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IASLC INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
Conquering Thoracic Cancers Worldwide

Volume 18, Number 4S, Supplement, April 2023 Alex A. Adjei, MD, PhD, FACP, Editor-in-Chief

Abstract Book

European Lung Cancer Congress (ELCC) 2023
29 March–1 April 2023

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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Guest Editors: European Lung Cancer Congress 2023 Scientific Committee

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ADVANCED NSCLC

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Osimertinib versus gefitinib followed by osimertinib in patients with EGFR-mutant non-small cell lung cancer (NSCLC): EORTC Lung Cancer Group 1613 APPLE trial

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Background: APPLE is a 3 arms phase II non-comparative trial exploring the sequential treatment approach of gefitinib followed by osimertinib or osimertinib frontline in patients with advanced EGFR-mutant NSCLC. Here we report the exploratory analysis of the outcome with osimertinib frontline compared to a sequential approach.

Methods: Patients were randomized to: arm A (osimertinib until RECIST progression -PD-), arm B (gefitinib until the emergence of circulating tumor DNA EGFR T790M mutation or RECIST PD) or arm C (gefitinib until RECIST PD), and then switch to osimertinib in both arms B and C. In this analysis, arms B and C were pooled. Primary endpoint: Progression Free Survival rate "on osimertinib" at 18 months (PFSR-OSI-18) in arm B (H_0: PFSR-OSI-18 of ≤40%). Secondary endpoints: overall survival (OS) and Brain PFS (BPFS). Primary analyses were performed in per-protocol population (PPP). In all arms, contrast-enhanced brain CT-scan was performed every 8 weeks.

Results: From 11/2017 to 02/2020, 156 patients were randomized (arm A:53, arm B/ C:103), and 136 were included in the PPP. Most patients were females (56.6% and 69.9%), with EGFR Del19 (66% and 64%). Baseline brain metastases: 19% and 29.1%, respectively. In pooled arms B/C, 70% of patients received osimertinib at PD. In arm A, PFS on osimertinib was 19.5 months. The PFSR-OSI-18 was 51.1% in Arm A and 61% in pooled arms B/C. The median OS was NR in arm A vs 42.8 (95% CI: 28.6-NR) months (mo) in pooled arm B/C, with 18-months OS of 84.4% and 82.3%, respectively. In all arms, 68 brain progression events were observed. Median time to brain PD in arm A and B/C were 34.3 mo (95% confidence interval, CI:26.9-NR) and 22.3 mo (95%CI:18.6–22.3), and corresponding hazard ratio was 0.54 (90% CI: 0.34–0.86) with 18-months BPFS of 82.2% and 63.5%, respectively.

Conclusions: In advanced EGFR mutant-NSCLC, upfront treatment with osimertinib shows a significant reduction in the risk of brain progression, with comparable OS versus the sequential treatment approach.

Clinical trial identification: NCT02856893.

Legal entity responsible for the study: EORTC.

Funding: AstraZeneca.

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Phase II randomized study of osimertinib (OSI) with or without local consolidative therapy (LCT) for metastatic EGFR mutant non-small cell lung cancer (NSCLC): Analysis of adverse events (AEs)

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Background: Most patients with EGFR mutant NSCLC who have an initial response to OSI exhibit persistent residual disease that may enable emergence of acquired resistance. Eliminating residual disease with LCT may delay resistance and improve clinical outcomes. Safety of OSI with LCT, however, is not well defined. Here we report safety data from a multicenter randomized phase II study of OSI with or without LCT for patients with EGFR mutant NSCLC.

Methods: Metastatic NSCLC patients with tyrosine kinase inhibitor naïve EGFR mutation (L858R/Exon 19 deletion) or T790M resistance mutation after prior therapy received 6–12 weeks of induction OSI. Patients without progression per RECIST 1.1 were randomized to OSI alone vs LCT plus OSI until progression. Primary objective was progression free survival. Secondary objective was safety. Patients were evaluated every 8 weeks using CTCAE v4.0. All possible, probable, and definite treatment related AEs were analyzed.

Results: From 2018 to 2022, 122 patients (median age: 65, range: 30–88) were randomized (63 to OSI alone; 59 to OSI plus LCT). Among 59 patients who received LCT, 35 (59%) received RT alone, 17 (29%) received surgery alone, and 7 (12%) received both RT and surgery. At median follow up of 16 months (range: 2–49), there were no grade 4/5 AEs. There was no significant difference in grade 3 AEs between OSI alone and OSI plus LCT (16% vs 29%; p = 0.08). The most common grade 3 AEs with OSI alone were hyponatremia (4.8%), transaminitis (4.8%), and pneumonitis (3.4%). The most common grade 3 AEs with OSI plus LCT were hyponatremia (6.8%), diarrhea (3.4%), empyema (3.4%), and pneumonitis (1.7%). Among 42 patients that received RT, 1 (2%) had a grade 3 AE possibly related to RT (non-cardiac chest pain). Among 24 surgical patients, 3 (13%) had surgery related grade 3 AEs (1 arterial injury, 2 empyema). Common grade 1–2 AEs with OSI plus LCT were fatigue (56%), diarrhea (45%), dyspnea (31%), cough (29%), pneumonitis (10%), dysphagia (12%), and esophagitis (7%).

Conclusions: OSI plus LCT is well tolerated in EGFR mutated metastatic NSCLC patients without significant increase in serious AEs compared to OSI alone.

Clinical trial identification: NCT03410043.

Legal entity responsible for the study: The University of Texas MD Anderson Cancer Center.

Funding: National Comprehensive Cancer Network (NCCN).

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Long-term efficacy, safety, and predictors of response to amivantamab among patients with post-platinum EGFR Ex20ins-mutated advanced NSCLC

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Background: Amivantamab (ami), an EGFR and MET bispecific antibody with immune cell-directing activity, is approved to treat patients (pts) with advanced non-small cell lung cancer (NSCLC) harboring EGFR exon 20 insertion mutations (Ex20ins) who progressed on prior platinum-based chemotherapy. This report presents long-term results for this population.

Methods: Pts with EGFR Ex20ins advanced NSCLC whose disease progressed on platinum-based chemotherapy were recruited in CHRYSALIS. Pts who received the approved phase II dose of 1050 mg (1400 mg, ≥80 kg) by 08 Jun 2020 were included. Response was assessed by investigator per RECIST v1.1.

Results: As of Sep 2022, among 114 pts included, the median follow-up was 19.2 months and 48 (42%) pts alive. Investigator-assessed overall response rate (ORR) was 37% (95% CI, 28–46), with median duration of response of 12.5 months (95% CI, 6.9–19.3), median progression-free survival of 6.9 months (95% CI, 5.6–8.8), and median overall survival of 23 months (95% CI, 18.5–29.5). Activity was observed across subgroups, including the elderly (ORR of 32% and 33% for age ≥65 and ≥75, respectively), heavily pretreated pts (ORR of 53% for >2 prior lines, 42% for prior immunotherapy, and 52% for prior EGFR TKI therapy), or those sensitive or resistant to prior platinum-based chemotherapy (ORR of 36% and 31%, respectively). No new safety signals were detected, with rash (all grades, 89%) and infusion-related reactions (67%) remaining the most frequent toxicities. There are 48 (42%) pts on ami for ≥12 (28-day) cycles. Treatment is ongoing in 15 (13%) pts (11 responders and 4 with stable disease as best response) who have received ami for a median of 2.6 years. An analysis comparing pts without and with sustained clinical benefit (≥12 cycles on ami) will presented at the meeting, including plasma ctDNA data.

Conclusions: Ami demonstrated robust efficacy that was consistently observed across post-platinum patients with EGFR Ex20ins NSCLC, including the elderly, those with multiple prior lines, or those who were platinum sensitive or refractory. A subgroup derived long-term benefit; the mechanisms for which will be explored further.

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Patient-reported outcomes from the CodeBreaK 200 phase III trial comparing sotorasib versus docetaxel in KRAS G12C-mutated NSCLC

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Background: In the CodeBreaK 200 phase III trial, sotorasib significantly improved PFS (primary endpoint) versus docetaxel in previously treated $KRAS^{G12C}$-mutated NSCLC. Previously described patient-reported outcomes (PROs) favored sotorasib over docetaxel for global health status, physical functioning, dyspnea, and cough (ESMO 2022, LBA10). Here, we report the severity and impact of symptoms on patients' quality of life (QOL) in response to treatment.

Methods: In this trial, 345 patients who progressed after receiving platinum-based chemotherapy and a checkpoint inhibitor were randomized 1:1 to receive sotorasib (960 mg orally QD) or docetaxel (75 mg/m^2 intravenously Q3W). Well-established, validated

questionnaires captured patients' perception of their QOL and symptom burden: EuroQOL-5 Dimension Visual Analogue Scale (EQ-5D VAS), PRO-Common Terminology Criteria for Adverse Events (CTCAE), Brief Pain Inventory (BPI), and question GP5 from the Functional Assessment of Cancer Therapy Tool General form (FACT-G). For ordinal outcomes, change from baseline to week 12 was assessed with generalized estimating equations.

Results: Compared with patients receiving sotorasib, those receiving docetaxel were more severely bothered by their side effects (odds ratio [OR] 5.71) and experienced symptoms at a higher severity (pain: OR 2.94, aching muscles: OR 4.40, aching joints: OR 4.17, mouth or throat sores: OR 4.26). Further their symptoms more strongly interfered with their usual/daily activities (pain: OR 3.18, aching muscles: OR 3.90, aching joints: OR 10.68). QOL worsened five days after initial docetaxel treatment while remaining stable with sotorasib (change from baseline in VAS score: −8.4 vs 1.5). The VAS showed a long-term worsening of QOL with docetaxel while the VAS remained stable with sotorasib (−5.8 vs 2.2 at week 12).

Conclusions: Patients treated with sotorasib reported less severe symptoms than those treated with docetaxel; hence, their daily lives were positively affected. In addition to improving clinical efficacy outcomes, sotorasib maintained QOL versus docetaxel suggesting that sotorasib may be a more tolerable treatment option for patients with pretreated, $KRAS^{G12C}$-mutated advanced NSCLC.

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Cemiplimab plus chemotherapy versus chemotherapy alone in non-small cell lung cancer: Longer follow-up results from the phase III EMPOWER-Lung 3 trial

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Background: EMPOWER-Lung 3, a randomized, double-blind, placebo-controlled phase III trial, examined cemiplimab (anti-PD-1) plus chemotherapy (chemo) in patients with advanced non-small cell lung cancer (NSCLC) without EGFR, ALK or ROS1 aberrations, with either squamous or non-squamous histology and any level of PD-L1 expression. Previously we reported that, after 16.4 months follow-up, cemiplimab + chemo improved median overall survival (OS) over chemo alone (21.9 vs 13.0 months, HR = 0.71, 0.53–0.93). Here, we report longer-term data after 28.4 months follow-up.

Methods: Patients were randomized 2:1 to receive 4 cycles of platinum-doublet chemo, with 350 mg cemiplimab (n = 312) or placebo (n = 154) every 3 weeks for up to 108 weeks. The primary endpoint was OS; secondary endpoints included progression-free survival (PFS) and objective response rates (ORR).

Results: After a median of 28.4 months follow-up, cemiplimab + chemo continued to show significantly improved OS and PFS vs chemo alone. Median OS was 21.1 months for cemiplimab + chemo vs 12.9 months for chemo alone (HR = 0.65, 0.51–0.82, p = 0.0003). Median PFS was 8.2 months for cemiplimab + chemo vs 5.5 months for chemo alone (HR = 0.55, 0.44–0.68, p < 0.0001). ORRs were 43.6% vs 22.1%, with a duration of response of 16.4 and 7.3 months, respectively. Safety profiles for longer-term use of cemiplimab + chemo were generally consistent with previously reported data; Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 48.7% of patients in cemiplimab + chemo and 32.7% in chemotherapy alone.

Table: 5O

m = Median	Cemiplimab + chemo (N = 312)	Chemo alone (N = 154)
mDuration of follow-up	28.3	28.7
mOS, months	21.1	12.9
HR (95% CI)	0.65 (0.51, 0.82); P < 0.0003	
mPFS, months	8.2	5.5
HR (95% CI)	0.55 (0.44, 0.68); P < 0.0001	
ORR, %	44%	22%
Odds ratio (95% CI)	2.82 (1.80-4.41); P < 0.0001	
Complete response, n (%)	13 (4%)	0
Partial response, n (%)	123 (39%)	34 (22%)
Kaplan-Meier estimated mDOR (95% CI), months	16.4 months	7.3 months
≥Grade 3 TEAEs	152 (48.7%)	50 (32.7%)

CI, confidence interval; DOR, duration of response; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TEAEs, treatment-emergent adverse events.

Conclusions: At 28.4 months of follow-up, the EMPOWER-3 Lung trial continues to show an improvement in benefit of cemiplimab in combination with chemo, compared to chemo alone, for patients with advanced squamous and non-squamous NSCLC, regardless of PD-L1 expression level and without EGFR, ALK or ROS1 aberrations.

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CONTACT-01: Efficacy and safety from a phase III study of atezolizumab (atezo) + cabozantinib (cabo) vs docetaxel (doc) monotherapy in patients (pts) with metastatic NSCLC (mNSCLC) previously treated with checkpoint inhibitors and chemotherapy

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Background: Despite treatment (tx) with anti–PD-L1/PD-1 (αPD-(L)1) and platinum-based chemo, mNSCLC often progresses, suggesting a need for new second/third-line tx options. The TKI cabo may enhance αPD-(L)1 efficacy by promoting an immune-permissive environment. CONTACT-01 is a multicentre, randomised, open-label Ph3 study of atezo (anti–PD-L1) + cabo vs doc in pts with mNSCLC previously treated with αPD-(L)1 + chemo.

Methods: Eligible pts had ECOG PS 0-1, histologically or cytologically confirmed mNSCLC with progression after αPD-(L)1 + chemo (concurrent or sequential; regardless of response to prior αPD-(L)1) and any known PD-L1 status (or available tissue for central testing). Pts were randomised 1:1 to atezo 1200 mg IV q3w + cabo 40 mg PO qd or doc 75 mg/m^2 IV q3w. Stratification factors were sq vs nsq histology and sequence of prior NSCLC regimens. The primary EP was OS (ITT). Key secondary EPs were PFS, ORR, DOR and safety.

