research. Research Sponsor: NIH.

9042 **Poster Session**

Brigatinib in Japanese patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC): First results from the J-ALTA tyrosine kinase inhibitor (TKI)-naive expansion cohort.

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Background: Brigatinib is a next-generation ALK inhibitor with demonstrated activity against ALK mutations. We report primary analysis results with brigatinib in Japanese patients with ALK-positive NSCLC who have not previously been treated with an ALK TKI in the phase 2 J-ALTA study (NCT03410108). **Methods:** J-ALTA, a multi-cohort study, included a TKI-naive expansion cohort. Patients in the TKI-naive cohort received brigatinib 180 mg qd with 7-day lead-in at 90 mg. Primary endpoint was 12-month progression-free survival (PFS) as assessed by an independent-review committee (IRC). Secondary endpoints included confirmed objective response rate (ORR; IRC- and investigator-assessed); IRC-assessed PFS and duration of response (DoR); overall survival (OS); intracranial PFS (iPFS by IRC); and safety. **Results:** A total of 104 patients were enrolled in the whole study; of these, 32 patients had TKI-naive NSCLC (median age, 60.5 y; 94% had adenocarcinoma; 22% had baseline brain metastases; 25% received prior chemotherapy). As of September 29, 2020, median follow-up was 14.2 months and 27 patients remained on treatment. IRC-assessed 12-month PFS was 93% (90% CI, 79–98). Confirmed ORR was 97% (90% CI, 84–100) by IRC, with 2 complete responses and 29 partial responses. Median DoR as assessed by the IRC was not mature; median PFS, iPFS, and OS were not reached. In the TKI-naive cohort, treatment-emergent adverse events (TEAEs) were reported in all 32 patients (most common: increased creatine phosphokinase, 81%; hypertension, 59%; diarrhea, 47%). Grade ≥3 TEAEs were reported in 91% of patients in this cohort (most common: increased creatinine phosphokinase, 44%; hypertension, 34%; increased lipase, 19%) and 75% of all patients. Three cases (9.4%) of interstitial lung disease/pneumonitis were reported in the TKI-naive cohort; all were grade 1 and occurred after day 15 of brigatinib treatment. Dose discontinuations/interruptions/reductions due to AEs in the TKI-naive cohort were 0%/94%/66%, respectively, and in the total study population were 5%/72%/41%. AE frequency and profile were similar in the TKI-naive and overall cohorts. **Conclusions:** In the J-ALTA TKI-naive cohort, brigatinib demonstrated substantial efficacy and manageable safety in the Japanese patient population. Brigatinib remains one of the treatment options in Japanese patients. Clinical trial information: NCT03410108. Research Sponsor: ARIAD Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

9043 **Poster Session**

A large real-world study on the effectiveness of the combined inhibition of *EGFR* and *MET* in *EGFR*-mutant advanced non-small cell lung cancer (NSCLC).

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Background: *MET* amplification is an important mechanism mediating acquired resistance to EGFR tyrosine kinase inhibitors (TKI). Until now, no consensus exists on the standard treatment strategy for this subset of patients due to the lack of clinical data from large cohort or controlled trials. In our clinical practice, three regimens were commonly administered to patients after *MET* amplification-mediated EGFR-TKI progression: EGFR-TKI and MET-TKI combination therapy, MET-TKI monotherapy, or chemotherapy. Our study aimed to compare the effectiveness of these three regimens. **Methods:** Seventy patients with *EGFR*-mutant advanced NSCLC who progressed from prior EGFR-TKI through the acquisition of *MET* amplification and received treatment between March 2015 and March 2020 were included in this study. Of them, 38 received EGFR-TKI plus crizotinib, 10 received crizotinib monotherapy, and 22 received platinum-based doublet chemotherapy. Somatic mutation profiling was performed on blood and tissue biopsy samples. Resistance mechanisms to the combination targeted therapy were also explored in 12 patients. **Results:** The objective response rate (ORR) and disease control rate (DCR) were 47.5% and 84.0% for EGFR-TKI+crizotinib group, 40.0% and 70.0% for crizotinib monotherapy group, and 18.2% and 50.0% for chemotherapy group, respectively. The EGFR-TKI+crizotinib group had significantly better ORR (P = 0.026) and DCR (P = 0.016) than the chemotherapy group but was not statistically different from the crizotinib monotherapy group (ORR, P = 0.73; DCR, P = 0.39). Progression-free survival (PFS) was significantly longer for the EGFR-TKI+crizotinib group than those who received crizotinib monotherapy (5.0 vs 2.3 months, P = 0.004) or chemotherapy (5.0 vs 2.9 months, P = 0.036), but overall survival was comparable (10.0 vs 4.1 vs 8.5 months, P = 0.088). *TP53* mutation (58.5%) and *EGFR* amplifications (42.9%) were the two common concurrent mutations in the three cohorts. PFS was significantly longer for patients with either concurrent *TP53* mutation (n = 17) (6.0 vs 2.3 vs 2.9 months, P = 0.009) or concurrent *EGFR* amplification (n = 13) (5.0 vs 1.2 vs 2.4 months, P = 0.016) who received EGFR-TKI+crizotinib. Potential molecular mechanisms of acquired resistance to EGFR-TKI+crizotinib therapy included *EGFR* T790M (n = 2), *EGFR* L718Q (n = 1), *EGFR* S645C (n = 1), *MET* D1228H (n = 1), *BRAF* V600E (n = 1), *NRAS* Q61H (n = 1), and amplifications in *KRAS* (n = 2), *ERBB2* (n = 1), *CDK4* (n = 1), and *MYC* (n = 2). **Conclusions:** Our study provides real-world clinical evidence, in the largest cohort to date, that simultaneous inhibition of *EGFR* and *MET* improves clinical outcomes of patients with *EGFR*-mutant NSCLC who acquired *MET* amplification from prior EGFR-TKI therapy, indicating that combinatorial regimen of EGFR-TKI and MET-TKI could be a more effective therapeutic strategy in this subset of patients. Research Sponsor: National Natural Science Foundation of China, Other Foundation.

Differential immune-related microenvironment determines PD-1/PD-L1 blockade efficacy in advanced non-small cell lung cancer patients.

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Background: Programmed death ligand-1 (PD-L1) expression is not a completely reliable predictive marker of the efficacy of anti-programmed cell death protein-1 (PD-1)/anti-PD-L1 therapy in advanced non-small cell lung cancer patients (NSCLC). Immune-related tumor microenvironment (TME) is classified into four different types based on the status of tumor-infiltrating lymphocytes (TILs) and PD-L1 expression. **Methods:** We retrospectively reviewed advanced NSCLC patients treated with anti-PD-1/anti-PD-L1 therapy between 2015 and 2019, and investigated the association between the efficacy of anti-PD-1/anti-PD-L1 therapy, the types of TME based on PD-L1 (clone: 22C3) expression, and the density of CD8-positive TILs by immunohistochemistry (/mm^2), and mutational profiles assessed by next-generation sequencing. **Results:** Overall, 228 patients without driver mutation (*EGFR*, *ALK*, *ROS1,* and *RET*) were included in the analysis. The patients were classified into four following groups: Type I: PD-L1$_{High}$ (tumor proportion score [TPS]≥50%)/TIL$_{High}$ (≥85/mm^2; n = 73), Type II: PD-L1$_{Low}$ (TPS < 50%)/TIL$_{Low}$ (< 85/mm^2; n = 70), Type III: PD-L1$_{High}$/TIL$_{Low}$ (n = 37), and Type IV: PD-L1$_{Low}$/TIL$_{High}$ (n = 48). The progression-free survival (PFS) and objective response rate (ORR) of anti-PD-1/anti-PD-L1 therapy clearly differed according to the different tumor microenvironment (TME) types (ORR and median PFS; Type I: 64%, 14.5 months, Type II: 12%, 2.1 months, Type III: 24%, 3.6 months, Type IV: 41%, 10.8 months). In patients with PD-L1$_{High}$ tumors, Type I tumors had significantly better ORR and PFS than Type III(ORR: $p < 0.001$, and PFS: $p < 0.001$) tumors. Regarding the association between mutational profiles, histology and the TME types, the presence of *TP53* mutation and *KRAS* mutation significantly related to TIL$_{High}$ (Type I and IV) and PD-L1$_{High}$ tumors (Type I and III), respectively. Pleomorphic and NSCLC- not otherwise specified histology were associated with Type I tumors, while LCNEC was associated with PD-L1 low tumors (Type II and IV). **Conclusions:** Various factors (mutational profile and histology) are related to TME classification based on the status of TILs and PD-L1 expression. Differential types of TME, including PD-L1 expression and TILs status, can accurately predict the efficacy of anti-PD-1/anti-PD-L1 therapy. Research Sponsor: None.

	ORR (95% CI) (%)	PFS (95% CI) (months)
All patients (n = 228)	36 (30-43)	5.5 (3.7-7.3)
Type I (PDL-1$_{High}$CD8$_{High}$, n = 73)	64 (52-75)	14.5 (8.3-NA)
Type II (PDL-1$_{Low}$CD8$_{Low}$, n = 70)	12 (5-21)	2.1 (1.8-2.4)
Type III (PDL-1$_{High}$CD8$_{Low}$, n = 37)	24 (12-41)	3.6 (2.3-4.9)
Type IV (PDL-1$_{Low}$CD8$_{High}$, n = 48)	41 (27-57)	10.8 (8.1-13.5)

9045 **Poster Session**

Predicting response to pembrolizumab in non-small cell lung cancer, by analyzing the spatial arrangement of tumor infiltrating lymphocytes using deep learning.

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Background: Immune checkpoint inhibitors (ICI) have become the standard treatment for metastatic NSCLC, although only a small proportion of patients derive durable benefit. PDL1 expression is the only approved biomarker to select NSCLC patients for treatment with single-agent pembrolizumab, however its predictive value is limited and better predictive biomarkers are needed. The spatial arrangement of immune cells in the tumor microenvironment (TME), namely tumor infiltrating lymphocytes (TILs), emerges as a potential biomarker for ICI efficacy. In this work, we utilized deep-learning (DL) models to extract TME features from digitized H&E slides and evaluated their predictive and prognostic role in patients with mNSCLC treated with Pembrolizumab. **Methods:** NSCLC patients (n=90) treated with single-agent 1st line pembrolizumab in two centers were identified. 47 patients from one center were used to train the model, and 43 patients from another center were used for validating the model. Pre-treatment H&E whole slide images (WSI) were analyzed using a deep-learning model to identify and classify tumor cells, TILs, tumor and stromal areas, and spatial features were calculated. Spatial features were correlated with clinical outcome data to train a binary classifier that identifies patients with a favorable clinical outcome. The resulting classifier combined three spatial features and three clinical features. The classifier was then applied to the validation set and differences in duration of treatment (DOT), and overall survival (OS) between patients with positive and negative scores were assessed. **Results:** The classifier identified patients in the validation set to have either positive (n=18) or negative (n=25) scores. Baseline patient characteristics and PDL1 score were similar between the positive and negative groups. In a Kaplan-Meier (KM) analysis, OS was significantly higher in patients with a positive score compared to patients with a negative score (HR=0.35, 95% CI 0.13-0.98; $p<0.05$). Positive patients had a significantly higher median OS (NR vs.17.8m, $p<0.05$) and 2-year OS (70.8% vs. 33%, $p=0.02$) than negative patients. Median DOT was also higher in positive patients compared to negative patients (10.1m vs. 6.5m). **Conclusions:** Deep-learning models that analyze the TME from H&E whole-slide images can identify NSCLC patients with durable benefit on Pembrolizumab. Identifying NSCLC patients who are exceptionally sensitive to anti-PD-1 therapy as monotherapy may improve clinical decision making and spare patients the unnecessary adverse effects associated with the addition chemotherapy or another IO agent. Research Sponsor: Nucleai.

Results from a phase II study of eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab in patients with PD-L1 unselected metastatic non-small cell lung carcinoma.

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Background: Eftilagimod alpha (efti) is a soluble LAG-3 protein that binds to a subset of MHC class II molecules to mediate antigen presenting cell (APC) activation and CD8 T-cell activation. The stimulation of the dendritic cell network and subsequent T cell recruitment with efti may lead to stronger antitumor responses in combination than observed with pembrolizumab alone. We hereby report results of the 1st line non-small cell lung carcinoma (NSCLC) part of the phase II trial (NCT03625323). **Methods:** Patients (pts) with untreated, immunotherapy naïve, advanced NSCLC unselected for PD-L1 expression were recruited into part A. The study used a Simon's 2-stage design (17 pts planned for stage 1 and 19 pts for stage 2), with objective response rate (ORR) by iRECIST as the primary endpoint (EP). Secondary EPs include tolerability, disease control rate (DCR), progression free survival (PFS), overall survival (OS), PK, PD and immunogenicity. Efti is administered as 30 mg subcutaneous injection every 2 wks for 8 cycles and then every 3 wks for 9 cycles with pembrolizumab (200 mg intravenous infusion every 3 wks for up to 2 yrs). Imaging was performed every 8 weeks locally and with blinded independent central review (BICR) retrospectively. The study was approved by ethic committees and institutional review boards. **Results:** In total 36 pts were enrolled. At data cut-off (Jan 2021; median FU of 14 months), the median age was 69 yrs (range 53-84) and 69 % were male. The ECOG PS 0 and 1 was 42% and 58% respectively. Patients had squamous (42%) and non-squamous (58%) NSCLC and 95% presented with metastatic disease. All PD-L1 subgroups (TPS < 1 %, ≥ 1 % to ≤ 49 %; ≥ 50 %) were represented with 36% pts having ≥ 50% TPS. Pts received a median of 7.0 (range 1 – 31) pembrolizumab and 11.5 (range 1-22) efti administrations. Responses as per BICR and local read are shown in the table. ORR (local, iRECIST) by different PD-L1 subgroups was 27% for pts with TPS<1%, 39 % for TPS ≥ 1 %and 54% for ≥ 50 % TPS. Median PFS (n=36) was 8.2 months while median OS was not yet reached. The most common (> 20 %) treatment emergent adverse events (AEs) were asthenia (47 %), cough (36 %), decreased appetite (36 %), dyspnea (32 %), pruritus (31 %), fatigue (28 %), diarrhea (25 %), anemia (25 %), constipation (25 %) and back pain (22%). Two patients discontinued treatment due to adverse reactions (Grade 4 immune-mediated hepatitis, Grade 3 AST+ALT increase). **Conclusions:** Efti in combination with pembrolizumab is safe and shows encouraging antitumor activity in 1st line advanced NSCLC patients across all PD-L1 (TPS) levels. Clinical trial information: NCT03625323. Research Sponsor: Immutep S.A.

N=36	iRECIST (BICR)	iRECIST (local read)
CR	2 (6 %)	2 (6%)
PR	13 (36%)	11 (31%)
SD	10 (28 %)	10 (28%)
PD	6 (17%)	9 (25%)
NE/NA	5 (14%)	4 (11%)
ORR (95 % CI)	42% (95 % CI 25.5-59.2)	36 % (95 % CI 20.8-53.8)
DCR	69 %	64 %

9047 **Poster Session**

Safety and efficacy of the anti-CD73 monoclonal antibody (mAb) oleclumab ± durvalumab in patients (pts) with advanced colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDAC), or EGFR-mutant non-small cell lung cancer (EGFRm NSCLC).

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Background: Upregulation of CD73 in multiple cancers increases adenosine production, leading to local immunosuppression. Oleclumab, a human IgG1λ mAb, inhibits CD73 function and may increase antitumor immunity. Initial data from a Phase I, first-in-human, dose-escalation and expansion study showed that oleclumab ± durvalumab had manageable safety and encouraging clinical activity in pts with advanced CRC or PDAC. We report updated safety and activity in these cohorts and the first results in an expansion cohort of pts with advanced EGFRm NSCLC. **Methods:** Previously treated pts with histologically or cytologically confirmed microsatellite stable CRC, PDAC, or EGFRm NSCLC received oleclumab 5–40 mg/kg (escalation) and 40 mg/kg (expansion) IV Q2W, alone (escalation only) or with durvalumab 10 mg/kg IV Q2W. The primary objective was safety; secondary efficacy objectives included objective response (OR) per RECIST v1.1 and duration of response (DoR). **Results:** 66 pts were enrolled in the escalation phase (35 CRC, 31 PDAC) and 126 in the expansion phase (42 CRC, 42 PDAC, 42 EGFRm NSCLC). At data cutoff (DCO; June 9, 2020), the median number of oleclumab doses was 4 in pts on monotherapy (range 1–26) and 4 in pts on combination therapy across both phases (range 1–76). In the escalation phase, there were no DLTs in pts on monotherapy or combination therapy; treatment-related adverse events (TRAEs) occurred in 54.8% of pts on monotherapy (Grade 3–4 in 7.1%) and 54.2% of pts on combination therapy (Grade 3–4 in 20.8%); fatigue was the most common TRAE with both regimens. No TRAEs resulted in death. In previous interim analyses before this DCO, no ORs were reported in the escalation phase. In the expansion phase, 5 pts were treated for ≥12 mos; 6 pts were ongoing at DCO. TRAEs occurred in 54.0% (Grade 3–5 in 15.1%); the most common TRAEs were fatigue (15.1%), diarrhea (9.5%), and rash (7.1%). One pt had a TRAE resulting in death (systemic inflammatory response syndrome). ORs were seen in 1 CRC pt (DoR 35.9+ mos [+ = ongoing response]), 2 PDAC pts (DoR 22.1+ and 28.6+ mos), and 4 EGFRm NSCLC pts (DoR range 5.6 to 15.7+ mos, median not reached; only 1 of the 4 pts had ≥25% programmed cell death ligand-1 [PD-L1]+ tumor cells). Nine CRC pts, 8 PDAC pts, and 9 EGFRm NSCLC pts had SD. Of 6 pts with matched biopsies who received combination therapy, 5 had increases in CD8+ T cells, PD-L1, and granzyme B. Baseline tumor CD73 expression and association with clinical response will be presented. **Conclusions:** Oleclumab ± durvalumab had a tolerable safety profile and combination therapy showed promising antitumor activity in EGFRm NSCLC. ORs and SD were durable, even in tumor types that are generally immunotherapy-resistant. Clinical trial information: NCT02503774. Research Sponsor: AstraZeneca.

9048 **Poster Session**

Phase 1b/2 study of capmatinib plus gefitinib in patients with EGFR-mutated, MET-dysregulated non-small cell lung cancer who received prior therapy: Final overall survival and safety.

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Background: Primary findings from the phase 1b/2 study (NCT01610336) demonstrated clinical activity of combination therapy with capmatinib, a potent and selective MET inhibitor, and gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) in heavily pre-treated patients with EGFR-mutated and MET dysregulated non-small cell lung cancer (NSCLC). The objective response rate (ORR) was 27% in patients across phase 1b/2 of the study. At the recommended phase 2 dose (R2PD) of capmatinib 400 mg twice-daily (bid) and gefitinib 250 mg once-daily (qd), the ORR was 47% in patients with high *MET*-amplified tumors (*MET* gene copy number ≥6). Here, we report the updated data on the efficacy and safety from the NCT01610336 study. **Methods:** Patients with locally advanced or metastatic NSCLC harboring *EGFR* exon 19 deletion or L858R mutation with a recorded clinical benefit on prior single-agent EGFR-TKI before progression and confirmed dysregulated MET pathway after progression on EGFR TKIs were included. Patients in phase 1b received capmatinib 100 to 800-mg capsules qd or 200 to 600-mg capsules or tablets bid, plus gefitinib 250 mg qd. Patients in phase 2 received the R2PD dose. Data on the overall survival (OS) and cumulative safety endpoints are reported in this final analysis. **Results:** Overall, 161 patients received the combination treatment in this study; phase 1b (n = 61) and phase 2 (n = 100). The median age of patients was 60.0 years, mostly Asian (67.1%) with an Eastern Cooperative Oncology Group performance status of 0/1: 18.0%/78.3%. At data cut-off on May 27, 2020, all patients had discontinued the study; 82 out of the 100 patients in phase 2 had died and 18 were censored (mostly lost to follow-up [n = 15]). One patient was still on treatment with a partial response and rolled over to another study. The median (range) follow-up time for OS was 12.2 (0.9-70.2) months. The median OS was 13.9 months (95% confidence interval, 11.6-15.7 months). The median (range) duration of exposure for capmatinib plus gefitinib was 16 weeks (0.4-209.7 weeks) during phase 1b and 18.5 weeks (0.4-268.0 weeks) during phase 2. Majority of the patients (98.8%) experienced ≥1 adverse event (AE); 87% of the patients had treatment-related AEs. Most common treatment-related AEs (reported in ≥20%) were nausea (28.0%), peripheral edema (23%), rash (21.7%), and decreased appetite (21.1%). Grade 3 or 4 treatment-related AEs occurred in 51 patients (31.7%) across both phases, of which, the most frequent (reported in ≥5%) were increased amylase and increased lipase (6.2% each) and peripheral edema (5%). **Conclusions:** Capmatinib 400 mg bid in combination with gefitinib 250 mg qd was well-tolerated and showed encouraging clinical activity in patients with EGFR-mutant and MET-dysregulated NSCLC. Clinical trial information: NCT01610336. Research Sponsor: Novartis.

9049 **Poster Session**

Response to immune checkpoint inhibition as monotherapy or in combination with chemotherapy in metastatic *ROS1*-rearranged lung cancers.

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Background: *ROS1* fusions are oncogenic drivers in various cancers types, including 1-3% of non-small cell lung cancers (NSCLCs). Immunotherapy approvals for NSCLC include *ROS1*-rearranged carcinomas, but the activity of immune checkpoint inhibition (ICI) as monotherapy or in combination with chemotherapy (chemo-ICI) therapy, as well as the immunophenotypic characteristics of these tumors, have not been described in a large data set. **Methods:** In this multi-institutional study, patients with *ROS1*-rearranged NSCLC were identified retrospectively. Tumor PD-L1 expression and tumor mutational burden (TMB) were assessed as part of routine clinical care. In patients who received ICI monotherapy or chemo-ICI in the metastatic setting, time to treatment discontinuation (TTD) and objective response rate (ORR; RECIST v. 1.1) were calculated. TTD was assessed with Kaplan-Meier methods; patients remaining on treatment were censored at last follow up. **Results:** 184 patients with *ROS1*-rearranged NSCLC were identified. Among 146 PD-L1 evaluable cases, PD-L1 expression was $< 1\%$ in 60 (41%), 1-49% in 35 (24%) and $\geq 50\%$ in 51 (35%) tumors. Ninety-two of 100 (92%) TMB-evaluable tumors had $<$ 10 mutations/megabase (mut/Mb). TMB was significantly lower for *ROS1*-rearranged NSCLCs (n = 97) vs. *ROS1*-wild type tumors (n = 5,380) evaluated with next-generation sequencing using MSK-IMPACT (median 2.6 vs. 5.9 mut/Mb, $p < 0.001$). Twenty-eight patients received ICI monotherapy and 11 patients received chemo-ICI. The median TTD was 2.1 months (95% CI: 1.0-4.2; n = 28) for single-agent ICI therapy and 10 months (95% CI: 4.7-14.1; n = 11) for chemo-ICI therapy. The ORR was 13% (2/16 RECIST-evaluable; 95% CI: 2-38%) for ICI monotherapy and 83% (5/6 RECIST-evaluable; 95% CI: 36-100%) for chemo-ICI therapy. There was no difference in PD-L1 tumor expression ($p = 0.9$) or TMB ($p = 0.8$) between responders and non-responders and no correlation between PD-L1 tumor expression (rho = 0.16, $p = 0.6$) or TMB (rho = 0.03, $p = 0.9$) and maximum change in sum of target lesions. **Conclusions:** Most *ROS1*-rearranged NSCLCs have low or no PD-L1 expression and low TMB. The activity of checkpoint inhibitor monotherapy is disappointing in ROS1-driven NSCLC. In contrast, combination chemoimmunotherapy can achieve clinically meaningful activity. Research Sponsor: None.

9050 **Poster Session**

Complete metabolic response in advanced non-small cell lung cancer patients with prolonged response to immune checkpoint inhibitor therapy.

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Background: Recently reported, extended follow-up data from KEYNOTE-024 or -010 indicates that non-small-cell lung cancer (NSCLC) patients can experience long-term benefit from immunotherapy irrespective of discontinuation (per protocol: 35 cycles ~24 months) or type of response in computed tomography (CT). Similar results were observed in the pooled analysis of 5-year follow-up data from CheckMate-017 and -057. This raises the question, whether patients may safely discontinue immunotherapy after achieving durable response. However, recently published results from CheckMate-153 demonstrated inferior survival rates in patients ceasing immunotherapy after one year, therefore optimal treatment duration of immunotherapy in advanced NSCLC remains unknown. Protocols from published Phase-III trials implemented treatment for a period of approximately 24 months or until evidence of disease progression or unbearable toxicity. Therefore, the ideal duration of immunotherapy remains unclear, and finding markers of beneficial outcome is of great importance. Here, we determine the proportion of complete metabolic responses (CMR) in patients that have not progressed after 24 months of immunotherapy. **Methods:** This is a retrospective analysis of forty-five patients with positron emission tomography using 2-[18F]fluoro-2-deoxy-D-glucose (FDG-PET) imaging for assessment of residual metabolic activity after at least 24 months of immunotherapy. Lesion-uptake in FDG PET on or below background level (using mediastinum as reference) was considered as CMR. Time until best objective morphological response including disease stabilization was measured from start of immunotherapy until first stable CT-scan (i.e. no progression or further response compared to previous scan) using RECIST 1.1. **Results:** Out of 45 patients, 29 patients had a CMR (64%). CMR was observed more frequently in non-first line patients. Patients with CMR were younger (median 65.7 vs. 75.5, $P = 0.03$). Fourteen patients with CMR have discontinued therapy and have not progressed until time of analysis; however median follow-up was only 5.6 (range 0.8-17.0) months. **Conclusions:** After a minimum of 24 months of palliative immunotherapy for NSCLC, CMR occurred in almost two thirds of patients. Potentially, achievement of CMR might identify patients, for whom palliative immunotherapy may be safely discontinued. Research Sponsor: None.

9051 **Poster Session**

Comprehensive investigation of mutational features of adenocarcinoma in situ and invasive adenocarcinoma among Chinese lung cancer patients.

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Background: Lung adenocarcinoma (LUAD) is further classified into several histological subtypes with adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma (IAC) as the three major subtypes according to the extent of invasion. AIS has been considered as a precursor of IAC. Considering the significantly higher mutation burden among IAC tumors than AIS tumors, it seems likely that AIS tumors undergo a process of accumulating various somatic mutations to gain invasive ability. To understand the gene mutations involved in this transformation, we compared the mutational features of AIS and IAC tumors. **Methods:** This retrospective study included 2,769 Chinese patients diagnosed with stage 0-IIIA LUAD. Targeted sequencing was performed on tissue DNA isolated from 246 AIS tumors and 2,523 IAC tumors using 68 lung cancer-related genes (Lung Core, Burning Rock Biotech). **Results:** Analysis of mutation profiles revealed that mutation count was significantly lower for AIS ($P< 0.01$) as compared to IAC tumors. Moreover, AIS tumors had significantly higher mutation detection rates for *ERBB2* exon 20 insertion (20ins) ($P\leq0.05$), *EGFR* 20ins ($P\leq0.05$), non-V600E *BRAF* mutations ($P\leq0.05$), and *MAP2K1* small insertion-deletion variants ($P\leq0.05$). These 4 gene mutations were grouped and referred to as AIS-like mutations for further analysis. Detection rates of AIS-like mutations were 54.9% for AIS tumors and 7.8% for IAC tumors. Patients with AIS-like mutation-positive AIS tumors were significantly younger than those with AIS tumors without AIS-like mutations ($P =0.018$), while age were similar for IAC tumors with or without AIS-like mutations. Mutation count was similar between AIS tumors with or without AIS-like mutations. Interestingly, IAC tumors harboring AIS-like mutations had a significantly higher mutation count than those harboring known oncogenic drivers ($P= 0.045$). Further investigation of the molecular profiles of IAC tumors harboring AIS-like mutations (n = 198) revealed the presence of various concurrent mutations in 8 genes including *TP53* (39.4%), *EGFR* (non-20ins) (16.7%), *RB1* (7.1%), *PIK3CA* (6.6%), *MET* (5.1%), *ROS1* (4.0%), *FLT3* (4.0%), and *PTEN* (3.5%), which were absent among AIS tumors, particularly those that harbor AIS-like mutations. In addition to *TP53* (35.8%), *PIK3CA* (4.5%), and *RB1* (4.0%), IAC tumors without AIS-like mutations (n = 2,324) had additional concurrent mutations in 2 other genes *CDK4* (5.7%) and *STK11* (3.9%) as compared to AIS tumors. **Conclusions:** Our data suggest that AIS-like mutations could be involved in the early stages of tumorigenesis by initiating the accumulation of other gene mutations that are required for the transformation of AIS tumors into IAC tumors. Our study contributes to a deeper understanding of the distinct gene mutations between AIS and IAC tumors among Chinese LUAD patients. Research Sponsor: Shanghai Municipal Health Commission Intelligent Medical Research Project, Other Foundation.

9052 **Poster Session**

Amivantamab compared with real-world therapies in patients with NSCLC with EGFR Exon 20 insertion mutations who have progressed after platinum doublet chemotherapy.

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Background: Amivantamab is an epidermal growth factor receptor (EGFR)-MET bispecific antibody with immune cell-directing activity. Amivantamab has demonstrated efficacy and safety in patients (pts) with EGFR exon 20 insertion (Exon20ins) in the ongoing CHRYSALIS phase 1 study in advanced non-small cell lung cancer (aNSCLC). Because CHRYSALIS is a non-randomized, single arm study, external controls (EC) can add valuable context in interpreting amivantamab's efficacy and appreciating the unmet needs given real-world therapies. A protocol-driven treatment comparison was conducted of amivantamab vs real-world therapies in pts with Exon20ins aNSCLC who progressed after platinum chemotherapy. **Methods:** Custom curated, real-world data abstracting clinically relevant measures that are not typically available from off-the-shelf datasets were obtained from 3 US-based companies: Flatiron, COTA, and ConcertAI. Datasets were de-duplicated via a tokenization procedure, analyzed separately and as a single pooled database. Key eligibility for the EC included: Exon20ins aNSCLC, prior platinum chemotherapy, $\geq$1 line after platinum therapy, and ECOG PS 0 or 1. Propensity score weighting (average treatment effects on the treated) was used to adjust for differences in age, brain metastases, ECOG PS, and number of prior lines of therapy (LOT). **Results:** The amivantamab-treated population (N = 81) included post-platinum pts with EGFR Exon20ins aNSCLC treated at the recommended phase 2 dose (Sabari WCLC 2020 Abs #3031). After de-duplication of the custom real-world datasets, 126 unique pts formed the EC. Most frequent treatments after platinum doublet chemotherapy in the EC group were checkpoint inhibitors (CPI; 25%), single-agent, non-platinum chemotherapies (25%), and EGFR tyrosine-kinase inhibitors (TKIs; 16%). Baseline demographics were generally similar between amivantamab and the EC pts; notable differences included a higher percentage of Asian pts (56% vs 9%) and more prior LOT (median 2 vs 1) among the amivantamab compared to the EC pts. Median overall survival (OS) among amivantamab pts was 22.8 months and EC pts was 13.1 months (HR = 0.53 [95% CI, 0.33, 0.86]). Similarly, amivantamab pts had longer progression-free survival (8.3 vs 2.9 months; HR = 0.46 [95% CI, 0.33, 0.63]) and time to next treatment (14.8 vs 4.8 months; HR = 0.42 [95% CI, 0.29, 0.6]) compared to the EC pts. Confirmed overall response rate was 40% among amivantamab pts and 10% for the EC pts (odds ratio = 4.44 [95% CI 2.42, 8.14]). **Conclusions:** Amivantamab demonstrated a 10-month higher OS than real-world therapies in the post-platinum setting. The poor performance of the EC, frequently treated with CPI, single chemotherapies, and EGFR TKI, highlights the ineffectiveness of these agents and the urgent need to find more alteration-specific treatments in aNSCLC. Research Sponsor: Janssen R&D.

9053 **Poster Session**

Totality outcome of afatinib sequential treatment in patients with EGFR mutation-positive NSCLC in Korea: KCSG LU-19-22.

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Background: While osimertinib showed impressive efficacy and safety profile in 1st-line setting for EGFR mutation-positive (EGFR M+) NSCLC patients, there are no standard targeted therapy following progression. Thus, interest has been growing on sequential treatment of osimertinib as 2nd-line treatment for patients acquiring T790M resistance mutation after 2nd generation EGFR TKIs. We did a retrospective study to support the hypothesis that sequential approach of afatinib followed by osimertinib represents a practical treatment option in 'real-world' practice. **Methods:** In this non-interventional, multicenter study, EGFR M+ NSCLC patients had to start 1st-line afatinib treatment ≥ 13 months prior to data entry. They were categorized into 4 cohorts according to 2nd-line treatments with retesting results: T790M+ patients sequentially treated with osimertinib in cohort A, T790M patients treated with chemotherapy or other treatments in cohort B, and patients with unknown mutation status in cohort C. Cohort D included patients who were still ongoing with afatinib. Primary outcome was the time on treatment (TOT) of patients receiving 1st-line afatinib (TOT-1) followed by 2nd-line treatments (TOT-2). Secondary endpoints were acquisition rate of T790M after progression, objective response rates of afatinib (ORR-1) and 2nd-line treatments (ORR-2), and overall survival (OS). **Results:** Among a total of 761 enrolled patients, 737 patients excluding 24 screening failures were allocated into cohort A (n=116), B (n=143), C (n=111), and D (n=367). Median age was 62 years (22 - 90) with 53.05% of female proportion. Brain metastasis was discovered in 38.94% at initial diagnosis. Regarding genotypes of EGFR mutations, del19 was 57.53%, 31.48% for L858R, 7.33% for uncommon mutations, and 3.66% for compound mutation. Median TOTs in cohort A, B, C, and D were 35.09 months (95% CI, 30.09 to 43.53), 18.76 months (95% CI, 16.92 to 20.20), 12.02 months (95% CI, 10.22 to 14.98), and 42.61 months (95% CI, 30.95 to 59.23), respectively. Particularly, in cohort A, median TOT-1 and TOT-2 were 17.43 months (95% CI, 15.21 to 19.32) and 11.04 months (95% CI, 7.10 to 14.13), respectively. Retesting was attempted in 262 of 370 patients (70.81%) with 44.27% of T790M detection rate. ORR-1 and -2 in cohort A, B, and C were 84.48% and 56.03%, 82.52% and 29.08%, 54.95% and 21.70%, respectively and 68.94% of ORR for cohort D. Median OS has was not reached. **Conclusions:** These data suggest that, in real-world practice, sequential afatinib followed by osimertinib be a feasible and effective therapeutic strategy for EGFR M+ NSCLC patients acquiring T790M during the period of afatinib treatment. Of note, median TOT in cohort D is over 3.5 years, suggesting that 1st-line afatinib potentially allow certain patients to maintain long-term, chemotherapy-free state. Further analysis is currently being undertaken and will be presented. Research Sponsor: Boehringer Ingelheim.

Clinico-pathological and genomic features of *NRAS*- or *HRAS*-mutated non-small cell lung cancer (NSCLC) identified in large-scale genomic screening project (LC-SCRUM-Asia).

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Background: *RAS* (*KRAS*, *NRAS* and *HRAS*) is a targetable oncogene family in several cancers, including NSCLC, and the clinical development of various RAS-targeted therapies are ongoing. However, the clinical relevance of uncommon *RAS* mutations, such as *NRAS* and *HRAS* mutations, in NSCLC patients (pts) remains unclear. **Methods:** In a large-scale genomic screening project (LC-SCRUM-Asia), we have prospectively analyzed lung cancer pts for genomic alterations by a targeted next-generation sequencing (NGS) system, Oncomine Comprehensive Assay. We evaluated clinico-pathological and genomic characteristics in *NRAS*- or *HRAS*-mutated NSCLC pts comparing with those in *KRAS*-mutated pts based on the LC-SCRUM-Asia database. **Results:** Since March 2015 to December 2020, 9131 NSCLC pts were enrolled in the LC-SCRUM-Asia, and 8374 of them (92%) were successfully analyzed by NGS. The *RAS* mutation frequencies were 1134 *KRAS* (14%), 50 *NRAS* (0.6%), and 15 *HRAS* (0.2%). The most frequent variant of *NRAS* and *HRAS* mutations was Q61X (78%) and G13X (80%), respectively, whereas that of *KRAS* was G12X (84%). Patient characteristics were summarized in Table. Male was significantly frequent in *NRAS*- than in *KRAS*-group (p=0.03), and smokers were frequent in all the three groups (overall, 79%). The majority of *NRAS* (70%) and *KRAS* mutations (89%) were detected in adenocarcinoma (Ad), whereas 60% of *HRAS* mutations were in squamous cell carcinoma (Sq). Tumor mutation burden (TMB) was significantly higher in *NRAS*-mutated tumors than in *KRAS*-mutated tumors (p=0.03). Concomitant *TP53* mutations were significantly frequent in *HRAS*-mutated pts than in *KRAS*-mutated pts (53% vs. 30%, p=0.05), and *STK11* mutations were also tended to be frequent in *HRAS*-mutated pts than in *KRAS*-mutated pts (20 vs. 7%, p=0.10). Therapeutic efficacy of PD-1/PD-L1 inhibitors was not different among the three groups in the current follow-up data, but *HRAS*-mutated tumors did not respond to PD-1/PD-L1 inhibitors (response rate, 0%; median PFS, 1.6 months). **Conclusions:** *NRAS*- or *HRAS*-mutated NSCLCs were different from *KRAS*-mutated NSCLCs in clinico-pathological and genomic profiles. In particular, the immunotherapies were not effective for *HRAS*-mutated NSCLCs. Research Sponsor: Japan Agency for Medical Research and Development.

		KRAS	***NRAS***		***HRAS***	
		N=1134 (%)	N=50 (%)	p-value(vs. *KRAS*)	N=15 (%)	p-value(vs. *KRAS*)
Age	Median [range]	69 [25-91]	69 [36-87]	0.67	67 [30-84]	0.64
Sex	Male	737 (65)	40 (80)	0.03	13 (87)	0.10
Smoking status	Ever	895 (79)	41 (82)	0.72	13 (87)	0.75
Histology	Ad	1008 (89)	35 (70)	<0.01	4 (27)	<0.01
	Sq	42 (4)	1 (2)		9 (60)	
	Other	84 (7)	14 (28)		2 (13)	
TMB (N=477)	Mean [SD]	6.2 [9.4]	9.4 [11.6]	0.03	7.4 [8.4]	0.70

9055 **Poster Session**

SHR-1701, a bifunctional fusion protein targeting PD-L1 and TGF-β, for advanced NSCLC with *EGFR* mutations: Data from a multicenter phase 1 study.

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Background: Despite the development of targeted therapies for advanced NSCLC harboring *EGFR* mutations (*EGFR*+), acquired resistance remains inevitable. Immune checkpoint inhibitor as monotherapy has limited efficacy. Blockade of the TGF-β pathway which plays a key role in immune suppression may enhance the tumor response to anti-PD-1/PD-L1 antibodies. Here, we assessed SHR-1701, a novel bifunctional fusion protein composed of a mAb against PD-L1 fused with the extracellular domain of TGF-β receptor II, in advanced NSCLC pts including one separate *EGFR+* cohort. **Methods:** This phase 1 study includes a 3+3 dose-escalation and dose-expansion period of pretreated advanced NSCLC and multiple clinical expansion cohorts of different tumor types, genetic aberrations, or prior therapies. During the dose-escalation and dose-expansion period, pathologically confirmed pts received SHR-1701 at 3, 10, or 20 mg/kg Q3W or 20 mg/kg Q2W by intravenous infusion. The primary objectives were to determine the safety profile, maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D) of SHR-1701. In the *EGFR*+ NSCLC clinical expansion cohort, histologically or cytologically confirmed advanced pts after at least 1L standard EGFR TKI received SHR-1701 at RP2D, and the primary endpoint was objective response rate (ORR). Treatment beyond progression was allowed. **Results:** During the dose-escalation and dose-expansion period, 30 pts were recruited: all stage IV; 83.3% had ≥2 metastasis sites; 76.7% had received ≥2L prior systemic therapy. One dose-limiting toxicity (immune-mediated pneumonitis) in the 20 mg/kg Q2W group was observed, and the MTD was not reached. Population pharmacokinetics and exposure-response analysis of SHR-1701 based on this study and another phase 1 study for advanced solid tumors (NCT03710265) demonstrated 30 mg/kg Q3W as the RP2D. In the *EGFR*+ NSCLC cohort, 27 pts were enrolled: all stage IV; 77.8% had ≥2 metastasis sites; 70.4% had received ≥2L prior systemic therapy; 29.6% had 19-Del, 14.8% 19-Del and T790M, 7.4% 20-ins, 29.6% L858R, 18.5% L858R and T790M. With a median SHR-1701 exposure of 8.7 weeks (range, 3.0-24.0), 4 of the 24 pts who had at least one post-baseline radiographic assessment achieved objective responses, including 3 ongoing confirmed and 1 unconfirmed partial response. ORR was 16.7% (95% CI, 4.7%-37.4%), and disease control rate was 50.0% (95% CI, 29.1%-70.9%). Grade 3 treatment-related adverse events (TRAEs) occurred in 2 (7.4%) pts, including anemia, hypokalemia, and asthenia (1 [3.7%] for each). There were no grade 4 or 5 TRAEs. No pts discontinued treatment due to TRAEs. **Conclusions:** SHR-1701 monotherapy shows a manageable safety profile and encouraging antitumor activity in advanced *EGFR*+ NSCLC pts after failure of at least 1L standard EGFR TKI. Further investigation of SHR-1701 combination therapy for *EGFR+* NSCLC is warranted. Clinical trial information: NCT03774979. Research Sponsor: Jiangsu Hengrui Medicine Co., Ltd.

9056 **Poster Session**

Patient-reported outcomes in capmatinib-treated patients with *MET*ex14-mutated advanced NSCLC: Results from the phase II GEOMETRY mono-1 study.

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Background: Capmatinib, a potent, selective MET inhibitor, showed substantial antitumor activity and manageable tolerability in patients with *MET*ex14-mutated advanced non-small cell lung cancer (aNSCLC) in the GEOMETRY mono-1 trial (NCT02414139). Patient-reported outcomes (PROs) from this study are reported here. **Methods:** GEOMETRY mono-1 enrolled patients ≥18 years with *MET*ex14-mutated or *MET*-amplified, *ALK*-negative and *EGFR* wild-type, treatment-naïve (1L) or pre-treated (2L+) aNSCLC, to receive capmatinib orally 400 mg bid during 21-day treatment cycles. Here we report results for patients with *MET*ex14 mutations. PROs (EORTC QLQ-C30, QLQ-LC13 and EQ-5D-5L) were collected at baseline (BL) and every 6 weeks (Wks) until end of treatment. Key PROs (in patients with BL and ≥1 post-BL value) included change from BL in QLQ-C30 global health status (GHS), QLQ-LC13 symptoms (cough, chest pain and dyspnea), and EQ-5D-5L visual analogue scale (VAS), with a ≥10-point change from BL considered clinically meaningful. Time to definitive deterioration (TTDD) in QLQ-LC13 symptoms (time from treatment initiation to first date of ≥10% symptom change from BL with no later reduction) was assessed using Kaplan-Meier. QLQ-LC13 symptoms over time were explored by BIRC-assessed clinical response to capmatinib. **Results:** By Jan 6, 2020 cut-off, median capmatinib exposure was 48.2 (4.0 117.4) Wks and 22.1 (0.4 136.0) Wks for 1L and 2L+ patients, respectively. A total of 27/28 1L patients and 65/69 2L+ patients completed PROs at BL, and completion rate remained high (mostly > 70%) through treatment cycles. Mean [SD] BL PRO scores were moderate-to-high in 1L and 2L+ patients (GHS: 64.7 [21.6] and 58.8 [21.0.]; cough: 35.9 [32.6] and 28.7 [28.2]; chest pain: 12.8 [23.2] and 17.2 [22.7]; dyspnea: 23.5 [23.4] and 22.2 [20.8]; VAS: 67.7 [20.8] and 61.9 [18.8], respectively). Overall change from BL in PROs was maintained over time. Cough improved early, with meaningful improvements observed through cycles, notably in 1L patients (mean change from BL [SD] at Wk 7: 1L -13.0 [39.9], 2L+ -8.2 [28.4]; Wk 25: 1L -15.6 [33.0], 2L+ -6.0 [31.5]; Wk 43: 1L -28.2 [26.7], 2L+ -10.5 [27.3]). Median TTDD in GHS was 16.6 months (95% CI: 9.7, NE [not estimated]) and 12.4 months (95% CI: 4.2, 19.4) in 1L and 2L+ patients, respectively. Median TTDD for cough and chest pain was NE in both 1L and 2L+ patients, and for dyspnea was 19.4 months (95% CI: 12.4, NE) and 22.1 months (95% CI: 9.9, NE), respectively. QLQ-LC13 symptoms improved at all cycles in patients achieving clinical complete response or partial response, while symptom worsening was seen in those with no clinical response. **Conclusions:** Capmatinib was associated with clinically meaningful improvements in cough, delayed time to lung symptom deterioration, and preserved QoL, supporting its use as a treatment option in patients with *MET*ex14-mutated aNSCLC. Clinical trial information: NCT02414139. Research Sponsor: Novartis.

9057 **Poster Session**

Patient-reported outcomes (PRO) from the phase 2 CodeBreaK 100 trial evaluating sotorasib in *KRAS* p.G12C mutated non-small cell lung cancer (NSCLC).

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Background: In the registrational phase 2 CodeBreaK 100 trial, sotorasib demonstrated a response rate of 37.1% with median duration of 10.0 months, a median progression-free survival of 6.8 months, and a tolerable safety profile in patients with pretreated *KRAS* p.G12C mutated NSCLC. Patients received a median of 2 prior lines of therapy. Here, we report PRO measures of health-related quality of life (QoL), physical functioning, and key lung cancer symptoms from this trial. **Methods:** Eligible patients had *KRAS* p.G12C mutated advanced NSCLC and received prior standard therapies. Sotorasib was given at an oral daily dose of 960 mg with 21-day treatment cycles until disease progression. Disease-related symptoms and health-related QoL were evaluated as exploratory endpoints on day 1 of each cycle from baseline to discontinuation, using the European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30) and its lung cancer module, EORTC QLQ-LC13. The single item, 5-point scale GP5, of the Functional Assessment of Cancer Therapy-General version was used to evaluate the impact of side effects. Predefined analyses included change from baseline using descriptive statistics and mixed model for repeated measures for global health status/QoL, physical functioning, and key lung cancer symptoms of cough, dyspnea and chest pain. **Results:** Of 126 patients enrolled, compliance rates for each of the questionnaires were high throughout the study ($>$ 70%). Data up to cycle 11 (where n $>$ 20) are presented. EORTC QLQ-C30 global health status/QoL and physical functioning were maintained over time (least-square mean changes ranged from -3.5 to 0.2 and 0.1 to 3.9, respectively). EORTC QLQ-C30 symptoms of fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, and constipation were stable or improved. Similarly, key lung cancer-related symptoms, as measured by EORTC QLQ-LC13, remained stable or improved from baseline, with the greatest least-square mean change of -11.2 (95% CI: -16.2, -6.1) for cough, -4.9 (95% CI: -10.3, 0.4) for chest pain, and -3.4 (95% CI: -7.8, 1.0) for dyspnea. Most patients reported on the GP5 that they were "not at all" (54.2%-79.2%) or "a little bit" (8.3%-33.3%) bothered by side effects from sotorasib, with 0%-7.4% reporting being bothered as "quite a bit" and 0% as "very much". **Conclusions:** In patients from the single-arm phase 2 trial of sotorasib, PRO measures suggested maintenance or improvement of global health status/QoL, physical functioning, and the severity of key lung cancer-related symptoms, including cough, dyspnea, and chest pain. Self-reported side effect bother was minimal. These data, together with the encouraging efficacy and safety profiles, strongly support the use of sotorasib in this population. Clinical trial information: NCT03600883. Research Sponsor: Amgen Inc.

9058 **Poster Session**

TROPION-PanTumor01: Dose analysis of the TROP2-directed antibody-drug conjugate (ADC) datopotamab deruxtecan (Dato-DXd, DS-1062) for the treatment (Tx) of advanced or metastatic non-small cell lung cancer (NSCLC).

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Background: Datopotamab deruxtecan (Dato-DXd; DS-1062) is an ADC composed of a humanized anti-TROP2 IgG1 monoclonal antibody conjugated to a topoisomerase I inhibitor via a tetrapeptide-based cleavable linker. **Methods:** TROPION-PanTumor01 (NCT03401385) is a multicenter dose-escalation/expansion study evaluating Dato-DXd administered Q3W in patients (pts) with advanced NSCLC (since expanded to other tumor types, excluded from this analysis). Efficacy and safety were evaluated in 175 pts for dose analysis. Pharmacometric analyses (population pharmacokinetics [popPK] and exposure-response modeling) were conducted across doses to inform dose selection for further development. **Results:** At data cutoff (Sept 4, 2020), median follow-up was 7.4 mo (range, 0.10-21.7 mo). Select all-grade TEAEs were 1.5- to 2-fold higher in the 8 mg/kg vs 4 and 6 mg/kg cohorts: vomiting (34% vs 12% and 18%), anemia (28% vs 4% and 16%), diarrhea (20% vs 6% and 11%), and mucositis (29% vs 6% and 13%). Rates of grade ≥3 drug-related TEAEs and serious drug-related TEAEs were ≥2-fold higher with the 8 mg/kg dose (n = 80; 34% and 20%) relative to the 4 mg/kg (n = 50; 10% and 8%) and 6 mg/kg (n = 45; 16% and 9%) doses. Rates of drug-related interstitial lung disease (ILD), as determined by an independent adjudication committee, were higher in the 8 mg/kg cohort (15% vs 2% and 2% in the 4 and 6 mg/kg cohorts); 3 pts in the 8 mg/kg cohort experienced grade 5 ILD. Dose interruptions and reductions due to TEAEs increased with dose (4 mg/kg: 4% and 2%; 6 mg/kg: 20% and 9%; 8 mg/kg: 20% and 31%). More pts in the 8 mg/kg cohort discontinued Tx early due to AEs (15%) compared with those in the 4 mg/kg (4%) and 6 mg/kg (7%) cohorts. ORRs determined by blinded independent central review were similar: 8 mg/kg, 25% (20/80); 6 mg/kg, 21% (8/39); and 4 mg/kg, 23% (9/40). Preliminary median PFS (95% CI) was 5.4 mo (4.1-7.1 mo) in the 8 mg/kg cohort, 8.2 mo (1.5-11.8 mo) in the 6 mg/kg cohort, and 4.3 mo (2.0 mo-NE) in the 4 mg/kg cohort. PFS was limited by early censoring due to immature duration of follow-up, with the majority of pts having ≤3 mo of follow-up in the 4 (66%) and 6 mg/kg (67%) cohorts vs 8 mg/kg (46%) cohort. In pharmacometric analyses, tumor-size change from baseline and probability of complete response/partial response positively correlated with exposure (AUC) of Dato-DXd. Incidences of dose reduction and grade ≥2 stomatitis/mucositis were also positively correlated with exposure; projected probabilities in a virtual population bootstrapped from pts with NSCLC in the popPK data confirmed these trends. Updated results will be presented. **Conclusions:** A Dato-DXd dose of 6 mg/kg was selected for the randomized, phase 3, TROPION-Lung01 trial (NCT04656652) based on better tolerance and improved efficacy, including a trend toward increased PFS. Clinical trial information: NCT03401385. Research Sponsor: Daiichi Sanko Co., Ltd.

9059 **Poster Session**

The role of chemotherapy plus immune checkpoint inhibitors in oncogenic driven non-small cell lung cancer: A University of California Lung Cancer Consortium retrospective study.

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Background: Immune checkpoint inhibitors (ICIs) have demonstrated limited efficacy in patients (pts) with actionable oncogenic drivers. As a result, pts with the prototypic oncogenic drivers (EGFR and ALK) have purposefully been excluded from many NSCLC ICI trials although ICI is commonly used in combination with chemotherapy for these pts. Data from one randomized trial that included pts with known EGFR and ALK alterations did not show a survival benefit with an ICI plus a platinum doublet. We sought to gain further insight into the role of chemotherapy plus ICI in pts with oncogenic driven tumors. **Methods:** We conducted a retrospective analysis of pts with oncogenic drivers (EGFR, ALK, ROS1, BRAF, MET, RET, HER2 and KRAS) who were treated with chemotherapy (C) or chemotherapy plus ICI (C+ICI) between 2018 and 2019 at the five University of California (UC) NCI Designated Cancer Centers (UC Irvine, UC Davis, UC Los Angeles, UC San Diego and UC San Francisco). Descriptive statistics were used. Kaplan-Meier plots and confidence intervals summarize PFS and OS in the overall cohort and oncogenic subgroups. **Results:** 125 pts were identified. Median age 64.1 years; M/F (45%/55%); White/Asian (59%/33%); Current/Former/Never Smokers (4%/39%/57%); PS 0/1/2(22%/68%/10%); prior number of tyrosine kinase inhibitors 0/1/2/ $>$ 3 (46%/23%/19%/11%); Oncogenic driver: EGFR mutations (60%), KRAS mutations (23%), ALK fusions (8%), MET mutations (2.4%), RET fusions (1.6%), ROS1 fusions (1.6%), HER2 mutations (1.6%), and BRAF mutations (0.8%). The table below displays the efficacy outcomes. **Conclusions:** There was no survival benefit for pts with oncogenic drivers treated with chemotherapy plus an immune checkpoint inhibitor in the overall cohort or any of the subsets. Pts with KRAS mutations treated with C+ICI had a numerically longer median PFS than their counterparts treated with C. Updated data and additional analyses including PD-L1, TMB, co-mutations and toxicity will be presented. Research Sponsor: None.

Cohort	# of Pts (C/C+ICI)	PFS (HR)	Median PFS (C/C+ICI)	OS (HR)	Median OS (C/C+ICI)
All patients	70/55	1.07 (0.72, 1.59) P = 0.72574	225 days/219 days	0.80 (0.48, 1.33) P = 0.38655	555 days/653 days
EGFR	50/25	1.13 (0.67, 1.91) P = 0.64177	213 days/178 days	0.77 (0.40, 1.49) P = 0.44319	496 days/574 days
KRAS	8/22	0.85 (0.33, 2.19) P = 0.73898	176 days/249 days	0.82 (0.21, 3.21) P = 0.77742	NR/NR
Non-EGFR/ KRAS	12/8	1.37 (0.50, 3.71) P = 0.53906	285 days/200 days	1.34 (0.35, 5.13) P = 0.66511	944 days/653 days
Never smoker	41/30	1.14 (0.68, 1.90) P = 0.62813)	246 days/232 days	0.77 (0.40, 1.48) P = 0.43269	555 days/599 days
Current/Former smoker	29/25	1.00 (0.54, 1.85) p = 0.99526	206 days/214 days	0.83 (0.36, 1.92) P = 0.66541	546 days/NR

PFS – Progression Free Survival; HR – Hazard Ratio; OS – Overall Survival; NR – Not Reached.

9060 **Poster Session**

A phase 2, open-label, multicenter study to evaluate the efficacy, safety, and tolerability of KN046 in combination with chemotherapy in subjects with advanced non-small cell lung cancer.

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Background: Dual blockade of PD-1 and CTLA-4 has shown improved overall survival (OS) in combination with a short course of chemotherapy. KN046 is a novel bispecific antibody that blocks both PD-L1 interaction with PD-1/CD80 and CTLA-4 interaction with CD80/CD86. We hypothesized that KN046 could be combined with a full course of chemotherapy and build more durable clinical benefit. **Methods:** This study enrolled systemic treatment naive, stage IV NSCLC patients (pts). Eligible pts received KN046 plus platinum doublet chemotherapy until progressive disease, unacceptable toxicity, withdrawal of informed consent or death. Efficacy evaluation was performed by investigators per RECIST 1.1. Safety and tolerability were assessed per NCI-CTCAE v5.0. **Results:** As of the Jan. 19, 2021, 87 pts [Cohort 1 (n = 51), Cohort 2 (n = 36)] have been enrolled with 83 pts having tumor PD-L1 expression data (PD-L1 $\geq$1%: 55.4%; PD-L1 $<$ 1%: 44.6%). 33.3% pts remained on the study treatment and 66.7% pts discontinued treatment due to disease progression (27.6%), TEAE (13.8%), death (9.2%) and other reasons (16%). The median treatment duration of KN046 was 21 weeks (range: 1.6~68.7 weeks). Treatment related TEAE (TRAE) occurred in 92% pts. 25.3% pts experienced Grade$\geq$3 TRAE [diarrhoea (5.7%), alanine aminotransferase increased (4.6%), infusion related reaction (3.4%), rash (3.4%), aspartate aminotransferase increased, dermatitis allergic and immune-mediated pneumonitis (2.3%, respectively), anaphylactoid reaction, autoimmune hepatitis, back pain, bilirubin conjugated increased, hypertension, neutrophil count decreased, platelet count decreased, pneumonitis, rash maculo-papular, septic shock and white blood cell count decreased (1.1%, respectively). In 81 efficacy evaluable pts, the overall objective response rate (ORR) was 50.6% (95% CI: 39.3%,61.9%) and disease control rate (DCR) was 87.7% (95% CI: 78.5%-93.9%). The ORR and DCR in pts with non-squamous NSCLC (n = 48) were 45.8% (95% CI: 31.4%, 60.8%) and 89.6% (95% CI: 77.3%, 96.5%). The ORR and DCR in pts with squamous NSCLC (n = 33) were 57.6% (95% CI: 39.2%, 74.5%) and 84.8% (95% CI: 68.1%, 94.9). Progression free survival (PFS) and OS events have occurred in 53% and 18% patients. Median PFS was 5.9 (95%CI: 5.3, 8.7) months. Median OS was not reached. OS rate at 12 and 15 months were both 74.9%. Similar OS curves have been observed in PD-L1 $\geq$1% and PD-L1 $<$ 1% pts. In PD-L1 $\geq$1% patients, median PFS was 6.7 months (10.8 months for PD-L1 $\geq$1% squamous NSCLC pts). **Conclusions:** KN046 combined with platinum doublet chemotherapy is tolerated and has shown promising clinical benefit as IL treatment for stage IV NSCLC particularly in PD-L1$\geq$1% tumors and squamous histology. Pivotal Phase III trial in advanced unresectable or metastatic squamous NSCLC is currently ongoing. Clinical trial information: NCT04054531. Research Sponsor: Alphamab oncology.

Comparison of time to failure of pembrolizumab plus chemotherapy versus pembrolizumab monotherapy: A consecutive analysis of NSCLC patients with high PD-L1 expression.

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Background: There are two types of pembrolizumab-containing strategies for patients with non-small cell lung cancer (NSCLC) exhibiting a high expression level of programmed death-ligand 1 (PD-L1) (tumor proportion score [TPS] ≥50%): the early combination of pembrolizumab plus chemotherapy, and chemotherapy after pembrolizumab failure. Which strategy is superior, however, remains unclear. Comparing progression-free survival (PFS) or progression after the next therapy line (PFS2) in previous clinical trials has not allowed any conclusions regarding superiority to be made. Instead, the time to failure of strategy (TFS), which represents the time until disease exacerbation when the same number of drugs has been used, should be used to compare the two strategies. **Methods:** We consecutively reviewed the efficacy and safety of first-line, pembrolizumab-containing regimens administered between December 2017 and November 2020. We divided the patients who received pembrolizumab as a first-line treatment into two groups according to whether they received chemotherapy: a pembrolizumab plus chemotherapy group (combo group), and a pembrolizumab monotherapy group (mono group). TFS was defined as the PFS in the combo group and the PFS2 in the mono group. We used the propensity score matching (PSM) method to reduce the bias. **Results:** Of the 964 patients with advanced NSCLC who underwent first-line treatment, 126 with a PD-L1 TPS ≥50% were eligible for inclusion in this analysis (89 in mono group, 37 in combo group). PSM matched 36 people from each of the two groups. The median follow-up period was 16.2 months (range, 0.1-34.3 months). The patient backgrounds were similar. The overall response rate (ORR) of the combo group was higher than that of the mono group (69.4% vs. 50.0%). The median PFS (mPFS) in the combo group was longer (11.4 months vs. 6.0 months). However, the median TFS (mTFS) of the two groups was almost the same (11.4 months vs. 11.7 months). At the time of the analysis, the median overall survival had not been reached. The frequency of all immune-related serious adverse events (irSAE) was similar, however, that of all SAE and AE leading to treatment discontinuation were larger in the combo group. **Conclusions:** The ORR of the combo group was higher than that of the mono group; however, the TFS was similar. We suggest that pembrolizumab plus chemotherapy, which can increase toxicity, might be of value in patients, producing a clinically meaningful increase in the ORR. Research Sponsor: None.

Characteristics, efficacy, and safety of two groups after PSM.

	Combo group (n = 36)	Mono group (n = 36)
Age in years, median (range)	64 (46-78)	66 (45-80)
PS over 2, n	5	3
ORR, % (95% CI)	68.8 (50.0-83.9)	50.0 (32.9-67.1)
mPFS in months, n (95% CI)	11.4 (7.0-NR)	6.0 (3.2-10.7)
mTFS in months, n (95% CI)	11.4 (7.0-NR)	11.7 (9.1-21.5)
SAE, n	12	6
irSAE, n	11	12
Treatment discontinuation, n	18	11

9062 **Poster Session**

EGFR Exon 20 insertion: Prognostic and predictive values in advanced non-small cell lung cancer, a real-world study.

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Background: In Europe, 10-15% of non-squamous non-small cell lung cancer (nsqNSCLC) have EGFR mutations of which 5-12% are an Exon 20 insertion (20ins). **Methods:** Analysis of Epidemio-Strategy and Medical Economics (ESME) Advanced and Metastatic Lung cancer (AMLC) Data Platform (NCT03848052), a multicenter real-life database using a supervised, retrospective data collection process. The database includes 13737 advanced nsqNSCLC treated from January 2015 at participating centres. The cut-off date for patient follow-up for this analysis was June 30, 2020. The aim of the study was to assess real-world patient characteristics, treatment patterns and clinical outcomes of advanced nsqNSCLC EGFR 20ins. Overall survival (OS) of EGFR cohorts (20ins, 19del/L858R without 20ins, other EGFR mutations) and EGFR wild-type/not tested cohort were assessed. **Results:** 1549 (11.3%) nsqNSCLC had an EGFR mutation, 61 (3.9%) of whom being an EGFR 20ins. These 61 patients (pts) are mainly female (68.9%), non-smoker (55.7%), with de novo stage IIIB/IV disease (78.6%), PS 0-1 (76.9%). Median age was 68.0 years (q1-q3: 54-74). PD-L1 status was assessed in 34 (55.7%) pts, mainly (n = 20) before first line and 22 (64.7%) had negative result. Most (63.9%) pts had EGFR 20ins positive result available before first line. Almost all pts (95.1%, n = 58) received a systemic therapy with a median number of 3 (q1-q3: 1-4) lines. In first line setting, 74% of the pts received chemotherapy (mainly chemotherapy combination), 13.7% received EGFR TKI (mainly as monotherapy) and 8.6% received immunotherapy only. Median treatment duration for pts treated with CarboPem (n = 19), CisplatinPem (n = 16) and CarboTaxol (n = 6) were 4.7 (q1-q3: 2.6-6.6), 7.4 (q1-q3: 5.0-12.8) and 3.3 (q1-q3: 2.8-3.8) months, respectively. For afatinib (n = 3), erlotinib (n = 2) and gefitinib (n = 1), median treatment durations were 1.6 (q1-q3: 0.5-2.8); 1.8 (q1-q3: 1.4-2.1) and 2.3 months, respectively. After a median follow up of 36.3 (95%CI: 34.1-39.8) months, median OS was 24.3 (95%CI: 19.1-32.6) months; 1 and 2-years OS rates were 82.5% (95%CI: 69.7-90.2) and 52.6% (95%CI: 37.3-65.9), respectively. For pts with 19del/L858R without 20ins (n = 1049) and those with other EGFR mutations (n = 439) median OS were 35.4 (95%CI: 32.6-37.5) and 41.7 (95%CI: 31.9-53.5), respectively compared to 20.7 (95%CI: 20.0-21.8] months for pts EGFR wild type/not tested (n = 12188). **Conclusions:** This large, national real-world analysis based on medical chart data's confirm that EGFR 20ins is a rare disease (0.4% of advanced nsqNSCLC). Currently available EGFR TKIs appear to have low efficacy and response to chemotherapy seems identical to that of EGFR wild-type/not tested pts. Prognosis for NSCLC pts with EGFR 20ins mutations was in line with that of EGFR wild type/not tested but worse than common EGFR mutations highlighting the need for advancements for this rare population. Research Sponsor: This work was supported by UNICANCER. The ESME AMLC database is supported by an industrial consortium (AstraZeneca, MSD, BMS, Janssen, Amgen and Roche). Data collection, analysis and publication are fully managed by UNICANCER independently of the industry.

9063 **Poster Session**

Features in genomics and tumor immune microenvironment in NSCLC treated with neoadjuvant PD-1 blockade.

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Background: Results from several clinical trials have preliminarily demonstrated the safety and effectiveness of single PD-1 inhibitors in neoadjuvant setting for resectable non-small cell lung cancer (NSCLC). However, only around 40% patients could achieve Major Pathological Response. How to select patients who could benefit from single PD-1 blockade remains elusive. **Methods:** In this study, we aimed to assess the association of PD-L1 expression, tumor mutation burden (TMB), copy number alteration (CNA, including copy number gain and loss) burden with the pathological response to neoadjuvant PD-1 blockade. We also evaluated the dynamic changes of tumor immune microenvironment (TIME) by analyzing pre-immunotherapy treatment tumor biopsy samples from twenty-nine NSCLC patients as well as the matched post-surgery samples after neoadjuvant sintilimab treatment and resection. Targeted DNA sequencing (543 genes), PD-L1 immunochemistry staining (22C3) and multiplex immunofluorescence (CD4, CD8, CD9) were applied. **Results:** The degree of pathological regression and major pathological response (MPR), were positively correlated with tumor proportion score (TPS) of PD-L1 ($R = 0.40$, $p = 0.04$) and negatively correlated with copy number gain (CNgain) burden ($R = -0.44$, $p = 0.04$). Of note, the combination of CNgain burden and TPS can better stratify MPR patients compared to CNgain or TPS alone. Whereas, TMB only had a marginal association with pathological response ($R = 0.32$, $p = 0.15$). Additionally, PD-1 blockade led to an increase in $CD8^+$PD-1-T cells in the tumor region ($p = 0.04$, Mann-Whitney U test for paired samples) and a reduction in Tregs and M2 macrophages in the stromal region ($p < 0.05$, Mann-Whitney U test for paired samples). Further investigation showed that the degree of $CD8^+$PD-1-T cell increase was significantly associated with MPR ($p < 0.05$, Mann-Whitney U test). Intriguingly, we also observed a substantial reduction in $CD19^+$ cells in the non-MPR group but not in the MPR group, indicating the involvement of B cells in improving neoadjuvant immunotherapy response in NSCLC patients. **Conclusions:** TPS and CNgain burden were correlated with pathological response to neoadjuvant immunotherapy in NSCLC patients. This may provide potential selective indicators for future clinical trials of neoadjuvant immunotherapy. The dynamic changes of components in the tumor immune microenvironment may provide novel insight into the immune responses induced by neoadjuvant PD-1 blockade therapy. Research Sponsor: Chinese Academy of Medical Sciences (grants 2016-I2M-1-001, 2017YFC0907903, 2016-12M-1-005, and 2016-12M-1-001).

9064 **Poster Session**

Subgroup-level network meta-analysis for efficacy of first-line immunotherapy-based treatments in advanced non-small cell lung cancer.

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Background: Immunotherapy has unequal efficacies in populations with different clinical or histological features. This study aims to explore inter-subgroup differences in responses to immunotherapy in patients with advanced non-small cell lung cancer (NSCLC) and find the optimal treatments for each subgroup. **Methods:** We performed (network) meta-analyses of phase III random controlled trials, in which efficacies of 10 immunotherapy-based treatments were compared, including anti-programmed death receptor-1 (PD-1) (+chemotherapy), anti-programmed death ligand-1 (PD-L1) (+chemotherapy), anti-PD-L1+anti-cytotoxic T-lymphocyte protein 4 (CTLA-4), anti-PD-1+anti-CTLA-4 (+chemotherapy), anti-CTLA-4+chemotherapy, anti-PD-1+anti-angiogenic therapy (AT)+chemotherapy, and anti-PD-L1+AT+chemotherapy, for 19 subgroups by sex, age, smoking status, metastatic site (liver/brain/bone), histological type (squamous/non-squamous cancer), and PD-L1 expression, using hazard ratios (HRs) for overall survival (OS) and progression-free survival (PFS) and their 95% confidence intervals (CIs). **Results:** 22 studies comprised of 12678 patients with advanced NSCLC were included in our study. The results showed OS and PFS advantages of immunotherapy-based treatments in 16 out of 19 subgroups comparing with chemotherapy. Never-smokers (OS-HR 0.81, 95% CI 0.55-1.18; PFS-HR 0.73, 95% CI 0.51-1.07), ¡Ý75-year-old patients (OS-HR 0.9, 95% CI 0.71-1.13), and patients with liver metastases (OS-HR 0.88, 95% CI 0.77-1) showed indisposed responses to immunotherapy. In patients with PD-L1 tumor proportion score (TPS)$<$1%, anti-CTLA-4+anti-PD-1 and anti-PD-1+anti-CTLA-4+chemotherapy had significant OS benefit comparing with anti-PD-L1 monotherapy (HR 0.6, 95% CI 0.44-0.81; HR 0.6, 95% CI 0.41-0.87; respectively) and anti-PD-L1+AT+chemotherapy (HR 0.66, 95% CI 0.48-0.92; HR 0.66, 95% CI 0.45-0.98; respectively). In patients with liver metastases, anti-PD-L1+AT+chemotherapy showed significant PFS advantage comparing with anti-PD-L1+chemotherapy (HR 0.51, 95% CI 0.33-0.77). As for other populations, anti-PD-1+chemotherapy showed wide-ranging promising efficacies in multiple subgroups. **Conclusions:** Patients with advanced NSCLC generally benefit from immunotherapy. Specific immunotherapy treatments should be applied according to different clinical or histological features. Meanwhile, we expect more preclinical and clinical studies to focus on therapeutic strategies for populations with impaired responses towards immunotherapy. Funding: CSCO-BMS Oncologic Research Foundation (Grant No. Y-BMS2019-100); Guangdong Provincial Key Lab of Translational Medicine in Lung Cancer (Grant No. 2017B030314120) and Guangdong Association of Clinical Trials (GACT); Changsha Science and Technology Bureau (Grant No. kq1907077). Research Sponsor: CSCO-BMS Oncologic Research Foundation (Grant No. Y-BMS2019-100), Other Foundation.

9065 **Poster Session**

Updated overall efficacy and safety of selpercatinib in patients (pts) with *RET* fusion+ non-small cell lung cancer (NSCLC).