Results: Of 366 pts assigned to either atezo + cabo (n = 186) or doc (n = 180), 61% and 71% had ECOG PS 1, and 74% and 76% had nsq histology, respectively; median age was 64 and 66 y. At data cutoff 28 Sep 2022, minimum follow-up was 10.9 mo. No statistically significant OS benefit was seen with atezo + cabo vs doc (table). Median tx duration was 4.2 mo (range, 0–20; atezo), 3.9 mo (0–21; cabo) and 2.1 mo (0–19; doc). All-cause AEs occurred in 98% (G3-4, 48%) of safety-evaluable pts in the atezo + cabo arm and 94% (G3-4, 45%) in the doc arm and led to discontinuation in 17% and 14% of pts, respectively. G3-4 AEs of special interest for atezo were seen in 15% and 4% (G5 in 1% and 0%) and for cabo in 14% and 2% (G5 in 2% and 2%), respectively. G5 tx-related AEs occurred in 4 pts (2%) in the atezo + cabo arm and 1 pt (<1%) in the doc arm.

Table: 6O

Endpoint	Atezo + cabo (n = 186)	Doc (n = 180)
OS events, n (%)	114 (61)	106 (59)
Median OS, months (95% CI)	10.7 (8.8, 12.3)	10.5 (8.6, 13.0)
Stratified HR (95% CI)	0.88 (0.68, 1.16)	
P value	0.3668	
PFS events, n (%)	162 (87)	150 (83)
Median PFS, months (95% CI)	4.6 (4.1, 5.6)	4.0 (3.1, 4.4)
Stratified HR (95% CI)	0.74 (0.59, 0.92)	
ORR, % (95% CI)	11.8 (7.6, 17.4)	13.3 (8.7, 19.2)
DOR, months (95% CI)	5.6 (3.1, 10.3)	4.3 (3.3, 5.6)

AE, adverse event; DOR, duration of response; EP, endpoint; G, Grade; HR, hazard ratio; ITT population, intent-to-treat population; nsq, nonsquamous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; sq, squamous; TKI, tyrosine kinase inhibitor.

Conclusions: In this final OS analysis of CONTACT-01, atezo + cabo was not superior to doc in the ITT population. No new safety signals arose.

Clinical trial identification: NCT04471428.

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7MO

Sotorasib in *KRAS* G12C–mutated advanced non-small cell lung cancer (aNSCLC): Overall survival (OS) data from the global expanded access program (EAP study-436)

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Background: Amgen study 20190436 (study-436) is a global protocol under the sotorasib EAP which allowed compassionate use of sotorasib, a first-in-class *KRAS* G12C inhibitor, in previously treated patients (pts) with *KRAS* G12C-mutated aNSCLC. The median real-world progression-free survival previously reported in study-436 was 6.7 (95% CI, 4.6–8.3) months. Here we present the median OS data from study-436.

Methods: Pts, including those with Eastern Cooperative Oncology Group performance status (ECOG PS) 2, a history of CNS metastases, additional co-morbidities, and who had exhausted other treatment options, were enrolled in 6 countries (USA, ARG, BRA, ISR, SAU, TWN) across 49 centers. The primary endpoint assessed the safety of oral sotorasib 960 mg once daily. Median OS, a key secondary endpoint, was estimated based on the time from the start of sotorasib treatment until death due to any cause.

Results: A total of 147 pts received sotorasib. At baseline, pts had received a median of 2 (range, 0–8) prior lines of anticancer therapy, 37 (25%) pts had ECOG PS 2, and 48 (33%) had a history of CNS metastases. With a median follow-up of 13.6 (95% CI, 11.1–14.6) months, the median OS was 9.5 (95% CI, 8.6–12.0) months. Among the subgroups, the median OS was numerically longer in pts with ECOG PS 0 or 1 vs ECOG PS 2; with up to 2 vs > 2 prior lines of anticancer therapies; and in pts with former vs current smoking history (table). The median OS was numerically similar between patients with vs without a history of CNS metastases.

Table: 7MO

	Median OS, months (95% CI)
All pts (N = 147)	9.5 (8.6–12.0)
Subgroups (at baseline)	
ECOG PS	
0 or 1 (n = 110)	10.3 (8.8–12.2)
2 (n = 37)	7.9 (6.6–NE)
Prior line of anticancer therapy	
1 (n = 56)	10.5 (7.9–12.5)
2 (n = 47)	11.3 (8.6–NE)
> 2 (n = 42)	7.2 (5.7–12.0)
Smoking history	
Never (n = 13)	18.0 (12.2–NE)
Current (n = 23)	5.8 (3.4–7.9)
Former (n = 111)	10.5 (8.9–12.5)
History of CNS metastases	
Yes (n = 48)	9.5 (6.7–12.0)
No (n = 99)	10.3 (8.6–12.5)

Data cut-off date: November 8, 2022.

Conclusions: In the first report of survival in an EAP pt population treated with sotorasib, the median OS was similar to that observed in trials. The difference in median OS was minimal in pts with or without a history of CNS metastases at baseline.

Clinical trial identification: NCT04667234.

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Adagrasib (MRTX849) in patients with advanced/metastatic KRAS G12C-mutated non-small cell lung cancer (NSCLC): Preliminary analysis of mutation allele frequency

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Background: $KRAS^{G12C}$ mutations occur in ∼14% of NSCLC adenocarcinomas. Adagrasib (ada), a $KRAS^{G12C}$ inhibitor, was selected for favorable properties, including long half-life (23 h), dose-dependent pharmacokinetics, and central nervous system penetration. In the KRYSTAL-1 registrational phase II Cohort A, ada showed clinical activity with manageable tolerability in patients (pts) with previously treated $KRAS^{G12C}$-mutated NSCLC.

Methods: Pts with previously treated $KRAS^{G12C}$-mutated NSCLC received ada 600 mg orally BID. Study objectives included objective response rate [ORR], progression-free survival [PFS], overall survival [OS], safety and exploratory correlative analyses. An exploratory analysis of clinical response for pts with detectable circulating tumor (ct) DNA at baseline, cycle 2 day 1, and cycle 4 day 1 (C4D1), who comprise the mutation allele frequency clearance (MAFC)-evaluable population, was also performed; $KRAS^{G12C}$ ctDNA was assessed by digital droplet polymerase chain reaction.

Results: At data cutoff, 15 Oct 2021, Cohort A included 116 pts (median follow-up 12.9 months): median age 64 years, 56% female, median 2 prior systemic therapies. ORR by blinded independent central review (BICR) was 42.9%, disease control rate 79.5%, median PFS 6.5 months (95% CI 4.7–8.4) and, with longer follow-up (cutoff 15 Jan 2022), median OS 12.6 months (95% CI 9.2–19.2). Any grade treatment-related adverse events (TRAEs) occurred in 97% of pts (most commonly [>40%] diarrhea [63%], nausea [62%], vomiting [47%], and fatigue [41%]), and Grade 3–4 TRAEs in 43% (most commonly [≥5%] serum lipase increase [6%] and anemia [5%]). Two grade 5 TRAEs occurred; 8 (7%) TRAEs led to discontinuation. In MAFC-evaluable pts (n = 35), ORR by BICR was 60% (21/35) and all responses correlated with MAFC >90% by C4D1.

Conclusions: Ada showed promising efficacy and manageable tolerability in previously treated pts with $KRAS^{G12C}$-mutated NSCLC. Additional analyses are needed to further evaluate whether clinical response with ada correlates with MAFC in ctDNA. A phase III trial evaluating ada monotherapy vs docetaxel in previously treated pts with $KRAS^{G12C}$-mutated NSCLC is ongoing (NCT04685135).

Clinical trial identification: NCT03785249.

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Profile of immunorecognition related markers including HLA-1 expression to predict response to immunocheckpoint inhibitors in non-small cell lung cancer

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Background: The incorporation of immunotherapy (IT) with immune-checkpoint inhibitors (ICIs) into clinical practice has represented a major breakthrough in non-small cell lung cancer (NSCLC) treatment, particularly in cases where the cancer has no druggable genetic alterations. The human histocompatibility complex (HLA-1) is essential for antigen presentation capability and immune response. Here we evaluate HLA-1 and other immune-related markers as potential predictive factors of response to ICI in NSCLC.

Methods: We evaluated the immunophenotype in a cohort of 140 metastatic NSCLC patients who received treatment with ICI based regimens for metastatic setting at ICO Badalona from 2014 to 2019. We profiled the expression levels by immunohistochemistry (IHC) of HLA-1, and other immune-related markers including CD73, CD8, and PD-L1 (Ventana SP263) from formalin-fixed paraffin-embedded (FFPE) human tissue samples. We evaluated the response and clinical outcomes to ICI. The Chi-Square test for categorical variables and Kaplan Meier method for survival analysis were performed.

Results: In our cohort of 140 patients: 86% males and 14% females, 63% were lung adenocarcinomas (LuAD) and 37% squamous cell carcinoma (SCC). They received IT treatment as a 1st line (29%), 2nd (46%), and 3rd or further lines (25%). PD-L1≥50% was present in 25% of cases. 67 patients were evaluable for HLA-1 at the moment of the analysis. Our work reveals that ∼45% of NSCLC in our cohort express low staining levels of HLA-1 (down regulation or total absence) compared to normal/high staining (55%). Those patients present worse clinical outcomes: mPFS to IT 9.1 (6.5–20.2) vs 21 (13.9-NR) months (p-value 0.028), respectively. We also report that HLA-1 is co-expressed with PD-L1 ($p < 0.005$), regardless of histological subtype.

Conclusions: Down-regulation of HLA-1 expression is a mechanism of immune-evasion and affects a subset of NSCLC, which abrogates the response to ICI. HLA-1 IHC is an emerging immunomarker in NSCLC and predictor of response to ICI. In addition, we observed that HLA-1 is co-expressed with PD-L1 and represents a surrogate marker of immune-inflamed phenotype which might predict better outcomes to PD(L)-1 blockade.

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10MO

EMPOWER-Lung 1: Cemiplimab (CEMI) monotherapy as first-line (1L) treatment of patients (pts) with brain metastases from advanced non-small cell lung cancer (aNSCLC) with programmed cell death-ligand 1 (PD-L1) ≥50% — 3-year update

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Background: In phase III EMPOWER-Lung 1 study, 1L CEMI monotherapy resulted in significantly longer OS and PFS versus chemotherapy (CHEMO) for pts with aNSCLC with no actionable genomic aberrations, whose tumours express PD-L1 ≥50%. The study included pts with treated, clinically stable, baseline brain metastases, a hard-to-treat and underrepresented population in clinical trials. We previously reported improved OS and PFS with 1L CEMI versus CHEMO for this subgroup. In this post hoc analysis, we report 3-year outcomes.

Methods: In EMPOWER-Lung 1, pts were randomised 1:1 to CEMI 350 mg IV Q3W or investigator's choice of CHEMO. The overall median follow-up duration from randomization to data cut-off (4 March 2022) was 37.1 months (mo; range 24.0–56.5). Here, we analyzed pts with treated, clinically stable brain metastases (radiological stability not required).

Results: In all, 69/565 (12.2%) pts with PD-L1 ≥50% had treated, clinically stable brain metastases at randomization. Baseline characteristics in CEMI (n = 34) vs CHEMO (n = 35) groups were: median age, 60.0 (range: 45–76) vs 62.0 (range: 48–77) yrs; male, 97.1% vs 82.9%; and non-squamous histology, 85.3% vs 74.3%. CEMI showed superior efficacy outcomes vs CHEMO: longer median OS (not reached vs 20.7 mo; HR = 0.42, 0.20–0.87), longer median PFS (12.5 vs 5.3 mo; HR = 0.34, 0.18–0.63), a higher ORR (55.9% vs 11.4%) and a longer median duration of response (31.7 mo vs 12.5 mo; table). After baseline, disease progression in brain occurred in 5 (14.7%) pts with CEMI vs 7 (20%) with CHEMO. Incidence of grade ≥3 TEAEs was 35.3% in the CEMI group vs 60.0% in CHEMO.

Table: 10MO

Clinical outcomes	Cemiplimab (n = 34)	Chemotherapy (n = 35)	HR (cemiplimab vs chemotherapy)
OS, mo, median (95% CI)	NR (20.6–NE)	20.7 (9.1–29.9)	0.42 (0.20–0.87); P = 0.0168†
PFS, mo, median (95% CI)	12.5 (6.1–33.5)	5.3 (2.2–6.5)	0.34 (0.18–0.63); P = 0.0004†
ORR, %, (95% CI)	55.9 (37.9–72.8)	11.4 (3.2–26.7)	NA
Median (95% CI) duration of response (CR or PR), mo	31.7 (14.7–NE)	12.5 (4.4–NE)	NA

Data cutoff date 4 March 2022.
†Stratified log-rank test P-value.
CI, confidence interval; CR, complete response; ORR, objective response rate; OS, overall survival; mo, months; NA, not applicable; NE, not evaluable; NR, not reached; PFS, progression-free survival; PR, partial response.

Conclusions: Three-year follow up data shows durable clinical benefits and an acceptable safety profile with 1L CEMI monotherapy in subgroup analysis of pts with aNSCLC and brain metastases. CEMI is generally well tolerated in this subgroup.

Clinical trial identification: NCT03088540.

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11MO

Final data from a phase II study (TACTI-002) of eftilagimod alpha (soluble LAG-3) and pembrolizumab in 2nd-line metastatic NSCLC pts resistant to PD-1/PD-L1 inhibitors

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Background: Eftilagimod alpha (E), a soluble LAG-3 protein, acts as an MHC class II agonist triggering activation of antigen-presenting cells (APC) and CD8 T-cells. Stimulating APCs and subsequent T cell recruitment with efti may revert PD-1/PD-L1 resistance. We report updated results from Part B of the TACTI-002 trial: 2nd-line PD-1/PD-L1-resistant non-small cell lung carcinoma (NSCLC) patients (pts) treated with efti plus pembrolizumab (P).

Methods: Pts with metastatic NSCLC unselected for PD-L1 expression and with resistance to 1st-line PD-1/PD-L1 inhibitor-based therapy were enrolled. Primary endpoint (EP) was objective response rate (ORR) by iRECIST. Secondary EPs were disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and tolerability. Post-hoc analysis included tumor growth kinetics (TGK). Pts received E (30 mg SC Q2W for eight 3-week cycles and then Q3W up to 1 yr) with P (200 mg IV Q3W up to 2 yrs). Imaging was performed every 9 wks and locally evaluated. PD-L1 TPS was assessed using IHC 22C3 kit.