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Background: Selpercatinib, a first-in-class highly selective and potent, CNS-active RET kinase inhibitor, is approved in multiple countries for treatment of *RET* fusion+ lung or thyroid cancers. Here we report an update of efficacy and safety results which provide a longer follow up and increased number of patients (safety population: N = 345 vs N = 329). **Methods:** Pts with *RET* fusion+ NSCLC enrolled in the global, multicenter, ongoing LIBRETTO-001 trial (NCT03157128; 16 countries, 89 sites) were included in this analysis. Pts with the opportunity to be followed ≥6 months from their first dose were included in the efficacy-evaluable population for these analyses. Integrated analysis set (IAS) included 218 NSCLC pts with prior platinum-chemotherapy. Primary analysis set (PAS) was a subset of the IAS and included the first 105 consecutively enrolled pts. The treatment-naïve population included 48 efficacy-evaluable pts. Primary endpoint was objective response rate (ORR, RECIST v1.1) by independent review committee (IRC). Secondary endpoints included ORR by investigator, duration of response (DoR), progression-free survival (PFS), clinical benefit rate (CBR; CR+PR+SD ≥16 weeks), and safety. Safety population (N = 345) included all pts with NSCLC who received ≥1 selpercatinib dose by data cutoff (30 Mar 2020). **Results:** In pts with prior treatment (N = 218) and treatment-naïve (N = 48) pts, 56% and 60% were female, with a median pt age of 61 and 64 years, respectively. The ORR with selpercatinib was 57% in the IAS, 64% in the PAS, and 85% in the treatment-naïve population (Table). In both the IAS and PAS, the median DoR was 17.5 months, median PFS was 19.3 months at median follow-up of 12.0 and 15.7 months, respectively (Table). The most common treatment-emergent adverse events (TEAEs) reported in ≥25% of pts were dry mouth, diarrhea, hypertension, increased ALT/AST, edema peripheral, and fatigue. Twenty-five pts (7%) permanently discontinued due to TEAEs, with 10 pts (3%) discontinuing selpercatinib due to treatment-related AEs as per investigator. **Conclusions:** In this updated data set, selpercatinib continued to demonstrate durable antitumor activity in pts with *RET*-fusion+ NSCLC. Selpercatinib was well-tolerated with a safety profile consistent with previous reports. A global, randomized, phase 3 trial (LIBRETTO-431) evaluating selpercatinib compared with standard frontline therapy is ongoing. Clinical trial information: NCT03157128. Research Sponsor: Eli Lilly and Company.

	IAS (N = 218)	PAS (N = 105)	Treatment-naive (N = 48)
Best response by IRC, n (%)			
ORR, % (95% CI), n	57 (50.0, 63.6), 124	64 (53.9, 73.0), 67	85 (72.2, 93.9), 41
CBR% (95% CI), n	84 (78.9, 89.0), 184	85 (76.4, 91.0), 89	94 (82.8, 98.7), 45
DoR, median (95% CI), months	17.5 (12.1, NE)	17.5 (12.1, NE)	NE (12.0, NE)
PFS, median (95% CI), months	19.3 (16.5, NE)	19.3 (13.9, NE)	NE (13.8, NE)
Duration of follow-up, median (25^{th}, 75^{th} percentiles), months	12.0 (7.4, 15.9)	15.7 (12.1, 18.2)	9.8 (7.0, 13.1)

9066 **Poster Session**

Taletrectinib (AB-106; DS-6051b) in metastatic non-small cell lung cancer (NSCLC) patients with ROS1 fusion: Preliminary results of TRUST.

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Background: Taletrectinib (AB-106; DS-6051b) is a potent, selective ROS1/NTRK inhibitor. In two phase I trials, NSCLC patients (pts) with ROS1 fusion who received taletrectinib as first line ROS1 TKI had an objective response rate (ORR) of 66.7% (6/9) and median progression-free survival (PFS) of 29.1 mo (Sai-Hong Ignatius Ou et al., *JTO Clinical and Research Reports*, 2020). TRUST (NCT04395677) is an ongoing, multicenter, phase II study of taletrectinib in Chinese NSCLC pts with ROS1 fusion. **Methods:** The ROS1 TKI naïve or crizotinib pre-treated NSCLC patients with ROS1 fusion were treated with taletrectinib 400 or 600 mg QD. ROS1 testing was performed in each center and confirmed by central lab using RT-PCR. The primary endpoint was ORR (complete response [CR] + partial response [PR]) by IRC assessment. Secondary endpoints were disease control rate (DCR; CR + PR + stable disease), PFS and safety, etc. The pharmacokinetics (PK) of taletrectinib following 400 or 600 mg QD regimen was also evaluated. **Results:** As of the data cutoff (15 Jan 2021), 22 pts had received taletrectinib treatment. Median age was 54.5 years (range, 32-77 years;); 18.2% (4/22) had central nervous system metastases; ECOG performance status was 0 in 13.6% (3/22) of pts and 1 in 86.4% (19/22) of pts. Most pts (54.5%, 12/22) had prior systematic chemotherapy; 31.8% (7/22) of pts had prior crizotinib treatment. ORR by investigator among the crizotinib naïve pts with tumor assessment (N = 11) was 100% (95% CI, 72%-100%); 81.8% (18/22) of pts had treatment-emergent adverse events (TEAEs), including nausea, vomiting, diarrhea, transaminase elevation, white blood cell count decrease/neutrophil count decrease, etc. 13.6% (3/22) were grade $\geq$ 3, including fatigue (4.5%, 1/22), white blood cell decrease (4.5%, 1/22) and transaminase elevation (4.5%, 1/22).TEAEs led to dose interruption in 3 pts (13.6%), including dose reduction in 2 pts (9.1%). Taletrectinib in plasma approximately reached steady state on Cycle 1 Day 8 with 2- to 3- fold accumulations of exposure, which was consistent with results observed in the phase I trials. **Conclusions:** Taletrectinib demonstrated promising clinical activity with high ORR and good tolerability in ROS1 fusion positive NSCLC patients. The safety and PK profiles following taletrectinib treatment was generally consistent with the phase I trials. Clinical trial information: NCT04395677. Clinical trial information: NCT04395677. Research Sponsor: An-Heart Therapeutics.

9067 **Poster Session**

Physician concern about delaying lung cancer treatment while awaiting biomarker testing: Results of a survey of U.S. oncologists.

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Background: With rapid advancements in biomarker testing informing lung cancer treatment decisions, clinicians are challenged to maintain knowledge of who, what and when to test and how to treat based on test results. An ASCO taskforce including representatives from the American Cancer Society National Lung Cancer Roundtable and patient advocates conducted a study to assess biomarker testing and treatment practices for patients with advanced non-small cell lung cancer (aNSCLC) among U.S. oncologists. **Methods:** A survey was sent to 2374 ASCO members – lung cancer specialists and general oncologists. Eligibility required treating $\geq$1 lung cancer patient/month. Proportions were estimated across groups and compared using chi-square tests. **Results:** 170 responses were analyzed. 59% of respondents work at an academic center (i.e., have a fellowship program), while 41% work at a community (non-academic hospital/health system/private practice). Nearly all (98%) believe biomarker results should be received within 1 or 2 weeks of ordering, yet 37% wait an average of 3 or 4 weeks for results. Of respondents who usually wait 3 or 4 weeks, 37% initiate a non-targeted systemic treatment while waiting. Respondents from community practices were more likely to initiate non-targeted systemic treatment if results were not available after 2 weeks (59% compared to 40% of academic respondents; $p = 0.013$).). When asked about reasons for not testing, respondents $<$5 years since training were more likely to report that delaying treatment while waiting for results was always/often a concern compared to those $>$6 years from training (41% vs 19%). Respondents reported high testing rates in both non-squamous and squamous aNSCLC. Roughly equal representation of generalists/specialists and academic/community respondents helps mitigate potential concerns about external validity. **Conclusions:** Respondents indicated that treatment decisions are impacted by delays in biomarker test results. Clinicians should be informed about when it is safe and appropriate to defer treatment while biomarker testing is pending. Respondents suggest that diagnostic biomarker testing companies should strive to expedite results. Research Sponsor: ASCO.

Respondents Characteristics (N=170) N(%).

	All	Academic Setting	Community Setting
1-50% / 51-100% lung cancer pts (row %)	7 (51) / 82 (49)	35 (35) / 65 (65)	52 (75) / 17 (25)
Order multigene panel aNSCLC squamous	154 (91)	96 (62)	58 (38)
Order multigene panel aNSCLC non-squamous	160 (95)	97 (61)	63 (39)
Access to Molecular Tumor Board	142 (84)	91 (64)	51 (36)
Time Since Training (column %)			
<5 yrs	32 (19)	20 (20)	12 (17)
6-15	63 (38)	44 (45)	19 (28)
16+	72 (43)	34 (35)	38 (55)
Avg Time – Biomarker Results			
1 or 2 wks	107 (63)	60 (60)	47 (68)
3 or 4 wks	62 (37)	40 (40)	22 (32)

9068 **Poster Session**

Neratinib efficacy in a subgroup of patients with *EGFR* exon 18-mutant non-small cell lung cancer (NSCLC) and central nervous system (CNS) involvement: Findings from the SUMMIT basket trial.

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Background: The phase 2 SUMMIT basket trial (NCT01953926) demonstrated efficacy of neratinib in patients with *EGFR* exon 18-mutant NSCLC [Boni et al. WCLC 2020]. Neratinib also has documented activity in HER2+ metastatic breast cancer with CNS metastases [Saura et al. SABCS 2020 & J Clin Oncol 2020]. Here we report neratinib efficacy in a subgroup of patients with *EGFR* exon 18-mutant NSCLC and CNS involvement from SUMMIT. **Methods:** Patients with *EGFR* exon 18-mutant NSCLC were treated with single-agent neratinib (240 mg po daily). Prior EGFR tyrosine kinase inhibitors (TKIs), chemotherapy, and checkpoint inhibitors (IO) were allowed. Patients with stable, asymptomatic CNS metastasis were enrolled. Study endpoints: objective response rate (ORR) at week 8 (±1 week); ORR (RECIST 1.1 confirmed); duration of response (DOR); clinical benefit rate (CBR); progression-free survival (PFS); safety; biomarkers. **Results:** Baseline characteristics of 11 patients with *EGFR* exon 18-mutant NSCLC: median age 67 (range 56–83) years; ECOG PS 0/1 (45%/55%). Prior lines of therapies: 2 (range 1–3): EGFR TKIs (91%); chemotherapy (55%); IO (27%). 3/11 patients had baseline CNS metastasis and received radiation 8–22 months prior to study enrollment. Best CNS response in these 3 patients was stable disease with overall individual PFS of 1.9 (censored), 6.9 and 9.1 months and OS of 2.6 (censored), 17.7 (censored), and 17.9 months. Efficacy is summarized in Table. Efficacy summary: TKI-pretreated *EGFR* exon 18-mutant NSCLC cohort receiving neratinib monotherapy. **Conclusions:** Activity of single-agent neratinib was observed in prior TKI-exposed patients with *EGFR* exon 18-mutant NSCLC. Despite the small sample size of only 3 patients with baseline CNS metastases, findings suggest a potential role for neratinib as a systemic treatment option for patients with NSCLC and difficult-to-treat uncommon mutations with CNS involvement. The SUMMIT trial continues to enroll patients with *EGFR* exon 18-mutant NSCLC. Clinical trial information: NCT01953926. Research Sponsor: Puma Biotechnology Inc.

	TKI-pretreated subgroup (n=10)[a]
ORR (confirmed),[b,†] n	4
CR	0
PR	4
ORR, % (95% CI)	40 (12–74)
Best overall response, n	6
CR	0
PR	6
Best overall response rate, % (95% CI)	60 (26–88)
Median DOR,[c] months (95% CI)	7.5 (4.0–NE) (1.9*, 4.0, 7.5, 9.2*)
CBR,[d] n	8
CR or PR	4
SD ≥16 weeks	4
CBR, % (95% CI)	80 (44–97)
Overall median PFS,[c] months (95% CI)	9.1 (3.7–NE)
Overall median OS,[c] months (95% CI)	17.9 (5.7–NE)
PFS in patients with CNS metastases, months	1.9[#], 6.9, 9.1
OS in patients with CNS metastases, months	2.6[#],17.7[#], 17.9

Data cut: Aug 2020. [a]10/11 patients had prior EGFR TKIs. [b]ORR = CR/PR (confirmed ≥4 weeks after criteria for response initially met). [c]KM analysis in safety population. [d]CBR = confirmed CR/PR + SD for ≥16 weeks ±7 day. [†]ORR at week 8 (ORR_{first}) and ORR (RECIST 1.1 confirmed) are identical and only presented once. *Response ongoing; [#]Censored.

9069 **Poster Session**

The effects of tislelizumab treatment on the health-related quality of life of non-small cell lung cancer patients who progressed on a prior platinum-containing regimen.

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Background: Anti-PD-1/L1 therapies have improved overall survival (OS) by 2-4 months vs docetaxel in patients with advanced non−small cell lung cancer (NSCLC) who progressed after receiving a platinum regimen. Tislelizumab, an anti-PD-1 antibody, has been tested as monotherapy in the RATONALE (NCT 03358875) trial, which found that tislelizumab prolonged OS (median OS difference 5.3 months in ITT population) as compared to docetaxel, improved progression-free survival (median 4.1 vs 2.6 months), as well as overall response rate (ORR difference = 14.9%).Here we report health-related quality of life (HRQoL) of patients receiving tislelizumab vs docetaxel in this clinical trial. **Methods:** NSCLC patients in this open-label, multicenter Phase 3 study were randomized to either the tislelizumab or docetaxel. HRQoL was measured using the QLQ-C30 global health status/quality of life score (GHS/QoL) from EORTC QLQ-C30 as well as the lung cancer specific subscales of the EORTC QLQ-LC13. Descriptive analysis for the GHS/QoL score was performed for baseline through cycle 10; changes from baseline to cycle 12 were examined for the symptom subscales. **Results:** 805 patients were randomized to tislelizumab (n = 535) or docetaxel (n = 270). Patients were 77% male with an average age of 60 years (range 28-88 years). The compliance rates were mostly $>$ 98% and were similar across arms. The GHS/QoL score in the tislelizumab arm improved relative to baseline from cycles 5 through 10 while declining in cycles 6 through 10 in the docetaxel arm. The tislelizumab arm showed a reduction from baseline at cycle 12 in the symptom scores of coughing, chest pain, and dyspnea while patients in the docetaxel arm experienced an increase in symptoms. **Conclusions:** The study results show that tislelizumab monotherapy improved HRQoL in patients who previously failed treatment with a platinum containing chemotherapy; this is especially important as the NSCLC patients treated with tislelizumab not only experienced improvements in OS, but also reductions in their symptomology. Clinical trial information: NCT 03358875. Research Sponsor: BeiGene LTD.

9071 **Poster Session**

Brigatinib (BRG) in ALK+ crizotinib (CRZ)-refractory non-small cell lung cancer (NSCLC): Final results of the phase 1/2 and phase 2 (ALTA) trials.

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Background: BRG is a kinase inhibitor approved for the treatment of patients (pts) with ALK+ metastatic NSCLC; specific details for BRG use vary by indication and country. We report long-term efficacy and safety results of the Phase 1/2 and Phase 2 (ALTA) trials of BRG. **Methods:** The Phase 1/2 study was a single-arm, open-label trial (NCT01449461) of BRG 30–300 mg/d in pts with advanced malignancies. ALTA (NCT02094573) randomized pts with CRZ-refractory ALK+ NSCLC to receive BRG at 90 mg qd (arm A) or 180 mg qd with 7-d lead-in at 90 mg (arm B). For the Phase 1/2 study, investigator assessments of confirmed objective response rate (cORR; RECIST v1.1), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety in pts with ALK+ NSCLC are reported. The primary endpoint of ALTA was cORR per investigator; secondary endpoints included cORR per independent review committee (IRC), DoR, PFS, and OS. **Results:** In the Phase 1/2 study, 137 pts received BRG; of these, 79 pts had ALK+ NSCLC (71/79 had prior CRZ; 28/79 received 180 mg qd [7-d lead-in at 90 mg]; 14/79 received 90 mg qd). In ALTA, 222 pts with CRZ-refractory ALK+ NSCLC were randomized (n = 112/110, arm A/B). At the end of the Phase 1/2 study (Feb 18, 2020), with median 27.7 mo follow-up (~67 mo after last pt enrolled), 4 pts remained on BRG. At the end of ALTA (Feb 27, 2020), with median 19.6/28.3 mo follow-up in arm A/B (~53 mo after last pt enrolled), 10/17 pts in arm A/B were still on treatment. Table shows efficacy results from final analyses with long-term follow-up. In ALTA, the IRC-assessed intracranial cORR in pts with measurable baseline brain metastases was 50% (13/26) in arm A and 67% (12/18) in arm B; Kaplan-Meier (KM) estimated median intracranial DoR was 9.4 mo (95% CI, 3.7, not reached [NR]) in arm A and 16.6 mo (3.7, NR) in arm B. With long-term follow-up, no new safety signals were identified. Treatment-emergent adverse events led to dose interruption (Phase 1/2: 59%; ALTA arm A/B: 49%/61%), dose reduction (13%; 8%/33%), or discontinuation (10%; 4%/13%). **Conclusions:** BRG showed sustained long-term activity, PFS, and manageable safety in pts with CRZ-refractory ALK+ NSCLC. The 180 mg/d dose after 7-d lead-in at 90 mg/d led to numerically higher median PFS and OS. Final results are similar to those reported for other approved ALK tyrosine kinase inhibitors in this setting. Clinical trial information: NCT01449461, NCT02094573. Research Sponsor: ARIAD Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

	Phase 1/2 (n = 79)	ALTA: A (n = 112)	ALTA: B (n = 110)
cORR, n (%) [95% CI] Per investigator	53 (67) [56, 77]	51 (46) [36, 55]	63 (57) [48, 67]
Per IRC	—	58 (52) [42, 61]	62 (56) [47, 66]
Median DoR (95% CI),[a] mo Per investigator	14.9 (9.9, 29.5)	12.0 (9.2, 19.4)	13.8 (10.8, 17.6)
Per IRC	—	19.4 (9.2, 24.9)	15.7 (13.6, 22.1)
Median PFS (95% CI),[a] mo Per investigator	14.5 (10.8, 21.2)	9.2 (7.4, 11.1)	15.6 (11.1, 18.5)
Per IRC	—	9.9 (7.4, 12.8)	16.7 (11.6, 21.4)
Median OS (95% CI),[a] mo	47.6 (28.6, NR)	25.9 (18.2, 45.8)	40.6 (32.5, NR)
OS at 5 years[a]	42%	31%	43%

[a]KM estimates.

Activity of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) in patients (pts) with NSCLC with uncommon *EGFR* mutations: A real-world cohort study (UpSwinG).

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Background: EGFR TKIs are an established treatment (tx) option for pts with *EGFR* mutation-positive NSCLC with common mutations (Del19 or L858R); however, 7–23% of NSCLC tumors harbor uncommon *EGFR* mutations, where EGFR TKI efficacy is less established. These mutations are highly heterogeneous, and developments in detection by NGS are helping to identify mutations with little or no clinical data. **Methods:** In this non-interventional, global, multi-center study (NCT04179890), existing medical or electronic health records were identified for consecutive EGFR TKI-naïve pts with uncommon *EGFR* mutations (T790M, ex20ins, major uncommon [G719X, L861Q or S768I], 'other' or compound mutations) treated with erlotinib, gefitinib, afatinib, osimertinib or other systemic therapy. Endpoints were time to tx failure (TTF), ORR, OS and duration of response (DoR). **Results:** Overall, 246 pts (median age: 69.5 yrs; Asian: 84%; brain metastases: 8%; ECOG PS $\geq$2: 16%) were recruited from 9 countries. Most pts (n=226; 92%) received an EGFR TKI as 1st-line therapy; 132 (54%), 105 (43%) and 7 (3%) received afatinib, 1st-gen TKIs and osimertinib, respectively. 57% of pts received $>$1 line of therapy. Most pts (73%) had a major uncommon mutation, 9% had other mutations and 33% had a compound mutation; these were detected using PCR (75%) or sequencing (25%), mainly based on tissue biopsy (86%). Pathology reports varied in quality, often lacking detail on specific mutations e.g. 21% of ex18 and 72% of ex20ins were undefined. Median TTF and OS with EGFR TKIs were 9.9 and 24.4 mos; ORR was 42%. In pts treated with 1st-line chemotherapy (n=20), median TTF and ORR were 6.6 mos and 41%. Outcomes were most favorable in major uncommon and compound mutations (Table). TTF appeared to be higher with afatinib vs 1st-gen EGFR TKIs. In most mutation categories, median OS was $>$2 yrs, possibly reflecting high subsequent therapy uptake. **Conclusions:** In a real-world setting, EGFR TKIs were the preferred tx option in pts with uncommon *EGFR* mutations; strongest outcomes were seen in major uncommon and compound mutations, and in pts treated with afatinib. Data were in line with recent analyses of afatinib in uncommon mutations. Tx with an EGFR TKI should be considered as standard for most pts with uncommon mutations. Optimal tx for pts with uncommon mutations requires improvements in pathology reports, with more emphasis on NGS methodology and precise definition of mutations. Clinical trial information: NCT04179890. Research Sponsor: Boehringer Ingelheim.

Pts treated with afatinib	Median TTF, mos	Median OS, mos	ORR, %	Median DoR, mos
All (n=132)	11.3	24.5	44	12.0
Major uncommon (n=94)	14.3	24.5	51	12.0
Compound (n=46)	12.6	23.4	53	10.0
Other (n=9)	10.8	20.2	29	10.5
Ex20ins (n=18)	8.4	22.5	19	5.5
Pts treated with 1st-gen EGFR TKI				
All (n=106)	8.8	24.2	44	6.0
Major uncommon (n=80)	9.8	28.5	47	6.5
Compound (n=32)	12.4	31.3	48	6.0
Other (n=12)	7.3	12.8	56	4.5
Ex20ins (n=10)	5.2	21.0	17	33.0

9073 **Poster Session**

A phase II trial of chemotherapy plus pembrolizumab in patients with advanced NSCLC previously treated with a PD-1 or PD-L1 inhibitor: Big Ten Cancer Research Consortium BTCRC-LUN15-029.

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Background: Chemoimmunotherapy with a platinum doublet plus a checkpoint inhibitor (CPI) is a standard of care for pts with advanced NSCLC. While some pts experience prolonged responses to initial CPI therapy, the majority of pts will eventually experience PD. It is unknown if continuing CPI treatment beyond progression has any advantages in this setting. We report the results of a phase 2 trial of chemotherapy plus pembrolizumab in pts with advanced NSCLC previously treated with a PD-1 or PD-L1 inhibitor. **Methods:** Pts experiencing PD after clinical benefit to CPI (PFS $>$ 3 months) were enrolled. Pts received pembrolizumab 200 mg q3wks plus next-line chemotherapy (gemcitabine 1000 mg/m^2 IV D1 and D8 q3wks, or docetaxel 60-75 mg/m^2 IV D1 q3wks, or pemetrexed 500 mg/m^2 IV D1 q3wks [nonsquamous histology only]). The primary endpoint was PFS by RECIST 1.1. Key secondary endpoints included ORR, OS, and toxicity. The null hypothesis was median 3-month PFS with pembrolizumab plus next-line chemotherapy and the alternative hypothesis was median 6-month PFS with pembrolizumab plus chemotherapy. **Results:** 35 pts were enrolled. Median follow-up was 18.1 months and median age 63 (44-80). 51.4% male and 48.6% female. 82.9% were current or former smokers. Histology included 74.3% with adenocarcinoma, 20% with squamous cell carcinoma, 5.7% with NSCLC NOS. Treatment regimens included pembrolizumab/docetaxel (40%), pembrolizumab/gemcitabine (45.7%), or pembrolizumab/pemetrexed (14.3%). Median number of cycles of pembrolizumab was 6 (1-31). Median PFS using RECIST 1.1 and irRECIST was 5.2 months (95% CI 3.6-11.2, $p < 0.05$) and 6.9 months (95% CI 3.8-12), respectively. Median OS was 26.8 months (95% CI 13.4-30.9). Best response using RECIST 1.1 was PR (23.5%) and SD (53%). 45.7% of pts experienced G3 or higher treatment-related AEs (TRAEs). Most common TRAEs were fatigue (60%), anemia (51.4%), and nausea (42.9%). There were no treatment related deaths. **Conclusions:** Pembrolizumab plus next-line chemotherapy in pts with advanced NSCLC who experienced PD after clinical benefit to CPI was associated with prolonged PFS compared with historical controls of single agent chemotherapy. Further investigations into which pts would benefit from continued CPI treatment after progression is warranted. Clinical trial information: NCT03083808. Research Sponsor: Merck.

9074 **Poster Session**

Phase I study of the aurora kinase A inhibitor alisertib in combination with osimertinib in EGFR-mutant lung cancer.

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Background: The 3rd generation EGFR tyrosine kinase inhibitor (TKI) osimertinib is effective for the treatment of advanced EGFR-mutant (mt) lung adenocarcinoma (LUAD). However, tumor resistance to osimertinib monotherapy invariably occurs. Activation of Aurora Kinase A (AURKA) drives resistance to osimertinib treatment in preclinical models of EGFR-mutant LUAD and is associated with TKI resistance in patients. Alisertib is a selective AURKA inhibitor with an acceptable safety profile established in early phase clinical trials. **Methods**: We performed a single institution phase Ia clinical trial of alisertib in combination with the 3rd generation EGFR inhibitor osimertinib in patients with metastatic EGFR-mutant LUAD who had experienced disease progression on osimertinib monotherapy (NCT04085315). The primary objective of the study was to determine the safety and tolerability of alisertib in combination with osimertinib in order to define the maximum tolerated dose (MTD) and to identify a recommended phase 2 dose (RP2D). Secondary efficacy endpoints included objective response rate (ORR), disease control rate (DCR) and progression-free survival (PFS). Utilizing a 3+3 trial design, patients receiving osimertinib 80 mg daily were treated with alisertib using an intermittent dosing strategy of 20-50 mg twice daily (BID) oral alisertib on days (d) 1-3, 8-11, and 15-17 of a 28-day cycle. **Results:** A total of 10 patients were treated with osimertinib 80 mg and received at least one dose of alisertib. 6 patients were treated at the 30 mg BID and 4 patients at the 40 mg BID intermittent dosing schedule of alisertib. The most commonly reported adverse events (AEs) were diarrhea (70%), fatigue (60%), alopecia (50%) and neutropenia (50%). All AEs, except neutropenia, were grade 1 or 2. Two patients (20%) experienced grade 3 or grade 4 neutropenia; both patients were treated at the 40 mg BID intermittent dose of alisertib. Intermittent alisertib 30 mg BID was identified as the MTD and RP2D in combination with osimertinib 80 mg daily. The ORR was 10% (1/10) and DCR 70% (7/10), with the majority of patients, 60% (6/10), achieving stable disease (SD). 30% (3/10) experienced progressive disease (PD) as their best response. The median PFS was 9.4 months (2.0 months - N.R.). **Conclusions:** Intermittent dosing of alisertib 30 mg BID on d1-3, 8-11, and 15-17 of a 28-day cycle in combination with osimertinib 80 mg daily demonstrates an acceptable toxicity profile. Preliminary efficacy analysis suggests that alisertib + osimertinib may result in clinically meaningful disease control in EGFR-mt LUAD patients whose disease is resistant to osimertinib monotherapy. Clinical trial information: NCT04085315. Research Sponsor: Takeda, Other Foundation.

9075 **Poster Session**

Phase II randomized study of ramucirumab plus pembrolizumab versus standard of care for advanced non-small cell lung cancer previously treated with a checkpoint inhibitor: Toxicity update (Lung-MAP non-matched sub-study S1800A).

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Background: The therapeutic landscape in metastatic NSCLC has dramatically changed with approvals of immunotherapy agents in both treatment-naïve and previously treated cancer patients (pts) and irrespective of histology. Pts with tumors that develop resistance is a significant area of unmet need. Vascular endothelial growth factor (VEGF) has been shown to modulate the tumor immune microenvironment and combination immune checkpoint and VEGF/VEGF receptor inhibition have shown benefit in multiple tumor types. Lung-MAP is a master protocol for pts with stage IV, previously treated NSCLC. Pts who were not eligible for a biomarker-matched substudy enrolled in S1800A. The adverse event profile will be presented. **Methods:** S1800A is a phase II randomized trial for pts who previously received PD-1 or PD-L1 inhibitor therapy for at least 84 days and platinum-based doublet therapy with ECOG 0-1 stratified by PD-L1 expression, histology and intent to receive ramucirumab in the standard of care (SOC) arm. Pts were randomized 1:1 to pembrolizumab and ramucirumab P+R or SOC (docetaxel +R [SOC w R]; docetaxel, pemetrexed or gemcitabine [SOC wo R]). The primary endpoint was overall survival. Secondary endpoints included response, duration of response, investigator assessed-progression free survival and evaluation of toxicity. **Results:** From May 17, 2019 to November 16, 2020, 166 pts enrolled and 140 determined eligible [69 (49%) P+R; 46 (33%) SOC w R; 25 (18%) SOC wo R]. Treatments for those who received SOC wo R included 3 on docetaxel (19%); 12 on gemcitabine (75%); and on 1 on pemetrexed (6%). 131 were eligible for adverse event (AE) assessment. The most common AE were fatigue (38%), proteinuria (28%), hypertension (23%), diarrhea (22%) and hypothyroidism (22%) on P+R; fatigue (61%), anemia (48%), diarrhea (41%) and neutropenia (39%) on SOC w R and anemia (56%), leukopenia (56%), fatigue (44%) and neutropenia (44%) on SOC wo R. Grade $\geq$ 3 treatment-related AEs occurred in 32% of pts on P+R, 54% of pts on SOC w R and 56% of pts on SOC wo R. Cardiac and thromboembolic events occurred in 12% of pts on P+R, 11% of pts on SOC w R and 0% of pts on SOC wo R. Grade 5 AE occurred in 2 pts on P+R (respiratory failure and cardiac arrest), 3 pts on SOC w R (2 respiratory failure and sepsis) and 1 pt on SOC wo R (sepsis). Four patients were diagnosed with COVID-19 (1 on P+R and 3 on SOC) and 3 died (1 on P+R and 2 on SOC). **Conclusions:** Grade 3 toxicities were lower in P+R compared to SOC arms with or without R. Cardiac and thromboembolic events were similar in arms that included R. P+R was generally well-tolerated. Efficacy outcomes will be presented when data matures. Clinical trial information: NCT03971474. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Eli Lilly and Company and MSD International GmbH.

9076 **Poster Session**

PD-(L)1 inhibitors as monotherapy for the first-line treatment of non-small cell lung cancer patients with high PD-L1 expression: A network meta-analysis.

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Background: PD-L1 has emerged as a potential biomarker for predicting responses to immunotherapy and as a prognostic factor in non-small cell lung cancer (NSCLC). In this network meta-analysis, we aimed to evaluate the efficacy of first-line PD-(L)1 monotherapy in advanced NSCLC patients with high PD-L1 expression. **Methods:** We conducted a systematic search in PubMed to identify all eligible trials from inception until 1 November 2020, with no start date limit applied. Only phase III trials evaluating the efficacy of first-line (1L) PD-(L)1 monotherapy in patients with stage IIIB/stage IV NSCLC and high PD-L1 expression were included. **Results:** Six clinical trials (KEYNOTE-024, KEYNOTE-042, EMPOWER Lung-01, IMpower110, MYSTIC and CheckMate-026) with 2,111 patients were included. In head-to-head comparisons, immunotherapy showed a significant improvement in progression-free survival (PFS: $HR_{pooled} = 0.69$, 95% CI: 0.52-0.90, $p = 0.007$), overall survival (OS: $HR_{pooled} = 0.69$, 95% CI: 0.61-0.78; $p < 0.001$) and overall response rate (ORR) (Risk ratio $[RR]_{pooled} = 1.354$, 95% CI: 1.04-1.762, $p = 0.024$) compared to chemotherapy (CT). In the assessment of relative efficacy for PFS through indirect comparisons, pembrolizumab (results from KEYNOTE-024) ranked highest followed by cemiplimab and atezolizumab, with statistical significance determined across some of the drugs. In terms of OS, cemiplimab ranked highest followed by atezolizumab and pembrolizumab, although non-significant OS was determined across these drugs. Overall, 1L PD-(L)1 monotherapy improved OS in almost all subgroups, reaching statistical significance in men ($HR_{pooled} = 0.624$, 95% CI: 0.51-0.72, $p < 0.001$), non-Asian patients ($HR_{pooled} = 0.66$, 95% CI: 0.55-0.79, $p < 0.001$), all patients regardless of age (< 65 years [$HR_{pooled} = 0.72$, 95% CI: 0.57-0.90, $p = 0.005$]; ≥ 65 years [$HR_{pooled} = 0.61$, 95% CI: 0.48-0.77, $p < 0.001$]), ECOG PS status (ECOG PS = 0 [$HR_{pooled} = 0.68$, 95% CI: 0.56-0.82, $p < 0.001$; ECOG PS = 1 [$HR_{pooled} = 0.59$, 95% CI: 0.43-0.82, $p = 0.001$) and histological tumour type (Squamous [$HR_{pooled} = 0.49$, 95% CI: 0.37-0.67, $p < 0.001$; Non-squamous [$HR_{pooled} = 0.67$, 95% CI: 0.52-0.87, $p = 0.003$). In the case of smokers and NSCLC stage, only current/former smokers ($HR_{pooled} = 0.623$, 95% CI: 0.47-0.83, $p = 0.001$) and patients with stage IV disease* ($HR_{pooled} = 0.687$, 95% CI: 0.59-0.81, $p < 0.001$) benefited from single PD-(L)1 monotherapy over CT. **Conclusions:** PD-(L)1 inhibitor monotherapy improves efficacy outcomes in the 1L setting of advanced NSCLC patients with high PD-L1 expression. Current/former smokers ≥65 years, with ECOG PS = 1 and squamous NSCLC benefited most from this therapy. *KEYNOTE-042 was the only study including patients with stage IIIB NSCLC. Research Sponsor: ROCHE FARMA.

9077 **Poster Session**

Safety and activity of CLN-081 (TAS6417) in NSCLC with EGFR Exon 20 insertion mutations (Ins20).

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Background: NSCLC with EGFR ins20 represents a significant area of unmet need, with no approved targeted therapies. While several agents targeting EGFR ins20 are in development, wild-type (WT) EGFR-related adverse events (AEs) have been common and challenging to manage. CLN-081 is a novel oral EGFR TKI with broad activity against clinically relevant EGFR mutations, including ins20, and has attenuated activity against WT EGFR relative to EGFR ins20 *in vitro*, suggesting that CLN-081 may have a more favorable clinical therapeutic window. We present interim results of a multicenter, Phase (Ph) 1/2a trial evaluating CLN-081 in advanced, EGFR ins20 NSCLC (NCT04036682). **Methods:** Patients (pts) with EGFR ins20 previously treated with platinum-based therapy (tx) were eligible to enroll. Ph 1 dose escalation in this adaptive trial began with an accelerated titration (AT) design, and converted to a rolling six design based upon pre-specified safety criteria or at clinically active doses. Cohort expansion in Ph 1 occurred at any dose where responses were seen. Transition from Ph 1 to 2a was based on a Simon-Two Stage design. Prior tx with EGFR ins20-specific inhibitors was allowed in AT cohorts only. CLN-081 was dosed twice daily (BID) in 21-day cycles. **Results:** As of 10 November 2020, 37 pts [median age 64 years (44-82); median 2 (1-9) prior lines of tx] received CLN-081 at doses of 30 mg (n = 8), 45 mg (1), 65 mg (12), 100 mg (13), and 150 mg (3) BID. The most common all-grade (gr) treatment-related AEs (TRAEs) were rash (49%), diarrhea (24%), paronychia (16%), nausea (14%), stomatitis (14%), and dry skin (11%). Gr 3 TRAEs included anemia (5%), diarrhea (3%), and increased alkaline phosphatase (ALP) (3%). There was 1 DLT, gr 3 diarrhea at 150 mg BID. No gr $\geq$ 3 rash or gr 4/5 TRAEs were reported. Four pts (11%) required dose reductions for rash (2), diarrhea (1), and increased ALP (1). Two pts (5%) discontinued tx due to TRAEs of gr 2 hypersensitivity reaction (1) and gr 2 pneumonitis (1); the latter also experienced pneumonitis while receiving prior osimertinib. Among the 25 response evaluable pts (RECIST 1.1), 10 (40 %) had a partial response (PR) (6 confirmed, 2 pending confirmation, 2 unconfirmed), 14 (56%) had stable disease (SD), and 1 (4%) had progressive disease as best response. Of the 4 pts that received prior EGFR ins20 inhibitors, 2 had PR and 2 SD. Of pts with SD or PR as best response, 20/24 (83 %) experienced tumor regression [median regression: -18 % (-100 to +3)]. Enrollment is ongoing and updated data will be presented. **Conclusions:** CLN-081 has an acceptable safety profile, including diarrhea in $<$ 25% of pts treated to date. CLN-081 has demonstrated encouraging preliminary anti-tumor activity across the full dose range tested, in multiple distinct EGFR ins20 variants, and in heavily pre-treated pts that are either naïve or refractory to other EGFR ins20 inhibitors. Since the time of the data cut, a Ph 2a expansion has been initiated at 100 mg BID. Clinical trial information: NCT04036682. Research Sponsor: Cullinan-Pearl.

9078 **Poster Session**

Patient-reported symptoms, functioning, and quality of life (QoL) in patients treated with cemiplimab monotherapy for first-line treatment of advanced NSCLC with PD-L1 $\geq$ 50%: Results from EMPOWER-Lung 1 study.

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Background: Cemiplimab, a PD-1 inhibitor, improved survival and progression-free survival vs platinum doublet chemotherapy (chemo) in patients (pts) with advanced NSCLC and PD-ligand(L)1 expression $\geq$50% in the EMPOWER-Lung 1 Phase 3 study (NCT03088540). Since pts with advanced NSCLC have a high symptom burden that adversely impacts QoL and functioning, these outcomes were evaluated as secondary endpoints in the clinical trial. **Methods:** Pts with advanced NSCLC with PD-L1 expression $\geq$50% and ECOG performance status $\leq$1 were randomized to IV cemiplimab 350 mg Q3W (n=356) or platinum doublet chemo (n=354). At baseline (BL) and day 1 of each treatment cycle (C) to C15, pts were administered the EORTC core questionnaire (QLQ-C30) and its lung cancer specific module (QLQ-LC13) to assess symptoms, functioning, and Global Health Status (GHS)/QoL. In the intent-to-treat population, mixed-effects repeated measures models were used to estimate least squares (LS) mean change from BL on all scales. Kaplan–Meier analysis estimated time to definitive deterioration, defined as worsening $\geq$10 points from BL observed at all subsequent time points or patient withdrawal after worsening; hazard ratios (HR) with 95% CIs estimated the likelihood of definitive deterioration. **Results:** BL scores showed moderate to high levels of functioning and low symptom burden. Cemiplimab-treated pts had lower likelihood of definitive deterioration vs chemo on key symptoms of dyspnea, cough, pain in chest, pain in other body parts, fatigue, nausea/vomiting, appetite loss, constipation, and diarrhea vs chemo (all $P<.05$). Treatment-related symptoms of peripheral neuropathy and alopecia had a lower likelihood of definitive deterioration with cemiplimab vs chemo (both $P<.05$). Cemiplimab resulted in significantly greater improvements vs chemo on all functioning scales and reduced the likelihood of definitive deterioration as indicated by HR <1 (Table). GHS/QoL improvements with cemiplimab at C2 were maintained to C15; LS mean change (SE) from BL across all timepoints was 7.1 (1.0) for cemiplimab vs 1.7 (1.2) for chemo ($P<.0001$). **Conclusions:** In pts with advanced NSCLC and PD-L1 expression $\geq$50%, cemiplimab significantly improved GHS/QoL, functioning, and most symptoms vs chemo. Over 1 year of treatment, cemiplimab delayed worsening of key lung cancer symptoms and functioning. Clinical trial information: NCT03088540. Research Sponsor: Regeneron Pharmaceuticals, Inc, and Sanofi.

	Difference in LS mean change from BL (95% CI)[a]	HR (95% CI) for definitive deterioration
GHS/QoL	5.4 (2.7–8.1)*	0.73 (0.52–1.03)
Physical functioning	4.2 (1.6–6.7)*	0.59 (0.42–0.84)*
Role functioning	3.3 (0.2–6.3)*	0.65 (0.46–0.92)*
Emotional functioning	3.4 (1.0–5.9)*	0.49 (0.30–0.79)*
Cognitive functioning	2.5 (0.4–4.5)*	0.64 (0.44–0.93)*
Social functioning	5.2 (2.5–7.9)*	0.50 (0.35–0.72)*

[a]Cemiplimab minus chemo.
*$P<.05$.

9079 **Poster Session**

Real-world patterns of biomarker testing and targeted therapy in metastatic non-small cell lung cancer (mNSCLC) in the community oncology setting.

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Background: National guidelines recommend biomarker testing in mNSCLC, and targeted therapy is associated with improved outcomes. The aim of this study was to understand the real-world biomarker testing and treatment patterns in the community setting. **Methods:** This was a retrospective study of adult patients diagnosed with de novo mNSCLC between 01-Jan-2016 and 30-Sep-2019, with follow-up through 31-Dec-2019 using The US Oncology Network structured electronic health records data. Patients who received systemic treatment for mNSCLC were included. **Results:** A total of 3213 patients were identified with median age 68 years (24, 90+); 52.7% were male and 10% were current smokers. ECOG score was 0-1 in 55.2%; 60% had adenocarcinoma, 16% had squamous cell carcinoma, and the rest had other/unknown histology. Since most of the biomarker-guided therapies were approved after 2016, testing patterns are described for 2017-2019 (n=2257). Overall, 23.6% were not tested for any biomarker (PD-L1 or driver mutation [DM]) at any time during the study period, and only 49% had a biomarker test result prior to 1L treatment. We observed similar patterns when assessing DM specifically; 35.8% were never tested for DM, and only 39.3% had a DM test result prior to 1L treatment. As an example, out of 42 ALK+ patients in this study population, only 5 had test results prior to 1L treatment and only 3 received an ALK inhibitor as their 1L treatment (Table). Similar patterns were observed for the other biomarkers. **Conclusions:** Despite availability of promising biomarker-based therapies, the lack of adequate testing in the community oncology setting means that not all eligible patients are receiving the most effective therapies upfront. Nearly 61% of patients had no DM test reported before 1L treatment in this mNSCLC cohort (all histologies), and some were determined to be DM positive at a later time, highlighting a missed opportunity to employ the most effective biomarker-directed front-line treatment. Next steps in this study will include assessing patterns by histology. Structured data, which are recorded for clinical management, might have gaps; future research with chart reviews could provide a more comprehensive assessment. Research Sponsor: Genentech.

N=2257	PD-L1		ALK		EGFR		BRAF		ROS1	
	Study observation period	Before/ at 1L	Study observation period	Before/ at 1L	Study observation period	Before/ at 1L	Study observation period	Before/ at 1L	Study observation period	Before/ at 1L
Tested (n, %)	1481 (65.6)	982 (43.5)	1300 (57.6)	801 (35.5)	1316 (58.3)	794 (35.2)	634 (28.1)	385 (17.1)	1187 (52.6)	750 (33.2)
Results positive (n, % of tested)	586 (39.6)	516 (52.5)	42 (3.2)	5 (0.6)	503 (38.2)	230 (28.9)	25 (3.9)	10 (2.6)	15 (1.3)	6 (0.8)
Biomarker-directed treatment (n, % of positive)	532 (90.8)	394 (76.4)	40 (95.2)	3 (60.0)	206 (40.9)	33 (14.3)	6 (24)	0	6 (40)	1 (16.7)

9080 **Poster Session**

Identification of recurrence-associated gene signature and tumor immune microenvironment features in resected stage I NSCLC.

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Background: Surgery is the primary treatment for stage I NSCLC, but postoperative recurrence leads to poor prognosis. Alterations of tumor genes and immune microenvironment may be crucial factors for tumor recurrence; however, the detailed mechanisms remain unclear. **Methods:** A total of 130 resected stage I NSCLC patients were enrolled, 69 developed recurrence within three years and 61 without recurrence over five years. Whole exome sequencing (WES) was performed to evaluate genomic alterations. Immunohistochemistry was carried out to assess the expression of PD-L1, CD3 and CD8. We calculated density of CD3+ and CD8+ T cells in the center of tumors (CT) and invasive margins (IM), defined six immunoscore types based on the location and density of both cells, and performed ROC analysis to evaluate prognostic value of them. We further verified our results using stage I NSCLC cohorts from the Cancer Genome Atlas (TCGA) and Tumor immune estimation resource (TIMER) database. **Results:** In univariate analysis, lung adenocarcinoma (LUAD) patients showed significantly higher risk of recurrence ($p = 0.008$). There was no statistically significant correlation between recurrence and other clinical factors, including TNM stage. Although driver gene mutations, such as those of EGFR, had no correlation with recurrence, *MUC4* mutation and high tumor mutation burden (TMB) were significantly associated with higher risk of recurrence ($p = 0.001$ and 0.0032, respectively). Enrichment analysis of KEGG pathways showed that Ras pathway mutations were significantly enriched in *MUC4* mutant group and recurrence group ($p = 0.02$ and 0.05, respectively). 9.6% patients had PD-L1 positive expression (TPS$\geq$1%), but showed no association with recurrence. Recurrence group had much lower density of $CD8_{CT}$, $CD8_{IM}$ and $CD3_{CT}$ +T cells($p = 0.0026$, 0.0022 and 0.0308, respectively). Immunoscore type V, based on the average of $CD8_{CT}$, $CD8_{IM}$ and $CD3_{CT}$ + T cells, had the highest prognostic value (AUC = 0.764) and was used as the final immunoscore in our study. In multivariate analysis, we found *MUC4* mutation and low immunoscore were independent predictors of higher risk of recurrence. Smoking history was also an independent prognostic factor in LUAD. While in LUSC, only immunoscore correlated with recurrence. In TCGA cohort, *MUC4* mutation rate was significantly lower (3.6% vs. 24.3%, $p < 0.001$) and had no correlation with risk of recurrence ($p = 0.765$). Besides, the tumor infiltrating CD8+ T cells also had no correlation with risk of recurrence ($p = 0.469$). **Conclusions:** In this study, we established a refined immunoscore with high prognostic value for tumor recurrence in stage I NSCLC. In addition, we showed for the first time a strong association between *MUC4* mutation and recurrence, which might be mediated by the Ras pathway. Finally, the recurrence mechanisms might vary among different histological subtypes. Research Sponsor: 1) The Health Commission of Hunan Province (Grant No. 202103100948); 2) CSCO-BMS Oncologic Research Foundation (Grant No. Y-BMS2019-100) and 3) Guangdong Provincial Key Lab of Translational Medicine in Lung Cancer (Grant No. 2017B030314120) and Guangdong As.

9081 **Poster Session**

Update analysis of NEJ009: Gefitinib alone (G) versus gefitinib plus chemotherapy (GCP) for non-small cell lung cancer with mutated EGFR.

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Background: NEJ009 study is the first randomized phase III trial that compared gefitinib plus chemotherapy with gefitinib in patients with untreated NSCLC harboring EGFR mutations. We report an updated OS and long-term tolerability analysis, including subgroup analyses focusing on a type of EGFR mutation and metastatic sites. **Methods:** Patients were randomly assigned to gefitinib (gefitinib 250 mg PO, QD) and GCP regimen (gefitinib 250 mg PO, QD combined with carboplatin AUC 5 and pemetrexed 500 mg/m2 in a 3-week cycle for up to six cycles, followed by concurrent gefitinib and pemetrexed maintenance). This study tested multiple primary endpoints, PFS, PFS2, and OS, which were analyzed using a preplanned hierarchical sequential testing method. **Results:** Three hundred forty-five patients were randomly assigned (gefitinib, n = 172; GCP, n =170). At latest data cut-off (May 22, 2020), although there was no significant difference in OS between the groups (HR, 0.82; 95% CI, 0.64 to 1.06; P=0.13), GCP still demonstrated significantly better PFS and PFS2 compared to G. The updated median PFS, PFS2, and OS was 11.2 months, 18.0 months, and 38.5 months in the gefitinib group and 20.9 months, 20.9 months, and 49.0 months in the GCP group, respectively. No severe adverse events occurred in the period since the first report. **Conclusions:** This updated analysis confirmed that the GCP regimen achieved significantly better PFS and PFS2 with an acceptable safety profile compared with gefitinib alone. The efficacy outcome of GCP is more favorable than gefitinib monotherapy as first-line treatment of NSCLC with EGFR mutation. Clinical trial information: UMIN000006340. Clinical trial information: UMIN000006340. Research Sponsor: grant-in-aids from the Japan Society for Promotion of Science and Japanese Foundation for the Multidisciplinary Treatment of Cancer.

	GCP	Gefitinib	HR(95% CI)
Median PFS(95% CI), mo	20.9(18.0-24.0)	11.2(9.0-13.4)	0.50(0.40-0.63)
Median PFS2(95% CI), mo	20.9(18.0-24.0)	18.0(16.3-20.7)	0.77(0.62-0.97)
Median OS(95% CI), mo	49.0(41.8-56.7)	38.5(31.1-47.1)	0.82(0.64-1.06)

9082 **Poster Session**

Discontinuation of immune checkpoint inhibitor (ICI) above 18 months of treatment in real-life patients with non-small cell lung cancer (NSCLC): INTEPI, a multicentric retrospective study.

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Background: The optimal treatment duration of ICIs for patients with NSCLC remains uncertain. In phase 3 clinical trials, treatment continued for two years or until disease progression, and results from CheckMate 153 trial suggest to continue beyond one year. Real life data are missing. **Methods:** This multi-centric retrospective study presents data on real-life patients who discontinued treatment after at least 18 months of ICI monotherapy, their tumour being still controlled. Their characteristics, the causes of discontinuation of ICI, and their outcome are described. **Results:** Between July 2015 and May 2018, 107 patients had their tumour controlled after at least 18 months of treatment. Among them, 54 (50%) patients discontinued ICI: 76% male, median age 63, 91% PS 0-1, 54% adenocarcinoma, 20% with brain metastases, PD-L1 expression level available for 18 (33%) patients (2 $<$ 1%, 8 btw 1-50% and 8 $>$ 50%), 93% treated after 1st line. The median duration of treatment was 26 months. Treatment was stopped by choice of the prescriber and toxicity in 46% and 22% respectively. With a median follow up of 21 months from ICI discontinuation, 18 (33%) patients had a tumor progression with a median time of 10 months (2-33). From discontinuation, overall survival (OS) and progression free survival (PFS) were 90% and 71% respectively at 12 months and 84% and 63% respectively at 24 months. Duration of disease control after ICI cessation seemed to be correlated to the best tumor response at treatment discontinuation, with a PFS rates at 12 months of 73% for complete response (CR n = 11), 77% for partial response (PR n = 37), 22% for patients with stable disease (SD n = 6), 80% for CR and/or complete metabolic response with 18F-FDG PET/CT (CMR) and 65% for others. Fourteen patients out of the 18 in the relapse group received a subsequent treatment : 7 were retreated with ICI (with best response 14% PR and 86% SD) and 5 received a localized therapy with 60% CR. **Conclusions:** Our study in real life provides new insight into the long-term outcomes of patients treated with ICI for at least 18 months before discontinuation in the absence of PD. CR and CMR with FDG-PET before therapy discontinuation may be a positive factor for a prolonged disease control upon discontinuation. Research Sponsor: None.

9084 **Poster Session**

Intracranial activity of tepotinib in patients (pts) with *MET* exon 14 (*MET*ex14) skipping NSCLC enrolled in VISION.

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Background: Brain metastases (BMs) are reported in 20–40% of pts with *MET*ex14 skipping NSCLC and present a high unmet need with poor prognosis. Tepotinib is a highly selective MET inhibitor that has demonstrated intracranial activity in preclinical MET-driven lung cancer orthotopic BM models, and has high binding in brain tissue with 25% of free tepotinib levels in brain, relative to plasma. In VISION Cohort A (N = 152), tepotinib had robust and durable clinical activity in pts with *MET*ex14 skipping NSCLC, with an objective response rate (ORR) of 45% and a median duration of response (mDOR) of 11.1 months. Here, we report the intracranial activity of tepotinib. **Methods:** In the Phase II VISION study, pts with *MET*ex14 skipping NSCLC received 500 mg QD (450 mg active moiety) oral tepotinib. Study eligibility allowed for pts with BM (neurologically stable on symptomatic therapy with stable steroids, and pts with asymptomatic BM). Primary endpoint: systemic OR per RECIST v1.1; subgroup analysis in pts with BM (determined by RECIST v1.1) was predefined. An *ad hoc* retrospective analysis of brain lesions determined by CT/MRI was conducted by an IRC using Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria, which accounts for pts' clinical status and steroid use. Responses were determined in pts with $\geq$1 evaluable post-baseline tumor assessment (due to the retrospective nature and resulting incomplete data, confirmation was not required). For pts with non-measurable lesions per RANO-BM (enhancing and non-enhancing non-target lesions [NTL]), disease control in the brain was defined as non-complete response/non-progressive disease. Data cut-off: July 1, 2020. **Results:** Based on RECIST v1.1, 23 pts in Cohort A had BM at baseline. Systemic efficacy in pts with BM (ORR 47.8% [95% CI: 26.8, 69.4], mDOR 9.5 months [95% CI: 5.5, not estimable]) was consistent with the overall population. 15 pts were evaluable by RANO-BM; 12 received prior radiotherapy for BM (median 6.4 weeks before tepotinib initiation [range 2.6–44]). Systemic best objective responses (BORs) were partial response (PR, n = 9), stable disease (SD, n = 3), and progressive disease (PD; n = 3). Of 7 pts with measurable CNS disease per RANO-BM (all of whom received prior radiotherapy), intracranial BORs were PR (n = 5; including 3 with complete disappearance of target lesions), SD (n = 1) and PD (n = 1). Of 8 pts with NTL only, 7 achieved intracranial disease control and 1 had PD. Of the 7 pts with disease control, 3 had CR of the enhancing NTL. **Conclusions:** Tepotinib demonstrated robust systemic activity in pts with *MET*ex14 skipping NSCLC with BM; this is complemented by intracranial activity in an *ad hoc* analysis using RANO-BM. Small pt numbers, a large proportion of pts with prior radiotherapy for BM, and the retrospective nature of analysis should be considered. Prospective evaluation of intracranial activity data from VISION Cohort C is ongoing. Clinical trial information: NCT02864992. Research Sponsor: Merck KGaA, Darmstadt, Germany.

9085 **Poster Session**

Cemiplimab monotherapy as first-line (1L) treatment of patients with brain metastases from advanced non-small cell lung cancer (NSCLC) with programmed cell death-ligand 1 (PD-L1) ≥ 50%: EMPOWER-Lung 1 subgroup analysis.

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Background: In the Phase 3, EMPOWER-Lung 1 study, cemiplimab monotherapy provided significant survival benefit and an acceptable safety profile vs chemotherapy in patients with advanced NSCLC and PD-L1 ≥50%. EMPOWER-Lung 1 included patients with brain metastases at baseline who are typically underrepresented in clinical trials. Other published exploratory analyses in single-cohort studies suggest benefit from immunotherapy in this patient population. Here, we present subgroup analysis of patients with brain metastasis from EMPOWER-Lung 1. **Methods:** Patients were randomized 1:1 to cemiplimab 350 mg IV every 3 weeks or investigator's choice of chemotherapy (NCT03088540). Patients with treated, clinically stable brain metastases (radiological stability not required) were eligible to enroll and are the focus of this subgroup analysis from the PD-L1 ≥50% population (n=563) of the EMPOWER-Lung 1 study. **Results:** A total of 68 of 563 (12.1%) cases had treated stable brain metastases at time of randomization. Patients were evenly distributed between cemiplimab (n=34) and chemotherapy (n=34), with similar median duration of follow-up (Table). Baseline characteristics were generally similar; median (range) age: 60.0 (45–76) vs 62.0 (48–77); male: 97.1% vs 85.3%; and non-squamous histology: 85.3% vs 76.5%; between cemiplimab vs chemotherapy, respectively. Per independent review committee, median overall survival (OS, 18.7 vs 11.7 months), median progression-free survival (PFS, 10.4 vs 5.3 months), and objective response rate (ORR, 41.2% vs 8.8%) were superior with cemiplimab vs chemotherapy (Table). After baseline, central nervous system (CNS) disease progression occurred in 2 (5.9%) patients with cemiplimab vs 4 (11.8%) patients with chemotherapy; extra-CNS disease progression occurred in 9 (26.5%) patients with cemiplimab vs 15 (44.1%) patients with chemotherapy. **Conclusions:** 1L cemiplimab monotherapy improved OS, PFS, and ORR vs chemotherapy, in patients with advanced NSCLC with PD-L1 ≥50%, and clinically stable brain metastases at baseline. Cemiplimab monotherapy represents a suitable option for this subgroup of patients. Clinical trial information: NCT03088540. Research Sponsor: Regeneron Pharmaceuticals, Inc. and Sanofi.

Clinical outcomes in patients with advanced NSCLC and brain metastases.

	Cemiplimab (n=34)	Chemotherapy (n=34)	HR (cemiplimab vs chemotherapy)
Median duration of follow-up, weeks (IQR)	9.2 (3.7–16.3)	9.3 (6.1–13.3)	
OS, median, months (95% CI)	18.7 (17.3–NE)	11.7 (7.0–NE)	0.17 (0.04–0.76); P=0.0091
PFS, median, months (95% CI)	10.4 (4.2–NE)	5.3 (2.2–6.5)	0.45 (0.22–0.92); P=0.0231
ORR, %, (95% CI)	41.2% (24.6–59.3)	8.8% (1.9–23.7)	

HR, hazard ratio; IQR, inter-quartile range; NE, not evaluable.

9086 **Poster Session**

Real-world outcomes and clinical characteristics of patients with brain metastases from EGFR mutated non-small cell lung cancer: Data from a large retrospective study (REFLECT).

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Background: Brain metastases (BM) frequently occur in patients (pts) with epidermal growth factor receptor mutated non-small cell lung cancer (EGFRm NSCLC) and represent a poor prognostic marker. This study aimed to describe the clinical characteristics, treatment patterns and survival outcomes in EGFRm NSCLC pts treated with 1st or 2nd generation tyrosine-kinases inhibitors (TKIs) in first-line (1L). **Methods:** The retrospective real-world study REFLECT (NCT04031898) collected data from 896 pts initiating 1L TKI between 1 January 2015-30 June 2018 in Europe and Israel. Descriptive statistics were used to assess demographic and clinical characteristics in subgroups of patients with and without BM. Kaplan-Meier methods were used to estimate median real world progression free survival (mPFS) and overall survival (mOS) from start of 1L. **Results:** Out of 896 pts, 198 (22.1%) had BM at start of 1L, 134 (15%) developed BM later (any time), and 564 (62.9%) had no sign of BM at the time of data collection. Among pts who later developed BM the median time between the start of 1L and first diagnosis of BM was 13.5 months. Median duration of follow-up was 21.5 months. Of 332 pts with BM at any time 64.2% were female, similar to the ratio in pts without BM (64.0%). At diagnosis, median age was 65 years in pts with BM vs. 70 in those who never developed BM. Of pts with BM at any time, 50.9% had exon 19 deletion, 30.4% L858R point mutation and 18.7 % uncommon EGFR mutations at baseline, compared to 56.6%, 31.7% and 11.7% in pts without BM, respectively. At data collection, 94.9% of the pts with BM at diagnosis had progressed compared to 79.8% among those with no BM. Overall, whole brain radiation was the most frequently used treatment for BM (31.0%) followed by stereotactic radiosurgery (18.1%) and targeted therapies (13.3%). T790M testing rates were highest among pts developing BM later (85.7%) and lowest among those with BM from start (66.1%). The T790M positivity rate was highest in pts developing BM later (65.7%) and lowest among those with BM from start (50.4%). More pts received osimertinib in later lines among those with BM at any time compared to those without BM (51.3% vs 43.8%). Median real world PFS and OS (95% CI) were shorter among pts with BM at baseline compared to those never developing BM: 10.2 (8.8, 11.5) vs 15.2 (13.7, 16.1) months, and 19.4 (17.1, 22.1) vs 30.3 (27.1, 33.8) months, respectively. At the time of data collection, 77.3% of pts with BM at baseline were deceased compared to 52.5% pts with no BM. **Conclusions:** More than one third of pts included in REFLECT had BM at any time. Uncommon EGFR variants at baseline were observed more frequently in pts with BM. mPFS and mOS were shorter in pts with BM at baseline compared to those never developing BM. These data highlight the need for improved treatment and CNS control in pts with EGFRm NSCLC. Clinical trial information: NCT04031898. Research Sponsor: AstraZeneca.

9087 **Poster Session**

STK11/TP53 co-mutated non-small cell lung cancer (NSCLC) to display a unique tumor microenvironment (TME) and metabolic profile.

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Background: Recent data suggest inferior responses to immune checkpoint inhibitors (ICIs) in *STK11*-mt NSCLC. *TP53* is a critical tumor suppressor gene regulating DNA repair by arresting cells in the G1 phase in response to critical double strand breaks. We hypothesized that accumulated DNA damage from mutations in the *TP53* gene might increase immunogenicity and potentially enhance benefit of ICIs in *STK11-mt* NSCLC. **Methods:** A total of 16,896 NSCLC tumors submitted to Caris Life Sciences (Phoenix, AZ) for targeted NGS (DNA-Seq, 592 genes) were analyzed. A subset (N = 5034 tumors) had gene expression profiling (RNA-Seq, whole transcriptome). PD-L1 (TPS) was tested with 22c3 antibody (Dako). Exome-level neoantigen load for *STK11*-mt NSCLC was obtained from published TCGA Pan-immune analysis (Thorsson et al. 2018). Non-parametric tests were used for comparing differences in tumor mutational burden (TMB) and neoantigen load. Transcriptomic analysis included differential gene expression and hierarchical clustering. Tumor immune cell content was obtained from transcriptome using Microenvironment Cell Population-counter (MCP). Publicly available data from the POPLAR/OAK trials of atezolizumab in advanced NSCLC were used to model PFS and OS for *STK11*-mt with *TP53*-mt (n = 14) and without *TP53*-mt (n = 20). **Results:** Of 16,896 NSCLC samples, 12.6% had an *STK11*-mt with the proportions of TMB-high ($\geq$10 Mut/Mb), PD-L1 $\geq$ 50% and MSI-high being 55.9%, 11.8%, and 0.72%, respectively. *STK11*-mt vs. *STK11*-wt NSCLC did not differ in median TMB (Caris:10 vs. 10 Mut/Mb; $p > 0.1$) or neoantigen load (TCGA: 154.5 vs. 165; $p > 0.1$). Median TMB (13 vs. 9 Mut/Mb; $p < 0.001$) and neoantigen load (263 vs. 134; $p < 0.001$) were higher in *STK11*-mt/*TP53*-mt vs. *STK11*-mt/*TP53*-wt. MCP analysis showed higher CD8, NK-cell and lower myeloid dendritic cell infiltration in *STK11*-mt/*TP53*-mt vs. *STK11*-mt/*TP53*-wt ($p < 0.01$). Expression of *MYC* and *HIF-*α were increased in the *STK11*-mt/*TP53*-mt vs. *STK11*-mt/*TP53*-wt ($p < 0.01$) along with higher expression ($p < 0.01$) of genes associated with both glycolysis (*HK2, LDHA, ALDOA*) and glutamine metabolism (*GOT2, PPAT2*). Hierarchical clustering of *STK11*-mt adenocarcinomas (n = 463) for STING pathway genes (CCL5, CXCL10, cGAS) identified a STING-high and a STING low cluster. The STING high cluster was significantly enriched in *TP53*-mt (48 vs. 32%; $p < 0.01$).In the OAK/POPLAR cohort, median OS (HR is 1.14, 95% CI 0.53 - 2.48); $p > 0.1$) and PFS (HR 1.88, 95% CI 0.89-3.97, p = 0.098) were not statistically different between *STK11*-mt/*TP53*-mt vs. *STK*-mt/*TP53*-wt. However, the 15-months PFS was 21% in the *STK11*-mt/*TP53*-mt vs 0% in the *STK11*-mt/*TP53*-wt. **Conclusions:** *STK11*-mt NSCLC with *TP53*-mt are associated with an immunologically active TME with metabolic reprogramming. These intrinsic properties could be exploited to improve outcomes to ICIs in combination with metabolically directed agents. Research Sponsor: None.

9088 **Poster Session**

Chemo-immunotherapy outcomes of KRAS-G12C mutant lung cancer compared to other molecular subtypes of KRAS-mutant lung cancer.

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Background: *KRAS* mutations are identified in approximately 30% of NSCLC, with G12C mutations being the most common subtype and representing 12% of all non-small cell lung cancer cases. Novel direct inhibitors are in clinical development and have shown promising activity, although the efficacy of these agents compared to other standard therapies for lung cancer is not yet known. We hypothesized that patients with *KRAS*-G12C mutations may have distinct responses to chemo-immunotherapy regimens both with respect to STK11 and KEAP1 co-mutation status and compared to patients with non-G12C subtypes. **Methods:** Patients with KRAS-mutant lung cancers at Memorial Sloan Kettering Cancer Center and Dana Farber Cancer Institute treated with chemo-immunotherapy regimens as first line therapy for advanced/metastatic disease were identified. Subset with KRAS G12C mutations non-G12C subtypes were compared and response to therapy was assessed by investigator. Baseline characteristics were compared with the Chi-square and Fisher's exact test for categorical data and Wilcoxon rank-rum test for continuous data. Response evaluations where performed by investigators and compared between groups with the Fisher's exact test. Progression free survival and overall survival was calculated from start of therapy to date of progression or death/last follow up, respectively and compared between groups using the Cox proportional-hazards model. **Results:** We identified 137 patients with KRAS-mutant NSCLC treated with chemo-immunotherapy: 45% (62/137) had mutations in *KRAS*-G12C and 55% harbored non-G12C mutations (17% G12V, 15% G12D, 4% G12A, 4% G12S, 3% G13D). The median OS was 21 and 14 months for G12C and non-G12C patients, respectively ($p = 0.24$). ORR to chemo-immunotherapy for patients harboring a *KRAS*-G12C mutation was 40% (25/62) compared to 31% (23/75) in non-G12C subtypes ($p = 0.3$). Median PFS was similar for both G12C and non-G12C subtypes (7.3 vs 6.1 months, respectively, $p = 0.12$). Concurrent *STK11* mutation was identified in 40% of patients with *KRAS*-G12C and *KEAP1* alterations were observed in 32% of patients. In patients with *KRAS*-G12C, co-mutation in *STK11* and/or *KEAP1* was associated with shorter PFS (15.8 vs 5.1 months, $p = 0.01$). **Conclusions:** *KRAS*-G12C mutations are present in 12% of patients with NSCLC and represent a relevant subtype of NSCLC given KRAS G12C inhibitors now in clinical development. Treatment outcomes to chemo-immunotherapy are similar in patients with G12C and non-G12C subtypes. Outcomes are poor for patients with concurrent *STK11* and/or *KEAP1* mutations representing a significant unmet need. Research Sponsor: None.

9089 **Poster Session**

Safety and efficacy of pralsetinib in patients with advanced *RET* fusion-positive non-small cell lung cancer: Update from the ARROW trial.

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Background: *RET* fusions are targetable oncogenic drivers in 1–2% of non-small cell lung cancer (NSCLC). ARROW (NCT03037385) supported the US FDA approval of pralsetinib, a highly potent oral selective RET inhibitor for *RET*-altered NSCLC and thyroid cancer. Here, we present updated results for a larger population of patients with *RET* fusion–positive NSCLC enrolled in ARROW. **Methods:** ARROW is a phase 1/2 open-label study conducted at 84 sites in 13 countries. Phase 2 expansion cohorts included patients with *RET* fusion–positive NSCLC. Initially, all treatment-naïve patients were not candidates for platinum-based therapy, a requirement removed by protocol amendment in July 2019. Primary objectives are overall response rate (ORR; blinded independent central review [BICR] per RECIST v1.1), assessed for patients with baseline measurable disease, and safety. **Results:** Updated analyses were completed as of Nov 6, 2020 (data cut-off), for patients who initiated pralsetinib 400 mg QD by May 22, 2020 (enrollment cut-off). Efficacy results, including analyses for treatment-naïve patients enrolled after eligibility criteria were revised to allow candidates for platinum-based therapy, are shown in the Table. **Conclusions:** Pralsetinib showed rapid, potent, and durable clinical activity in patients with *RET* fusion-positive NSCLC (regardless of prior therapies), including poor prognosis patients not eligible for platinum-based therapy. Overall, pralsetinib was well-tolerated. These data highlight the need for *RET* testing early in the course of disease to identify candidates who may benefit from treatment with pralsetinib.Clinical trial information: NCT03037385. Research Sponsor: Blueprint Medicines Corporation.

	Prior Platinum[a] (n = 126)	Treatment-Naïve[a] (n = 68)	Treatment-Naïve: Subset Enrolled After Eligibility Revision[a] (n = 25)
ORR, % (95% CI)	62 (53–70)	79 (68–88)	88 (69–98)
Clinical benefit rate, % (95% CI)[b]	74 (65–81)	82 (71–91)	88 (69–98)
Disease control rate, % (95% CI)	91 (85–96)	93 (84–98)	96 (80–100)
Median duration of response, mo (95% CI)	22.3 (15.1–NE)	NR (9.0–NE)	NR (NE–NE)
Median time to response, mo (95% CI)	1.8 (1.3–11.4)	1.8 (0.9–6.1)	1.8 (1.7–6.1)
Median PFS, mo (95% CI)[c]	16.5 (10.5–24.1)[d]	13.0 (9.1–NE)[e]	NR (NE–NE)[f,g]

CI, confidence interval; mo, months; NE, not estimable; NR, not reached; PFS, progression-free survival. [a]Measurable disease population. [b]Confirmed response or stable disease of ≥16 weeks. [c]Assessed in full efficacy population. [d]n = 136. [e]n = 75. [f]n = 28. [g]Median follow-up for PFS in this population was 8.2 mo. In all patients enrolled in ARROW who received pralsetinib 400 mg QD by May 22, 2020 irrespective of tumor type (n = 471; data cut-off Nov 6, 2020), the most common (≥25%) treatment-related adverse events (TRAEs) were increased aspartate aminotransferase (39%), anemia (35%), increased alanine aminotransferase (27%), constipation (26%) and hypertension (25%). Overall, 6% of patients discontinued treatment due to TRAEs.

9090 **Poster Session**

Association between improvements in survival of metastatic NSCLC patients and targeted- and immuno-therapy.

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Background: Significant improvements in mortality among NSCLC cancer patients in the US over the past two decades have recently been reported based on SEER data. The timing of these improvements led to suggestions that they are primarily a result of the introduction of new and innovative treatments, however few studies have directly investigated this. **Methods:** We utilised the US Flatiron Health database to identify a cohort of non-biomarker (EGFR/ALK/ROS1/BRAF) positive metastatic NSCLC (mNSCLC) patients and a separate cohort of ALK positive (ALK+) patients diagnosed between 2012 and 2019. Multivariable Cox models adjusting for baseline characteristics and receipt of targeted and immunotherapy were utilised to explore the relationship between these variables and changes in the hazard of death by calendar year in each cohort. **Results:** We identified cohorts of 30,076 (54.7% Males) non-biomarker positive and 652 (45.4% males) ALK+ mNSCLC cancer patients in the database eligible for the analysis. Survival in both cohorts improved over time. After adjustment for differences in baseline characteristics the hazard of death in non-biomarker positive patients diagnosed in 2015, 2016, 2017, 2018 and 2019 was observed to be 14%, 13%, 16% 19% and 21% lower respectively than that in those diagnosed in 2012. Upon additionally adjusting for receipt of first line or second line immunotherapy the decrease in the hazard of death by calendar year was no longer observed, suggesting improvements in survival observed over time may be explained by the introduction of these innovative treatments. Similarly, decreases in the hazard of death were only observed in ALK+ patients diagnosed in 2018 and 2019 relative to 2012 and were no longer observed following adjustment for the use of ALK inhibitors. **Conclusions:** Our findings expand on the SEER data and provide direct evidence linking improvements in survival of NSCLC patients over the past decade with the introduction of innovative therapies. Research Sponsor: F. Hoffmann-La Roche AG.