Results: 36 pts enrolled between Apr 2019 – Aug 2021. Median age was 67 yrs (46–84) and 61% were male. ECOG PS was 0 and 1 in 33% and 67% of pts. Pts had squamous (19%) and non-squamous (78%) histology. All PD-L1 subgroups were included: 39% with TPS <1% and 82% with TPS <50%. Pts received a PD-1/PD-L1 inhibitor alone (28%) or combined with platinum-based chemo (72%) as 1st-line therapy. Pts received median of 5 (2–35) P and 7 (2–22) E doses. ORR and DCR (iRECIST) was 8.3% and 33%. All PRs were confirmed with pts on study 19+ m. TGK analysis was performed on pts with data available on the same lesions from prior failed therapy and post-baseline. Vast majority (83%) of pts showed deceleration (50%) in tumor growth or shrinkage (33%) of target lesions. Median PFS was 2.1 months with PFS rate at 6 m of 25%. 44% were alive at 12 m with median OS of 9.7 m. Most common (>15%) adverse events were decreased appetite (33%), dyspnea (31%), cough (28%), asthenia (22%), fatigue (19%), arthralgia (17%) and weight decreased (17%).

Conclusions: Efti + pembrolizumab is safe and shows encouraging signs of antitumor activity in NSCLC pts resistant to PD-1/PD-L1 inhibitors, warranting further investigation.

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12MO

Patterns of response in metastatic (m) NSCLC after 2 and 4 cycles of chemotherapy (CT), alone or with durvalumab (D) ± tremelimumab (T), in the phase III POSEIDON study

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Background: In POSEIDON, 1L T plus D and 4 cycles of platinum-based CT significantly improved PFS and OS vs CT in patients (pts) with EGFR/ALK wild-type mNSCLC leading to the approval of T+D+CT by the FDA; objective response rate (confirmed; 38.8% [95% CI, 33.6–44.3] and 41.5% [95% CI, 36.1–47.0] vs 24.4% [95% CI, 19.9–29.4]) and duration of response were also improved with both T+D+CT and D+CT vs CT. However, the relationship between number of CT cycles and patterns of response in pts with mNSCLC has not been fully established. Here we report outcomes in POSEIDON after 2 vs 4 CT cycles.

Methods: Pts (n = 1013) were randomised (1:1:1) to 1L T+D+CT, D+CT or CT. Exploratory analyses of objective response (intent-to-treat [ITT] population and subgroups with mutations [m] in STK11, KEAP1 or KRAS) and safety (safety population) were conducted after 2 vs 4 CT cycles (week 6 vs 12 scans, respectively).

Results: 78%, 82% and 74% of pts who received T+D+CT, D+CT or CT completed 4 CT cycles. 560 pts had stable disease (SD) after cycle (C) 2. Of these, 22.9% had partial response (PR) after C4 (table). A similar trend was observed in pts with STK11m, KEAP1m or KRASm mNSCLC; in these pts, improvement appeared greatest with T+D+CT, although 95% CIs were wide and overlapping. Of 252 pts in the ITT with CR/PR after C2, 89.7% remained in response after C4 (table). Reductions in median target lesion size occurred between C2 and C4 in all arms (data will be presented). The frequency of grade 3/4 adverse events (AEs) and serious AEs originating in C1–2 and C3–4 was similar (data will be presented).

Conclusions: These exploratory data support the use of 4 CT cycles, when given with T (limited course) and D (until progression), to optimise response and tumour shrinkage in pts with mNSCLC, including some harder to treat subgroups. Two further CT cycles did not meaningfully add to toxicity or compromise the ability to administer planned CT.

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Legal entity responsible for the study: AstraZeneca.

Table: 12MO

	T+D+CT	D+CT	CT	Total
ITT				
SD@C2 and PR@C4				
n/n	47/180	42/179	39/201	128/560
% (95% CI)	26.1 (19.9–33.2)	23.5 (17.5–30.4)	19.4 (14.2–25.6)	22.9 (19.4–26.6)
CR/PR@C2 and CR/PR@C4				
n/n	87/96	87/94	52/62	226/252
% (95% CI)	90.6 (82.9–95.6)	92.6 (85.3–97.0)	83.9 (72.3–92.0)	89.7 (85.2–93.1)
STK11m (NSQ)				
SD@C2 and PR@C4				
n/n	5/17	2/13	2/16	9/46
% (95% CI)	29.4 (10.3–56.0)	15.4 (1.9–45.4)	12.5 (1.6–38.3)	19.6 (9.4–33.9)
KEAP1m (any histology)				
SD@C2 and PR@C4				
n/n	4/11	4/14	0/5	8/30
% (95% CI)	36.4 (10.9–69.2)	28.6 (8.4–58.1)	0.0 (0.0–52.2)	26.7 (12.3–45.9)
KRASm (NSQ)				
SD@C2 and PR@C4				
n/n	13/31	9/33	2/26	24/90
% (95% CI)	41.9 (24.5–60.9)	27.3 (13.3–45.5)	7.7 (0.9–25.1)	26.7 (17.9–37.0)

NSQ, non-squamous.

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All other authors have declared no conflicts of interest.

13MO

Safety and efficacy of tusamitamab ravtansine in combination with pembrolizumab ± chemotherapy in patients with CEACAM5-positive nonsquamous NSCLC (CARMEN-LC05 phase II study)

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Background: Pembrolizumab (pembro) ± chemotherapy is currently standard-of-care (SoC) first-line treatment for advanced/metastatic nonsquamous (NSQ) non-small cell lung cancer (NSCLC) without EGFR, BRAF or ALK/ROS aberrations. Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) expression is often higher in cancerous vs healthy lung cells. Tusamitamab ravtansine (tusa rav) is a humanized CEACAM5-specific antibody-drug conjugate linked to DM4. Tusa rav monotherapy has shown encouraging antitumor activity and safety in patients with heavily pretreated CEACAM5-positive NSQ NSCLC.

Methods: CARMEN-LC05 assessed safety and antitumor activity of tusa rav in combination with SoC regimens: with pembro [T2]; with pembro + platinum-based chemotherapy (pCT) [T3]; and with pembro + pCT + pemetrexed [T4] in patients with advanced/metastatic NSQ NSCLC with CEACAM5 intensity of ≥2+ in ≥1% of tumor cells by immunohistochemistry. Tusa rav was given IV Q3W at 150 or 170 mg/m^2 in each treatment arm.

Results: As of Nov 28, 2022, 25 patients were treated for a median of 21 weeks (range 3–86); 12 (48%) were still on treatment. Dose-limiting toxicity of increased aspartate aminotransferase occurred in 1 patient in the T4 tusa rav 170 mg/m^2 group. The most frequent treatment-emergent adverse events (TEAE) were nausea (44%), diarrhea (36%), and asthenia (32%); Grade ≥3 events occurred in 68%; and Grade 5 events in 16% in the treatment period (all unrelated to tusa rav). Corneal TEAEs of any grade occurred in 24% of patients; but only 1 (keratitis) was Grade ≥3 in the T2 tusa rav 170 mg/m^2 group. Objective response rate (ORR) and disease control rate (DCR) for all patients were 40% and 88%, respectively.

Conclusions: Tusa rav combined with SoC showed encouraging antitumor activity across all treatment arms with a favorable safety profile, including in the T4 arm, and no new safety concerns, supporting ongoing evaluation of tusa rav.

Clinical trial identification: NCT04524689.

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Table: 13MO

Table of outcomes	T2		T3		T4		
Tusa rav dose, mg/m^2	150	170	150	170	150	170	All
Number of patients	3	2	4	1	12	3	25
Any TEAE, n (%)	3 (100)	2 (100)	4 (100)	1 (100)	12 (100)	3 (100)	25 (100)
Grade ≥3 TEAE, n (%)	2 (66.7)	2 (100)	2 (50.0)	1 (100)	8 (66.7)	2 (66.7)	17 (68.0)
Grade 5 TEAE, n (%)	0	0	0	0	4 (33.3)	0	4 (16.0)
TEAE leading to permanent discontinuation, n (%)	0	0	0	1 (100)	3 (25.0)	1 (33.3)	5 (20.0)
Corneal TEAE, n (%)	2 (66.7)	1 (50.0)	0	1 (100)	1 (8.3)	1 (33.3)	6 (24.0)
ORR (confirmed complete response [CR] or partial response [PR]), n (%; 95% CI)	3 (100)	0 (0.0)	2 (50.0)	0 (0.0)	3 (25.0)	2 (66.7)	10 (40.0; 21.1, 61.3)
DCR (confirmed CR, PR, or stable disease), n (%; 95% CI)	3 (100)	2 (100)	4 (100)	1 (100)	9 (75.0)	3 (100)	22 (88.0; 68.8, 97.5)

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14MO

Updated efficacy and safety of taletrectinib in patients (pts) with ROS1+ non-small cell lung cancer (NSCLC)

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Background: Taletrectinib is a potent, next-generation, CNS-active, ROS1 tyrosine kinase inhibitor (TKI) with selectivity over TRKB. In previous reports from TRUST-I, taletrectinib showed meaningful clinical efficacy and was well tolerated in pts with ROS1$^+$ NSCLC (n = 109) regardless of crizotinib (CRZ) pretreatment status. We report updated efficacy and safety data with ~1.5 yr follow-up.

Methods: TRUST-I is a multicenter, open-label, single-arm study with two cohorts: ROS1 TKI-naïve and CRZ-pretreated. Pts in both cohorts received taletrectinib 600 mg QD. Key study endpoints included IRC-confirmed ORR (cORR), DoR, disease control rate (DCR), PFS, and safety. A pooled analysis of ORR, PFS, and safety including pts from additional clinical trials was also conducted.

Results: In the 109 pts from TRUST-I (enrolled prior to Feb 2022) the median follow-up was 18.0 mo in TKI-naïve (n = 67) and 16.9 mo in CRZ-pretreated pts (n = 42). cORR was 92.5% in TKI-naïve and 52.6% in CRZ-pretreated pts (table). Median DoR (mDoR) and mPFS were not reached. Intracranial-ORR was 91.6%; ORR in pts with G2032R was 80.0%. In a pooled analysis with phase I studies, ORR was 89.5% and 50.0% for TKI-naïve and CRZ-pretreated pts, respectively; mPFS was 33.2 mo and 9.8 mo. In 178 pts treated at 600 mg QD, treatment-emergent adverse events (TEAEs) were 92.7%; most (64.0%) were grade 1–2. The most common TEAEs were increased AST (60.7%), increased ALT (55.6%), and diarrhea (55.6%). Neurological TEAEs (dizziness, 18.5%; dysgeusia, 12.4%) and discontinuations due to TEAEs (3.4%) were low. Further updated results will be presented.

Table: 14MO Efficacy in pts treated with taletrectinib

TRUST-1	ROS1 TKI-Naïve (n = 67)	CRZ-Pretreated (n = 38)
Median follow-up	18.0 (17.4–18.4)	16.9 (11.7–18.0)
Confirmed ORR	92.5 (83.4–97.5)	52.6 (35.8–69.0)
Confirmed DCR	95.5 (87.5–99.1)	81.6 (65.7–92.3)
Median time to response,mo (Min,Max)	1.4 (NE–NE)	1.4 (1.3–1.4)
Pooled data	**ROS1 TKI-Naïve (n = 78)**	**CRZ-Pretreated (n = 46)**
Confirmed ORR[a]	89.5 (80.3–95.3)	50.0 (34.6–65.4)
Median PFS[a]	33.2 (23.5–NE)	9.8 (5.6–18.4)

Data reported as mo (95% CI) unless specified.
[a]Data from evaluable patients from a pooled analysis from phase I and II studies. CRZ, crizotinib; DCR, disease control rate; NE, not evaluable; ORR, overall response rate; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Conclusions: With additional follow-up, taletrectinib continued to demonstrate meaningful efficacy outcomes including high response rates, prolonged PFS, robust intracranial activity, activity against G2032R, and tolerable safety with low incidence of neurological AEs.

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15MO
Efficacy and ctDNA analysis in an updated cohort of patients with TRK fusion lung cancer treated with larotrectinib

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Background: Neurotrophic tyrosine receptor kinase (NTRK) gene fusions are oncogenic drivers in various cancers, including lung cancer. Larotrectinib, a highly selective, central nervous system (CNS)-active tropomyosin receptor kinase (TRK) inhibitor, demonstrated a 73% objective response rate (ORR) in 15 patients (pts) with TRK fusion lung cancer (Drilon et al. JCO Precis Oncol 2022). We report efficacy and safety with circulating tumour DNA (ctDNA) analysis in pts with TRK fusion lung cancer treated with larotrectinib.
Methods: Pts treated with larotrectinib in 2 clinical trials were analysed. NTRK gene fusions were determined by local testing before enrolment. Larotrectinib was administered at 100 mg twice daily. Response was assessed by an independent review committee (IRC) per RECIST v1.1. ctDNA was analysed using Guardant360 and GuardantOMNI.
Results: As of 20 July 2021, 26 pts (12 pts with CNS metastases) were enrolled. Among 23 pts (10 pts with CNS metastases) evaluable per IRC, ORR was 83% (95% confidence interval [CI] 61–95; 2 complete response, 17 partial response, 4 stable disease). Median duration of response (DoR) was not reached (95% CI 9.5–not estimable [NE]), with a 12-month DoR rate of 72%. Median progression-free survival was not reached (95% CI 9.9–NE). Median overall survival was 40.7 months (95% CI 19.4–NE). Treatment-related adverse events were mostly Grade 1–2. ctDNA data were available for 14 pts. ctDNA analysis detected NTRK gene fusions in 6 of the 14 pts at treatment start. Assessment of baseline co-occurring mutations revealed the inclusion of 3 patients with mutation-positive NSCLC who had failed prior anti-EGFR therapy. By the data cut-off, 6 pts had progressed, with ctDNA data available for 5 pts. Potential acquired mutations were identified in 3 pts.
Conclusions: Larotrectinib demonstrated durable responses, extended survival benefit, and a favourable safety profile in patients with advanced lung cancer harbouring NTRK gene fusions, including those with treatment-naive NSCLC or with prior EGFR inhibitor therapy. ctDNA next-generation sequencing represents a promising technology to test NTRK gene fusions or resistance mutations.