Hazard ratios for death in metastatic NSCLC patients in years 2013 to 2019 relative to 2012, adjusting only for differences in baseline characteristics (model 1) and adjusting for baseline characteristics and treatment (model 2).

	Non-biomarker positive mNSCLC	Non-biomarker positive mNSCLC	ALK+ mNSCLC	ALK+ mNSCLC
	Model 1	Model 2	Model 1	Model 2
2012 vs 2013	0.95 (0.89 – 1.00)	0.94 (0.89 – 1.00)	1.06 (0.68 - 1.65)	1.13 (0.71 - 1.79)
2012 vs 2014	0.95 (0.89– 1.00)	0.93 (0.87 - 0.99)	0.98 (0.62 - 1.57)	1.34 (0.84 - 2.13)
2012 vs 2015	0.86 (0.81 - 0.91)	0.92 (0.86 - 0.98)	0.98 (0.63 - 1.52)	1.40 (0.88 - 2.25)
2012 vs 2016	0.87 (0.83 - 0.92)	0.93 (0.88 - 0.99)	1.12 (0.72 - 1.73)	1.45 (0.90 - 2.34)
2012 vs 2017	0.84 (0.79 - 0.89)	0.97 (0.90 - 1.03)	0.71 (0.45 - 1.10)	1.19 (0.69 - 2.04)
2012 vs 2018	0.81 (0.77 - 0.86)	1.01 (0.94 - 1.08)	0.51 (0.29 - 0.87)	1.15 (0.56 - 2.37)
2012 vs 2019	0.79 (0.74 - 0.85)	0.97 (0.89 - 1.05)	0.51 (0.28 - 0.95)	1.15 (0.56 - 2.38)

9091 **Poster Session**

First-line pembrolizumab monotherapy for PD-L1-positive (TPS ≥ 50%) advanced non-small cell lung cancer (aNSCLC) in the real world: A national French bispective multicentric cohort—ESCKEYP trial (GFPC 05-2018).

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Background: To determine real-world outcomes with first line pembrolizumab monotherapy, for aNSCLC with PD-L1 TPS ≥50%. **Methods:** Bispective, national and multicentric study including consecutively aNSCLC patients who initiated first-line pembrolizumab monotherapy from May 5, 2017 (marketing authorization of pembrolizumab monotherapy in France) to Nov 22, 2019 (marketing authorization of pembrolizumab-chemotherapy for non-squamous aNSCLC). Data were collected on medical charts. Responses were locally assessed according to RECIST v1.1; overall survival (OS) and real-world progression-free survival (rwPFS) were assessed by Kaplan-Meier method. **Results:** 845 patients (pts) were included by 33 centres: 67.8% were men, PS 0/1/≥2: 25.5%/46.9%/27.6%, active/former/non-smokers: 39.1%/51.7%/6.4%, adenocarcinoma: 70.8%; stage IV at diagnosis: 91.6%; median number of metastatic sites at baseline: 2±1 (brain (20.8%), liver (13.9%) and bone (35%)); KRAS mutated: 27.7%, PDL1 TPS > 75%: 53.7% At the cut off date (31 December 2020), on the 783/845 (92.7%) evaluable pts, CR, PR, disease stabilization and progression were reported on 4.7%, 42.6%, 24.1% and 28.6% of cases, respectively; 588 (69.6%) pts had discontinued pembrolizumab, 390 (66.4%) had a first disease progression; 320/390 (82.1%) received a second line treatment, mainly platinum-based chemotherapy (90.6%). With a median follow up of 25,8 [95%CI: 24,8-26,7] months, median rwPFS and median OS were 8,2 [95%CI: 6,9-9,5] and 22,6 [95%CI: 18,5-27,4] months, respectively; 6, 12, 18-months survival rates were 76,8%, 64,8% and 54,3%. 835 adverse events were reported in 48% of the patients, grade ≥3 in 13.8% of cases, mainly asthenia, colitis, pneumonitis. For evaluable patients receiving a platinum-based doublet in second line (266/290, 89%), CR, PR, disease stabilization and progression were reported on 1.9%, 41%, 35.3% and 21.8% of cases, respectively. Uni and multivariate analysis of factors related to OS will be presented at the congress. **Conclusions:** Despite a less stringent selection of patients, pembrolizumab as a single agent achieves similar tumor shrinkage, rwPFS and OS than those of pivotal clinical trials. Research Sponsor: GFPC.

9092 **Poster Session**

Beyond steroids: Immunosuppressants in steroid-refractory/resistant immune related adverse events.

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Background: The optimal management for immune related adverse events (irAEs) in patients who do not respond or become intolerant to steroids is unclear. Guidelines suggest additional immunosuppressants based on case reports and expert opinion. **Methods**: We examined patients with advanced lung cancers at MSK treated with immune checkpoint blockade (ICB) from 2011-2020. Pharmacy records were queried to identify patients who received systemic steroids as well as an additional immunosuppressant (eg TNFα inhibitor, mycophenolate mofetil). Patient records were manually reviewed to examine baseline characteristics, management, and outcomes. **Results**: Among 2,750 patients with lung cancers treated with ICB, 51 (2%) received both steroids and an additional immunosuppressant for a severe irAE (TNFα inhibitor (73%), mycophenolate mofetil (20%)). The most common events were colitis (53%), pneumonitis (20%), hepatitis (12%), and neuromuscular (10%). At 90 days after start of an additional immunosuppressant, 57% were improved from their irAE, 18% were unchanged, and 25% were deceased. Improvement was more common in hepatitis (5/6) and colitis (18/27) but less common in neuromuscular (1/5) and pneumonitis (3/10). All patients with hepatitis received mycophenolate mofetil 500-1000mg BID for a median of 3 months, range 2-5 months. Of the 18 patients with colitis who improved with a TNFα inhibitor, 10 needed just one dose. Of 13 patients who died, 4 were related to toxicity from immunosuppression (3, infection-related deaths; 1, drug-induced liver injury leading to acute liver failure). Those who died from immunosuppressive therapy received higher amounts of systemic steroids than those who did not (max median 525 vs 132 mg prednisone equivalent, Mann Whitney U $p = 0.004$, total median 5.9k vs 2.3k mg prednisone equivalent, $p = 0.004$). Of 31 patients who received at least 3 weeks of prednisone $\geq$ 20mg, most (90%, 28/31) had at least one side effect that was brought to clinical attention (most commonly altered mood/ sleep, 52%, increase in BMI $>$ 1kg/m2, 45%, and infection, 32%). **Conclusions**: Steroid-refractory/resistant immune related adverse events are rare. While existing treatments help patients with hepatitis and colitis, most patients with other irAEs remain refractory and/or experience toxicities from immunosuppression. Systemic steroid use likely contributed to side effects and mortality. A more precise understanding of the pathophysiology of specific irAEs is needed to guide biologically informed treatment regimens for severe irAEs to realize the true benefit of ICB therapy. Research Sponsor: U.S. National Institutes of Health.

9093 **Poster Session**

CNS activity of poziotinib in NSCLC with exon 20 insertion mutations.

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Background: Treatment addressing non-small cell lung cancer (NSCLC) harboring EGFR or HER2 exon 20 insertion mutations remains an unmet need. These tumors are associated with a high incidence of CNS metastases and unfavorable survival rates. Poziotinib is a potent, irreversible, tyrosine kinase inhibitor (TKI) with a structure that can overcome the steric hindrance of the exon 20 limited binding pocket. Preclinical data suggest poziotinib CNS penetration, and here we show meaningful poziotinib CNS activity in patients with NSCLC harboring exon 20 insertion mutations in an ongoing multi-cohort, multi-center Phase 2 study (ZENITH20; NCT03318939). **Methods:** ZENITH20 enrolled previously treated and naïve patients with advanced/metastatic NSCLC and EGFR or HER2 exon 20 insertion mutations in several cohorts: Cohort 1 (C1) EGFR previously treated; Cohort 2 (C2) HER2 previously treated and Cohort 3 (C3) EGFR treatment-naïve. All patients with stable CNS metastases at baseline were included. Poziotinib (16 mg) was administered orally QD, with follow-up for up to 24 months. The primary endpoint was Objective Response Rate (ORR) evaluated centrally using RECIST v1.1 by an independent image review committee. Secondary endpoints included Disease Control Rate (DCR), Duration of Response (DOR), Progression-Free Survival (PFS) and safety. Primary efficacy results have been previously released. Intracranial response was determined based on the modified RECIST criteria. **Results:** A total of 284 patients across 3 cohorts (C1 n=115; and C2 n=90; and C3 n=79) with a median age of 60.5 years were enrolled. The median follow-up was 7.3, 8.3, and 9.2 months for all patients in C1, C2, and C3, respectively. In NSCLC patients that had baseline CNS lesions (N=36), the analysis showed a patient-based ORR of 22.2% (8/36) and a DCR of 88.9% (32/36). One patient in each cohort had a complete intracranial response and stable disease was 80.6% across 3 cohorts and 92.9% in C2. Two patients each in C1 and C3 had progressive disease (PD) and none had CNS progression in C2 (Table). **Conclusions:** Poziotinib exhibited clinically meaningful CNS activity in patients with EGFR or HER2 exon 20 mutations in ZENITH20 Cohorts 1-3. The majority of the patients had no CNS progression and 3/36 patients had intracranial complete responses. The preliminary data suggest that poziotinib may provide a meaningful treatment alternative for patients with NSCLC that harbor EGFR or HER2 exon 20 mutations and who present with CNS metastases that have poor prognosis. Clinical trial information: NCT03318939. Research Sponsor: Spectrum Pharmaceuticals, Inc.

	Cohort 1 n=115	Cohort 2 n=90	Cohort 3 n=79	Total N=284
Patients with CNS Metastases at Baseline	12	14	10	36
ORR in CNS patients	1 (8.3)	4 (28.6)	3 (30.0)	8 (22.2)
Best Evaluable intracranial Response, n (%)				
Complete Response [a]	1 (8.3)	1 (7.1)	1 (10.0)	3 (8.3)
Stable Disease	9 (75.0)	13 (92.9)	7 (70.0)	29 (80.6)
Progressive Disease	2 (16.7)	0	2 (20.0)	4 (11.1)

a) ≥2 consecutive MRI scans with negative finding.

9094 **Poster Session**

Impact of rapid multigene assays with short turnaround time (TAT) on the development of precision medicine for non-small cell lung cancer (NSCLC).

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Background: A variety of oncogene drivers have been identified in NSCLC and molecularly-stratified precision medicine has led to improved survival in advanced NSCLC. Next-generation sequencing (NGS)-based testing is utilized to detect actionable gene alterations; however, the TAT of NGS is often too long to translate into clinical decision making. Thus, rapid multi-gene testing alternatives are needed. **Methods:** A lung cancer genomic screening project (LC-SCRUM-Asia) capturing clinical outcome was established in 2013 to identify patients with oncogene drivers and to support the development of novel targeted therapies. Since February 2013 to May 2019 (LC-SCRUM-Asia 1st-phase), single gene testing and/or a targeted NGS assay, Oncomine Comprehensive Assay (OCA), were used for the genomic screening. Since June 2019 to December 2020 (2nd-phase), a multi-gene PCR assay (Amoy 9-in-1 test) and a rapid NGS assay (Genexus/Oncomine Precision Assay [OPA]) were also implemented as rapid multigene testing. **Results:** A total of 10667 Japanese NSCLC patients, including 6826 in the 1st-phase and 3841 in the 2nd-phase, were enrolled in the LC-SCRUM-Asia. Success rate for OCA: 93%, for 9-in-1 test: 98%, for Genexus/OPA: 96%. Median TAT for OCA: 21 days, for 9-in-1 test: 3 days, for Genexus/OPA: 4 days. The frequencies of genetic alterations detected in the 1st-/2nd-phase were *EGFR*: 17/24%, *KRAS*: 15/16%, *HER2* ex20ins: 4/3%, *ALK* fusions: 3/3%, *RET* fusions: 3/2%, *ROS1* fusions: 3/2%, *MET* ex14skip: 2/2%, *BRAF* V600E: 1/1%, *NRG1* fusions: 0/0.2% and *NTRK3* fusions: 0.05/0.04%. Overall percent agreement of 9-in-1 test compared with OCA for *EGFR/KRAS/HER2/BRAF/MET/ALK/ROS1/RET/NTRK3* alterations was 98%, and that of OPA compared with OCA was 95%. The rate of patients who received targeted therapies as 1st-line treatment was significantly elevated in the 2nd-phase compared with the 1st-phase (510/3841 [13%] vs. 567/6826 [8%], $p < 0.001$). Through the genomic screening, 1410 (37%) and 1269 (18%) candidate patients for clinical trials of KRAS, HER2, BRAF, MET, ALK, ROS1, RET or TRK-targeted drugs were identified in the 2nd-phase and in the 1st-phase, respectively. The rate of patients who were actually enrolled into the genotype-matched clinical trials were also significantly higher in the 2nd-phase than in the 1st-phase (222 [6%] vs. 186 [3%], $p < 0.001$). In 1st-line treatments for advanced NSCLC patients, the median progression-free survival was 8.5 months (95% CI, 7.7−9.4) in the 2nd-phase (n = 1839) versus 6.1 months (95% CI, 5.9−6.3) in the 1st-phase (n = 4262) ($p < 0.001$). **Conclusions:** Both the 9-in-1 test and Genexus/OPA had short TATs (3−4 days), high success rates (96−98%) and good concordance (95−98%) compared with another NGS assay (OCA). These rapid multi-gene assays highly contributed to enabling precision medicine and the development of targeted therapies for advanced NSCLC. Research Sponsor: AMED (Japan Agency for Medical Research and Development), Pharmaceutical/Biotech Company.

9095 **Poster Session**

Maintenance targeted therapy compared to standard of care (SoC) in patients (pts) with metastatic non-small cell lung cancer (NSCLC): Results from the phase II randomized UNICANCER/IFCT1301- SAFIR02-LUNG intergroup trial.

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Background: Targeted therapies (TT) are approved in NSCLC based on a limited number of oncogenic drivers. Numerous additional TT can be matched to other molecular alterations found in comprehensive profiles. We investigated the effect of 8 TT compared to SoC as a maintenance strategy after chemotherapy in pts with metastatic NSCLC. **Methods:** In SAFIR02-LUNG trial (NCT: 02117167), open-label multicentric phase II randomized trials, PS 0-1 pts with *ALK/EGFR* WT NSCLC after a CR/PR/SD to 4 cycles of platinum-based chemotherapy were selected. All pts underwent a fresh biopsy, followed by targeted sequencing on 70 genes and SNP-array when $>$ 30% cancer cells were present on HES slides. In case of genomic alteration (including *KRAS*, *ERBB2*, *BRAF, BRCA* mutations), pts were randomized 2:1 between 8 TT and SoC. TT allocation was decided during weekly national tumor board, based on predefined guidelines. The primary endpoint was Progression-Free Survival (PFS) and the secondary endpoint was Overall Survival (OS). **Results:** 999 patients were enrolled and 394 had a molecular alteration eligible for the study. Among the 175 randomized pts (between July 2014 and May 2019), 116 received TT (65 selumetinib, 18 vistusertib, 9 capivasertib, 8 AZD4547, 5 AZD8931, 5 vandetanib, 4 olaparib, 1 savolitinib) and 59 SoC (54 pemetrexed, 4 gemcitabine and 1 erlotinib). Median age was 60, 40.6% were female, 4.6% never-smoker, 44% were PS 0, 88.6% had a non-squamous NSCLC and 26.9% a PR to chemotherapy. At data cut-off, 168 pts had progressed or died. With a median follow-up of 42.0 months (mo), median PFS was 2.7 mo (95% confidence interval (CI) 1.6 to 2.7) with TT vs. 2.7 mo (95%CI 1.6-4.1) with SoC (HR for disease progression or death 1.00; 95%CI = 0.73 to 1.38; p = 0.978). There was no significant PFS differences among the molecular subgroups; in the cohort with *KRAS* or *BRAF* mutation without *STK11* mutations the HR for disease progression or death was 0.76; 95%CI = 0.52 to 1.13; p = 0.17. Median OS was 14.3 mo (95%CI 11.0-18.3) with TT vs. 14.1 mo (95% CI 8.0-30.9) with SoC (HR for death 1.12; 95%CI = 0.75-1.65; p = 0.581). Grade 3 or 4 treatment-related adverse events occurred in 31 pts (26.7%) on TT (G3: 30 pts (25.9%), G4: 1 pt (0.8%)) and in 13 (22%) on SoC (G3 8 pts, G4 5 pts). **Conclusions:** The SAFIR02-LUNG trial demonstrated the feasibility of a routine precision medicine for advanced NSCLC. However, the monotherapy TT used as maintenance therapy after platinum-based chemotherapy failed to improve PFS or OS in this advanced *ALK/EGFR* WT NSCLC pts population. Newly available therapeutic options (ex. for *KRASG12C, RET, NTRK, ERBB2, NRG1*, etc) need to be evaluated. Clinical trial information: 2013-001653-27. Research Sponsor: Astrazeneca.

9096 **Poster Session**

Time-dependent efficacy of checkpoint inhibitor nivolumab in metastatic lung cancer patients.

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Background: Nivolumab (NIV) is a Programmed-cell-Death-1 inhibitor approved as 2nd line treatment for metastatic Non-Small Cell Lung Cancer (NSCLC). NIV mainly targets T(CD8) cells, whose functions and trafficking are regulated by circadian clocks (Nobis et al. PNAS 2019), hence suggesting possible dosing time-dependent changes in NIV efficacy. **Methods:** Consecutive metastatic NSCLC patients (pts) received single agent NIV (240 mg iv q 2 weeks) at a single institution. NIV timing slots were randomly allocated for each course by the day hospital coordinator on a logistics basis and recorded. The median NIV timing and its intra-pt coefficient of variation (CVar) were computed over the whole treatment span. The study population was split into two NIV timing groups based upon the median value of the median treatment times of all the pts. CTCAE-toxicity rates were compared between groups with c2 or Fisher exact. Progression free survival (PFS) and overall survival (OS) were compared between both NIV timing groups with Log Rank. **Results:** From 9/2015 to 11/2020, the study accrued 95 stage 4 NSCLC pts (males, 83%; PS 0-1, 96%), aged 41-83 years (median, 67). Primary histological types were adenocarcinoma (55 pts, 58%), squamous cell carcinoma (37 pts, 39%) or unspecified (3 pts, 3%). The pts had a median of 4 metastatic sites, including bone (52% of the pts), pleura (41%), liver (25%), brain (24%) and adrenal gland (20%). A total of 1818 NIV courses were given as 2nd line for 72 pts (76%), or as 3rd or later line for 22 pts (23%). Median PFS and OS (months, mo.) were 3.9 mo. [95% CL, 2.1 – 5.8], and 14.0 mo. [9.5 – 18.4] respectively, for the 95 pts. The majority of NIV administrations occurred between 9:27 and 12:54 for 48 pts ('morning' group) and between 12:55 and 17:14 for 47 pts ('afternoon' group), with intra-pt NIV timing CVar ranging from 2% to 21% (median, 10%). Main pts characteristics were similar for both groups, except for fewer females (8% vs 26%) and younger age (median, 66 vs 69 years) in the 'morning' group compared to the 'afternoon' one. Grade 3-4 fatigue, anorexia or myalgias were less in the 'morning' group compared with the "afternoon' one (6% vs 15%; 2% vs 6%; 0% vs 4%, respectively). Strikingly, median PFS [95% CI] were 11.3 mo. [5.5 - 17.1] for the 'morning' group as compared to 3.1 mo. [1.5 - 4.6] for the 'afternoon' one ($p<0.001$). Median OS were 34.2 mo. [15.1 - 53.3] for the 'morning' group *vs* 9.6 mo. [4.9 - 14.4] for the 'afternoon' group ($p<0.001$). Multivariate analyses identified NIV 'morning' timing and 2nd line administration, as significant independent predictors of longer PFS and OS. **Conclusions:** NIV was both less toxic and four times as effective following 'morning' as compared to 'afternoon' dosing in this study in Stage 4 NSCLC pts, possibly as a result of dosing time-dependent pharmacology. Translational and clinical nivolumab timing validation studies are needed, in order to optimize pts benefits from cancer immunotherapy. Research Sponsor: None.

9097 **Poster Session**

Optimal next-generation sequencing (NGS) panel for estimating tumor mutation burden (TMB) and its clinical implication for non-small cell lung cancer (NSCLC).

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Background: TMB estimation using targeted NGS panels is widely performed in clinical practice. The objective of this study was to determine the optimal NGS panel for estimating TMB and to evaluate its clinical implications for NSCLC. **Methods:** Two NGS panels, Oncomine Tumor Mutation Load Assay (OMLA) and FoundationOne (F1), were compared to select the most accurate TMB prediction panel. From February 2017 to May 2018, 350 lung cancer patients were analyzed by whole-exome sequencing (WES), and the concordance rate of OMLA and F1 to WES was examined. In addition, its clinical utility as a biomarker for immune checkpoint inhibitors (ICIs) was evaluated in our international genome screening network (LC-SCRUM-Asia). From June 2019 to December 2020, 3141 patients with NSCLC from 185 institutions were enrolled, and genomic analysis was successful. The clinico-genomic database of LC-SCRUM-Asia was used for this analysis. **Results:** The linear correlation with WES was 0.80 for OMLA and 0.78 for F1. This indicated that OMLA was more strongly correlated with WES. The cutoff value of F1 was 10 mut/Mb, which corresponded to 9 mut/Mb (OMLA) and 194 mutations (WES). The sensitivity of the OMLA for WES was 79%, and the specificity was 85%. Meanwhile, the sensitivity of the F1 was 74%, and the specificity was 80%. OMLA more accurately predicted TMB, and its clinical utility was evaluated. 3141 NSCLC patients, consisting of 2282 adenocarcinomas, 593 squamous cell carcinomas, and 266 others, were analyzed for TMB, estimated using OMLA. The median number of mutations was 4.2 mut/Mb (range, 0-718.4/Mb). High TMB (≥9 mut/Mb) was observed in 17.2% (393/2282) of adenocarcinoma cases and 25.8% (153/593) in squamous cell carcinoma cases. 778 patients were treated with ICI or ICI plus chemotherapy as the first-line treatment. Patients' characteristics were as follows: male/female; 595/183, median age (range); 67 (25-90), stage II/III/VI/recurrence; 11/90/649/28, TMB high/low; 177/601, ICI/ICI plus chemotherapy; 114/664. The progression-free survival (PFS) was significantly longer in patients with high TMB than in those with low TMB (median PFS, 7.5 vs. 5.9 months, $p = 0.0314$). The overall survival (OS) was significantly longer in patients with high TMB than in those with low TMB (median OS, 27.4 vs. 20.4 months, $p = 0.006$). **Conclusions:** The TMB estimated by OMLA correlated more strongly with the WES-derived TMB comparing with F1. TMB estimated by OMLA was correlated with PFS and OS in NSCLC patients treated with ICIs. Prospective clinical trials are needed to determine whether TMB estimated by OMLA is a biomarker for ICI. Research Sponsor: Ono Pharmaceutical Co., Ltd.

9098 **Poster Session**

Real-world response and outcomes in NSCLC patients with EGFR exon 20 insertion mutations.

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Background: There is currently no targeted therapy approved for patients with EGFR exon 20 insertion mutations (exon20ins) in NSCLC. Real world treatment outcome evidence for this rare population is limited. This study describes treatment patterns and outcomes in US patients with advanced NSCLC with EGFR exon20ins. **Methods:** The nationwide Flatiron Health electronic health record-derived deidentified database (cut-off 29 Feb 2020) was used to select 4 separate cohorts: (1) first-line (1L): patients receiving 1L therapy after documented exon20ins (1L start date as index date); (2) second or later line (≥2L): patients receiving ≥2L therapy after documented exon20ins (start date of ≥2L as index date); (3) ≥2L trial-aligned: ≥2L patients with baseline characteristics aligned with the key eligibility criteria of mobocertinib Trial NCT02716116 Part 3; and (4) ≥2L post platinum: ≥2L trial-aligned patients previously treated with platinum-based chemotherapy. Real-world endpoints were: confirmed overall response rate (cORR), PFS, and OS. Additional analyses were conducted for patients treated with immune-oncology therapy (IO). **Results:** Of 237 EGFR exon20ins patients, 129 patients were included in 1L cohort and 114 were in ≥2L cohort, including 63 ≥2L trial-aligned and 50 ≥2L post platinum patients. In 1L patients, EGFR TKI (28.7%) and platinum-based chemotherapy ± IO (56.6%) were the most common 1L regimens. In ≥2L patients, 28.1% received IO monotherapy, 17.5% received EGFR TKI, and 23.7% received platinum-based chemotherapy ± IO as index treatment. In the 1L setting, median PFS (mPFS) was 5.7 months for platinum-based chemotherapy and 4.5 months for IO + platinum-based chemotherapy. In the ≥2L setting, mPFS was 3.7 months for any therapy and 2.3 months for IO monotherapy. Full effectiveness data are provided in the accompanying table. **Conclusions:** This real world study provided a benchmark on the treatment outcome in patients with advanced NSCLC with EGFR exon20ins. Platinum-based chemotherapy was the most common 1L therapy and provided the longest mPFS. Immunotherapy, either as monotherapy or in combination with chemotherapy, appeared less effective for treatment of NSCLC with EGFR exon20ins. There is an unmet medical need for improved therapeutic options. Research Sponsor: Takeda Pharmaceutical Company Limited.

Cohort	N	cORR (95% CI)	Median OS (95% CI), months	Median PFS (95% CI), months
1L: any therapies	129	18.6% (12.3%, 26.4%)	17.0 (11.2, 19.5)	5.2 (3.1, 6.9)
1L: IO monotherapy	11	9.1% (0.2%, 41.3%)	11.0 (1.2, *n/r*)	3.1 (1.1, 5.2)
1L: IO + Platinum	16	18.8% (4.0%, 45.6%)	11.3 (5.6, *n/r*)	4.5 (1.2, 10.3)
1L: Platinum	41	19.5% (8.8%, 34.9%)	17.0 (10.5, 33.2)	5.7 (3.0, 10.9)
≥2L: any therapies	114	9.6% (4.9%, 16.6%)	13.6 (8.2, 15.4)	3.7 (2.7, 5.2)
≥2L: IO monotherapy	32	3.1% (0.1%, 16.2%)	8.1 (2.9, 15.0)	2.3 (1.9, 3.7)
≥2L post platinum: any therapies	50	14.0% (5.8%, 26.7%)	11.5 (7.9, 16.6)	3.3 (2.3, 5.9)
≥2L post platinum: IO monotherapy	20	5.0% (0.1%, 24.9%)	7.1 (2.5, 10.1)	2.2 (1.7, 3.0)

9099 **Poster Session**

Impact of immune checkpoint inhibitor (CPI) and EGFR tyrosine kinase inhibitor (TKI) sequence on time to treatment failure (TTF) among EGFR plus NSCLC treated in a community-based cancer research network.

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Background: The development of CPIs and driver-targeted TKIs has transformed the treatment of NSCLC and increased survival rates. However, the role of CPIs in patients with oncogenic-driven NSCLC remains an area of investigation. We sought to examine the impact of CPI sequence on treatment response among patients with oncogenic-driver mutation-positive NSCLC. **Methods**: Patients with NSCLC being treated within the Sarah Cannon Research Institute network were identified through Genospace, Sarah Cannon's clinico-genomic analytics platform. Advanced stage oncogenic-driven tumors (driver+) were defined as those with a record of receiving an FDA-approved TKI targeting EGFR, ALK, RET, ROS1, NTRK, MET, or BRAF. Kaplan-Meier estimates were used to examine TTF (defined as time from therapy start to start of next therapy, death, or loss to follow-up) and overall survival (OS). **Results**: We identified 12,352 patients with lung cancer and available therapy data (2005-2020), including 2,270 (18%) driver+ patients. Eleven percent (N=245) of driver+ patients received a CPI, including 120 (49%) with CPI prior to TKI, 122 (50%) with CPI post TKI, and 3 (1%) who received CPI both pre and post TKI. The CPI TTF was significantly longer for those who received CPI post TKI compared to those who received it prior (Table). EGFR+ tumors accounted for 82% (N=1,867) of driver+ patients, 10% of whom (N=188) received a CPI. Of the EGFR+/CPI+ patients, 78 patients (41%) received CPI prior to TKI, 107 (57%) received CPI post TKI, and 3 (2%) received CPI both pre and post TKI. EGFR+ tumors exposed to a CPI post TKI had a longer CPI TTF compared to patients who received it prior (Table). In contrast, there was no difference in length of benefit from TKI if it was received pre vs. post CPI (Table). There was also no difference in OS based on sequence of TKI and CPI (p=0.88). Larger sample sizes are needed for analysis of additional driver-stratified cohorts. **Conclusions**: Patients with oncogenic-driven NSCLC benefited from CPI longer when it was administered after TKI compared to before. Importantly, therapy sequence only affected length of benefit from CPIs and did not affect length of benefit from TKIs. This effect was present in EGFR+ NSCLC, but sample sizes were too small to determine if the same is true for other oncogenic-drivers. Therapy sequence had no impact on OS, indicating the presence of additional clinical, therapeutic, and/or genomic factors contributing to disease progression. Continued research is needed to better understand markers of CPI response in driver+ NSCLC. Research Sponsor: None.

Median TTF (mTTF) for driver+ NSCLC based on therapy sequence.

	mTTF (days)	P-value
Driver+		
CPI pre TKI	189	<0.005
CPI post TKI	280	
TKI pre CPI	418	0.40
TKI post CPI	486	
EGFR+		
CPI pre TKI	210	<0.005
CPI post TKI	280	
TKI pre CPI	450	0.88
TKI post CPI	436	

9100 **Poster Session**

Interim results of viagenpumatucel-L (HS-110) plus nivolumab in previously treated patients (pts) with advanced non-small cell lung cancer (NSCLC) in two treatment settings.

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Background: Viagenpumatucel-L (HS-110) is an allogeneic cell therapy derived from a human lung adenocarcinoma cell line incorporating multiple cancer testis antigens and transfected with a gp96-Ig fusion protein. **Methods:** We report interim results of cohort A (previously treated pts who had not received a checkpoint inhibitor [CPI]) and cohort B (pts who progressed after CPI treatment) in an ongoing phase 2 trial evaluating HS-110 plus nivolumab (NIVO) in advanced NSCLC pts (NCT02439450). Pts received HS-110 (1×10^7 cells) intradermally QW for 18 wk and NIVO Q2W until tumor progression. Stratified analyses were performed by injection site reaction (ISR), yes (+) or no (–); baseline blood tumor mutational burden (bTMB), bTMB-L (<10 mutations/ megabase [mut/Mb]) or bTMB-H (≥10 mut/Mb) by FoundationACT test; and baseline PD-L1 expression, – (<1%) or + (≥1%). **Results:** As shown in the Table, median progression-free survival (PFS) in cohort A (n=47) was 1.8 mo (95% CI 1.8-7.8) and median overall survival (OS) was 24.6 mo (95% CI 11.7-36.0) after a median follow-up (MFU) of 19.5 mo. We observed significantly longer PFS and OS in ISR+ pts (hazard ratio [HR] 0.43, p=0.01; HR 0.23, $p<0.001$) and longer OS in PD-L1+ pts (HR 0.25, p=0.02). In cohort B (n=68), median PFS was 2.8 mo (1.8-3.9) and median OS was 11.9 mo (9.7-16.3) after a MFU of 11.9 mo. We observed significantly longer OS in ISR+ pts (HR 0.48, p=0.03) and a trend toward extended OS in bTMB-L pts (HR 0.58, p=0.20). HS-110 TEAEs were reported in 21 (44.7%) pts in cohort A and 18 (26.5%) pts in cohort B. TEAEs in >5% of pts included fatigue, maculopapular rash, nausea, diarrhea, and pruritus. Few HS-110–related TEAEs led to discontinuation of treatment [cohort A, 5 (10.6%); cohort B, 3 (4.4%)], and no serious AEs were considered related to HS-110. **Conclusions:** HS-110 was well tolerated when administered in combination with NIVO. In previously treated pts with advanced NSCLC, we observed (1) significantly longer PFS and OS in ISR+ pts in both CPI naïve and CPI progressor cohorts; (2) significantly longer OS in PD-L1+ patients in the CPI naïve cohort; and (3) a trend of improved OS in bTMB-L pts in the CPI progressor cohort. Further clinical evaluation of HS-110 is warranted in both CPI naïve and CPI progressor NSCLC patients. Clinical trial information: NCT02439450. Research Sponsor: HEAT Biologics.

	All	ISR+	ISR–	Adj HR or OR; *p*	bTMB-L	bTMB-H	Adj HR or OR; *p*	PD-L1+	PD-L1-	Adj HR or OR; *p*
Cohort A, n	47	28	19	-	2	2	-	9	22	-
ORR, %	21.3	28.6	10.5	3.91†; 0.12	-	-	-	44.4	9.1	8.10†; 0.04
PFS‡	1.8	5.4	1.5	0.43; 0.01	-	-	-	4.8	1.8	0.46; 0.11
OS‡	24.6	36.0	4.5	0.23; <0.001	-	-	-	40.5	20.7	0.25; 0.02
Cohort B, n	68	52	16	-	32	11	-	23	29	-
ORR, %	10.3	11.5	6.3	1.99†; 0.60	15.6	9.1	2.25†; 0.50	13.0	10.3	1.27†; 0.80
PFS‡	2.8	3.0	1.7	0.63; 0.14	3.7	2.7	0.94; 0.90	3.2	2.9	1.11; 0.80
OS‡	11.9	12.1	6.4	0.48; 0.03	18.2	12.2	0.58; 0.20	12.1	12.3	0.99; 0.90

† OR. ‡median, mo. OR, odds ratio; ORR, objective response rate.

9101 **Poster Session**

Incidence and heterogeneity of C797S and other EGFR resistance mutations on routine comprehensive genomic profiling (CGP).

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Background: The emergence of osimertinib (osi) as standard of care therapy for *EGFR*-mutant NSCLC has led to investigations into understanding and overcoming drug resistance. There are now a number of therapeutic approaches aimed at overcoming *EGFR* resistance mutations (muts). We sought to understand the biology of *EGFR* C797S and other *EGFR* resistance muts through querying our clinico-genomic database (CGDB). **Methods:** CGP results from tissue (n = 60,889) or circulating tumor DNA (ctDNA; [n = 9,922]) samples from 70,811 NSCLC patients (pts) were queried for known osi resistance muts in *EGFR* (C797, L792, G796, L718, G724). Clinical outcomes were evaluated for a cohort of NSCLC pts with osi resistance from the Flatiron Health-Foundation Medicine CGDB, a nationwide de-identified EHR-derived database linked to CGP data. **Results:** Between 12/2014 and 11/2020, 261 osi resistance mutations in *EGFR* were detected in 228 samples. The most common were C797S (66%), L718X (14%), G724S (11%), and others (9%). 173 C797S muts were detected in 155 samples (123 ex19del, 30 L858R, 2 other *EGFR* muts); 100 tissue, 55 ctDNA (median VAF = 7.6%). *EGFR* T790M co-occurred with C797S muts (96% cis, 3.7% trans) in 118 (76%) samples and decreased over time, occurring in 92% (24/26) of C797S samples tested in 2017 vs 56% (20/36) of samples tested in 2020 (p = 0.002). In 19/155 (12%) samples with C797S (14 ctDNA), multiple changes resulting in *EGFR* resistance muts were present: 16 samples had $>$ 1 nucleotide changes resulting in C797S (100% trans), 3 samples had other resistance muts (L718Q/V, L792H, L792F) and 3 samples had multiple C797S changes with other resistance muts (C797G, L792H/F + G796S, L718Q + G796S+C797G). 29 pts (14 ctDNA) had C797S with potential off-target resistance (17 *PIK3CA* muts, 4 *BRAF* muts, 3 *CCDC6-RET* fusions, 3 *KRAS* muts, 2 *ERBB2* amplifications (amps), 1 *ERBB2* ex16 del, 1 *STRN-ALK* fusion, 1 *FGFR3-TACC3* fusion). In the CGDB, 527 *EGFR*-mut NSCLC pts had documented receipt of osi. Pre and post osi-treated specimens were available for 19 of these pts (12 ex19del, 6 L858R, 1 G719A/S768I). Heterogeneous acquired resistance mechanisms were observed in the post-osi specimen, including 2 *CCDC6-RET* fusions, 2 *MET* amps, 2 *BRAF* fusions, *BRAF* V600E, and secondary *EGFR* muts (C797S, L704F, L718V). 161/527 pts had a documented line of therapy after osi discontinuation and most frequently received platinum doublet + immunotherapy (27%) or platinum doublet alone (23%); 17 (11%) pts received another *EGFR* tyrosine kinase inhibitor. 214/527 had documented osi progression and median post-progression survival was 11.8 months. **Conclusions:** Osi resistance in *EGFR*-mutant NSCLC is a poor prognosis condition. *EGFR* C797S is a recurring resistance mut which, in a minority of cases, can co-occur with alternate on and off target resistance muts detected with tissue and liquid biopsy. Research Sponsor: Foundation Medicine.