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Clinical impact of plasma EGFR analysis: Results from the ETOP-BOOSTER randomized phase II trial

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Background: The ETOP-BOOSTER study explored the addition of bevacizumab to osimertinib as 2nd-line treatment in patients with pathologically confirmed advanced NSCLC harboring common sensitising EGFR (70% Exon 19 deletion; 30% Exon 21 L858R) and acquired EGFR T790M mutations (mt) and reported no difference in progression-free survival (PFS). An interaction of treatment outcomes by smoking status was previously identified. Pre-specified exploratory analysis of serial plasma samples using next generation sequencing (NGS) is reported.

Methods: Plasma circulating tumour DNA (ctDNA) analysis was conducted using Guardant360® on samples collected prospectively at baseline (BL), week 9 (w9) and at disease progression (PD). Multivariable Cox models, including interaction of treatment with smoking history, plasma EGFR T790M and TP53 mt at BL and longitudinally, and tumour EGFRmt status were analysed to assess their effect on outcome.

Results: From the 155 randomised patients, 136 (87%) had available blood samples at BL (68 in each arm), 110 (71%) at w9 and 65 (42%) at PD for plasma NGS analysis. EGFR T790M mt was detected in 71% (97/136) of BL samples and was not associated with PFS (table). At w9, EGFR T790M mt was undetected in 91% (of 80 available, initially mt, cases), while at PD it was present in 34% (of 47 cases available). Smoking status was found to be predictive for PFS (interaction p = 0.046), however it was not associated with TP53 mt, which was detected in 63% of BL samples. BL TP53 mt and tissue EGFR Exon 21 L858R were each found to be poor prognostic factors for PFS and overall survival independent of treatment.

Conclusions: The interaction of treatment with smoking, was confirmed for PFS in the current evaluation, and was not found to be driven by the presence of TP53 or EGFR T790M mt. BL TP53 mt and EGFR Exon 21 L858R were associated with poor outcome.

Table: 16MO

Median PFS (95%CI) months, log-rank p

	BEV-OSI	OSI	Whole cohort
BL EGFR T790M mt status (int p = 0.29)			
D – 97	14.9 (9.1–17)	9.9 (5.5–16.7)	12.4 (8.4–16.4)
ND – 39	16.5 (8.1–26.9) p = 0.15	13.4 (4.1–18.7) p = 0.97	14.4 (8.1–20.5) p = 0.32
EGFR T790M at BL/w9 (int p = 0.037)			
D at BL/9w – 7	NR (6.3–NE)	2.1 (0–15.1)	3.9 (0–15.1)
D at BL; not at 9w –73	13.3 (8.3–15.9)	9.0 (4.1–18.6)	10.5 (7.8–14.6)
ND at BL/9w – 27	7.1 (2.4–24.5) p = 0.39	7.5 (0.9–12.3) p = 0.051	7.5 (4.1–12.3) p = 0.82
BL TP53 mt status (int p = 0.67)			
D – 86	10.4 (6.2–16.4)	8.1 (4.2–12.4)	9.4 (6.2–12.4)
ND – 50	20.6 (14.1–26.6) p = 0.054	18.6 (6.2–25.1) p = 0.026	18.7 (14.4–24.4) p = 0.0033

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17P

Treatment sequence for non-small cell lung cancer with brain oligometastases does not impact overall survival

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Background: For patients with non-small cell lung cancer (NSCLC) presenting with brain oligometastases, the optimal treatment sequence

of thoracic and metastatic treatment is not well-established. This study sought to evaluate long-term survival of patients with NSCLC with brain oligometastases who received initial treatment of the primary site lung tumor versus brain metastases.

Methods: Patients with cT1-4, N0-3, M1b-c NSCLC with synchronous limited metastatic disease isolated to the brain who received systemic therapy with radical treatment (surgery, brain stereotactic radiosurgery, or lung radiation) to both the primary site and metastases in the National Cancer Database from 2010–2019 were included. Patients who received whole brain radiation therapy or palliative treatment were excluded. Long-term overall survival of patients who received initial treatment to the brain versus lung was evaluated using Kaplan-Meier analysis, Cox proportional hazards modeling, and propensity score matching, on 15 common prognostic variables including comorbidities, clinical T/N status, and the specific type of treatment to each site.

Results: Of the 1,044 patients diagnosed with NSCLC with brain oligometastases who met the study inclusion criteria, 893 (79.0%) received treatment of the brain metastases first, and 237 (21.0%) received treatment to the lung first. In unadjusted Kaplan-Meier analysis, overall survival was similar between patients who underwent initial treatment of brain metastases versus primary site. No significant difference in overall survival was found between the two groups after multivariable-adjusted Cox proportional hazards modeling (HR: 1.24, 95% CI: 0.91–1.70, p = 0.17). In a propensity score-matched analysis of 230 patients (115 in each arm), treatment sequence of brain metastases versus lung was not significantly associated with 5-year overall survival (Brain: 38.2% [95% CI: 27.5–34.4] vs Lung: 38.0% [95% CI: 29.9–44.7], p = 0.32).

Conclusions: The findings of this study suggest that for patients presenting with NSCLC with synchronous limited metastatic disease isolated to the brain who can tolerate aggressive treatment of the primary and metastatic sites, treatment sequence does not impact overall survival.

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18P

Stereotactic radiotherapy (SRT) in combination with aumolertinib to treat intracranial oligometastatic non-small cell lung cancer (NSCLC): An update of the phase II, prospective study

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Background: Aumolertinib is a tolerable third-generation EGFR-TKI that has CNS efficacy in patients with EGFR-mutant NSCLC. Stereotactic radiotherapy (SRT) is highly effective and less toxic for limited intracranial metastases. We aim to investigate the efficacy and safety of aumolertinib followed by SRT in patients with intracranial oligometastatic NSCLC.

Methods: Intracranial oligometastatic patients with EGFR sensitive mutations (EGFR-TKIs naive) were enrolled and received aumolertinib 110 mg daily until intracranial disease progression. Then SRT (32–40Gy total, 8Gy/f) was given to intracranial oligo-progression disease. After SRT the patients received continued aumolertinib if extracranial lesions were stable controlled. The primary endpoint was intracranial objective response rate (iORR). Secondary endpoints included intracranial progression-free survival (iPFS), intracranial duration of response (iDOR) according to RECIST 1.1, cerebral radiation necrosis rate (CRNR) and overall survival (OS). Safety was evaluated according to CTCAE v5.0.

Results: To January 6, 2023, a total of 35 patients were enrolled and 32 patients were assessed, and followed for 3 months to 16 months. All patients received 110 mg aumolertinib daily and received at least one independent imaging evaluation by a radiologist. After administration of aumolertinib, the best response of all patients in intracranial and extracranial lesions was partial response (PR), with an iORR of 100%. At data cut-off, one patient developed intracranial primary lesion progression at 12 months after aumolertinib treatment but stable in extracranial lesions. SRT treatment was given to this patient. No grade ≥3 adverse events occurred after continued aumolertinib. The most common adverse reactions were rash and abnormal liver enzymes.

Conclusions: This report showed pronounced intracranial objective response benefit with aumolertinib in patients with intracranial oligometastatic disease followed by SRT after intracranial oligo-progression and no new safety signals. Aumolertinib has promising efficacy and good tolerability in intracranial oligometastatic EGFR mutated NSCLC.

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Legal entity responsible for the study: The authors.
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19P

Mortality among EGFR-mutated advanced NSCLC patients after frontline osimertinib treatment: A real-world, US attrition analysis

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Background: The recommended frontline therapy for patients (pts) with epidermal growth factor receptor-mutated (EGFRm) advanced NSCLC is osimertinib (osi), a 3rd-generation (gen) EGFR tyrosine kinase inhibitor (TKI); however, most will develop resistance. Approximately 28% of frontline pts treated with a 1st/2nd-gen EGFR TKI die before receiving a 2nd line of therapy (LOT) (Nieva Drugs Real World Outcomes 2022; 9:333–345). This analysis estimated mortality in EGFRm NSCLC after starting frontline osi and before 2nd LOT to determine if there is an improvement to historical rates.

Methods: Data from the ConcertAI (Cambridge, MA) Patient360 NSCLC database (>100 geographically dispersed community US oncology practices) were analyzed descriptively. Included pts were diagnosed with advanced NSCLC between 1 Jan 2018 and 16 Aug 2022, had confirmed EGFR exon 19 deletions (ex19del) or exon 21 L858R mutations, and received osi (primary analysis) or 1st/2nd-gen EGFR TKI (ie, afatinib, erlotinib, or gefitinib) as frontline monotherapy.

Results: In the ConcertAI Patient360 database, 1,135 pts had confirmed EGFR ex19del or L858R; of which 467 (41%) received osi as frontline monotherapy. Among this frontline osi population, 119 (25%) died before receiving a subsequent LOT. Documented start of a 2nd LOT was observed in 133 (28%) of frontline osi-treated pts. The remaining 215 (46%) did not have documented start of a 2nd LOT, which could be due to ongoing frontline use. A similar proportion of frontline 1st/2nd-gen EGFR TKI pts died prior to a 2nd LOT (20%; table). Survival outcomes will be presented at the meeting. These results are also being evaluated in a 2nd dataset, which may be available at time of presentation.

Table: 19P Patient attrition

Of patients receiving frontline, n (%)	Osimertinib (n = 467)	1st or 2nd-gen EGFR TKI (n = 61)[a]
Median follow-up	2.1 years	2.9 years
Died during frontline	119 (25)	12 (20)
No documented start of 2nd LOT	215 (46)	8 (13)
Started 2nd LOT	133 (28)	41 (67)

[a]Cross-cohort analysis was not conducted, and therefore, confounding factors cannot be ruled out.

Conclusions: The proportion of EGFRm NSCLC pts dying while on frontline osi (25%) remains high, demonstrating many never get to a 2nd LOT. Further optimization of frontline therapy is needed to improve patient outcomes.

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20P

Efficacy and safety of AZD3759 in previously untreated EGFR-mutant non-small cell lung cancer with central nervous system metastases in a multi-center, phase II umbrella trial (CTONG1702)

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Background: Non-small cell lung cancer (NSCLC) had poor prognosis in patients with central nervous system (CNS) metastases. Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) has changed the treatment paradigm of advanced EGFR-mutant patients. However, limited benefit has been observed in patients with EGFR mutation and CNS metastases with available EGFR-TKIs.

Methods: We initiated an umbrella trial (CTONG1702), in the 8th arm to access the efficacy and safety of AZD3759, an EGFR-TKI with high capability to penetrate the blood-brain barrier, in untreated EGFR-mutant NSCLC with brain or leptomeningeal metastases. Patients received AZD3759 200 mg or 300 mg BID. The primary objective was objective response rate (ORR). To determine whether AZD3759 has sufficient activity, we used Simon's minimax two-stage to calculate sample size.

Results: 30 patients were enrolled and received AZD3759 at 200 mg (n = 15) or 300 mg (n = 15) BID. As of June 30 2022, the median follow-up is 31.6 months. The ORR was 70% (21/30), which was 80% (12/30) in 200 mg group and 60% (9/30) in 300 mg group, respectively. The median progression-free survival (PFS) was 13.9 months and median overall survival (OS) was 37.0 months. The survival benefit was greater in 200 mg than in 300 mg groups. Treatment-related adverse events with grade ≥3 occurred in 21 (70%) patients, which was (60.0%) in 200 mg group and 13 (86.7%) in 300 mg group, respectively. The most common adverse events are rash and diarrhea. Of 16 patients who had tumor or liquid biopsy to analyze acquired resistant mechanism, 10 (62.5%) developed EGFR T790M. Of 30 enrolled patients, 13 received osimertinib as 2nd-line therapy.

Conclusions: This is the first report to present phase II study outcome of AZD3759 with promising efficacy and tolerable safety in the selected population with CNS metastases. We suggested 200 mg BID was a better dose with superior response and lower toxicity. EGFR T790M was the most common resistant mutation, and these patients still have the opportunity to receive osimertinib after progression of AZD3759.

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Legal entity responsible for the study: Chinese Thoracic Oncology Group (CTONG).

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21P

Bevacizumab plus atezolizumab and chemotherapy in NSCLC harbouring EGFR mutation previously treated with EGFR tyrosine kinase inhibitor: The BACH-NET study

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Background: Atezolizumab (A)/Bevacizumab(B)/Carboplatin/Paclitaxel (CP) has been proposed as a second-line option in EGFR mutant (EGFRm) non-small lung cancer (NSCLC) patients (pts) progressing to EGFR tyrosine kinase inhibitors (TKIs) without druggable resistance targets on the basis of an exploratory analysis of the phase III trial IMpower150. A therapeutic named use program has been open in Italy (June 2019-July 2020), although this regimen has not been approved. A real-world study has been designed in order to acquire more solid data about its feasibility.

Methods: This is a retrospective-prospective observational multicenter study with the primary aim to assess the feasibility of ABCP (rate of ineligible patients/potentially candidates) according to clinicians' selection criteria in the real-world practice of 11 Italian centres. Secondary endpoints are overall survival (OS), progression free survival (PFS), response rate (RR), disease control rate (DCR), duration of response (DoR), time to treatment failure and discontinuation (TTF and TTD), safety and quality of life (QOL).

Results: We report preliminary data from 80 EGFRm NSCLC pts progressing to TKIs. Overall, twenty-two received the ABCP regimen, with an ineligibility rate of 80%, mostly because of poor performance status (PS) and age. After a median follow-up of 14.2 months (mos), median TTD and TTF of 8.0 and 8.7 mos, respectively, were observed. The RR was 32% and DCR was 82%, with a median DoR of 3.9 mos. The median PFS was 5.7 mos and the OS was 16.2 mos. Adverse events (AEs) occurred in 15 (68%) patients: 6 (27%) G3/G4, 1 (5%) G5 (pneumonia). The most frequent AEs were: fatigue (36.4%), hypertension (18.2%), non-febrile neutropenia (18.2%). The QOL assessment through EORTC, QLQ-C30 e QLQ-LC13 scales, showed a worsening of the global health, the person's ability and the symptoms after the first or second cycle of treatment.

Conclusions: This observational study included a more representative sample of patients of the clinical practice, (poor PS; comorbidities). The high rate of ineligibility confirms this combination regimen as not feasible for most patient. Median OS, PFS and the incidence of AEs are lower than in the IMpower150 trial.

Legal entity responsible for the study: University of Padova.
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Disclosure: All authors have declared no conflicts of interest.