RATIONALE-307: Tislelizumab plus chemotherapy versus chemotherapy alone as first-line treatment for advanced squamous NSCLC in patients aged ≥ 65.

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Background: Tislelizumab is a humanized, monoclonal antibody with high affinity and specificity for the programmed cell death protein 1 (PD-1). It has demonstrated antitumor activity in advanced lung cancers. We conducted a Phase 3, multicenter, randomized open-label study (NCT03594747) to assess the safety and efficacy of tislelizumab plus chemotherapy in patients (pts) with advanced squamous NSCLC. As previously reported, tislelizumab (TIS) significantly improved progression free survival (PFS) and reduced the risk of progression. Here, we report results from a sub-group of pts aged ≥ 65 years. **Methods:** Eligible pts (aged 18-75 years) enrolled in China were treatment-naive for locally advanced or metastatic squamous NSCLC. Pts were stratified by disease stage (IIIB vs IV), and programmed death-ligand 1 (PD-L1) expression (<1% vs 1-49% vs 50% tumor cells), and randomized 1:1:1 to Arm A: TIS 200 mg + paclitaxel (P) 175 mg/m^2 and carboplatin (C) area under the plasma concentration 5 (every 3 weeks [Q3W] on day 1); Arm B: TIS + *nab*-paclitaxel (*nab*-P) 100 mg/m^2 (Q3W on days 1, 8 and 15) + C (Q3W on Day 1); or Arm C: P + C (Q3W on day 1). P, *nab*-P and C were administered for 4 to 6 cycles. TIS was administered until loss of benefit, withdrawal of consent or start of a new anticancer therapy. In this sub-group analysis, pts aged ≥ 65 years were evaluated according to the primary endpoint (PFS) and key secondary endpoints (objective response rate and safety). **Results:** Overall, 127 pts aged ≥ 65 years were randomized to receive treatment. Median age of pts aged ≥ 65 was 68.0 years and 120 pts (94.5%) were male. In total, 18 (46.2%), 20 (38.5%), and 34 (94.4%) pts in Arms A, B and C, respectively, had discontinued treatment. In Arm C 22/34 pts had completed chemotherapy. The primary and secondary endpoints, PFS and ORR, were longer and higher, respectively, in Arms A and B, compared with Arm C (Table). Grade ≥ 3 treatment related adverse events (TRAEs) occurred in 33 (84.6%), 44 (84.6%) and 28 (82.4%) pts aged ≥ 65 years in Arms A, B and C, respectively, compared with 103 (85.8%), 99 (83.9%) and 94 (80.3%) pts aged ≥ 18 years enrolled in the study. The most commonly reported TRAEs in pts aged ≥ 65 years were anemia, decrease in neutrophil count, and alopecia. **Conclusions:** In this sub-group analysis, PFS and ORR were longer and higher, respectively, with TIS in pts aged ≥ 65 years with advanced squamous NSCLC. The safety profile of TIS in pts aged ≥ 65 years was similar to the safety profile for all aged pts aged ≥ 18 years. Clinical trial information: NCT03594747. Research Sponsor: This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Tamsin Grewal, MSc, of Ashfield Medcomms, an Ashfield Health Company, and funded by BeiGene, Ltd.

	Arm A (N = 39)	Arm B (N = 52)	Arm C (N = 36)
Median PFS, months (95% CI)	9.7 (5.59, NE)	9.7 (6.87, NE)	5.2 (4.14, NE)
HR (95% CI)	0.602 (0.309, 1.175)	0.564 (0.302, 1.052)	
ORR, % (95% CI)	69.2 (52.4, 83.0)	75.0 (61.1, 86.0)	50.0 (32.9, 67.1)

CI, confidence interval; HR, hazard ratio; NE, not estimable; ORR, objective response rate; PFS, progression free survival.

9103 **Poster Session**

Chronic immune checkpoint inhibitor (ICI) pneumonitis in patients (pts) with non-small cell lung cancer (NSCLC).

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Background: ICI pneumonitis is an immune-related adverse event (irAE) of the lung and often requires discontinuation of ICI. While some pneumonitis cases resolve within the recommended 4-6-week period of corticosteroid therapy, others either fail to improve or have multiple flares necessitating longer or repeated courses of steroids. We investigated the clinical features and courses of pts with chronic pneumonitis. **Methods:** We analyzed 869 pts with NSCLC initiated on ICIs at our institution between 2011 and 2019 for development of ICI pneumonitis. Chronic pneumonitis was defined as any pneumonitis requiring a total of $\geq$12 weeks of steroids, given either continuously or over multiple courses of treatment. Cases of chronic pneumonitis in which the initial course of steroids lasted $\geq$12 weeks without interruption were termed "primary refractory pneumonitis". Subsequent episodes of pneumonitis were categorized as either "recurrent pneumonitis" from ICI rechallenge or "pneumonitis flare" after steroid taper without ICI rechallenge. Chest CT scans were analyzed to classify the imaging patterns. **Results:** Of the 869 pts analyzed, 44 developed ICI pneumonitis (5.1%) and 22 of the 44 (50%) experienced chronic pneumonitis (Grade 2 in 11, Grade 3 in 9, and Grade 4 in 2). A cryptogenic organizing pneumonia (COP) pattern was the most common CT pattern among all pneumonitis cases (30/44) and in chronic pneumonitis cases (14/22). Among chronic pneumonitis cases, the median number of total weeks on corticosteroid therapy was 25.9 (range: 12.4 – 114.4 weeks). Four pts required additional immunosuppressive agents including mycophenolate or infliximab. Fourteen of 22 pts with chronic pneumonitis had primary refractory pneumonitis, while the remaining 8 pts were weaned off of steroids within 12 weeks but later developed additional episode(s) of pneumonitis, ultimately resulting in a total steroid duration of $\geq$12 weeks. The 14 pts with primary refractory pneumonitis had significantly shorter time to pneumonitis onset compared to the other 8 pts (median time to onset: 1.8 vs. 5.5 months, Wilcoxon ranksum p = 0.04). Seventeen of 22 patients had their ICI permanently discontinued; of these, 9 pts subsequently experienced pneumonitis flare after steroid taper, necessitating additional course(s) of steroid therapy. 5 of the 22 patients were rechallenged with ICI, and 4 of them had recurrent pneumonitis with ICI rechallenge. **Conclusions:** Half of the pts diagnosed with pneumonitis developed chronic pneumonitis requiring at least 12 weeks in aggregate of glucocorticoid therapy. Some patients had an initial prolonged steroid course while others initially improved and then flared, even after ICI discontinuation. Recognition of chronic pneumonitis as a distinct and common clinical entity is important in management of pts with ICI pneumonitis. Research Sponsor: None.

9105 **Poster Session**

Genomic markers associated with hyperprogression in patients with lung cancer treated with immune checkpoint inhibitors.

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Background: Immune checkpoint inhibitor (ICI) therapy has become a mainstay of non-small cell lung cancer (NSCLC) treatment. However, not all patients (pts) benefit with a subset paradoxically experiencing accelerated tumor growth while on ICI. Hyperprogression (HP) refers to accelerated tumor growth on ICI with worsening clinical status. Various gene alterations may be associated with HP including MDM2/MDM4 amplifications, EGFR alterations, and STK11/LKB1 mutations. Kato et al. (doi: 10.1158/1078-0432.CCR-16-3133) showed HP in 6/6 pts with MDM2/MDM4 amplification and in 2/10 pts with EGFR alterations. This report describes HP in pts with NSCLC treated with ICIs in a large health system. **Methods:** Pts with NSCLC treated with ICIs from Jan 2012 to Jan 2021 at Advocate Aurora Health were reviewed after IRB approval. Pts with NSCLC histology (ICD diagnosis codes and/or manual chart review), ICI treatment, and molecular testing were identified via the real world data integrated within the Syapse Learning Health Network platform. Additional chart review to ascertain HP was performed, and molecular results were analyzed. HP criteria include: 1) time-to-treatment failure $<$ 2 months (from start to discontinuation of ICI for any reason), 2) $>$ 50% increase in tumor burden by RECIST, 3) spread of the disease to a new organ between baseline and first radiologic evaluation or clinical deterioration, and 4) ECOG PS $\geq$ 2 during the first 2 months of treatment. Based on the number of criteria fulfilled, HP = $>$ 3, Progression = 1-2, and non-progressor = 0. Pts with and without HP were compared using Chi-squared and Fisher Exact tests. T-tests were performed for continuous variables. **Results:** Out of 7,078 NSCLC pts, 1,389 (20%) were treated with ICI including atezolizumab (40 pts, 3%), durvalumab (17 pts, 1%), nivolumab (167 pts, 12%), pembrolizumab (190 pts, 14%), and multiple ICIs (12 pts, 1%). Of those pts treated with ICIs, molecular testing was performed in427 (31%). 98 of 427 pts (23%)had HP and an additional 86 pts (20%) had progressive disease without meeting the definition of HP. Biomarker associations with HP are shown in the table. By tumor gene alterations, HP was seen in pts with: EGFR (20/60), STK11/LKB1 (16/25); and MDM2/4 (4/7). **Conclusions:** EGFR, STK11/LKB1, and MDM2/4 gene alterations were all statistically significantly associated with HP. Clinical and molecular predictors of HP need to be explored in order to optimize selection of pts for ICI therapy. Research Sponsor: None.

	Hyperprogression Status						
	No HP		+HP				
Molecular Alteration	N	%	N	%	N	%	P-Value*
EGFR							
No	367	86	289	88	78	80.59	
Yes	60	14	40	12	20	20	0.04
STK11/LKB1							
No	402	94	320	97	82	84	
Yes	25	6	9	3	16	16	< 0.0001
MDM2/4							
No	420	98	326	99	94	96	
Yes	7	2	3	1	4	4	0.03

*P-values were calculated using Chi-squared tests.

9106 **Poster Session**

Impact of *STK11* mutation on first-line immune checkpoint inhibitor (ICI) outcomes in a real-world KRAS G12C mutant lung adenocarcinoma cohort.

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Background: The introduction of KRAS G12C inhibitors into clinical trials has demonstrated promise and may provide a new therapeutic option for patients (pts) harboring *KRAS* G12C mutations. Recent data has also indicated that immune checkpoint inhibitors (ICI) have shown benefit in *KRAS* G12C mutant lung adenocarcinoma (LUAD); however, data on the impact of co-occurring *STK11* mutations on outcomes are conflicting. We utilized the Guardant INFORM real-world clinical-genomic database to assess the impact of co-occurring *STK11* mutations on outcomes in pts with *KRAS* G12C mutant LUAD treated with a first-line ICI containing regimen. **Methods:** This retrospective matched cohort observational study was conducted in a nationally representative clinical-genomic database covering over 137,000 pts with comprehensive ctDNA results and associated clinical information. Adult pts with metastatic LUAD who received $\geq$ 1 dose of first-line anti-PD1/PD-L1 ± chemotherapy and had at least 90 days follow-up after first *KRAS* G12C detection were included. A cohort of pts without *KRAS* G12C, including *KRAS* wildtype pts and pts with other *KRAS* mutations, were matched 3:1 for age, gender, year of index and baseline comorbidity. Time to next treatment (TTNT), time to discontinuation (TTD), real-world overall survival (rwOS) were compared with vs. without *STK11* mutations for both cohorts using cox proportional-hazards model. **Results:** Among 330 pts in the *KRAS* G12C cohort, 21% (n = 70) had an *STK11* mutation. Among the matched cohort (n = 938), 754 pts were *KRAS* wildtype, of whom 6% (n = 49) had *STK11* mutations. Within the *KRAS* G12C cohort, pts with *STK11* mutations had statistically significant shorter TTNT (hazard ratio [HR] 2.7, 95% confidence internal [CI] 1.8-4.0, $p < 0.0001$), TTD (HR 1.4, 95% CI 1.0-2.0, $p < 0.04$) and rwOS (HR 3.2, 95% CI 2.0-5.1, $p < 0.0001$) than pts without *STK11* mutations. Within the matched *KRAS* wildtype cohort, the differences in TTD (HR 1.4, 95% CI = 1.0-2.0, p = 0.08) and rwOS (HR 1.4, 95% CI = 0.8-2.4, p = 0.3) in patients with vs. without *STK11* mutation did not reach statistical significance (Table). **Conclusions:** This study provides real-world evidence that *STK11* co-mutations are associated with worse outcomes among pts with *KRAS* G12C mutant LUAD treated with first-line ICI. These inferior outcomes indicate a high unmet medical need among LUAD pts harboring co-occurring *KRAS* G12C and *STK11* mutations and demonstrate the need for effective targeted and/or combination therapies in this patient population. Research Sponsor: Mirati Therapeutics.

Cohort	Endpoints	HR (95% CI) No *STK11* vs *STK11*	P-value
***KRAS* G12C (N = 331)**			
	TTNT	2.7 (1.8, 4.0)	< .0001
	TTD	1.4 (1.0, 2.0)	0.03
	rwOS	3.2 (2.0, 5.1)	<.0001
Matched *KRAS* wildtype cohort* (N = 754)			
	TTNT	1.7 (1.1, 2.6)	0.02
	TTD	1.4 (1.0, 2.0)	0.08
	rwOS	1.4 (0.8, 2.4)	0.3

*Data on the full matched cohort to be presented.

9107 **Poster Session**

Association of concomitant NSAID and immunotherapy on outcomes in patients with non-small cell lung cancer: Analysis of the National Veterans Health Administration Database.

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Background: Preclinical data suggests the efficacy of immune checkpoint inhibitors (ICI) may be enhanced with concomitant nonsteroidal anti-inflammatory (NSAID) medications. Real-world evidence to support investigating this hypothesis in prospective randomized trials are needed. **Methods:** A retrospective cohort study queried the VA Corporate Data Warehouse (VA-CDW) to identify patients diagnosed with NSCLC who were treated with ICI between 2010-18. Exposure to concomitant NSAID was determined whenever NSAID prescriptions were released from the VA pharmacy within 90 days of the first ICI infusion. Chi-square and ANOVA tests were used to compare baseline characteristics. The outcome of overall survival (OS) was measured from the start of ICI. Cox proportional hazard regression was used to adjust for demographic, clinical, tumor, and treatment characteristics. **Results:** The study cohort consisted of 3,415 patients with NSCLC treated with ICI, and 2,336 (64%) were exposed to concomitant NSAID. The median age was 69, male 97%, race: white 73%, black 21%, and 66% lived in urban areas. Most patients were initially diagnosed with stage III or IV disease (68%); tumor histology: adenocarcinoma 48% and squamous cell 38%. Comorbidity counts were 0 in 40%, 1-3 in 30%, and 4+ in 30%. Chemotherapy was delivered before ICI in 54% and concurrently with ICI in 31%. The most commonly used NSAIDs were aspirin (35%), ketorolac (11%), and ibuprofen (7%); 44% were exposed to more than one NSAID. With a median follow-up of 8 months, exposure to concomitant NSAIDs was associated with a longer OS (HR = 0.90; 0.83-0.98, p = 0.01) after adjusting for all available potential confounders on multivariable analyses. Longer OS persisted following propensity score matching (HR = 0.89; 0.82-0.97 p = 0.007). Other factors significant for OS on multivariable testing included use of chemotherapy after ICI (HR = 0.53 [0.40-0.69], $p < 0.001$), concurrent chemotherapy during ICI (HR = 0.68 [0.62-0.74], $p < 0.001$), younger age, black race, female gender, and adenocarcinoma histology. Among the various NSAIDs analyzed on the multivariable analyses, only diclofenac approached statistical significance (HR = 0.78 [0.59-1.03], p = 0.08). Limiting the comparison to patients exposed to diclofenac (n = 101) versus no NSAIDs (n = 1,298), the comparison demonstrated a similar trend for OS (HR = 0.79 [0.60-1.04], p = 0.094), although the association was attenuated after propensity-score matching (HR = 0.90 [0.63-1.29], p = 0.57). **Conclusions:** This retrospective cohort study of Veterans with NSCLC who were treated with ICI identified that concomitant receipt of NSAIDs is associated with longer OS. Research Sponsor: Morningside Center for Innovative and Affordable Medicine, Emory Woodruff Health Sciences Center, Other Government Agency.

9108 **Poster Session**

Genomic landscape differences in patients with advanced non-small cell lung cancer by sex and age.

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Background: Non-small cell lung cancer (NSCLC) remains a leading cause of cancer-related death in the U.S. The median age at diagnosis is 70 years, and NSCLC is uncommon among younger individuals ($<$ 50 years).Overall, outcomes in NSCLC have improved significantly with targeted therapy. A prior study demonstrated patients $<$ 50 are more likely to have targetable alterations including EGFR, ALK, ERBB2, and ROS1. Another study reported an increased prevalence of EGFR mutations in females and KRAS mutations in males with NSCLC. The comprehensive genomic landscape of NSCLC patients in different age groups and genders remains largely unknown. In our study, we aim to investigate the genomic alterations in patients with advanced NSCLC according to age and sex. Efforts that are focused on identifying targetable alterations in NSCLC will likely help personalize treatment and improve outcomes. **Methods:** We performed a retrospective review of de-identified data from the Guardant Health database from March 2018 through October 2020. We reviewed 34,237 profiles from patients with NSCLC who underwent molecular profiling using the plasma-based circulating-tumor DNA (ctDNA) Next-Generation Sequencing (NGS) assay Guardant360. Single nucleotide variants (SNV), fusions, indels and copy number variations (CNV) of up to 83 genes were analyzed. We assessed for genomic differences among patients with advanced NSCLC by both sex and age ($\geq$70 and $<$ 70). We conducted two-tailed tests of equality of proportions comparing males to females and $\geq$70 to $<$ 70. **Results:** Of the 34,237 profiles reviewed, somatic alterations were seen in 81.7% (n = 27,972) of the patients. The median age was 70 (range 16-102) and 55% were female. Our study demonstrated that the most common genomic alterations in both age groups and genders were TP53, EGFR, KRAS, ATM, and MET. Patients $\geq$70 were more likely to have ATM (21% versus 14%, $p < 0.0001$) and MET (12% versus 10 %, $p < 0.0001$) mutations than those $<$ 70. Patients $<$ 70 were more likely to have EGFR (30% versus 27%, $p < 0.0001$), STK11 (14% versus 11%, $p = 0.0056$), and KRAS (26% versus 24%, $p < 0.0001$) alterations. EGFR was seen more frequently in females (33% versus 26%, $p < 0.0001$). ATM (11% versus 6%, $p < 0.0001$) and MET (8% versus 5%, $p = 0.0050$) were seen more frequently in males. **Conclusions:** Significant differences in the distribution of targetable genomic alterations were identified among different age groups and genders in patients with advanced NSCLC. These findings highlight the importance of taking personalized approaches to diagnostic testing and treatment of advanced NSCLC. Research Sponsor: None.

9109 **Poster Session**

Long-term efficacy and safety of larotrectinib in patients with TRK fusion-positive lung cancer.

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Background: Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions have been identified as oncogenic drivers in a diverse array of tumor types including lung cancer. Larotrectinib is a first-in-class, highly selective, central nervous system (CNS)-active tropomyosin receptor kinase (TRK) inhibitor approved for the treatment of adult and pediatric patients (pts) with TRK fusion cancer, with an objective response rate (ORR) of 78% across multiple non-CNS cancers (McDermott et al, ESMO 2020). Here, we report the updated data on pts with lung cancer treated with larotrectinib. **Methods:** Pts with lung cancer harboring a *NTRK* gene fusion enrolled in two clinical trials (NCT02576431 and NCT02122913) were identified for this analysis. Larotrectinib 100 mg PO BID was administered on a continuous 28-day schedule until disease progression, withdrawal, or unacceptable toxicity. Response was assessed by the investigator per RECIST v1.1. **Results:** As of July 20, 2020, a total of 20 pts with TRK fusion-positive lung cancer (19 with non-small cell lung cancer and 1 with small cell lung cancer) were enrolled. Median age was 48.5 years (range 25.0–76.0). The gene fusions involved *NTRK1* (n = 16; 80%) or *NTRK3* (n = 4; 20%). Pts were heavily pre-treated with a median of 3 systemic therapies (range 0–6). Among 15 evaluable pts, the confirmed ORR was 73% (95% CI 45–92): 1 complete response, 10 partial responses (PR), 3 stable disease (SD) and 1 progressive disease (PD). The median time to response was 1.8 months. Among 8 evaluable pts with baseline measurable and non-measurable CNS metastases, the ORR was 63% (95% CI 25–91): 5 PR, 2 SD, and 1 PD. In all evaluable pts, the 12-month rates for duration of response and progression-free survival were 81% and 65%, respectively. Median overall survival was 40.7 months (95% CI 17.2 to not estimable) at a median follow-up of 16.2 months. Duration of treatment ranged from 0.03+ to 51.55+ months. Adverse events (AEs) were predominantly Grade 1–2. Treatment-related AEs were reported in 16 pts, of which 2 experienced Grade 3 events (myalgia, hypersensitivity, weight increase). There were no treatment discontinuations due to AEs. **Conclusions:** These data confirm that larotrectinib is highly active with rapid and durable responses, extended survival benefit, and a favorable long-term safety profile in pts with advanced lung cancer harboring *NTRK* gene fusions, including in pts with CNS metastases. These results underscore the importance of screening for *NTRK* gene fusions in pts with lung cancer. Clinical trial information: NCT02576431 and NCT02122913. Research Sponsor: Bayer HealthCare and Loxo Oncology.

9110 **Poster Session**

Ph I/II study of oral selective AXL inhibitor bemcentinib (BGB324) in combination with erlotinib in patients with advanced EGFRm NSCLC: End of trial update.

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Background: AXL, a receptor tyrosine kinase, is over-expressed in many cancers, and has been identified as a marker of poor prognosis in NSCLC. AXL overexpression is implicated in development of resistance to EGFR inhibitors including erlotinib (Erl) and osimertinib. AXL inhibition by bemcentinib (Bem), a first-in-class, oral, selective and potent AXL kinase inhibitor, abrogates resistance to EGFR inhibitors *in vivo*. Bem is currently under evaluation as a monotherapy and in combination with EGFRi, CPIs and chemotherapy across several PhII trials. **Methods:** Phase I of this study was designed to confirm safety/tolerability of Bem in NSCLC pts as monotherapy and in combination with Erl in pts previously progressing on Erl (arm A). In Phase II, pts who had progressed on an approved EGFRi (arm B) or who were responding/stable on Erl in the 1L setting (arm C) were treated with Bem 200mg and Erl 150mg od to evaluate the safety and activity of the combination, assessing reversal or prevention of resistance to EGFR inhibition in these 2 groups, respectively. Plasma protein biomarker levels were sequentially measured using the DiscoveryMap v3.3 panel (Myriad RBM). **Results:** As of 7 Oct 2020, all arms have completed recruitment. Median exposure to Bem was 63d (mean: 200d, range: 2d-1175d). Treatment was generally well-tolerated. Common TRAEs (>20% pts) were diarrhea (70%; G3 20%), nausea (50%; G3 0%), QTc prolongation (35%; G3 3%), vomiting (35%; G3 0%), and fatigue (25%; G3 5%). 1 unrelated G4, 0 G5 reported. In the run-in arm (5 female, median age 61 yrs [57-76]), 2/8 pts achieved SD for ~1 yr, including 19% tumor shrinkage in 1 pt. In arm A (5 female, median age 58 yrs [38-67]), 1/8 pts (68 F) achieved tumor shrinkage of 38%, with treatment duration of 2 yrs until progression. A further 5 pts reported SD. In arm B, 11 pts (7 female, median age 63 yrs [49-78]) had received a median of 1 (0 - 4) prior lines of chemotherapy and a median of 2 prior lines of EGFRi. One achieved a PR (51M) and one a SD (62F) on the combination (CBR of 18%); durations on treatment were 1 yr, and 6 mos, respectively. Neither had EGFR T790M. mPFS was 1.4 mos. In arm C, 13 pts (10 female, median age 66 yrs [32-80]) were enrolled. 11/13 pts were evaluable for efficacy. 1 PR (58M) was reported with 47% tumor shrinkage, duration of treatment was 315d. 9 other pts achieved SD (CBR of 91%), including 4 (3 F/1 M, age range 64-71yrs) who continued on trial for 772+ to 1008+ d. mPFS is currently 12.2 mos. Protein biomarkers predictive of pt benefit upon Bem treatment are being explored. **Conclusions:** Bem with Erl combination is feasible and tolerable in NSCLC pts, with benefit was seen in a subset of pts who either progressed on an EGFRi or were receiving Erl concurrently in remission in the first line. Further studies of Bem + EGFRi are warranted to explore the potential benefits of this combination. Clinical trial information: NCT02424617. Research Sponsor: Privately.

9111 **Poster Session**

Capmatinib efficacy in patients with NSCLC identified as *MET*ex14 using an NGS-based liquid biopsy assay: Results from the GEOMETRY mono-1 study.

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Background: Capmatinib, a highly selective and potent MET inhibitor, was approved for patients (pts) with advanced MET exon 14 skipping mutation (METex14) NSCLC in the US and Japan, with the FoundationOne CDx (tissue NGS assay), based on results of the ongoing GEOMETRY mono-1 study (NCT02414139). Here, we report efficacy findings in pts from GEOMETRY mono-1, who were identified as *MET*ex14 using a next-generation sequencing (NGS)-based liquid biopsy test (LDx), which detects *MET*ex14 in circulating tumor (ct)DNA. **Methods:** During the GEOMETRY mono-1 study, pts were screened for *MET*ex14 status using a *MET*ex14 RT-PCR clinical trial assay (CTA) on FFPE tissue. Clinical validation of the LDx was performed using plasma samples from pts enrolled in the GEOMETRY mono-1 study, which include *MET*ex14-positive samples from Cohort (C)4 (pretreated) and C5b (treatment-naïve), in addition to *MET*ex14-negative samples from C1b, C2, and C3, and 21 tissue-matched NSCLC plasma samples from commercial sources to supplement the total number of *MET*ex14 deletion negative patients. Concordance of the CTA and LDx were evaluated by positive percent agreement (PPA) and negative percent agreement (NPA). This retrospective analysis reports overall response rate (ORR), duration of response (DOR), and progression-free survival (PFS), all by BIRC, and overall survival (OS) in pts identified as *MET*ex14 by the LDx (data cutoff: Sep 18, 2020). **Results:** Of the 97 pts with *MET*ex14 NSCLC in C4 (n = 69) and C5b (n = 28), 88 pts had plasma volume ≥2.5 mL and cell free DNA ≥20 ng (minimum input); of these 57 were LDx positive (C4, n = 41; C5b, n = 16), 26 were negative; 5 had invalid sequencing results. Of the 97 CTA *MET*ex14-negative patients who met minimum input requirements, 88 were LDx negative and 9 had invalid sequencing results; none of the CTA *MET*ex14-negative pts (N = 97) were reported as positive by the LDx. The PPA and NPA for these were 68.7% (95% CI: 57.6%, 78.4%) and 100% (95% CI: 95.9%, 100%), respectively, when excluding LDx invalid results. In pts identified as *MET*ex14 positive by LDx, the ORR (95% CI) was 81.3% (54.4–96.0; n = 16) in C5b and 48.8% (32.9–64.9; n = 41) in C4; median DOR (95% CI) was 20.3 (4.2, NE; n = 13) months in C5b and 9.8 (4.2–19.5; n = 20) months in C4; median PFS (95% CI) was 12.4 (4.5–NE; n = 16) months in C5b and 5.4 (4.0–6.6; n = 41) months in C4; median OS was 17.9 (9.8–NE; n = 16) months in C5b and 13.6 (6.6–23.3; n = 41) months in C4. Clinical findings in those identified as *MET*ex14 positive by LDx were comparable with those identified by the CTA. **Conclusions:** Current findings from the GEOMETRY mono-1 study support the activity of capmatinib in advanced NSCLC pts with *MET*ex14 identified using LDx. For pts identified as *MET*ex14-negative by the LDx, further testing should be performed on tissue samples, as a negative LDx result does not preclude a positive result by tissue biopsy. Clinical trial information: NCT02414139. Research Sponsor: Novartis.

9112 **Poster Session**

Interim results of a phase II single arm trial combining afatinib with cetuximab in patients with EGFRex20ins positive NSCLC.

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Background: Epidermal growth factor receptor exon 20 insertions (EGFRex20ins) are identified in 4-10% of all EGFR mutations in non-small cell lung cancer (NSCLC) and are associated with primary resistance to EGFR tyrosine kinase inhibitors (TKIs). Treatment options are limited. A case series showed that dual EGFR blockade with afatinib and cetuximab can induce tumor responses with manageable toxicity. We report on the first seventeen EGFRex20ins patients treated with afatinib in combination with cetuximab. **Methods:** In this Simon's two stage, single-arm, phase II trial, patients with advanced NSCLC harboring an EGFRex20ins mutation were treated with afatinib 40 mg once daily, in combination with cetuximab 500 mg/m^2, every two weeks, in five institutions in the Netherlands. Supportive medication consisted of minocycline, loperamide and skin creams. No previous line of treatment was required and asymptomatic brain metastases were allowed. The primary endpoint was disease control rate (DCR) after 18 weeks of treatment. Secondary endpoints included safety, response rate (RR), duration of response (DOR) and progression-free survival (PFS). Patients were treated until progression or unacceptable toxicity. A Simon's two stage optimal design was used in order to minimize the number of patients being treated in the event that the regimen proves to be inactive. The estimated sample size of the first stage was 17 patients. At least four successes were required to enter stage 2 of the trial (alpha = 0.10; power = 0.90). **Results:** Eighteen patients were enrolled between Jan 2019 and Aug 2020; one patient did not meet the eligibility criteria due to absence of measurable disease. Median age was 66.0 years, 65% female, 53% never smoker. 47% of patients were treated as first-line therapy. Median prior lines of treatment was 1 (range 0-6). 53% received prior platinum-based chemotherapy. The primary endpoint was met as disease control was achieved by 10 patients (59%) after 18 weeks of treatment. Median PFS was 5.5 months. Best responses were partial (n = 8, RR 47%), stable (n = 7) or progressive disease (n = 2). Four patients were still on treatment at the cut-off date (Feb 2021). Most common treatment-related adverse events (TRAEs) were diarrhea (71%), rash (65%), paronychia (59%) and dry skin (53%). Grade III TRAEs were reported in 59% of all patients. Grade III TRAEs $\geq$ 10% included rash (n = 3; 18%) and diarrhea (n = 3; 18%). No grade IV toxicity was observed. One patient died due to respiratory failure after infusion of study medication, probably related to disease progression, possibly treatment related. 82% of patients required a dose reduction. Rate of treatment discontinuation due to AEs was 12% (n = 2). **Conclusions:** Combination treatment with afatinib and cetuximab demonstrated antitumor activity with a DCR of 59% at 18 weeks and a 47% RR, with manageable toxicity. Clinical trial information: NCT03727724. Research Sponsor: Merck Healthcare, Schiphol-Rijk, Netherlands, an affiliate of Merck KGaA, Darmstadt, Germany, and Boehringer Ingelheim.

9113 **Poster Session**

DNMT3A mutation to identify a subset of non-small cell lung cancers with increased sensitivity to PD-(L)1 blockade.

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Background: Despite significant improvements in overall survival with PD-(L)1 inhibition, the majority of patients with metastatic NSCLC do not respond to immune checkpoint inhibition (ICI). Growing evidence suggests the importance of genomic alterations in modulating anti-cancer immune response and predicting ICI efficacy in solid tumors. However, the genomic correlates of response and resistance to ICI in NSCLC are still largely unknown. **Methods:** Patients with advanced NSCLC treated with PD-(L)1 blockade whose tumors underwent comprehensive genomic profiling were included. Mutation enrichment analysis was performed to identify genomic alterations enriched in responders versus (vs) non-responders to ICI. Loss-of function mutations annotated as oncogenic by OncoKB, and missense mutations predicted to be deleterious by SIFT/Polyphen-2 were considered. Cox proportional hazards models was used to estimate hazard ratios (HRs) in univariable and multivariable models. **Results:** : Among 600 NSCLCs, we identified deleterious mutations in the DNA methyltransferase 3A (*DNMT3A*) gene as the most significant alteration enriched in responders versus non-responders to PD-(L)1 blockade (q-Value < 0.05). *DNMT3A*^{MUT} (7.3%, N = 44) and *DNMT3A* wild-type (*DNMT3A*^{WT}) cases (92.7%, N = 556) were well balanced in terms of baseline clinicopathologic features, including PD-L1 expression, sex, performance status, age, concurrent genomic alterations, and smoking history. *DNMT3A*^{MUT} tumors had a significantly higher median TMB compared to *DNMT3A*^{WT} cases (12.1 vs 9.8 mutations/megabase, P = 0.03). *DNMT3A* loss was associated with significantly higher objective response rate (ORR, 50% vs 20.5%, $P < 0.001$), longer median progression-free (mPFS, 9.2 vs 2.9 months, HR 0.60, $P < 0.01$) and overall survival (mOS, 23.1 s 12.1 months, HR 0.59, P = 0.01) among *DNMT3A*^{MUT} compared to *DNMT3A*^{WT} NSCLCs. Loss-of function mutation in *DNMT3A* was confirmed be an independent predictor of improved PFS (HR 0.61, P = 0.01) and OS (HR 0.62, P = 0.04) at multivariable analysis. *DNMT3A* mutation had no impact on OS among patients with advanced NSCLC who did not receive ICI (HR 1.18, P = 0.22), nor among those with early-stage resected NSCLC (HR 1.17, P = 0.48), suggesting that *DNMT3A* mutation is predictive, rather than prognostic, of ICI efficacy. Although a subset of *DNMT3A* mutations could have potentially arisen from tumor-associated hematopoietic cells, the *DNMT3A* allele fraction-to-tumor purity ratio was ≥ 0.5 in more than 50% of cases, suggesting that a proportion of these mutations were derived from lung cancer cells. **Conclusions:** Loss-of-function mutation in DNMT3A may identify a new genomically defined subset of NSCLC with increased sensitivity to PD-(L)1 blockade. Additional studies are ongoing to determine the exact source of DNMT3A mutation (clonal hematopoiesis vs tumor) and their relative contribution to ICI efficacy. Research Sponsor: None.

9114 **Poster Session**

Nitroglycerin (NTG) plus whole intracranial radiotherapy for brain metastases (BM) in non-small cell cancer patient (NSCLC): A randomized open label, phase II clinical trial.