22P

Adding anlotinib in gradual or local progression on first-line EGFR-TKIs for advanced non-small cell lung cancer: A single-arm, multicenter, phase II trial

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Background: Anlotinib plus EGFR-TKIs continuation was a potential treatment strategy in selected advanced non-small cell lung cancer (NSCLC) after disease progression in first-line EGFR-TKIs. This study aimed to evaluate the efficacy and safety of combined EGFR-TKIs and anlotinib.

Methods: The trial aimed to enroll 120 patients after gradual or local progression in EGFR-TKIs treatment. All patients were treated with oral anlotinib 12 mg daily for 14 days every three weeks until disease progression or intolerable toxicity. The primary end-point was progression-free survival (PFS). The secondary end-points were 6 months and 12 months PFS rate, Overall response rate (ORR), disease control rate (DCR), overall survival (OS) and safety.

Results: From July 08, 2019 to December 15, 2022 the enrollment was completed, including 109 patients with gradual progression. Up to December 31, 2022, 114 patients were available for efficacy assessment (105 patients had confirmed evaluation). Median PFS of combined anlotinib and EGFR-TKIs treatment was 9.2 months (95% CI, 6.6–11.6). Confirmed ORR was 5.7% and DCR was 92.4%. The PFS rate at 6 and 12 months was 66.3% and 36.7% respectively. Safety assessment was available in 116 patients, 94% (109/116) patients were reported treatment related adverse events (TRAEs). The incidence of grade 3 or 4 TRAEs was 36.2% (42/116) and the treatment-related serious adverse event (SAE) was 7.8% (9/116). The common TRAEs were diarrhea (47.4%), hypertension (42.2%), proteinuria (39.7%), and hypertriglyceridemia (24.1%). 22.4% (26/116) of patients experienced anlotinib dose reduction.

Conclusions: EGFR-TKIs plus anlotinib demonstrated meaningful clinical control in advanced NSCLC after gradual or local progression in first-line EGFR-TKIs. And the toxicity was clinically manageable.

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Legal entity responsible for the study: Guangdong Association of Clinical Trials.
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Disclosure: All authors have declared no conflicts of interest.

23P

Impact of PDL1 expression on outcomes of patients with EGFR mutant NSCLC treated with EGFR TKIs: First results of the POET study

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Background: In EGFR mutant NSCLC, acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) inevitably occurs. To date, inconclusive results have been published or presented regarding the predictive/

prognostic role of PDL1 expression in EGFR mutant NSCLC treated with TKIs.

Methods: A retrospective analysis of patients treated with first (Erlotinib/Gefitinib), second (Afatinib) and third generation (Osimertinib) EGFR-TKIs was conducted. The main objective was to evaluate the potential correlation between levels of PDL1 expression and anti-EGFR treatment efficacy in terms of overall survival (OS) and progression-free-survival (PFS).

Results: Data from 171 patients (median age 69.0 years) who received EGFR TKIs were gathered. The most common EGFR alteration was ex19del (52.6%). 26 patients (15.2%) showed high PDL1 expression (≥50%). 105 patients (61.4%) were treated with Osimertinib, while 22.2%, 12.3% and 4.1% were treated with Gefitinib, Afatinib and Erlotinib, respectively. In the overall population, the objective response rate was 61%, mPFS 19.1 months (15.1–23.1) and 2-year OS 61.5%. Results of multivariate analysis are reported in the table. Patients with PDL1 <50% showed mPFS of 15.4 (9.3–21.5) versus 23.6 months (18.6–28.6) with first/second and third generation TKIs, respectively (p = 0.018). Patients with PDL1 ≥50% showed mPFS of 8.0 months (3.1–12.8) versus 10.2 months (0–30.5) with first/second and third generation TKIs, respectively (p = 0.03). In the high PDL1 subgroup, a significant difference in OS was observed (mOS 24.9 versus 31.3 months with first/second versus third generation TKIs; p = 0.030). No statistically significant differences were reported when the analysis was limited to the first-line setting.

Table: 23P

	Univariate HR (95% CI)	Multivariate HR (95% CI)
ECOG PS	P < 0.0001	P = 0.002
0	1.00	1.00
1	1.33 (0.80–2.21)	1.60 (0.95–2.72)
2–3	5.09 (2.70–9.60)	3.73 (1.78–7.82)
PDL1	P = 0.03	P = 0.073
<=49%	1.00	1.00
>=50%	1.87 (1.06–3.29)	1.71 (0.95–3.08)
Mutation	p = 0.11	
Esone 19	1.00	
Esone21	1.24 (0.77–2.00)	
Number of met sites	P = 0.40	
1	1.00	
2	1.69 (0.71–4.03)	
>=3	1.72 (0.78–3.79)	
Surgery	P = 0.03	P = 0.095
No	1.00	1.00
Yes	0.46 (0.23–0.93)	0.54 (0.26–1.12)
TKIs	P = 0.006	P = 0.001
Gefitinib/Erlotinib	1.00	1.00
Afatinib	0.62 (0.31–1.26)	0.48 (0.22–1.06)
Osimertinib	0.45 (0.27–0.73)	0.36 (0.21–0.61)
First-line	P < 0.0001	P = 0.08
No	1.00	1.00
Yes	0.14 (0.06–0.35)	0.39 (0.13–1.12)

Conclusions: Our study supports the survival benefit of Osimertinib compared to first/second generation TKIs, regardless of PDL1 expression. A larger data collection is ongoing and updated results will be presented at the Conference.

Legal entity responsible for the study: The authors.

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Disclosure: E. Bria: Financial Interests, Personal, Advisory Board: AstraZeneca, Roche, BMS, MSD, Eli Lilly, Amgen; Financial Interests, Institutional, Research Grant: AstraZeneca, Roche. S. Pilotto: Financial Interests, Personal, Invited Speaker: Bristol Myers Squibb, AstraZeneca, Merck & Co., Roche, Amgen, Novartis; Financial Interests, Personal, Advisory Board: Merck & Co., Amgen, AstraZeneca, Novartis; Financial Interests, Personal, Expert Testimony: Takeda; Financial Interests, Personal, Research Grant: Bristol Myers Squibb, AstraZeneca; Non-Financial Interests, Personal, Principal Investigator: AstraZeneca, Roche. All other authors have declared no conflicts of interest.

24P

Efficacy and safety of 1st generation EGFR TKI retreatment in EGFR mutation-positive, T790M-negative patients previously treated with 1st or 2nd generation EGFR TKI and cytotoxic chemotherapy

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Background: Although osimertinib has been approved as first-line therapy, 1st or 2nd generation EGFR TKIs are still being used as first-line therapy. Although T790M acquired resistance occurs 30 to 40% after the treatment of the 1st- or 2nd-generation EGFR TKIs, most cases of T790M mutation-negative patients undergo cytotoxic chemotherapy or other supportive treatment. There are several reports that EGFR TKI re-administration may be helpful in T790M-negative patients. We did prospectively undergo EGFR TKIs retreatment trial as a third or later line treatment.

Methods: The enrolled patients were resistant to 1st or 2nd generation EGFR-TKI as a 1st-line treatment and then treated with chemotherapy for more than 4 cycles because of T790M-negative at 2nd biopsy. The primary endpoint was objective response rate (RR), and the secondary endpoints were progression free survival (PFS), overall survival (OS), and safety.

Results: In total, 63 patients retreated with gefitinib (n = 34) or erlotinib (n = 29) after the progression of 2nd or more line chemotherapy. The median age was 65. The best RR and disease control rate were 14 and 51%, respectively. The median duration of treatment was 65 days (gefitinib 56 days vs. erlotinib 90 days). The median PFS was 2.8 months (gefitinib 1.8 vs. erlotinib 3.5 months), median OS was 8.5 months (gefitinib 8.3 vs. erlotinib 9.0 months). The development rate of T790M after the retreatment of EGFR TKIs was 32% (20/63). Acquired T790M mutation developed in 13 of 20 patients (65%) who had exon 19 del. The median duration from the start of EGFR TKI retreatment to the date of the T790M mutation development was 5.2 months. There was a statistical difference in OS between T790M-negative and induced patients (5.4 vs. 28.9 months, P < 0.001). The most common adverse events were diarrhea and skin toxicities.

Conclusions: Retreatment with EGFR-TKIs can be considered an option after the failure of chemotherapy for patients who were previously controlled by EGFR-TKI. The 1st generation EGFR TKIs retreatment may induce T790M mutation (32%) in patients who had not previously T790M mutation, leading to 3rd generation EGFR TKI sequential treatment and eventually prolong OS.

Clinical trial identification: NCT03382795.

Legal entity responsible for the study: The authors.

Funding: Chong Kun Dang Pharmaceutical Company.

Disclosure: All authors have declared no conflicts of interest.

25P
Furmonertinib plus icotinib for first-line treatment of EGFR-mutated non-small cell lung cancer

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Background: Furmonertinib is a highly brain-penetrant, pan epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) with activity against EGFR classical, T790M resistant and Ex20ins mutations. Icotinib is a first-generation EGFR TKI widely used in China and may overcome the resistance of furmonertinib due to EGFR C797S mutation. Furmonertinib plus icotinib may delay emergence of acquired resistance in the first-line setting.
Methods: This ongoing phase II study enrolled untreated advanced non-small cell lung cancer (NSCLC) patients with Ex19Del/L858R/Ex20ins mutation. Patients with stable central nervous system (CNS) metastases were allowed to enroll. The regimen consisted of furmonertinib (80 mg p.o, qd) and icotinib (125 mg p.o, tid). The primary endpoint was PFS. Secondary endpoints were ORR, DCR, OS, and safety.
Results: 40 patients were planned to be enrolled in this study. As of Nov 30 2022, 18 patients were enrolled and received study treatment. Patients' baseline characteristics included median age 61.5-years (range 43–82), female 55.6%, ECOG PS 0/1/2 0/88.9%/11.1%, Ex19Del/L858R/Ex20ins 55.6%/38.9%/5.6%, CNS metastases 83.3%. Median follow-up was 230 days and the median PFS was not yet reached. The confirmed ORR assessed by investigator based on RECIST 1.1 was 88.9% (16 PR), DCR was 100% (16 PR, 2 SD). In patients with CNS metastasis the ORR was 86.7%, and the DCR was 100%. Tumor shrinkage was observed in all patients with a median best percent change of −34.3% (range: −76.1, −27.1). The most commonly observed treatment-emergent adverse events (TEAEs) included diarrhea, liver enzyme elevation and rash. One patient experienced a grade 3 TEAE due to diarrhea, and no other grade≥3 TEAE was observed.
Conclusions: Furmonertinib plus icotinib as first-line treatment showed encouraging antitumor activity and well tolerated safety profile in EGFR-mutated NSCLC. The observed AEs were consistent with those previously reported. This study is still ongoing and more results will be evaluated in the future, which may contribute to definite the role of dual EGFR TKI therapy in first-line setting.
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26P
Real-world use of tyrosine kinase inhibitors (TKI) in epidermal growth factor receptor mutated (EGFRm) advanced non-small cell lung cancer (NSCLC) in nine countries

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Background: EGFR mutations occur in 10–50% of NSCLC patients globally. EGFR testing is recommended for NSCLC, with EGFR-TKIs recommended as the optimal first-line (1L) treatment for patients with advanced EGFRm NSCLC. This study investigated EGFR testing turnaround time and real-world treatment patterns in patients with advanced EGFRm NSCLC in nine countries.
Methods: A retrospective chart review was conducted from June to September 2021 in Argentina, Belgium, Brazil, India, Netherlands, Russia, Singapore, Switzerland, and Turkey. Overall, 947 case report forms were collected for patients who presented with advanced/metastatic (stage IIIB/C/IV) NSCLC who received a positive first EGFR test result between 01 April 2017–31 March 2018 (index date). Data on demographics, clinical characteristics, EGFR testing, and treatment patterns were abstracted from diagnosis until June 2020 (or death).
Results: Demographics and clinical characteristics are described in the table. Median EGFR test turnaround time was 14 days (Interquartile Range: 10–22). Overall, 69% of patients received a 1L (post-index) EGFR-TKI (48% 1st Generation), 13% received chemotherapy alone, 9% received another regimen, and 9% did not receive any treatment. Median time to first subsequent therapy (TTFST) after initiation of 1L EGFR-TKI was 22.2 months.

Table: 26P

	Overall n = 947
Median age at diagnosis, years (range)	61.4 (20.0–90.0)
Sex, n (%)	
Male	500 (53%)
Female	447 (47%)
Smoking status, n (%)	
Current smoker	141 (15%)
Ex-smoker	291 (31%)
Never smoked	393 (41%)
EGFR Test performed as single gene test or as part of a panel, n (%)	
Single gene test	606 (64%)
Part of a panel	341 (36%)
EGFR Mutation type recorded since diagnosis (most commonly reported), n (%)	
Exon 19 deletion	346 (37%)
L858R	310 (33%)
T790M	115 (12%)

Conclusions: Median EGFR test turnaround time was longer than the 10 working days recommended by guidelines; suggestive of the need to improve EGFR testing practices to ensure timely initiation of targeted therapy. As this study included dates up until 2020, testing practices may have improved since study end. For patients treated with an EGFR-TKI as 1L therapy, TTFST in this real-world study was favourable. However, 31% of EGFRm patients did not receive a 1L EGFR-TKI. The results suggest an unmet need to optimise treatment strategies for patients with advanced EGFRm NSCLC.
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27P

Amivantamab versus alternative real-world anti-cancer therapies in patients with advanced non-small cell lung cancer with epidermal growth factor receptor exon 20 insertion mutations in the US and Europe

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Background: Amivantamab was the first approved therapy for advanced/metastatic NSCLC harboring EGFR exon 20 insertion mutations (Ex20ins) who progressed on platinum chemotherapy (CT). Since Ex20ins is uncommon, it may be confused with activating EGFR mutations resulting in treatment with limited benefit. This study estimates the relative effectiveness of amivantamab versus alternative anti-cancer treatments used in real-world settings for NSCLC with Ex20ins.

Methods: Data from the single-arm CHRYSALIS trial were compared to an external cohort of patients derived from six US and European real-world data sources that met the CHRYSALIS Cohort D+ eligibility criteria. Amivantamab was compared to EGFR TKIs including osimertinib, immunotherapy, non-platinum CT, VEGFi + CT, and others. Patient-level data were used to adjust for differences in prognostic factors using inverse probability weighting (average treatment effect among the treated). Binary and time-to-event endpoints were analyzed using weighted logistic regression and proportional hazards regression, respectively.

Results: After adjustment, baseline characteristics between the two cohorts were balanced. For all individual treatment class comparisons, results were consistently in favor of amivantamab in overall survival (OS), progression free survival (PFS), time to next treatment (TTNT), and overall response rate by investigator (ORR-INV) (see table). Compared to osimertinib, amivantamab provided a significant advantage in ORR-INV (36.8% vs 0%), OS (HR [95% CI]: 0.37 [0.19, 0.73]) and TTNT (HR [95% CI]: 0.55 [0.31, 0.98]).

Conclusions: Based on this adjusted treatment comparison, amivantamab provides significant benefits compared to alternative therapies used in real world practice. Education on appropriate treatment choice is important to advance quality of cancer care.

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Table: 27P

			Adjusted Hazard Ratio (95% CI) for amivantamab vs. other treatment		
Treatment	N	ORR-INV	OS	PFS-INV	TTNT
Amivantamab	114	36.8%	–	–	–
All EGFR TKIs	69	5.3%	0.46 (0.30, 0.72)	0.51 (0.34, 0.76)	0.38 (0.26, 0.55)
Osimertinib subgroup	22	0.0%	0.37 (0.19, 0.73)	0.67 (0.33, 1.37)^	0.55 (0.31, 0.98)
Immunotherapy	91	13.2%	0.40 (0.27, 0.60)	0.42 (0.31, 0.58)	0.41 (0.29, 0.57)
Non-platinum chemotherapy	87	18.1%	0.45 (0.29, 0.70)	0.52 (0.36, 0.76)	0.36 (0.25, 0.53)
VEGFi + chemotherapy	57	21.4%^	0.54 (0.34, 0.85)	0.60 (0.42, 0.87)	0.53 (0.35, 0.79)
Other	79	27.2%^	0.58 (0.36, 0.92)	0.61 (0.43, 0.87)	0.51 (0.35, 0.75)

^No statistically significant difference vs. amivantamab; all other values significant.

28P

Generation and validation of a predictive model using pretreatment clinical factors for estimating survival and T790M mutation in EGFR-mutated non-small cell lung cancer in Taiwan

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Background: Although epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) have been the standard treatment for advanced EGFR-Mutated NSCLC, the generation and validation of a comprehensive platform in predicting survival of these patients remain rare.

Methods: From October 2010 to 2021, we collected potential prognostic factors from advanced stage NSCLC patients receiving EGFR-TKI treatment at National Chen-Kung University, Tainan, Taiwan (NCKUH). Using univariate and multivariate analyses, we identify potential prognostic factors and create a nomogram for risk stratification accordingly. Then we validated the platform in another cohort from Chang Gung Memorial Hospital.

Results: Records of 761 EGFR-Mutated NSCLC patients from NCKUH were retrospectively reviewed. Using univariate analysis, we identified 8 prognostic factors including sex, ECOG status, morphology, mutation, stage, the choice of EGFR-TKIs, and metastasis to liver, brain and multivariate analysis confirmed their independent significance. We established a nomogram based on these factors and successfully classified patients into different risk groups with different survival. This nomogram can be used to predict the possibility of 6-,9-, and 12-month PFS and stratify patients into different risk groups for PFS and OS. In addition, patients with shorter PFS predicted by the nomogram had significantly higher incidence of acquired T790M mutation upon disease progression, which implied the early emergence of T790M might be predicted by this nomogram. We then successful validated the risk score in another cohort including 751 EGFR-Mutated NSCLC patients from Chang-Gung Memorial Hospital. The calibration curves for the probability of survival at 6, 9, and 12 months after EGFR-TKI use revealed a good concordance between the nomogram prediction and actual observation. Moreover, the calibration curves of these two cohorts showed similar pattern.

Conclusions: Our risk stratification can provide additional information to clinicians to evaluate the prognosis and the chance of sequential therapy in patients with EGFR-Mutated NSCLC patients who received targeted therapy.

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29P

Real-world data of atezolizumab in combination with bevacizumab, and platinum-based chemotherapy for EGFR-mutant metastatic non-small cell lung cancer patients after failure of EGFR tyrosine kinase inhibitors

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Background: IMpower150 study showed that the combination of immune chemotherapy plus bevacizumab provided a favorable efficacy for patients with non-squamous lung cancer harboring EGFR mutations. Although its effectiveness has been approved, little is known about the clinical outcome of the combination therapy in routine practice, especially for the Asian population with high EGFR mutation incidence. The current study aimed to explore the clinical efficacy and prognosis of combinational treatment with atezolizumab, bevacizumab, and platinum-based chemotherapy in patients with EGFR-mutated lung cancer who progressed with standard EGFR-targeted therapies.

Methods: From April 2019 to June 2022, we retrospectively collected patient-level data on atezolizumab-bevacizumab-chemotherapy combination treatment in NSCLC patients with EGFR mutations after the failure of EGFR TKIs at the National Taiwan University Hospital. The patient's clinical characteristics and treatment outcomes were recorded.

Results: We collected 36 patients, including 28 females and 35 non-smokers. The median age was 59.5 (range 40.4–81.3) years. EGFR mutation types included 13 deletion in exon19, 19 L858R, and 4 uncommon types. Before the combination therapy, 24 (66.7%) patients and 11 (30.6%) patients have taken osimertinib and anti-angiogenesis, respectively. PD-L1 expression was ≧ 1% in 19 (52.8%) patients. The treatment outcomes included a response rate of 44.4% (16 of 36), median progression-free survival (mPFS) of 7.8 months, and median overall survival of 16.7 months. Patients with PD-L1 expression ≧ 1% have a loner mPFS than those with PD-L1 expression <1% or unknown (10.6 months vs. 2.5 months vs. 7.8 months; $p < 0.001$). There were no significant differences in response rates and PFS between patients with and without malignant pleural effusion, liver, or brain metastasis.

Conclusions: The combination treatment of atezolizumab, bevacizumab, pemetrexed, and cisplatin/carboplatin provided favorable efficacy in EGFR mutation-positive NSCLC after TKI failure, and higher PD-L1 expression (≧ 1%) was associated with longer PFS.

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30P

Real-world disease characteristics and treatment patterns in patients with advanced non-small cell lung cancer and EGFR in Brazil and Taiwan

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Background: Advanced non-small cell lung cancer (aNSCLC) treatment (tx) decision-making is complex, with prognosis and tx influenced by molecular alterations. Data are limited on how epidermal growth factor receptor mutation (EGFRm) subtypes influence tx choice in clinical practice. We aimed to describe disease characteristics and tx patterns in aNSCLC patients (pts) with EGFRm.

Methods: Data were drawn from the Adelphi NSCLC Disease Specific Programme™, a point-in-time survey of oncologists/pulmonologists, collected in Brazil and Taiwan from Jul-Nov 2020. Physicians reported characteristic and tx data for the next 5 consulting adult aNSCLC pts with EGFRm, including pts with point-mutation in exon 21 (exon 21) and/or deletion in exon 19 (exon 19). Data analysis was descriptive.

Results: Of 471 pts, 26% (n = 124) had exon 21 and 35% (n = 167) had exon 19. Median age was 65.0 years, 57% were female and 87% had adenocarcinoma. At aNSCLC diagnosis, 77% were stage IV and 69% had an Eastern Cooperative Oncology Group performance status of 0–1. EGFR tyrosine kinase inhibitor (TKI) monotherapy (mono) was the most common first-line (1L) tx; 41% of pts received first generation (1G), 21% second generation (2G) and 16% third generation (3G) EGFR TKI regardless of mutation type. 26% of exon 21 and 27% of exon 19 pts received 2G EGFR TKI, while 9% and 21%, respectively, received 3G EGFR TKI. Of pts who completed 1L tx (n = 55), most (84%) had partial response regardless of mutation type (94% of exon 21, n = 15; 84% of exon 19, n = 21). Median time to discontinuation (TTD) of 1L was 14.2 months (mo) overall (n = 61); 17.1 mo in exon 21 (n = 16) and 16.0 mo in exon 19 (n = 27). Median time to next tx was 15.0 mo overall (n = 61); 19.0 mo in exon 21 (n = 15) and 17.0 mo in exon 19 (n = 27). Median real-world progression free survival (excluding death; rwPFS) was 15.1 mo overall (n = 61); 19.2 mo in exon 21 (n = 15) and 16.6 mo in exon 19 (n = 27).

Conclusions: Pts with EGFRm generally received EGFR TKI mono, including those with exon 21 and exon 19. Exon 21 pts had longer TTD and rwPFS (no formal comparison was made between groups). Future research should examine whether different sensitizing EGFR mutations have an impact on pt outcomes.

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31P

EGFR mutation rate and spectrum in Ukrainian patients with advanced NSCLC: Relation to gender and PD-L1 expression

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Background: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) and immunotherapy are the core options for advanced non-small cell lung cancer (NSCLC) treatment. The efficacy of EGFR-TKI therapy was shown to vary depending on sex. And furthermore, EGFR alterations can impact PD-L1 expression and immunotherapy benefits. The aim of this study was to investigate the prevalence of clinically actionable EGFR mutations and their relation to PD-L1 expression with respect to gender in the Ukrainian cohort.

Methods: This retrospective study included 907 patients, diagnosed with advanced NSCLC who were tested for EGFR mutations and PD-L1 expression. There were 797 patients (87,9%) with adenocarcinoma (AC), 101 patients (11,1%) with squamous cell carcinoma (SCC) and 9 individuals (1%) with large cell neuroendocrine carcinoma (LC-NEC). EGFR mutation status in tissue samples was assessed by either NGS (n = 83) or qPCR (n = 824). PD-L1 testing was performed by IHC.

Results: SCC rate was higher in males (13,3% vs 8,4%), females demonstrated prevalence of AC (91,1% vs 85,3%; P = 0,022). 78 (21,5%) out of 363 women with AC were under 50 y.o., while only 65 out of 434 (15%) men were younger than 50 at the time of AC diagnosis (P = 0,027). 198 out of 907 patients (21,8%) had EGFR-mutant NSCLC. Patients with AC harbored EGFR mutations twice as frequently (187 out of 797 patients; 23,5%) as compared to SCC (9 out of 101; 8,9%; P = 0,004). There was no statistically significant difference in PD-L1 expression between NSCLC of different histology and EGFR status. EGFR mutation rate was higher in females (35,5%) compared to males (11,2%; P < 0,001). The Ex19del and L858R variants predominated in both males and females. However, females demonstrated a higher rate of sensitizing EGFR mutations (87,9% vs 71,9% in males). Males with NSCLC carried more exon 20 alterations, including in-frame insertions and T790M mutation (15,8% vs 4,3% in females) and presented uncommon variants including G719X, L861Q and S768I (10,5% vs 4,3%) more frequently (P = 0,009).

Conclusions: There are profound gender differences in the rates and spectrum of EGFR mutations in NSCLC with no relation to PD-L1 expression. Gender differences in EGFR mutation landscape can affect response to treatment.

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32P

Atezolizumab plus albumin paclitaxel-based regimens is an optional treatment for EGFR-mutant patients with SCLC transformation after EGFR-TKI

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Background: SCLC transformation is one of the acquired resistance mechanisms for epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) in EGFR mutation-positive non-small cell lung cancer (NSCLC) patients. It remains unclear whether the addition of

atezolizumab to chemotherapy could prolong PFS and OS of patients with SCLC transformation after EGFR-TKI treatment.

Methods: Three groups of advanced lung adenocarcinoma patients who relapsed after EGFR-TKI were analyzed in this retrospective study: cohort A included patients who did not undergo SCLC transformation and received atezolizumab plus chemotherapy after EGFR-TKI; cohort B included patients with SCLC transformation and following atezolizumab treatment; cohort C included patients who underwent SCLC transformation and did not receive atezolizumab treatment.

Results: Twenty-six patients were enrolled in this research (cohort A: N = 6; cohort B: N = 6; cohort C: N = 14). Five of six patients in group A and all patients of group B received atezolizumab plus albumin paclitaxel-based regimens. In addition, five of six patients received atezolizumab plus albumin paclitaxel-based regimens after conventional etoposide/platinum treatment. Etoposide/platinum +/− EGFR-TKI regimens were given to all patients in group C as first-line treatment after SCLC transformation. DCR (83.3% vs 100.0%, p = 0.224) and ORR (0% vs 16.7%, p = 0.224) were similar between cohort A and cohort B. Comparable median PFS (3.5 m vs 4.7 m, p = 0.086), median OS from diagnosis of advanced stage lung cancer (33.7 m vs 54.3 m, p = 0.077), and median OS from atezolizumab implementation (6.7 vs 7.6 m, p = 0.627) were observed between group A and group B. No significant differences in median PFS between group B and group C (4.7 m vs 3.5 m, p = 0.754). Patients in cohort B presented a tendency to have better median OS from diagnosis of stage IV lung cancer (45.4 m vs 22.5 m, p = 0.180) and better median OS from SCLC transformation (24.1 m vs 11.5 m, p = 0.092) compared with cohort C.

Conclusions: In patients with SCLC transformation after EGFR-TKI, atezolizumab plus albumin paclitaxel-based regimen was a treatment choice after conventional etoposide/platinum regimens.

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33P

Real-world experience of MET TKI-induced peripheral edema

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Background: Peripheral edema (PE), a class effect of MET TKIs, can impact treatment (tx) adherence. We conducted the Powerhouse Insights from Virtual Oncology Therapeutic Specialists (PIVOTS) survey of physicians' experience with MET TKIs to better understand associated PE and optimize its management.

Methods: An online survey assessed onset, time to resolution, symptoms, prevention, and management of PE during tx with four available MET TKIs for MET exon 14 skipping NSCLC (tepotinib, capmatinib, savolitinib and crizotinib).