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Background: Hypoxia has been associated with chemo-radioresistance secondary to Vascular Endothelial Growth Factor Receptor induced by Hypoxia Induced Factor (HIF). Nitroglycerin (NTG) can reduce HIF-1 in cell lines, and this may have anti-angiogenic, pro-apoptotic, and anti-efflux effects. Particularly, *EGFR* mutated (EGFRm) tumor cell lines have been shown to overexpress both VEGF and HIF. In this phase II study, we evaluated the effect of transdermal NTG on intracranial objective response rate (iORR), intracranial progression-free survival (ICPFS), and overall survival (OS) of NSCLC patients with BM. **Methods:** We performed an open-label, phase II clinical trial among ninety-six histologically confirmed NSCLC patients with BM. Patients were randomized 1:1 to receive NTG plus WBRT (30 Gy in 10 fractions) or WBRT alone. iORR and ICPFS were evaluated by MRI by two independent, blinded radiologists. Nitroglycerin was administered using a transdermal 36 mg patch, which released 10 mg in 24 hours with a rest interval of 12 hours from Monday-Friday throughout WBRT administration (10 days). **Results:** Fifty patients were allocated to the control group, while 46 were allocated to the experimental group (NTG); among these 26 (55.3%) had *EGFR*m in the control group and 21 (44.7%) had *EGFR*m in the NTG arm. In terms of the iORR, patients in the NTG group had a significantly higher response when compared to controls (56.6% vs. 43.5%; p = 0.024). Additionally, patients who received NTG in addition to WBRT had an independently prolonged ICPFS compared with those who received WBRT alone (27.7 vs. 9.6; HR: 0.470 [95%CI: 0.24-0.89]; p = 0.021). PFS was also positively impacted (HR: 0.519 [95%CI: 0.27-0.98]; p = 0.043). The benefit in terms of iORR and ICPFS (HR: 0.38 [95%CI: 0.16-0.91]; p = 0.030) was particularly important in the *EGFRm* patient subgroup. No differences were observed in OS. A significantly higher rate of vomiting presented in the NTG arm of the study (p= 0.016). **Conclusions:** The concurrent administration of NTG and chemo-radiotherapy improves iORR and ICPFS among NSCLC patients with BM. The benefit is particularly significant in the *EGFR*m patient subgroup. Clinical trial information: NCT04338867. Research Sponsor: Consejo Nacional de Ciencia y Tecnología (CONACyT).

9115 **Poster Session**

Stereotactic body radiation therapy and in situ oncolytic virus therapy followed by immunotherapy in metastatic non-small cell lung cancer.

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Background: The introduction of immunotherapy has altered the treatment paradigm for metastatic non-small cell cancer (mNSCLC). Unfortunately, many patients with mNSCLC have limited or no benefit from immune checkpoint inhibitors (ICIs). A variety of approaches have been explored to augment the efficacy of ICIs. Our study's aim was to determine whether the addition of stereotactic body radiation therapy (SBRT) and intratumoral injection of the oncolytic virus ADV/HSV-tk (adenovirus-mediated expression of herpes simplex virus thymidine kinase) to a monoclonal antibody targeting programmed cell death-1 (PD-1) would improve the ICI's efficacy in the treatment of mNSCLC. **Methods:** In this single-arm, open-label phase II study, patients with mNSCLC (squamous or non-squamous) who were ICI-naive or who were previously treated with a maximum of one line of therapy that included an ICI received an intratumoral injection of ADV/HSV-tk (5×10^{11} vp) followed by SBRT (30 Gy in 5 fractions) to the same tumor. An anti-PD-1 agent (pembrolizumab 200 mg IV every 3 weeks or nivolumab 240 mg IV every 2 weeks) was then given for up to 24 months (pembrolizumab) or 12 months (nivolumab), or until disease progression or intolerable toxicity. The primary endpoint was objective response rate (ORR) as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. A secondary endpoint was clinical benefit rate (CBR). **Results:** A total of 35 patients were enrolled, with 28 (80%) receiving pembrolizumab and 7 (20%) receiving nivolumab; 14 (40%) had previous ICI therapy while 21 (60%) were ICI-naive. The ORR and CBR were 28.5% and 61.9% in the ICI-naive group, and 14.2% and 64.2% in the group that previously received an ICI, respectively. Grade 3 or higher toxicity was seen in five patients (26.3%) in the ICI-naive group and in one patient (7.1%) in the previously ICI-treated group. No treatment-related deaths were observed. **Conclusions:** The addition of SBRT and intratumor injection of ADV/HSV-tk to anti-PD-1 therapy in mNSCLC resulted in a CBR of over 60% for both ICI-naive and previously ICI-treated patients without the use of chemotherapy. The combination was able to reinstitute sensitivity to ICIs in patients previously treated with an ICI, and also benefited some patients whose tumors did not express PD-L1. These findings should be further explored in a larger study population. Clinical trial information: NCT03004183. Research Sponsor: Merck.

PD-L1 expression and treatment response.

	ICI-naïve (N = 21)	Previous ICI (N = 14)	Total (N = 35)
Tumor PD-L1 - no. (%)			
< 1%	13 (61.9)	6 (42.8)	19 (54.3)
1-49%	7 (33.3)	6 (42.8)	13 (37.1)
≥ 50%	1 (4.8)	2 (14.3)	3 (8.6)
Best overall response – no. (%)			
Complete response (CR)	2 (9.5)	0 (0)	2 (5.7)
Partial response (PR)	4 (19.0)	2 (14.3)	6 (17.1)
Stable disease (SD)	7 (33.3)	7 (50.0)	14 (40.0)
Progressive disease (PD)	8 (38.1)	5 (35.7)	13 (37.1)
CBR	13 (61.9)	9 (64.2)	22 (62.8)

CBR = CR + PR + SD; PD-L1 = Programmed death-ligand 1.

Genomic landscape of non-small cell lung cancer (NSCLC) with methylthioadenosine phosphorylase (*MTAP*) deletion.

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Background: NSCLC remains a major cause of cancer-associated mortality despite major advancements in treatments. In addition to immune checkpoint inhibitors (ICPI), new strategies for clinically advanced NSCLC now include the development of new synthetic lethality targets focused on protein arginine methyl transferases such as PRMT5 that exploit the impact of tumor cell genomic loss of *MTAP*. **Methods:** 29,379 advanced/metastatic NSCLC cases underwent hybrid-capture based comprehensive genomic profiling to evaluate all classes of genomic alterations (GA). Tumor mutational burden (TMB) was determined on up to 1.1 Mb of sequenced DNA and microsatellite instability (MSI) was determined on up to 114 loci. PD-L1 tumor cell expression was determined by DAKO 22C3 immunohistochemistry (IHC); low positive was a tumor proportion score (TPS) 1-49% and high positive was a TPS $\geq$50%. **Results:** 3,928 NSCLC exhibited *MTAP* homozygous loss. Cases had the following subtypes: adenocarcinoma (59%), squamous cell ca (22%), NSCLC NOS (16%), and large cell neuroendocrine, sarcomatoid, adenosquamous ca (all 1%). GA/tumor were similar when *CDKN2A/B* losses associated with 9p21 co-deletion with *MTAP* loss are excluded. Significant differences in currently targetable GA included *KRAS* G12C higher in *MTAP*-intact NSCLC (P =.0003) and *EGFR* short variant mutations higher in *MTAP*-deleted NSCLC (P <.0001). *MTAP*-intact NSCLC had higher frequencies of GAs in *TP53* (P <.0001) and *RB1* and a lower frequency of *SMARCA4* (P <.0001). GAs frequencies in *ERBB2*, *MET*, *ALK, ROS1* and *NTRK1* were similar. Biomarkers for potential ICPI efficacy were higher in *MTAP*-intact including TMB $\geq$10mut/Mb (P =.0002) and low and high PD-L1 IHC staining (P =.01). Biomarkers potentially predictive of ICPI resistance (*STK11* and *KEAP1*) were similar in both groups. **Conclusions:** *MTAP* loss occurs in 13% of NSCLC, supporting the development of novel targeted therapies designed to exploit PRMT5 hyper-dependence in these tumors. *MTAP* loss in NSCLC is accompanied by differences in targeted and ICPI options for these patients which may impact future combination strategies. Further study of anti-PRMT5 drugs that are enabled by *MTAP* loss in NSCLC appears warranted. Research Sponsor: Foundation Medicine Inc.

	NSCLC *MTAP* Intact	NSCLC *MTAP* Loss	P Value
Number of Cases	25,843	3,928	
% Male	50%	50%	NS
Median age (range) yrs	68 (12-89+)	69 (18-89+)	NS
GA/tumor	5.5	8.2	NS*
CDKN2A	20%	98%	<.0001
CDKN2B	6%	95%	<.0001
TP53	70%	63%	<.0001
***KRAS* (all)**	31%	29%	NS
***KRAS* (G12C)**	12%	10%	=.0003
***EGFR* short variants only**	10%	13%	<.0001
ALK	3%	4%	NS
ROS1	1%	1%	NS
NTRK1	1%	1%	NS
STK11	15%	16%	NS
KEAP1	7%	7%	NS
PIK3CA	11%	12%	NS
SMARCA4	7%	10%	<.0001
PTEN	6%	6%	NS
MET	5% (3% amp)	6% (3% amp)	NS
ERBB2	4% (2%amp)	4% (2% amp)	NS
BRAF	5%	5%	NS
RB1	10%	2%	<.0001
MSI High	0.4%	0.2%	NS
Mean TMB	9.4	8.6	=.001
TMB>10 mut/Mb	35%	32%	=.0002
TMB>20 mut/Mb	10%	8%	<.0001
PD-L1 Low Positive	30% (13,931)	28% (2125)	=.01
PD-L1 High Positive	32%	30%	=.01

*when *CDKN2A/B* GA are excluded.

9117 **Poster Session**

Superior overall survival (OS), progression-free survival (PFS), and clinical response (CR) predictions for patients with non-small cell lung cancer (NSCLC) using Cellworks Singula: myCare-022-05.

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Background: The Cellworks Singula Therapeutic Response Index (TRI) has been developed to assist clinicians and NSCLC patients in choosing between competing therapeutic options. In contrast to approaches that consider single aberrations, which often yield limited benefit, Cellworks utilizes an individual patient's next generation sequencing results and a mechanistic multi-omics biology model, the Cellworks Omics Biology Model (CBM), to biosimulate downstream molecular effects of cell signaling, drugs, and radiation on patient-specific *in silico* diseased cells. For any individual patient and alternative therapy, Cellworks integrates this biologically modeled multi-omics information into a continuous Singula TRI Score, scaled from 0 (low therapeutic benefit) to 100 (high therapeutic benefit). We demonstrate that Singula is strongly associated with overall survival, progression-free survival and relative therapeutic benefit beyond standard clinical factors, including patient age, gender, and physician prescribed treatments (PPT). **Methods:** In this study, Singula's ability to predict response was evaluated in a retrospective cohort of 446 NSCLC patients with OS, PFS, and CR data from The Cancer Genome Atlas (TCGA) project, treated with PPT. As a primary analysis of the CBM and TRI Score, Cox Proportional Hazards (PH) regression and likelihood ratio (LR) tests were used to assess the hypothesis that Singula is predictive of OS, PFS, and CR above and beyond standard clinical factors. A p-value < 0.05 for the corresponding likelihood ratio statistic was required to be considered significant. **Results:** Multivariate analyses were performed to assess the performance of the Singula Therapy Response Index above and beyond physician's choice of treatment. The same Singula TRI algorithm and clinical cutoffs were used for all clinical outcome measures. For OS the median survival times for the high and low benefit groups were 60.16 and 28.57 months respectively, based on the median Singula value. Also, the hazard ratio per 25 Singula units for OS was 0.5103 (95% CI: 0.3337 - 0.7804) and the odds ratio for CR was 1.6161. These and further analyses, shown in Table, suggest that Singula TRI provides predictive value of OS, PFS, and CR above and beyond standard clinical factors. **Conclusions:** The Singula TRI Score provides a continuous measure for alternative NSCLC therapeutic options. In this retrospective cohort, Singula was strongly predictive of OS, PFS, and CR and provided predictive value of OS beyond PPT, patient age and gender. These results will be further validated in prospective clinical studies. Research Sponsor: None.

	OS	OS	PFS	PFS	CR	CR
LR Test	χ^{21}	p-value	χ^{21}	p-value	χ^{21}	p-value
Singula TRI	10.0120	0.0016	3.8579	0.0495	6.9185	0.0085

LR Analysis for TRI; OS and CR multivariate analysis; PFS univariate analysis.

9118 **Poster Session**

Use of brain radiotherapy as part of first course of treatment for NSCLC with de novo brain metastasis.

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Background: Loco-regional management of brain metastases from non-small cell lung cancer (NSCLC) are surgery and/or brain radiotherapy, either whole brain (WBRT) or stereotactic (SRS). We used a national registry to evaluate trends in the use of brain radiotherapy as part of the first course of management in patients diagnosed with de novo brain metastasis. **Methods:** We retrospectively analyzed the National Cancer Database (NCDB) to identify patients with NSCLC and de novo brain metastasis diagnosed from 2004-2016. We described the socio-demographic and clinical characteristics of this population, then used chi-squared testing to evaluate for an association between these variables and the use of brain radiotherapy (either SRS or WBRT). Significant variables ($p < 0.05$) were included in a multiple logistic regression model. **Results:** Of n = 41,454 patients with NSCLC and de novo brain metastasis, n = 27,949 (67.4%) received either SRS or WBRT as part of their first course of treatment, while n = 13,505 (32.6%) did not receive primary brain radiation. Of those that did not receive radiation: n = 9,927 (73.5%) were < 70 years old while n = 3,578 (26.5%) were ≥ 70. N = 11,081 (82.7%) were White, n = 1,550 (11.6%) were Black and n = 768 (5.7%) were Asian. Variables significantly associated with the use of primary brain radiotherapy at the multivariate level were: treatment facility type ($p = 0.004$), tumor histology ($p < 0.001$), clinical T-staging ($p < 0.001$), and clinical N-staging ($p < 0.001$). Age, sex, race, comorbidity, grade, insurance status, and setting (metro vs. rural vs. urban) were not significantly associated with the use of radiotherapy. Compared to patients treated at community cancer programs (CPs), those treated at comprehensive community CPs (OR 1.152, 95% CI 1.027-1.291, $p = 0.015$) and academic CPs (OR 1.242, 95% CI 1.104-1.398, $p < 0.001$) were more likely to receive primary brain radiotherapy. Patients with squamous NSCLC were less likely (OR 0.680, 95% CI 0.619-0.747, $p < 0.001$) to receive brain radiotherapy compared to those with adenocarcinoma. Finally, patients with advanced T-staging ($p < 0.001$) and N-staging ($p < 0.001$) were less likely ($OR < 1$) to receive brain radiotherapy as part of the first course of treatment. **Conclusions:** While insurance status and setting were not significantly associated with the use of brain radiotherapy, facility type was. Further research is needed to evaluate whether this is a true disparity in medical practice, or the differences can be explained by characteristics of the patient population undocumented by the NCDB (e.g. severity of brain metastasis). Additionally, patients with larger primary tumors were less likely to receive brain radiation as part of the first course of treatment, which may reflect the need for local therapy prior to treating metastatic sites. Research Sponsor: None.

9119 **Poster Session**

Clinicopathologic, genomic, and tumor microenvironment correlates of aneuploidy and immunotherapy outcomes in NSCLC.

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Background: Cancer aneuploidy, an unbalanced number of chromosomes, is associated with somatic mutation rate, expression of proliferative genes, and altered immune signaling. Whether aneuploidy correlates to a distinct immunophenotype or impacts clinical outcomes to immune checkpoint inhibitors (ICIs) in NSCLC is unclear. **Methods:** In NSCLCs which underwent targeted next-generation sequencing, we retrospectively analyzed the aneuploidy score (AS), defined as the sum of the number of altered chromosome arms. An unbiased recursive partitioning (URP) algorithm was used to investigate an AS cutoff to discriminate responders from non-responders to ICIs. Multiplexed immunofluorescence to quantify CD8+, Foxp3+, PD-1+, and PD-L1 expression was performed to determine differences in tumor immune cells subsets according to AS cutoff. **Results:** Among 436 NSCLCs identified, stage I tumors (median AS 1) had significantly lower median AS (mAS) than stage IV cancers (mAS 7, $P < 0.001$), stage III (mAS 4, $P = 0.03$), and numerically lower compared to stage II cancers (mAS 3, $P = 0.18$). We found no difference in the mAS across tumors with a PD-L1 tumor proportion score of $\geq$50%, 1-49%, or $<$ 1% (mAS 5 vs 7 vs 6, respectively, $P = 0.26$), nor was there any correlation between aneuploidy and TMB when taken as continuous variables (Spearman R: 0.074, $P = 0.12$). A total of 279 advanced NSCLCs with available aneuploidy scores were treated with ICIs. An URP analysis identified an AS of 2 as the strongest discriminator of objective response to ICI. Compared to pts with an AS $>$ 2 (N = 207, 74.2%), pts with AS $\leq$2 (N = 72, 25.8%) had a significantly higher objective response rate (ORR 43.0% vs 19.8%, $P < 0.001$), a significantly longer median progression-free survival (mPFS 6.2 vs 2.9 months, HR: 0.70 [95% CI: 0.52-0.94], $P = 0.02$), and a significantly longer median overall survival (mOS 19.8 vs 13.8 months, HR: 0.66 [95% CI: 0.47-0.94], $P = 0.02$) to treatment with ICIs. After adjusting for other variables such as performance status, presence of oncogenic driver mutation, PD-L1, TMB, and line of treatment, AS was significantly associated with improved mPFS (HR: 0.72 [95% CI: 0.52-0.99], $P = 0.04$) and mOS (HR: 0.64 [95% CI: 0.44-0.94], $P = 0.02$). By contrast, among pts who received first-line platinum doublet chemotherapy without ICI, an AS $\leq$2 (N = 29), when compared to an AS $>$ 2 (N = 56), did not correlate with improved ORR (55.2% vs 44.6%, $P = 0.4$) or PFS (5.3 vs 4.8 months, HR 0.83 [95% CI: 0.5-1.3], $P = 0.43$). Among 179 NSCLCs profiled by multiplex immunofluorescence, compared to cancers with an AS $>$ 2, those with low aneuploidy had significantly higher numbers of CD8+, Foxp3+, PD-1+ immune cells, and PD-1+ CD8+ T cell, both intratumorally and when looking at the total numbers of cells within the tumor and at the tumor-stroma interface. **Conclusions:** NSCLCs with low aneuploidy have a distinct immune microenvironment and more favorable outcomes to ICIs. Research Sponsor: None.

9120 **Poster Session**

Population-based impacts of new therapies on outcomes for stage IV non-small cell lung cancer.

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Background: Over 15 years, diagnostic and therapeutic algorithms for Stage IV non-small cell lung cancer (NSCLC) have dramatically progressed. While clinical trials demonstrate overall survival (OS) advantages, population level impact remains uncertain. Here we evaluate real world, population-based outcomes for Stage IV NSCLC to assess impact of changing therapies on referral, treatment patterns and OS, which may help explain ongoing stigma/nihilism. **Methods**: A retrospective cohort analysis was completed to evaluate *de novo* Stage IV NSCLC diagnosed in Manitoba from 2006 to 2015. We evaluated treatment received (not seen by specialist, saw a specialist but did not receive therapy, radiation therapy (RT) only, and systemic therapy (mutation unknown and known)) and treatment era of diagnosis (2006-2009, 2010-2013 and 2014-2015). Multivariable logistic regression assessed systemic therapy predictors. Kaplan-Meier curve and Cox proportional hazard models evaluated OS. **Results**: 3,601 patients were diagnosed with Stage IV NSCLC, 53% male. Only 21% received systemic therapy, mean age of 62. Within the cohort, 973 (27%) patients did not see a specialist, 610 (17%) saw a specialist but did not receive therapy, 1248 (35%) only received RT, and 771 (21%) received systemic therapy (17% mutation status unknown and 4% known). Younger patients and those with confirmed histology were more likely to see a specialist and receive treatment, each ($p < 0.001$). Patients who received systemic therapy had lower comorbidity and higher income quintile, each ($p < 0.001$). Median OS did not differ between treatment era with median OS of 3.0, 2.9 and 2.8 months for 2006-2009, 2010-2013 and 2014-2015 respectively, $p = 0.082$. When survival analysis was restricted to patients who received systemic therapy, median OS improved by era to 10.9, 11.2 and 15.6 months respectively, $p = 0.001$. Variables found to be independently associated with survival included treatment type, age, sex and comorbidity. **Conclusions**: Improved systemic therapy and molecular testing has improved OS for patients who receive systemic therapy. However, due to the large proportion of Stage IV NSCLC patients who never receive systemic therapy we do not see improved survival at a population level between treatment eras. Research Sponsor: CancerCare Manitoba Foundation.

9121 **Poster Session**

Clinicopathologic and genomic correlates of tumor-infiltrating immune cells and immunotherapy efficacy in NSCLC.

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Background: Tumor-infiltrating immune cells and PD-L1 expression are associated with improved clinical outcomes in patients (pts) with NSCLC treated with immune checkpoint inhibitors (ICIs). However, as tumor-infiltrating immune cells are not a well-established biomarker for NSCLC, further data are needed to integrate and identify clinicopathological and genomic factors that influence the tumor microenvironment. **Methods:** We collected clinicopathologic and genomic data from pts with NSCLC who underwent multiplexed immunofluorescence. Uniform Manifold Approximation and Projection (UMAP) was used to identify distinct immunophenotypic clusters according to the number of intratumoral PD-1+ immune cells (ICs), CD8+, and Foxp3+ T cells, as well as PD-L1 on tumor and immune cells. An unbiased recursive partitioning (URP) algorithm was used to investigate an optimal cluster with respect to objective response rate (ORR) in the subset of pts treated with ICIs. **Results:** Among 304 pts, UMAP identified 5 clusters: PD-L1-high with high vs low CD8+ and PD-1+ ICs (clusters A & B, respectively); PD-L1-low with high vs low CD8+ and PD-1+ ICs (clusters C & D respectively); PD-L1-low and moderate levels of CD8+ and PD-1+ ICs (cluster E). Clinicopathological characteristics of the clusters shown in Table. URP analysis identified immune rich clusters A and C as optimal responders to ICIs. From the start of ICIs, we observed a significantly higher ORR (53.3% vs 4.3%; P<0.001), a significantly longer median progression-free survival (mPFS 25.6 vs 3.7 months; HR: 0.12 [95% CI: 0.05-0.32]; P<0.001), and longer median overall survival (mOS 45.1 vs 22.3 months; HR: 0.25 [95% CI: 0.1-0.68]; P=0.006) in clusters A + C (N=15) vs other clusters (N=23). After adjusting for other variables such as performance status, histology, presence of oncogenic driver mutation, and line of treatment, clusters A + C were significantly associated with improved mPFS (HR: 0.08 [95% CI: 0.03-0.24], P<0.001) and mOS (HR: 0.11 [95% CI: 0.03-0.40], P<0.001). **Conclusions:** Incorporation of multiplex immunofluorescence may improve prediction of response and resistance to immunotherapy in NSCLC. Research Sponsor: None.

	Clusters					
Clinical Characteristics	A N=54	B N=53	C N=64	D N=67	E N=69	P
PD-L1 expression	High	High	Low	Low	Low	
CD8+, PD-1+	High	Low	High	Low	Moderate	
Smoking status	50 (92.6)	39 (73.6)	58 (90.6)	45 (67.2)	46 (67.7)	<0.001
Current/Former	4 (7.4)	14 (26.4)	6 (9.4)	22 (32.8)	23 (33.3)	
Never						
TMB, median (mut/Mb)	9.6	8.4	9.1	6.1	6.8	0.06
Oncogene Driver	14 (41.2)	10 (28.5)	22 (48.8)	9 (20.5)	14 (29.8)	<0.001
KRAS	4 (11.8)	9 (25.7)	3 (6.7)	9 (29.5)	21 (44.7)	
EGFR	4 (11.8)	0 (0.0)	3 (6.7)	0 (0.0)	2 (4.2)	
BRAF	4 (11.8)	8 (22.9)	4 (8.9)	8 (18.2)	4 (8.5)	
Other drivers	8 (23.4)	8 (22.9)	13 (28.9)	14 (31.8)	6 (12.8)	
None identified						
Stages						
I/II	30 (55.6)	18 (34.0)	45 (70.3)	24 (35.8)	39 (56.5)	0.02
III/IV	24 (44.4)	35 (66.0)	19 (29.7)	43 (64.2)	30 (43.5)	

Patterns of survival in NSCLC with de novo brain metastasis: SRS, WBRT, and no radiotherapy cohorts.

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Background: Prognostic determinants in metastatic non-small cell lung cancer (mNSCLC) include numerous sociodemographic and clinical characteristics. We provide granular, real-world survival data in different cohorts of this heterogeneous population, stratifying by: age, Charlson/Deyo scoring (CDS) of comorbidity, tumor histology, and use of immunotherapy. **Methods**: This retrospective analysis uses the National Cancer Database (NCDB) to explore patterns of survival in patients diagnosed between 2010-2016 with mNSCLC involving the brain. Kaplan-Meier (KM) modeling was used to evaluate for differences in overall survival (OS) between 3 cohorts of patients: those undergoing 1) stereotactic radiosurgery (SRS), 2) whole-brain radiotherapy (WBRT), and 3) those not undergoing brain radiotherapy (NR) as part of the first course of treatment. As per Table, we ran 8 KM models to generate median OS (mOS) data across stratifications for age (<70 vs. ≥ 70), CDS (0-1 vs. 2-3), tumor histology (adenocarcinoma vs. squamous), and use of immunotherapy (yes vs. no). We provide a ranked order of these 3 cohorts by mOS ('survival sequence', or 'SS'), as well as differences in mOS ('ΔmOS') between NR and WBRT – the two cohorts most comparable in life expectancy. **Results:** A total of n=38,119 patients were included in this study. Most received WBRT (n=18,052, 47.4%), n=6,562 (17.2%) received SRS, while n=13,505 (35.4%) did not receive brain radiation as part of their first course of treatment. In all subgroups, patients treated with SRS for brain metastasis had the highest mOS. Survival for those receiving WBRT was better or comparable (difference in mOS <0.5 months) to those that did not receive radiotherapy, except in patients aged ≥ 70 (SS: NR $>$ WBRT; KM p-value <0.05; ΔmOS of 1.6 months), those with Charlson-Deyo comorbidity scores of 2-3 (SS: NR $>$ WBRT; KM p-value <0.05; ΔmOS: 0.6 months), those with squamous carcinoma (SS: NR $>$ WBRT; KM p-value <0.05; ΔmOS: 0.7 months), and those already receiving immunotherapy (SS: NR $>$ WBRT; KM p-value <0.05; ΔmOS: 0.6 months). **Conclusions:** SRS for de novo brain metastases is associated with improved OS in mNSCLC. In contrast, the burden of WBRT may outweigh the survival benefit it affords in patients ≥ 70, and those with comorbidities. Squamous cell carcinomas may be associated with more radio-resistance than adenocarcinomas to WBRT. Finally, as previously described in melanoma, the survival benefit afforded by brain radiotherapy may be lower in patients on immunotherapy. Research Sponsor: None.

Stratifications	Kaplan Meier Models	NR mOS	SRS mOS	WBRT mOS	SS	ΔmOS (WBRT-NR)
Age	1) <70	8.9	14.5	9.2	SRS > WBRT > NR	0.3
	2) ≥ 70	7.7	11.7	6.1	SRS > NR > WBRT	-1.6
CDS	3) 0-1	8.8	13.8	8.7	SRS > NR = WBRT	-0.1
	4) 2-3	7.1	10.6	6.5	SRS > NR > WBRT	-0.6
Histology	5) Adenocarcinoma	9.9	15.5	9.5	SRS > NR > WBRT	-0.4
	6) Squamous	6.9	9.3	6.2	SRS > NR > WBRT	-0.7
Immunotherapy	7) None	8.5	13.3	8.4	SRS > NR = WBRT	-0.1
	8) Received	11.5	15.7	10.9	SRS > NR > WBRT	-0.6

9123 **Poster Session**

Analysis of patterns of care and benefit of thoracic radiotherapy for patients with stage IV NSCLC in the immunotherapy-era from a national hospital-based registry.

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Background: Metastatic non-small cell lung cancer (mNSCLC) has classically been treated with platinum-doublet chemotherapy. Recent studies have established immunotherapy as an integral part of therapy for mNSCLC without targetable mutations. There are limited data on the role of consolidative thoracic radiotherapy (TRT) for patients with mNSCLC in the immunotherapy-era. A secondary analysis of KEYNOTE-001 showed significant improvement in overall survival in patients who received radiotherapy with pembrolizumab compared to patients not previously receiving radiotherapy. **Methods:** We queried the National Cancer Database (NCDB) for patients with metastatic presentation, stage IVA/IVB non-small cell lung cancer between the ages of 18-90 years treated between 2012-2017 with a combination of chemotherapy, immunotherapy, and thoracic radiotherapy. Patients with unknown treatment status, follow up time, or vital status were excluded. Overall survival (OS) was estimated using the Kaplan-Meier method and compared between treatment groups utilizing log-rank testing. A 3:1 nearest-neighbor propensity-score matching was performed utilizing clinical and demographic covariates to reduce the impact of potential confounders of overall survival on the probability of receipt of TRT. Cox proportional hazards regression was used to identify predictors of overall survival. **Results:** A total of 81,382 patients were identified that met inclusion criteria. The median age was 68 (18-90) years. The majority of patients (n = 51,681, 64%) had chemotherapy, while 7,929 (10%) patients received immunotherapy, and 15,984 (20%) received TRT. The median follow-up was 6.18 (range 0-76.9) months. For the entire cohort of patients receiving immunotherapy, 2 year OS was 29.4% with TRT compared to 32.7% without. Following propensity matching by age, sex, race, and comorbidity score, a total number of 4,264 patients receiving immunotherapy were matched. The 2 year OS was 27.7% in patients receiving TRT and immunotherapy vs. 22.2% in patients with immunotherapy alone ($p = 0.004$). On multivariable analysis receipt of TRT was a significant predictor of OS after adjustment for age, race, comorbidity score, sex, and median income ($p = 0.0003$, HR 0.87, 95% CI 0.80 - 0.94). For patients receiving BED10 $>$ 39 Gy (equivalent to 30 Gy in 10 fractions), 2 year OS was significantly improved at 37.0% vs 18.1% ($p < 0.0001$). **Conclusions:** In patients with mNSCLC, the addition of TRT to immunotherapy is associated with improved overall survival at 2 years. Receipt of a higher BED10 is associated with further improved survival. Selection of mNSCLC patients receiving immunotherapy for TRT approaching definitive doses warrants further investigation. Data from prospective, randomized trials may better elucidate this benefit and identify a potential mechanism. Research Sponsor: None.

Effect of continuing osimertinib with chemotherapy in the post-progression setting on progression-free survival among patients with metastatic epidermal growth factor receptor (EGFR) positive non-small cell lung cancer.

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Background: Continuing a 1st generation EGFR TKI with chemotherapy upon TKI progression was not shown to be beneficial in the IMPRESS trial. However, the validity of this approach with osimertinib remains under explored. We attempted to characterize the efficacy of continuing osimertinib with chemotherapy in the post-progression setting. **Methods:** A single-center retrospective review of patients with metastatic EGFR mutant NSCLC who had progressed on osimertinib was performed. Clinical characteristics and treatment outcomes were noted. Progression free survival (PFS), duration of treatment (DOT), overall survival (OS) and rates of intracranial progression were captured. ANOVA or a Fisher exact test were used to identify associations between cohort characteristics and treatment outcomes. Differences in PFS, DOT and OS were assessed using a log-rank test. A Cox proportional hazard model was used to adjust for potential confounders. **Results:** 73 patients with EGFR mutant NSCLC with post-osimertinib treatment outcomes were identified. Cohort characteristics are summarized in Table. Median duration of follow up was 41 months. Upon progression, osimertinib was discontinued in 34 patients (Cohort A) and continued with next line of therapy in 39 patients (Cohort B). Survival analyses were adjusted for prior lines of therapy, use of platinum doublet chemotherapy, and use of immune checkpoint inhibitors in the post-progression setting. After adjusting for covariates, continuing osimertinib post-progression was associated with an improved PFS (7 vs 4 months; HR 0.58; 95% CI 0.34 – 1.00; p = 0.003) and DOT (7 vs 4 months; HR 0.52; 95% CI 0.31 – 0.87; p = 0.006). There was no difference in OS between Group A and B (52 vs 41 months; HR 0.73; 95% CI 0.43 – 1.24; p = 0.234). Rates of intracranial progression were similar between Group A and B (28% vs 23%; p = 0.649). **Conclusions:** After adjusting for covariates, continuing osimertinib with chemotherapy in the post-progression setting was associated with a significant difference in PFS and DOT, but with no differences in OS. Continuing osimertinib does not appear to influence the rate of subsequent intracranial progression. Prospective studies are needed to identify the optimal practice pattern. Research Sponsor: International Association for the Study of Lung Cancer (IASLC).

Variables	Values	Osimertinib discontinued (%)	Osimertinib continued (%)	P-value
Sex	Female	22 (64%)	27 (69%)	0.803
	Male	12 (35%)	12 (30%)	
Age (years)		61 (36 – 86)	61 (30 – 78)	0.512
Smoking Status	Never	28 (82%)	29 (74%)	
	Former	6 (18%)	10 (26%)	0.317
EGFR	Drug-sensitizing	32 (94%)	33 (85%)	0.110
	Atypical	2 (6%)	6 (15%)	
Prior lines of therapy		2 (1 – 6)	2 (1 - 8)	0.934
ECOG	0-1	32 (94%)	31 (79%)	0.468
	>2	2 (6%)	8 (21%)	
Brain metastases upon osimertinib progression	Present	6 (18%)	6 (15%)	0.704
	Absent	16 (47%)	15 (38%)	
	Not evaluated	12 (35%)	18 (46%)	

9125 **Poster Session**

Lung cancer in HIV versus non-HIV population: Nationwide analysis of mortality, morbidity, demographics, and healthcare utilization.

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Background: Lung cancer (LC) is the most common non-AIDS defining cancer with a high cancer-related mortality in patients with HIV. With improving survival in HIV patients, the incidence of LC is increasing. We attempted to evaluate the characteristics and outcomes, including healthcare utilization in patients with HIV-LC compared to non-HIV-LC using a national sample. **Methods:** Healthcare Cost and Utilization Project National Inpatient Sample (HCUP-NIS) was queried to identify HIV and non-HIV-LC admissions between 2016-2018. We studied socio-demographic differences, medical comorbidities (including hypertension (HTN), diabetes (DM), Coronary artery disease (CAD), Chronic kidney disease (CKD), Heart failure (HF), dialysis (HD), COPD), all-cause mortality, mean length of stay (LOS), mean total hospital charges (THC). Secondary outcomes included sepsis, septic shock, acute kidney injury (AKI), influenza, pneumonia, respiratory failure, lung collapse, ICU care, hemoptysis, anemia, pain, and protein energy malnutrition (PEM). Statistics were performed using the t-test, univariate and multinomial logistic regression. **Results:** A total 4,105 HIV-LC and 1,204,365 non-HIV-LC admissions were identified. HIV-LC were younger (mean age 48.7 vs 53.4 $p<0.05$), male (67% vs 51%, $p<0.01$), African American (52% vs 12% $p<0.01$), on Medicaid (35% vs 10% $p<0.01$), from lowest quartile income zip codes (51% vs 30% $p<0.01$). HIV-LC had significantly high rates of CKD and HD ($p<0.05$) while non-HIV-LC had significantly higher rates of HTN, DM, Dyslipidemia, CAD, COPD, obesity, HF and smoking (all $p<0.05$). Odds of adjusted all-cause mortality were significantly lower in HIV-LC (aOR 0.47 CI 0.36-0.63 $p<0.001$). HIV-LC had higher LOS (8.1 vs 6 days $p<0.001$) and higher THC ($83,328 vs $65,642 $p<0.001$), amounting to over $72 million over 3 years. Significantly different secondary outcomes between the two groups are shown in Table, the rest were similar between the groups. **Conclusions:** HIV-LC patients were younger, minority with a significantly lower all-cause mortality despite higher rates of complications and significantly higher LOS and THC compared to non-HIV-LC cohort. A higher comorbidity burden may be responsible for higher mortality in the non-HIV group while higher rates of secondary complications, CKD, HD may be driving up healthcare utilization in HIV-LC. More studies are needed to clarify these findings. Research Sponsor: None.