Results: In total, 26 physicians participated: Asia (14), Europe (6), UK (2) and North America (4). 24 physicians had experience with tepotinib, 10 with savolitinib, 20 each with capmatinib and crizotinib, and 7 with all four MET TKIs. Six physicians had experience with >20 patients (pts), 9 with 10–20 pts, 6 with 5–10 pts and 5 with <5 pts treated with a MET-TKI. 77% of physicians reported that >50% of pts had PE with MET TKIs. Low mobility, age, and time on tx were reported as common risk factors, and cardiac disease as the most common comorbidity. PE onset, which may take >6 months, and time to improvement was considered similar among MET-specific TKIs, with crizotinib (a multi-kinase TKI) resulting in less frequent, less severe, and less durable PE. Swollen extremities were reported by 96% of physicians as the most bothersome symptom followed by pain (46%) and weight gain (31%), with a resolution time of up to 3 months in mild-moderate PE and up to 6 months in severe PE. Pain (81% vs 23%) and skin lesions (50% vs 23%) were reported as more common in severe vs mild-moderate PE, respectively. 62% of physicians incorporated multiple preventive measures simultaneously (bed/feet elevation [88%], compression stockings [69%], massage [63%], salt intake reduction [50%], exercise/diuretics [25%]); only 13% incorporated at tx initiation. The most common tx were diuretics (89%), non-pharmacologic measures (85%), MET TKI interruption (73%) and dose reduction (65%); 4/5 Chinese physicians reported consulting vascular specialists.

Conclusions: The PIVOTS survey indicates the most important unmet needs for PE management are developing effective tx, incorporating preventive measures at MET TKI initiation (not only at PE onset), and clarity of its mechanism of action associated with MET TKI.

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Treatment sequencing in the VISION study of tepotinib in patients with MET exon 14 (METex14) skipping NSCLC

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Background: Tepotinib is a MET TKI approved for METex14 skipping NSCLC. We report Tx sequencing prior/post tepotinib of immunotherapy (IO), chemotherapy (CT) and METi (post only) in VISION (data cut-off: Feb 20, 2022).

Methods: Pts with advanced/metastatic METex14 skipping NSCLC received 500 mg (450 mg active moiety) tepotinib QD. Primary endpoint: objective response (RECIST 1.1) by IRC. Prior/post tepotinib Tx was investigator's choice; outcomes were reported per investigator.

Results: Of 313 pts (median age 72), 164 were Tx naïve (median age 74) and 149 previously treated (median age 70.8). Among previously treated pts, the most common 1L regimen prior to enrolling in VISION was platinum-CT without IO (58%), then IO monotherapy (23%) and IO-CT (13%). Across all prior 1L regimens, median duration of Tx was 4 mo (IQR 1.8–7.3), with an ORR of 24.8%, mDOR of 6.0 mo (IQR 4–12) and mPFS of 4.0 mo (IQR 2–8.5) (outcomes by Tx regimen in table). In contrast, 1L outcomes to tepotinib were greatly improved with an ORR of 56.1%, mDOR of 46.4 mo and mPFS of 12.6 mo. Overall, 265 pts (84.7%) discontinued tepotinib; 124 pts (46.8%) received subsequent Tx. 48 pts received subsequent METi (20 crizotinib, 15 capmatinib, 4 bozitinib, 3 tepotinib, 3 amivantamab, 3 cabozantinib, 4 other; 4 pts received different METi in subsequent lines). 31 pts received subsequent METi immediately after tepotinib (11 1L and 20 2L+ pts). BOR across all subsequent METi was 3 PR (1 pt received METi immediately after tepotinib, 2 pts received CT/IO regimens followed by METi), 11 SD; longest mDOR and mPFS were 4.0 and 2.5 mo, respectively. Outcomes to subsequent CT/IO were comparable to outcomes of prior CT/IO as well as those reported in literature.

Table: 34P

Outcomes with:	No. pts receiving Tx	ORR, %	mDOR, mo	mPFS, mo
1L Tx* prior to tepotinib by investigator assessment				
IO+platinum CT	19	26.3	5.0	5.0
IO mono	34	23.5	7.5	5.0
Platinum-CT without IO	87	27.6	5.0	4.0
Tepotinib by IRC				
1L	164	56.1	46.4	12.6
2L	92	45.7	12.6	10.9
+3L	57	43.9	10.8	11.0
Post tepotinib Tx by investigator assessment				
Subsequent CT	31	6.5	3.0	2.0
Subsequent IO	43	14.0	8.0	3.0

*9 patients received other 1L Tx. CT, chemotherapy; IO, immunotherapy; Tx, treatment.

Conclusions: Robust and durable efficacy, particularly in the 1L setting, support early use of tepotinib in Tx sequence. Almost half of this elderly population received subsequent Tx, higher than the 20–30% reported for 1L CT/IO IPSOS trial in elderly pts (median age 75). METi Tx sequencing analyses ongoing.

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35P
Drug treatment management of advanced ALK-positive non-small cell lung cancer in Spain: A real-world cross-sectional analysis

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Background: In Spain, new generation ALK inhibitors have been added as new therapeutic options, with specific indications, to those already available for advanced or metastatic ALK-positive non-small cell lung cancer (mNSCLC ALK+). In this context it is key to understand current treatment management of this subpopulation by line in clinical practice, as well as the most prescribed treatment sequences, as in most cases they have not been fully established.

Methods: This is a cross-sectional, population-based observational study, based on IQVIA Oncology Advantage dataset, that includes drug-treated anonymized mNSCLC ALK+ patient cases in real clinical practice reported by senior physicians at a quarterly basis in Spain. The sample of 368 mNSCLC ALK+ patients reported between July 2021 and June 2022 was selected for the study. Patients participating in phase II or III clinical trials were excluded (N = 29). A descriptive analysis of all therapeutic regimens prescribed by line was performed (1L, 2L, and 3L+, respectively), using absolute and relative frequencies, as well as an identification of main treatment sequences across lines based on the subpopulation currently on 2L+.

Results: A sample of 339 patients was analyzed, 163 in 1L, 90 in 2L and 86 in 3L+. Patients were mostly treated in 1L with alectinib (N/%) (138/85%), followed by brigatinib (8/5%), the share of the first ALK inhibitor commercialized, crizotinib, of being 4% nowadays. In 2L, alectinib (29/32%), lorlatinib (27/30%), and brigatinib (9/10%) were the most prescribed treatments; and in 3L+, immunotherapy (IO) (27/31%), lorlatinib (18/21%), and platinum-based regimens (18/21%). The most common sequence from 1L to 2L among patients currently on 2L was alectinib-lorlatinib (27/30%). Among patients currently on 3L+, the most prescribed sequences 1L-2L-3L+ were crizotinib-alectinib-lorlatinib (12/14%), and crizotinib-alectinib-IO or alectinib-lorlatinib-IO both in the same proportion (8/9%).

Conclusions: New drugs marketed in Spain for mNSCLC ALK+ patients seem to have gained importance in 2L and 3L. Additional approvals are expected so clinical practice could continue evolving.

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36P
Prevalence, clinical characteristics, and treatment outcomes of patients with BRAF-mutated advanced NSCLC in China: A real-world multi-center study

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Background: BRAF mutation is one of the targetable oncogenic driver mutations in non-small-cell lung cancer (NSCLC). However, the prevalence, real-world treatments and clinical outcomes are rarely reported in Chinese BRAF-mutated NSCLC patients.

Methods: The next-generation sequencing (NGS) data of 137,798 Chinese NSCLC patients from the Lung Cancer Big Data Precise Treatment Collaboration Group (LANDSCAPE) project (Cohort I) were analyzed to derive the prevalence of BRAF mutations. We also retrospectively collected clinical and survival data of 129 advanced NSCLC patients with primary BRAF mutation from two centers between December 2015 and September 2022 (Cohort II). Baseline characteristics, treatment pattern and outcomes were analyzed in Cohort II.

Results: In Cohort I, 4409 patients (3.2%) were confirmed to harbor a BRAF mutation. BRAF V600E accounted for 28.7% of all BRAF mutation. In Cohort II, 62% (80/129) were BRAF V600 mutation with median age of 63.0 years. Of 99 patients who receive NGS, 79 (79.8%) patients had concomitant mutations, with TP53 of the highest incidence (33.3%). For patients received first-line dabrafenib plus trametinib (dab-tram) (N = 38), the median progression-free survival (PFS) was 25.0 months (95% CI: 13-NA), which is significantly longer than chemotherapy (N = 38, mPFS 8.4 months, 95%CI: 6.3–19.2, P = 0.023) and other regimens (N = 11, mPFS 8.0 months, 95%CI: 7.8-NA, P = 0.046). A numerically longer mPFS was also observed with dab-tram versus immunotherapy based therapy (N = 22, mPFS 11.4 months, 95%CI: 7.8-NA, P = 0.25). After applying inverse probability of treatment weighting (IPTW), the above differences still existed.

Conclusions: In the study with the largest sample size so for, 3.2% of Chinese NSCLC patients were observed to have BRAF mutations. The more favorable PFS benefit demonstrated by first-line dabrafenib plus trametinib compared with all other therapy regimens indicates the optimal treatment choice for Chinese BRAF-mutated NSCLC patients.

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37P

Pralsetinib in acquired RET fusion-positive advanced non-small cell lung cancer patients after resistance to EGFR/ALK-TKI: A China multi-center, real-world data (RWD) analysis

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Background: RET-fusion was reported contribute about 2% of acquired resistance mechanisms of EGFR/ALK-TKIs. Selective RET inhibitor pralsetinib demonstrated impressive improvement of survival in patients with RET+ aNSCLC in the I/II ARROW study. However, the efficacy in patients with acquired RET-fusion after resistance to EGFR/ALK-TKIs was only reported by case, and the strategy of overcome the acquired RET-fusion has not been fully investigated.

Methods: This multicenter, retrospective, real-world data analysis enrolled thirty-one aNSCLC with acquired RET-fusion after resistance to EGFR/ALK-TKIs in 23 centers across China from Jan 1st, 2015 to Nov 23rd, 2022. Cohort 1 including 20 patients who received pralsetinib immediately after RET-fusion was detected, of which 15 patients received pralsetinib combined with EGFR/ALK-TKI. Eleven patients who underwent standard chemotherapy in combination with or without immunotherapy or antiangiogenesis therapy on acquired RET+ occurred were enrolled in Cohort 2. Molecular profile, objective response rate (ORR), disease control rate (DCR), progression free survival (PFS), time to treatment failure (TTF), toxicity was assessed.

Results: 25.8% (8/31) patients lost EGFR mutation when RET-fusion was detected. EGFR 19del (64.5%) was more likely to develop acquired RET+ compared with L858R mutation (29.0%). CCDC6 was the most common RET-partners (38.7%), followed by KIF5B (19.4%), and NCOA4 (16.1%). In Cohort 1, ORR was 35.0% and DCR was 75.0%, which were higher than Cohort 2 (18.2% and 54.6%, respectively). Patients who received pralsetinib-based therapy had a longer PFS and TTF compared with patients in cohort 2 (PFS: 8.42 months vs. 6.97 months, TTF: 6.48 months vs. 4.24 months). Pralsetinib and EGFR-TKI combination therapy was generally well tolerated, with AEs consistent with known profile of the two drugs.

Conclusions: Pralsetinib-based therapy may be a potential strategy to overcome the acquired RET-fusion after resistance of EGFR/ALK-TKIs.

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38P

Matching-adjusted indirect comparison (MAIC) of treatment outcomes for selective RET inhibitors, selpercatinib and pralsetinib, in non-small cell lung cancer (NSCLC)

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Background: Selpercatinib (SELP) and pralsetinib (PRAL) are approved for RET fusion-positive advanced NSCLC, based on the LIBRETTO-001 and ARROW trials. No randomized direct comparison of SELP and PRAL is available or ongoing.

Methods: MAIC was conducted between the NSCLC data from LIBRETTO-001 (June 2021 datacut) and ARROW (March 2022 datacut). LIBRETTO-001 results were weighted to match ARROW baseline characteristics. Objective response rate (ORR), progression-free and overall survival (PFS and OS) were compared for treatment-naive (TN) and platinum-pretreated (PP) cohorts using 95% confidence intervals for hazard ratios (HR) and odds ratios (OR). Safety was also compared.

Table: 38P Comparative efficacy and safety for SELP and PRAL in RET fusion-positive NSCLC estimated by MAIC

	SELP		PRAL		OR/HR Comparison (SELP vs PRAL)	
Study measure, (95% CI)	TN (N_{eff} = 37)	PP (N_{eff} = 193)	TN (n = 116)	PP (n = 141)	TN	PP
ORR, %	77.1 (67.4, 90.1)	59.2 (53.5, 64.7)	72.4 (63.3, 80.3)	59.6 (51.0, 67.7)	1.29 (0.67,4.06)	0.98 (0.70,1.43)
Median PFS, mo	17.1 (11.5, 22.0)	24.9 (19.3, NR)	12.5 (9.2, 16.5)	16.3 (10.8, 22.2)	0.81 (0.52, 1.26)	0.67 (0.50, 0.90)*
Median OS, mo	32.3 (18.5, NR)	NR (30.3, NR)	NR (31.9, NR)	44.3 (25.0, NR)	1.20 (0.69, 2.09)	0.68 (0.48, 0.97)*
	SELP NSCLC Safety Population (N_{eff} = 247)		PRAL NSCLC Safety Population (N = 281)		OR (95% CI)	
Grade ≥3 TRAEs, %	39.3 (34.8, 43.9)		62.6 (56.7, 68.3)		0.39 (0.29,0.49)*	
Discontinuation due to TRAEs, %	3.6 (1.4, 5.4)		10.0 (6.7, 14.1)		0.34 (0.14,0.58)*	

PRAL is the reference group when calculating OR/HR. *statistically significant; N_{eff}- effective sample size; NR = not reached.

Results: Weighted ORRs were similar for SELP and PRAL, as were PFS and OS in TN patients (table). In PP patients, PFS and OS were significantly longer for SELP. There were fewer grade ≥3 treatment-related adverse events (TRAE) and lower rates of treatment discontinuation due to TRAE in patients receiving SELP. The difference in % of Asian patients impacted weighted results.

Conclusions: The efficacy of SELP and PRAL was similar. SELP was associated with fewer grade ≥3 TRAE and treatment discontinuations due to TRAE. Inherent limitations of MAIC are acknowledged.

Clinical trial identification: LIBRETTO 001 NCT03157128 ARROW NCT03037385.

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Preliminary clinical investigations and mechanism exploration of furmonertinib in NSCLC with EGFR exon 20 insertion

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Background: Here we analyzed the clinical efficacy of furmonertinib, a novel 3rd generation EGFR TKI, in advanced NSCLC patients (pts) who harboring EGFRex20ins and explored mechanism.

Methods: A retrospective single-arm analysis was performed to evaluate the efficacy of 20 NSCLC pts harboring EGFRex20ins receiving furmonertinib treatment from three institutions. Meanwhile, we investigated the clinical efficacy of furmonertinib versus osimertinib as second-line treatment, because pts about furmonertinib as first-line treatment were immature. In addition, the binding activity of different EGFR TKIs to EGFRex20ins were computationally constructed based on the crystal structure of EGFR_D770_N771insNPG/V948R (PDB ID: 7LGS) by the Schrödinger software (2021–2 Release).