	HIV-LC	non-HIV-LC	p-value
Sepsis	18.5%	12.6%	0.00
Septic shock	19%	14.2%	0.00
AKI	16.5%	3.2%	0.00
Pneumonia	27.8%	21.1%	0.00
Hemoptysis	5%	3.4%	0.01
Anemia	42.4%	35.6%	0.00
ICU care	7.7%	5.9%	0.049
PEM	37.2%	23.2%	0.00

TPS9126 **Poster Session**

Blood-based biomarker analysis in high PD-L1 expressing NSCLC treated with PD-1/PD-L1 based therapy with or without the addition of platinum-based chemotherapy.

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Background: Immunotherapy directed against the programmed death-1 / ligand-1 (PD-1/L1) axis has revolutionized the treatment of advanced non-small cell lung cancer (aNSCLC). Tumor PD-L1 is currently the only biomarker validated for predicting patient response to front line PD-1/L1 directed immunotherapy, yet 20% of patients with ≥50% PD-L1 expression die within six months of starting therapy (Reck et al. 2016). Blood-based agents such as autoantibodies and circulating inflammatory biomarkers have stratified patient outcomes on anti-PD-1/L1 immunotherapy in preliminary studies (Tarhoni, Kollipara et al. 2019; Tarhoni, Fidler et al. 2019). Moreover, a serum-based proteomic test that uses mass spectrometry and machine learning to provide three classifications (Good, Intermediate and Poor) has stratified non-treatment naïve aNSLCC patients treated with nivolumab based on their outcomes (Mueller et al. 2020) and identified a subset of patients who progressed rapidly. This study will evaluate these blood-based biomarkers as predictors of response and early progression in patients with >50% PD-L1 positive aNSCLC treated with immunotherapy regimens. **Methods:** This is a prospective, observational, multicenter study (NCT04676386) designed to assess biomarkers (serum and plasma) as predictive of early progression in 390 patients with aNSCLC treated with anti-PD 1/PD-L1 immunotherapy with or without platinum-based chemotherapy. Key eligibility criteria are treatment naïve aNSCLC with tumor biopsy PD-L1 tumor proportion score > 50%, Eastern Cooperative Oncology Group performance status (ECOG PS) 0-2, and ability to consent to participate. Prior to enrollment, tumor specimens will be tested for PD-L1 expression according to participating centers' standard operating procedures. For each treatment cohort of 195 patients, enrollment will proceed in sub-cohorts to ensure a population with 20% patients with ECOG PS2 and a total of 40 patients with squamous cell carcinoma per treatment arm. Patients will be followed for a maximum of 3 years. Blood draw for biomarker assessment will be performed prior to treatment initiation, start of 3rd cycle and investigator assessed progression. Biomarker analysis will be performed retrospectively. As a secondary objective, this study will evaluate proteomic test performance in predicting early overall survival (OS) and rapid progression, and in stratifying patient survival and response. Exploratory analyses will correlate baseline and serial circulating protein analytes and autoantibodies with the proteomic test, response measures (RECIST 1.1) and toxicities. Enrollment opened in February 2021. Clinical trial information: NCT04676386. Research Sponsor: Biodesix, Inc.

TPS9127 **Poster Session**

A randomized, phase 3 study of datopotamab deruxtecan (Dato-DXd; DS-1062) versus docetaxel in previously treated advanced or metastatic non-small cell lung cancer (NSCLC) without actionable genomic alterations (TROPION-Lung01).

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Background: Treatment options are limited for patients with advanced/metastatic NSCLC without driver genomic alterations after failure of a platinum-based chemotherapy and immunotherapy; median survival is < 1 year. Datopotamab deruxtecan (Dato-DXd; DS-1062) is an antibody-drug conjugate consisting of a humanized anti-TROP2 IgG1 monoclonal antibody attached to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker. Results from the ongoing phase 1 study (TROPION-PanTumor01; Spira, WCLC 2020) demonstrated an overall response rate (ORR) of 21%, a disease control rate (DCR) of 67%, and a preliminary median progression-free survival (PFS) of 8.2 months (all by blinded independent central review [BICR]), with a manageable safety profile, in patients with NSCLC who were treated with 6 mg/kg of Dato-DXd. This phase 3 study (NCT04656652) will compare the efficacy of Dato-DXd with that of docetaxel as 2/3L therapy in patients with advanced/metastatic NSCLC.
Methods: TROPION-Lung01 is an open-label, phase 3, randomized study of Dato-DXd vs docetaxel in patients with advanced/metastatic NSCLC without *EGFR*, *ALK*, or other actionable genomic alterations. Patients must have been previously treated with platinum-based chemotherapy and a PD-(L)1 monoclonal antibody in combination or sequentially and have radiographic disease progression on or after the most recent therapy. Those with asymptomatic and stable/treated brain metastases are eligible. A tumor specimen is required for biomarker analyses. Patients (N = 590) are randomized 1:1 to either Dato-DXd 6 mg/kg or docetaxel 75 mg/m^2 given intravenously on day 1 of each 3-week cycle. Randomization is stratified by histology (squamous vs nonsquamous), immunotherapy in last regimen (yes vs no), and region (US/Japan/Western Europe vs rest of world). Treatment continues until disease progression or intolerance or other discontinuation criteria are met. The study will be conducted globally at approximately 184 study sites. Dual primary endpoints are PFS by BICR and overall survival. Secondary outcome measures include PFS by investigator, ORR, duration of response, DCR, and time to response (all assessed by BICR and by investigator per RECIST version1.1), patient-reported outcomes, safety, pharmacokinetics, and proportion of patients who develop antidrug antibodies. Biomarkers will be evaluated for potential associations with efficacy. Clinical trial information: NCT04656652. Research Sponsor: Daiichi Sankyo, Inc.

TPS9128 **Poster Session**

AdvanTIG-302: Anti-TIGIT monoclonal antibody (mAb) ociperlimab (OCI) plus tislelizumab (TIS) versus pembrolizumab (PEM) in programmed death ligand-1 (PD-L1) selected, previously untreated, locally advanced, unresectable or metastatic non-small cell lung cancer (NSCLC).

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Background: Monotherapy with programmed death 1 (PD-1)/PD-L1 antibodies has improved clinical outcomes for patients (pts) with non-oncogenic driven NSCLC but clinical responses are limited by primary and secondary resistance, and improvements in durability of response are required. T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain (TIGIT) is a co-inhibitory, immune checkpoint receptor upregulated on T-cells and natural killer cells in multiple solid tumors, which can inhibit anticancer immune responses. OCI (BGB-A1217) is a novel, humanized mAb that binds to TIGIT with high affinity and specificity, which has demonstrated competent binding with C1q and all Fcγ receptors while inducing antibody-dependent cellular cytotoxicity. Preclinical and clinical studies suggest that dual targeting with anti-TIGIT and anti-PD-1 antibodies produces synergistic immune cell activation and enhanced antitumor activity. **Methods:** AdvanTIG-302 is a Phase 3, multicenter, international, randomized, double-blind study (NCT04746924) investigating OCI in combination with TIS compared with PEM in adult pts ($\geq$ 18 years of age) with PD-L1 selected, previously untreated, locally advanced, unresectable or metastatic NSCLC without oncogenic *EGFR* or *ALK* mutation. Approximately 605 pts will be randomized 5:5:1 to receive: OCI 900 mg intravenously (IV) plus TIS 200 mg IV every three weeks (Q3W; Arm A), PEM 200 mg IV plus placebo IV Q3W (Arm B) or TIS 200 mg IV plus placebo IV Q3W (Arm C). Pts will be treated until disease progression, loss of clinical benefit, intolerable toxicity or withdrawal of consent. Stratification factors include histology (squamous vs non-squamous) and region (Asian vs non-Asian). Cross-over is not permitted. Key eligibility criteria include histologically confirmed disease, PD-L1 expression $\geq$ 50%, no known *EGFR* or *ALK* mutations and no prior checkpoint inhibitor therapy. Dual primary endpoints are investigator-assessed progression-free survival (PFS; RECIST v1.1) and overall survival (Arms A and B) in the Intention-to-Treat population. Secondary endpoints include PFS (assessed by Blinded Independent Review Committee), investigator-assessed overall response rate and duration of response, safety and tolerability, and patient-reported health-related quality of life (EORTC-QLQ-C30, QLQ-LC13 and EQ-5D-5L; Arms A and B). Exploratory endpoints include disease control rate, clinical benefit rate and time to response. This study will also evaluate the association between biomarkers and response or resistance. Study enrollment has begun and recruitment is ongoing. Clinical trial information: NCT04746924. Research Sponsor: This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Jessica Jones, PhD, of Ashfield Medcomms, an Ashfield Health company, and funded by BeiGene, Ltd.

TPS9129 **Poster Session**

KRYSTAL-12: A randomized phase 3 study of adagrasib (MRTX849) versus docetaxel in patients (pts) with previously treated non-small-cell lung cancer (NSCLC) with KRAS^{G12C} mutation.

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Background: Despite significant advances in chemotherapy and immunotherapy for advanced NSCLC, the majority of pts ultimately develop progressive disease associated with poor outcomes. KRAS is a key mediator of the RAS/MAPK signaling cascade that promotes cell growth and proliferation. KRAS^{G12C} mutations occur in 14% of NSCLC (adenocarcinoma), and mutations in KRAS are associated with a poor prognosis. Although KRAS has historically been undruggable, recent research into the development of agents that specifically bind mutant KRAS has led to the development of direct inhibitors of KRAS^{G12C}. Adagrasib, an investigational agent, is a potent, covalent inhibitor of KRAS^{G12C} that irreversibly and selectively binds to and locks KRAS^{G12C} in its inactive state. Adagrasib was optimized for favorable pharmacokinetic (PK) properties, including oral bioavailability, long half-life (~24 h), and extensive tissue distribution. Initial results have demonstrated encouraging antitumor activity and tolerability of adagrasib monotherapy in pts with NSCLC harboring a KRAS^{G12C} mutation. **Methods:** KRYSTAL-12 is a multicenter, randomized Phase 3 study evaluating the efficacy of adagrasib (600 mg BID) vs docetaxel in pts with advanced NSCLC harboring a KRAS^{G12C} mutation who have progressed during or after treatment with a platinum-based regimen and an immune checkpoint inhibitor. The study is designed to demonstrate improvement in the dual primary endpoints of progression-free survival (PFS) and overall survival (OS). Secondary endpoints include safety, objective response rate (ORR) per RECIST 1.1, duration of response (DOR), plasma PK parameters of adagrasib, and patient-reported outcomes (PROs). The study will also explore correlations between gene alterations (at baseline and upon development of treatment resistance) and efficacy. Approximately 450 patients will be randomized in a 2:1 ratio to receive adagrasib or docetaxel and will be stratified by region (United States/Canada vs other countries) and sequential vs concurrent administration of prior platinum-based chemotherapy and anti–PD-1/PD-L1 antibody. The planned sample size is sufficiently powered for the hypothesized treatment effect of the endpoints. Pts will receive study treatment until disease progression, unacceptable adverse events, investigator decision to terminate treatment, or patient withdrawal. This study is currently enrolling and will be open at sites in the United States, Europe, and Asia. Clinical trial information: NCT04685135. Research Sponsor: Mirati Therapeutics, Inc.

TPS9130 **Poster Session**

Camrelizumab monotherapy or in combination with apatinib for PD-L1-positive advanced pulmonary sarcomatoid carcinoma: A multicenter, open-label, single-arm, phase II study.

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Background: Pulmonary sarcomatoid carcinoma (PSC) is a rare subtype of non-small cell lung cancer (NSCLC) with a fairly poor prognosis. As a highly aggressive malignancy, PSC is insensitive to conventional chemotherapy or radiotherapy and no optimal treatment for PSC has been established yet. Immune checkpoint inhibitors (ICIs) were documented to possess encouraging therapeutic efficacy in PSC patients, which is demonstrated to be associated with high expression of programmed death-ligand 1 (PD-L1) in PSC. However, because of the rarity of PSC, most of the existed data were derived from case repots which could not reflect the true clinical efficacy of ICIs for PSC treatment. This clinical trial was designed to investigate the clinical outcomes of camrelizumab in treating PD-1-positive PSC. Apatinib may be used simultaneously based on the expression level of PD-L1 in PSC as the combination of camrelizumab and apatinib exhibited treatment potential in NSCLC in previous researches. **Methods:** In this multicenter, open-label, single-arm, phase II study conducted in 44 sites in China, 30 patients with an age of 18-80 years old, an Eastern Cooperative Oncology Group (ECOG) performance score of 0–2, positive PD-L1 expression, no EGFR, ALK, ROS1, and MET gene mutations, and histologically or cytologically confirmed stage IIIB-IV PSC regardless of prior lines of standard therapy will be enrolled. Patients with PD-L1 expression 1-49% will receive Camre (200 mg, IV, Q3W) and Apa (250mg, QD). Patients with PD-L1 expression≥50% receive Camre (200 mg IV Q3W) alone. The treatment will continue until a maximum treatment duration of 36 months, disease progression, intolerable toxicity, death or consent withdrawal. The primary endpoint is objective response rate (ORR). The secondary endpoints are progression-free survival (PFS), overall survival (OS), disease control rate (DCR), time to objective response (TTR), duration of response (DOR) and safety. This study is ongoing. Clinical trial information: ChiCTR2000032649, China. Research Sponsor: None.

TPS9131 **Poster Session**

A multicenter, randomized, double-blind study of gefitinib in combination with anlotinib or placebo in previously untreated patients with EGFR mutation-positive advanced non-small cell lung cancer (FL-ALTER).

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Background: Preclinical and clinical evidence has demonstrated that the dual blockade of the EGFR and VEGF pathways is a viable strategy in the EGFR-mutated advanced NSCLC population. Anlotinib is an oral multi-targeted tyrosine kinase inhibitor (TKI) that effectively inhibits VEGFRs, FGFRs, PDGFRs, c-kit and MET. It has been proved to be safe and effective in advanced lung cancer after second-line standard chemotherapy failure. A cohort study of Anlotinib plus Erlotinib has shown a favorable safety profile and promising antitumor activity with an objective response rate (ORR)92.6%. This phase III study aims to evaluate the efficacy and safety of Anlotinib or placebo plus Gefitinib in patients(pts) with untreated EGFR-mutated metastatic NSCLC. **Methods:** Eligible pts were aged 18~75 years old, had stage IIIB or IV NSCLC, with an EGFR 19del or 21L858R mutation, an ECOG PS of 0 or 1, measurable lesion according to RECIST v1.1 and adequate organ function. We randomly assigned eligible pts in a 1:1 ratio to receive oral Gefitinib (250 mg QD) plus either Anlotinib (12 mg QD from day 1 to 14 of a 21-day cycle) or matching placebo until progressive disease or unacceptable toxicity. Randomization was done by an interactive web response system with a computer-generated sequence and stratified by EGFR mutation status, gender, ECOG PS and pathological type. The primary endpoint is progression-free survival(PFS). Secondary endpoints include overall survival, ORR, disease control rate, time to progression, duration of response, quality of life and the safety profile. The peripheral blood of the pts will be detected three times by polygenic detection to monitor the resistance mechanism (before treatment, during the first evaluation, during tumor progression, each time 10ml peripheral blood). Independent Data Monitoring Committee and Independent Review Committee will be used in this study. According to previous report (Erlotinib plus Bevacizumab vs. Erlotinib alone: 16.0 vs. 9.7 mos, HR 0.54, *Lancet Oncol, 15(11):1236-1244*), the sample size was determined based on a median PFS of 15 months for the Anlotinib + Gefitinib group and median PFS of 10 months for the Placebo + Gefitinib group. To achieve 80% power at a two-sided $\alpha = 0.05$ and an anticipated dropout rate of 20%, 310 patients (with 192 events required for the analyses) were needed. In total, 310 patients will be enrolled in this trial at 16 sites in China. From April 2019, 224 patients have been enrolled. Clinical trial information: NCT04028778. Research Sponsor: None.

TPS9132 **Poster Session**

CHRYSALIS-2: A phase 1/1b study of lazertinib as monotherapy and in combination with amivantamab in patients with EGFR-mutant NSCLC.

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Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have improved clinical outcomes for patients with EGFR mutant (EGFRm) non-small cell lung cancer (NSCLC); however, patients will inevitably progress due to acquired resistance mutations. Lazertinib is a potent, brain-penetrant, 3rd-generation EGFR TKI with efficacy against activating EGFR and resistance T790M mutations. Amivantamab is an EGFR-MET bispecific antibody with immune cell-directing activity that targets activating EGFR and MET mutations. Synergistic inhibition of the EGFR by targeting the receptor's extracellular domain with amivantamab and the kinase domain with lazertinib, may lead to more potent inhibition of the EGFR pathway and potentially delay resistance. In the ongoing CHRYSALIS phase 1 study (NCT02609776), preliminary antitumor activity has been demonstrated with the combination of lazertinib and amivantamab in patients with treatment-naïve and osimertinib-relapsed EGFRm NSCLC (Cho *Ann Oncol* 2020;31:S813). **Methods:** CHRYSALIS-2 is an ongoing phase 1/1b open-label study of lazertinib as monotherapy and in combination with amivantamab in patients with advanced EGFRm NSCLC (NCT04077463; https://clinicaltrials.gov/ct2/show/NCT04077463). Phase 1 of the study has confirmed the safety and tolerability of lazertinib monotherapy in Japanese patients. The objective of phase 1b is to characterize the preliminary efficacy of lazertinib in combination with amivantamab in subpopulations of patients with EGFRm NSCLC (Phase 1b Expansion Cohorts) at the recommended combination dose of 1050 mg (1400 mg, ≥80 kg) IV amivantamab dosed weekly in cycle 1 (28-day cycle), every other week thereafter, and 240 mg oral lazertinib QD. Global enrollment in Phase 1b Expansion Cohorts is currently ongoing. Expansion Cohort A is enrolling patients who have progressed on 1st or 2nd-line osimertinib followed by platinum chemotherapy; Expansion Cohort B is enrolling patients with EGFR exon 20 insertion (Exon20ins) mutation who have progressed on prior therapy; and Expansion Cohort C is enrolling patients with uncommon non-Exon20ins EGFR mutations (i.e., S768I, L861Q, G719X) who are treatment-naïve or received 1st or 2nd-generation EGFR TKI as last therapy. The primary endpoints of the study are frequency of dose-limiting toxicity for phase 1 and 1b combination cohorts, and overall response rate for phase 1b expansion cohorts. Key secondary endpoints include safety (adverse events), pharmacokinetics, duration of response, clinical benefit rate, progression-free survival, and overall survival. Safety assessments will include monitoring AEs, clinical laboratory tests, ophthalmologic examination, ECG, and ECHO/MUGA. Blood samples will be collected to access PK. Tumor response will be assessed every 6 weeks by the investigator using RECIST, v1.1. Clinical trial information: NCT04077463. Research Sponsor: Janssen R&D.

TPS9134 **Poster Session**

CONTACT-01: A phase III, randomized study of atezolizumab plus cabozantinib versus docetaxel in patients with metastatic non-small cell lung cancer (mNSCLC) previously treated with PD-L1/PD-1 inhibitors and platinum-containing chemotherapy.

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Background: Patients with mNSCLC who progress on anti–PD-L1/PD-1 therapy administered in combination with or after platinum-based chemotherapy (PBC) are mainly treated with docetaxel or pemetrexed monotherapy. These therapies only have modest clinical activity, leaving a high unmet medical need. Cabozantinib, a tyrosine kinase inhibitor (TKI), promotes an immune-permissive environment and may enhance the efficacy of PD-L1/PD-1 inhibitors, offering a promising second/third-line therapeutic opportunity for patients with mNSCLC. In a Phase Ib multi-cohort study (COSMIC-021; NCT03170960), cabozantinib plus atezolizumab (anti–PD-L1) showed an acceptable safety profile and promising efficacy (ORR: 27%; mDOR: 5.7 mo [range: 2.6-6.9]; disease control rate [CR + PR + SD]: 83%) in 30 patients with mNSCLC who had progressed after prior anti–PD-L1/PD-1 therapy plus chemotherapy (Neal et al. J Clin Oncol 2020). The Phase III CONTACT-01 study will further evaluate the efficacy and safety of atezolizumab plus cabozantinib versus docetaxel monotherapy in patients with mNSCLC who have progressed during or after prior treatment with anti–PD-L1/PD-1 therapy and PBC. **Methods:** CONTACT-01 (NCT04471428) is a Phase III, multi-center, randomized, open-label study that will enroll ≈350 patients from 150 to 200 sites internationally. Key eligibility criteria include histologically or cytologically confirmed mNSCLC, disease progression with concurrent or sequential anti–PD-L1/PD-1 treatment and PBC, measurable disease (RECIST 1.1), ECOG PS of 0-1 and the availability of tissue specimens for centralized PD-L1 testing or known PD-L1 status using a health authority–approved PD-L1 assay. Patients with NSCLC previously treated with cabozantinib, docetaxel or anti–PD-L1/PD-1 + VEGFR TKIs are excluded. Patients with known sensitizing *EGFR/ALK* mutations and active or untreated CNS metastases are also excluded. Patients will be randomized 1:1 to receive either atezolizumab (1200 mg IV every 3 weeks) + cabozantinib (40 mg orally once daily) or docetaxel (75 mg/m^2 IV every 3 weeks). The primary endpoint is OS. Secondary endpoints include investigator-assessed PFS, ORR and DOR per RECIST 1.1; TTD in patient-reported physical function and global health status (EORTC QLQ-C30); investigator-assessed PFS rates at 6 months and 1 year; OS rates at 1 and 2 years; safety and PK. Clinical trial information: NCT04471428. Research Sponsor: F. Hoffmann-La Roche.

TPS9135 **Poster Session**

Phase I trial of *in situ* vaccination with autologous *CCL21*-modified dendritic cells (CCL21-DC) combined with pembrolizumab for advanced NSCLC.

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Background: Effective immunotherapy options are lacking for patients with advanced non-small cell lung cancer (NSCLC) who progress on a programmed cell death-(ligand)1 [PD-(L)1] inhibitor and for those that are epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement positive after progression on tyrosine kinase inhibitor (TKI) therapy. One potential approach to improve immune checkpoint efficacy in these patient populations is to promote cytolytic T cell infiltration into tumors. This can be accomplished via *in situ* vaccination with functional antigen presenting cells (APCs) which can take advantage of the full repertoire of tumor antigens and convert the tumor into a lymph node-like environment promoting both local and systemic T cell activation. The chemokine CCL21 promotes co-localization of naive T cells and antigen-experienced dendritic cells (DCs) to facilitate T cell activation. Our preclinical studies and phase I trial of intratumoral (IT) administration of DC genetically modified to overexpress CCL21 (CCL21-DC) revealed augmentation of tumor antigen presentation *in situ*, resulting in systemic antitumor immunity. However, increased PD-L1 expression was observed in some patient tumors, suggesting that tumor-mediated impairment of T cell function may be forestalling a more robust CCL21-DC mediated antitumor response. Similarly, improved PD-(L)1 inhibitor efficacy may be possible with enhanced T cell infiltration and augmented APC function following IT CCL21-DC. Therefore, we are conducting a phase I trial, combining IT CCL21-DC with pembrolizumab in patients with advanced NSCLC that are either (1) EGFR/ALK wild-type after progression on a PD-(L)1 inhibitor or (2) EGFR/ALK mutant after progression on TKI therapy. **Methods:** Phase I, dose-escalating, multi-cohort trial followed by dose expansion. Maximum of 24 patients (9-12 escalation + 12 expansion) with stage IV NSCLC will be evaluated who have tumors accessible for IT injection and are either (1) EGFR/ALK wild-type after progression on a PD-(L)1 inhibitor or (2) EGFR/ALK mutant after progression on TKI therapy. Three IT injections of autologous CCL21-DC (days 0, 21, 42) will be concurrently administered with pembrolizumab, followed by q3wk pembrolizumab up to 1 year. Primary objective of dose escalation is safety and determination of maximum tolerated dose (MTD) of IT CCL21-DC ($5x10^6$, $1x10^7$, or $3x10^7$) when combined with pembrolizumab. Primary objective of dose expansion is objective response rate at MTD. Secondary objectives include adverse event profiling and determination of drug target activity by immune monitoring studies. This trial, NCT03546361, is currently open for enrollment. Clinical trial information: NCT03546361. Research Sponsor: California Institute for Regenerative Medicine (CIRM).

TPS9136 **Poster Session**

Phase II two-arm study of tepotinib plus osimertinib in patients with *EGFR*-mutant NSCLC and acquired resistance to first-line osimertinib due to *MET* amplification: INSIGHT 2.

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Background: *MET*amp is a mechanism of acquired resistance to EGFR tyrosine kinase inhibitors (TKIs). *MET*amp occurs in ~30% of patients who progress on EGFR TKI therapy as measured using fluorescence in situ hybridization (FISH). There is an unmet need for targeted treatment options in these patients. Combination treatment with a MET TKI may overcome *MET*-related osimertinib resistance. Tepotinib is an oral, once daily (QD), highly selective, potent MET TKI. In the INSIGHT study (NCT01982955), the combination of tepotinib and the EGFR TKI gefitinib improved outcomes in patients with *EGFR*-mutant *MET*amp NSCLC and EGFR TKI resistance compared to chemotherapy (INSIGHT). Median progression-free survival (PFS) was 16.6 vs 4.2 months (hazard ratio [HR] = 0.13; 90% confidence interval [CI]: 0.04, 0.43) and median overall survival (OS) was 37.3 vs 13.1 months (HR = 0.08; 90% CI: 0.01, 0.51). **Methods:** INSIGHT 2 is a global, open-label, Phase II trial of tepotinib + osimertinib in patients with advanced *EGFR*-mutant NSCLC. Following a protocol amendment in Apr 2020, the study is enrolling patients with acquired resistance to 1L osimertinib (radiological documentation of disease progression following previous objective clinical benefit) due to *MET*amp by FISH (GCN $\geq$5 or MET/CEP7 ratio $\geq$2). Patients must be $\geq$18 years old, have an Eastern Cooperative Oncology Group performance status of 0/1, and normal organ function. Both tissue and liquid biopsy, obtained at the time of progression to osimertinib, will be sent for central confirmation of *MET*amp. Liquid biopsy samples will also be used for exploratory biomarker evaluation. Enrollment is allowed based on local FISH testing while awaiting central confirmation of *MET*amp. Patients will receive 500 mg QD (450 mg active moiety) tepotinib + 80 mg QD osimertinib until disease progression, unacceptable toxicity, or consent withdrawal. The study is anticipated to enroll 120 patients. The primary endpoint is objective response rate (ORR) by independent review (RECIST v1.1) in patients with *MET*amp, centrally confirmed by FISH. Secondary endpoints include ORR by investigator assessment, duration of response, disease control, PFS, OS, pharmacokinetics, health-related quality of life, tolerability, and safety. An exploratory tepotinib monotherapy arm will enroll 12 patients to assess the contribution of tepotinib to the activity of the combination. At progression (determined by independent review committee), monotherapy patients can switch to combination treatment. These patients will be analyzed separately. Recruitment is ongoing, with $>$ 300 patients prescreened. Approximately 100 sites in 17 countries in Europe, Asia, and North America are expected to participate. Approximately 15 sites will recruit patients in the US. Clinical trial information: NCT03940703. Research Sponsor: Merck KGaA, Darmstadt, Germany.

TPS9137 **Poster Session**

Phase 2 study of PD-1 inhibitor JTX-4014 alone and in combination with vopratelimab, an ICOS agonist, in biomarker-selected subjects with metastatic NSCLC after one prior platinum-containing regimen (SELECT).

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Background: Immune checkpoint inhibitors have led to durable remissions for some patients with advanced malignancies, including NSCLC; however, only a minority of patients benefit. The field of oncology is addressing this via the development of novel therapies, combinations and identification of biomarkers to select patients most likely to derive clinical benefit. ICOS, a novel therapeutic target, is a costimulatory molecule upregulated on activated T cells. Vopratelimab is an investigational IgG1 ICOS agonist monoclonal antibody that results in activation and proliferation of primed CD4 T effector cells. The preliminary efficacy of vopratelimab +/- nivolumab was assessed in the phase 1/2 ICONIC study in which durable responses were observed in a subset of patients who demonstrated on treatment emergence of peripheral ICOS hi CD4 T effector cells. Patients with peripheral ICOS hi CD4 T cells achieved significantly greater clinical benefit than patients whose CD4 T cells remained ICOS lo. An RNA based tumor inflammation signature (TIS) comprised of 18 genes associated with immune cell infiltration was previously identified as a predictive biomarker of response to anti-PD-1 therapy (Ayers et al, 2017); it was also associated with ICOS hi CD4 T cell emergence in ICONIC (ASCO-SITC 2020). The pre-treatment tumor TIS score, coupled with a specific threshold established by Jounce, referred to as TIS^{vopra}, was predictive of ICOS hi CD4 T cell emergence. TIS^{vopra} positive patients had improved RECIST response, PFS, and OS compared to those with a TIS^{vopra} negative score. Therefore, we hypothesize that patient selection by TIS^{vopra} will identify those who will display emergence of ICOS hi CD4 T cell populations and importantly, improved clinical outcomes when treated with vopratelimab in combination with JTX-4014 (a novel PD-1 inhibitor in development by Jounce) vs JTX-4014 alone. **Methods:** This Phase 2 open-label multicenter study is investigating JTX-4014 alone and in combination with vopratelimab in TIS^{vopra} selected patients with metastatic NSCLC after one prior platinum-containing regimen (NCT04549025). Patients must be PD-1/L1 inhibitor naïve and negative for activating EGFR mutations. TIS^{vopra} eligibility is determined using RNA isolated from a tumor sample. Eligible patients will be randomized to receive either JTX-4014 as monotherapy or in combination with one of two dose levels of vopratelimab. The primary endpoint is mean percent change from baseline tumor size of all measurable existing and new lesions averaged over 9 and 18 weeks. Secondary endpoints include ORR and PFS according to RECIST v1.1, OS, safety, and association of baseline TIS score with clinical outcomes. The study has a target enrollment goal of approximately 75 patients; the first patient was dosed October 2020. Clinical trial information: NCT04549025. Research Sponsor: Jounce Therapeutics.

TPS9138 **Poster Session**

An open-label, multicenter phase I/IIa study evaluating the safety and clinical activity of clonal neoantigen reactive T cells in patients with advanced non-small cell lung cancer (CHIRON).

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Background: Lung cancer is the most common cause of cancer-related death worldwide with over 1.6 million deaths per year. Non-small cell lung cancer (NSCLC) accounts for 80% of cases, the majority of which are adenocarcinomas. 75% of patients present with inoperable tumours and/or with distant metastatic spread, with 5-year survival for stage IV disease as low as 5%. Treatment options include chemotherapy, targeted therapies for specific mutations, and - increasingly - immune checkpoint inhibitors (CPI). Adoptive cell therapies (ACT) can produce durable responses in pre-treated NSCLC. Evidence also suggests potential benefit of combining ACT with CPIs, even after acquired resistance. Efforts to improve efficacy include the expansion of T cells able to recognise patient-specific clonal tumour neoantigens. Clonal tumour neoantigens arise early in cancer evolution and represent a subset of patient-specific mutations present in all cancer cells. Developing ACTs that target clonal neoantigens represents a personalised approach to treating all cancer cells concurrently, minimising the risk of tumour escape and reducing potential for off-target toxicities. Insights gained from applying the PELEUS bioinformatic platform (developed using UK TRACERx study data) to matched tumour and blood samples from NSCLC patients – as part of a tissue acquisition study (NCT03517917) – has enabled the manufacture of a personalized clonal neoantigen-reactive T cell (cNeT) product (ATL001), which is now in clinical development. **Methods:** The CHIRON Study (NCT04032847), is a first-in-human, open-label, multi-centre, phase I/IIa study to characterise the safety and clinical activity of ATL001 administered intravenously in up to 40 adults with advanced unresectable or metastatic NSCLC. Following consent and screening, patients enter the study for procurement of tumor tissue and blood to manufacture ATL001. Tissue may be procured during treatment with standard systemic therapies. Patients in Cohort A receive cyclophosphamide/fludarabine on days -6 to -4, followed by a single dose of ATL001 and 10 daily doses of subcutaneous IL-2; Patients in Cohort B will additionally receive one dose of pembrolizumab between days -13 and -6 before receiving ATL001, then restart pembrolizumab 2 weeks after receiving ATL001 and continue for up to 12 months. Key eligibility criteria include treatment with at least one prior systemic therapy (including a PD-1 inhibitor). Primary endpoints are the safety and tolerability of ATL001 as a monotherapy and in combination with pembrolizumab. Secondary endpoints include change in tumor size and response rate by RECIST 1.1 and imRECIST. Correlative studies will investigate the effects of cNeT dose and engraftment kinetics on clinical activity. The study began enrolling patients in Cohort A in August 2019. Clinical trial information: NCT04032847. Research Sponsor: Achilles Therapeutics.

TPS9139 **Poster Session**

HERTHENA-Lung01: A randomized phase 2 study of patritumab deruxtecan (HER3-DXd) in previously treated metastatic *EGFR*-mutated NSCLC.

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Background: Few treatment options have demonstrated therapeutic benefit in epidermal growth factor receptor–mutated (*EGFR*m) non–small cell lung cancer (NSCLC) that has progressed after treatment with EGFR tyrosine kinase inhibitors (TKIs) and platinum-based chemotherapy. HER3, a member of the human epidermal growth factor family, is detectable in most *EGFR*m NSCLC, and its expression has been linked to worse clinical outcomes. There are no approved HER3 directed therapies for the treatment of NSCLC. HER3-DXd is a novel, potentially first-in-class HER3 directed antibody drug conjugate that has demonstrated preliminary evidence of safety and antitumor activity in patients (pts) with *EGFR*m TKI–resistant NSCLC in an ongoing Phase 1 study, providing proof of concept of HER3-DXd. The Phase 2 study (HERTHENA-Lung01) is further evaluating HER3-DXd in pts with previously treated metastatic or locally advanced *EGFR*m NSCLC. **Methods:** This randomized, open-label Phase 2 study will enroll up to 420 pts at approximately 135 study sites in North America, Europe and the Asia-Pacific region. Eligible pts will have metastatic or locally advanced NSCLC with an activating *EGFR* mutation (exon 19 deletion or L858R), progression during or after systemic treatment with $\geq$1 EGFR TKI and $\geq$1 platinum-based chemotherapy regimen, and $\geq$1 measurable lesion confirmed by blinded independent central review (BICR) per RECIST v1.1. Pts with an *EGFR* T790M mutation must have received and progressed on prior osimertinib. Pts with stable brain metastases are eligible. Exclusion criteria include evidence of previous small cell or combined small cell/non–small cell histology or any history of interstitial lung disease. Tumor tissue will be assessed retrospectively for HER3 expression and molecular mechanisms of TKI resistance. HER3 expression will not be used to select pts for enrollment. Pts will be randomized 1:1 to receive 1 of 2 HER3-DXd Q3W dose regimens that will be independently evaluated: a 5.6 mg/kg fixed-dose regimen (Arm 1) or an up-titration dose regimen (Arm 2: Cycle 1, 3.2 mg/kg; Cycle 2, 4.8 mg/kg; Cycle 3 and beyond, 6.4 mg/kg). After review of data from an ongoing Phase 1 study with similar patients treated with either of these dose regimens, a decision could be made to continue enrollment into 1 or both arms. The primary objective is to evaluate the efficacy of HER3-DXd as measured by objective response rate (ORR) by BICR. Secondary objectives are to evaluate the efficacy and safety/tolerability of HER3-DXd and to assess the relationship between efficacy and HER3 expression. Secondary endpoints include duration of response, progression-free survival, ORR by investigator, disease control rate, time to response, best percentage change in the sum of diameters of measurable tumors, and overall survival. The study is enrolling and is planned to finish in 2023. Clinical trial information: NCT04619004. Research Sponsor: Daiichi Sankyo.