Results: Of the 20 pts selected, we found that EGFRex20ins p.S768_D770dup (n = 5) variants were more common. Six first-line pts all achieved PR (ORR: 100%), five of the eight second-line pts achieved PR (ORR: 62.5%), and three of the six multiple-line pts achieved PR (ORR: 50.0%). We observed 14 pts with PR and six pts with SD as best response to furmonertinib (ORR: 70.0%, DCR: 100%). All pts showed tumor shrinkage in target lesions (median best percent change, −36.43% [−74.78%, −5.56%]). Median PFS was 10.2 (95% CI, 7.19–13.21) months (mo). Median DOR was 8.5 (95% CI, 4.97–12.03) mo. Comparative analysis of the efficacy of different groups showed that median PFS was significantly longer in furmonertinib group than in osimertinib (10.2 vs 3.8 mo, p = 0.008). Median OS was numerically longer in furmonertinib group than in osimertinib (18.9 vs 11.7 mo, p = 0.207). No grade 3 or above adverse events were observed. Furthermore, rather than erlotinib (GlideScore: −5.564; MM/GBSA: −52.8044), gefitinib (−7.68; −47.317), and afatinib (−5.075; −44.64), furmonertinib (−11.085; −68.1575) and osimertinib (−10.031; −63.87) revealed favorable binding activity to EGFRex20ins, with furmonertinib being the most significant.

Conclusions: Furmonertinib has positive clinical efficacy to advanced NSCLC pts with EGFRex20ins probably based on its favorable binding activity to EGFRex20ins. Furmonertinib may be the optimal choice for these pts in the future.

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Updated data from the phase I Beamion Lung 1 trial of BI 1810631, a HER2 TKI, in patients (pts) with advanced solid tumours with HER2 aberrations

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Background: This ongoing phase Ia/Ib trial determines the safety, MTD, PK, PD and preliminary efficacy of BI 1810631 in pts with HER2 aberration-positive solid tumours.

Methods: Phase Ia: Pts with HER2 aberration-positive (overexpression, gene amplification/rearrangements or somatic mutation) advanced/unresectable/metastatic solid tumours refractory/unsuitable for standard therapy were enrolled. Pts received escalating doses of BI 1810631 BID (starting dose 15 mg) or BI 1810631 QD (starting dose 60 mg). Phase Ib will initially include 30 pts with advanced HER2 TK domain mutation-positive, pre-treated NSCLC. Primary endpoints: MTD based on number of DLTs; number of pts with DLTs (phase Ia); ORR (phase Ib). Secondary endpoints: number of pts with DLTs throughout entire treatment period and PK parameters (phase Ia/Ib); DoR, DCR, duration of disease control and PFS (phase Ib).

Results: As of 21 Dec 2022, 34 pts have been treated in the US, Netherlands, Japan and China. Pts had NSCLC (n = 21), colorectal cancer (n = 3), or other tumours (n = 10). Most pts had a pathological HER2 mutation (n = 25). Pts received BI 1810631 15, 30, 60, 100, 150 mg BID (n = 3/3/4/4/3) or 60, 120, 180, 240 mg QD (n = 5/4/5/3). Median number of cycles: 4 (range 1–14). Treatment ongoing: n = 23. To date, 3 DLTs has been observed (grade [G] 2 oedema [60 mg BID]; G3 anaemia [60 mg QD]; G3 elevated ALT [180 mg QD]). The MTD has not been

reached with either schedule. Treatment-related adverse events (TRAEs) reported in 23 pts (68%). The most common TRAEs were diarrhoea (n = 9), anaemia (n = 5), increased alkaline phosphatase, increased ALT and hypoalbuminemia (all n = 4). Three pts had G3 TRAEs (anaemia/elevated GGT [n = 1]; increased ALT [n = 2]). In 29 pts evaluable for response the ORR (regardless of confirmation) was 34% (n = 10, all PRs; NSCLC: n = 8; oesophagus, cholangiocarcinoma: n = 1). The DCR was 90%. In 19 evaluable NSCLC pts the ORR was 42% and the DCR was 95%. Updated data will be presented at the meeting.

Conclusions: Preliminary data indicate that BI 1810631 is well tolerated and shows encouraging anti-tumour activity in pts with HER2 aberration-positive solid tumours. Phase Ia recruitment is ongoing.

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41P

Efficacy of first-line (1L) nivolumab (N) + ipilimumab (I) by tumor histologic subtype in patients (pts) with metastatic nonsquamous NSCLC (mNSQ-NSCLC)

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Background: Tumor histologic subtype (THS) has been reported to be a prognostic indicator for NSCLC; the solid subtype is associated with poor prognosis. 1L N + I has demonstrated durable, long-term clinical benefit vs chemotherapy (C) in pts with mNSCLC. Here we report exploratory analyses of overall survival (OS) with 1L N + I and association of biomarkers by mNSCLC THS using data from the CheckMate (CM) 227 and 568 trials.

Methods: THS was assessed in pts with evaluable mNSQ-NSCLC tissue in CM 227 Part 1 (NCT02477826; ph 3; N + I vs C; n = 675) and in CM 568 Part 1 (NCT02659059; ph 2; N + I, single arm; n = 170) by 3 independent pathologists using a modified version of the WHO NSCLC classification system. Samples were classified as solid, acinar, or other THS per consensus on the predominant THS. Exploratory assessments included OS, tumor PD-L1, TMB, select somatic mutations (muts; TP53,

Table: 41P Biomarkers and OS by THS

	CM 227 Part 1[a] N + I		CM 568 Part 1[a] N + I	
	Solid (n = 192)	Acinar (n = 91)	Solid (n = 77)	Acinar (n = 48)
Median tumor PD-L1 expression, % (range)	50 (0–100)	1 (0–100)	30 (0–100)	0 (0–80)
Median TMB, mut/Mb (range)	8.8 (0–66.8)	6.3 (0–44.1)	10.1 (1.3–98.4)	5.7 (1.3–17.6)
OS				
Median, mo (95% CI)	18.7 (13.5–28.4)	13.3 (10.0–17.1)	26.5 (14.6–47.3)	12.9 (8.6–24.0)
HR, solid vs acinar (95% CI)	0.60 (0.45–0.80)	–	0.67 (0.44–1.02)	–
5-y rate, % (95% CI)	31.0 (24.9–38.4)	6.0 (2.6–14.0)	31.1 (21.9–44.1)	18.4 (9.9–34.3)

[a]THS-evaluable pts: CM 227 (N + I and C), 675 pts and CM 568 (N + I), 170 pts; solid, 59% and 45%; acinar, 26% and 28%; other, 10% and 7%; not specified, 5% and 19%, respectively.

KRAS, and STK11; FoundationOne CDx™), and gene expression analysis (GEA) by THS.

Results: Baseline characteristics were generally consistent across THS and treatment groups. Minimum follow-up was 61.3 and 61.2 mo in CM 227 and 568, respectively. In both trials, greater OS benefit was observed in N + I-treated pts with solid vs acinar THS (CM 227: HR 0.60, 95% CI 0.45–0.80; CM 568: HR 0.67, 95% CI 0.44–1.02; table). In contrast, among C-treated pts, OS was similar in pts with solid or acinar THS in CM 227 (HR 1.01, 95% CI 0.77–1.32). Further exploratory analysis identified a trend toward higher tumor PD-L1 expression and TMB in pts with solid vs acinar THS (table). A higher frequency of TP53 muts and lower frequencies of KRAS and STK11 muts were also observed in the solid THS. These results and findings from GEA by THS will be presented.

Conclusions: Greater long-term OS benefit with N + I was seen in pts with the solid mNSCLC THS, a subgroup with poor prognosis, vs pts with the acinar THS. Exploratory PD-L1, TMB, and mut analysis may provide insight into the clinical benefit of 1L dual immunotherapy by THS.

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42P

Pembrolizumab vs chemotherapy in Chinese patients with non-small cell lung cancer (NSCLC) and PD-L1 TPS ≥1%: 5-year update from KEYNOTE-042

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Background: After 4 y of follow-up in patients (pts) enrolled in China in the phase III KEYNOTE-042 study, pembrolizumab (pembro) improved OS vs chemotherapy (chemo) in pts with previously untreated advanced or metastatic NSCLC without EGFR/ALK alterations in the PD-L1 tumor proportion score (TPS) ≥50% (HR, 0.66; 95% CI, 0.45–0.95), ≥20% (0.68, 0.49–0.93), and ≥1% (0.67, 0.51–0.89) groups. We report results after 16 mo of additional follow-up.

Methods: Eligible pts were randomized 1:1 to receive pembro 200 mg Q3W for ≤35 cycles or carboplatin + paclitaxel or pemetrexed with optional pemetrexed maintenance (nonsquamous only). Primary endpoints were OS in pts with PD-L1 TPS ≥50%, ≥20%, and ≥1%. No alpha was assigned to this exploratory analysis of pts enrolled in China in KEYNOTE-042 global (NCT02220894) and China extension (NCT03850444) studies.

Results: Of 262 pts enrolled in China, 128 were randomized to pembro and 134 to chemo. Median time from randomization to database cutoff (Sep 12, 2022) was 63.7 (range, 56.3–72.6) mo. Pembro prolonged OS vs chemo in pts with PD-L1 TPS ≥50% (HR 0.65, 95% CI 0.45–0.93), ≥20% (0.67, 0.49–0.91), and ≥1% (0.66, 0.51–0.87). 5-y OS rates were ~2 fold higher with pembro vs chemo across all 3 PD-L1 TPS groups (table). Grade 3–5 treatment-related AEs occurred in 19.5% of pts in the pembro arm and 68.8% in the chemo arm. Of 22 pts who completed 35 cycles of pembro, ORR was 81.8% (95% CI, 59.7%–94.8%) and 3-y OS rate after completion of 35 cycles (~5 y after randomization) was 56.6%. At data cutoff, 80 pts in the pembro arm and 79 in the chemo arm had begun subsequent therapy; 5 pts began second-course pembro.

Conclusions: Similar to the global KEYNOTE-042 study, after 5 y of follow-up, pembro continued to demonstrate improved OS vs chemo with manageable safety in Chinese pts with previously untreated advanced or metastatic NSCLC without EGFR/ALK alterations with PD-L1 TPS ≥1%. These data further support pembro monotherapy as a standard of care for these pts.

Clinical trial identification: NCT02220894 and NCT03850444.

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43P

Camrelizumab plus famitinib as first-line treatment in advanced NSCLC patients with PD-L1 TPS ≥1%: A report from a multicenter, open-label, phase II basket trial

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Background: The combination of immune-checkpoint inhibitors and antiangiogenic agents can modulate the microenvironment in a synergistic manner and represents a promising treatment option for

Table: 42P

	PD-L1 TPS ≥50%		PD-L1 TPS ≥20%		PD-L1 TPS ≥1%	
	Pembro n = 72	Chemo n = 74	Pembro n = 101	Chemo n = 103	Pembro n = 128	Chemo n = 134
OS, median (95% CI), mo	24.5 (17.4–34.3)	13.8 (10.1–18.3)	21.9 (17.4–27.0)	13.5 (10.1–17.9)	20.2 (17.4–25.3)	13.5 (10.1–17.9)
OS HR (95% CI)	0.65 (0.45–0.93)		0.67 (0.49–0.91)		0.66 (0.51–0.87)	
5-y OS rate (95% CI), %	18.4 (10.2–28.5)	8.3 (3.3–16.2)	19.1 (12.0–27.5)	10.2 (5.2–17.1)	19.0 (12.6–26.4)	9.5 (5.2–15.5)
ORR (95% CI), %	41.7 (30.2–53.9)	24.3 (15.1–35.7)	34.7 (25.5–44.8)	24.3 (16.4–33.7)	32.0 (24.1–40.9)	24.6 (17.6–32.8)
DOR, median (range), mo	16.5 (1.4+ to 64.1+)	11.7 (1.6+ to 63.4+)	16.5 (1.4+ to 64.1+)	10.9 (1.6+ to 63.4+)	16.0 (1.4+ to 64.1+)	10.9 (1.1+ to 63.4+)

NSCLC. The efficacy and safety of camrelizumab (an anti-PD-1 antibody) plus famitinib (a receptor tyrosine kinase inhibitor) as first-line therapy for advanced NSCLC with PD-L1 TPS ≥1% was explored in an open-label, multicenter, phase II basket trial.

Methods: Eligible patients (pts) received camrelizumab (200 mg once every 3 weeks by intravenous infusion) plus oral famitinib (20 mg once daily). Primary endpoint was confirmed objective response rate (ORR) assessed by investigator per RECIST v1.1. Disease control rate (DCR), duration of response (DoR), time to response (TTR), progression-free survival (PFS), overall survival (OS), 6-, 9-, 12-month OS rates and safety profile were secondary endpoints.

Results: Among all enrolled 41 pts, 21 (51.2%) had PD-L1 TPS 1–49% and 20 (48.8%) had PD-L1 TPS ≥50% per local laboratory testing. As of data cutoff on Jun 22, 2022, 22 (53.7%) pts had achieved a confirmed objective response. This combination regimen achieved an ORR of 53.7% (95% confidence interval [CI], 37.4–69.3), and the DCR was 92.7% (95% CI, 80.1–98.5). Median DoR had not been reached yet and the median TTR was 2.1 mos (range, 1.4–8.3). With the median follow-up duration of 12.5 mos (range, 1.0–24.2), the median PFS was 16.6 mos (95% CI, 8.3-NR), median OS was 20.4 mos (95% CI, 20.4-NR; data not mature), and the estimated 12-month OS rate was 76.8% (95% CI, 60.0–87.3), respectively. The most common ≥ grade 3 treatment-related adverse events were hypertension (22.0%), increased alanine aminotransferase (12.2%) and decreased neutrophil count (9.8%). One patient (2.4%) died from grade 5 hemoptysis, which the investigator considered possibly related to the study treatment.

Conclusions: Camrelizumab plus famitinib exhibited encouraging antitumor activity in advanced NSCLC pts whose tumor expressed PD-L1 TPS ≥1% with an acceptable safety profile. In this patient population, this combination regimen might offer an alternative treatment strategy that deserves further investigation.

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44P

Dostarlimab (Dos) or pembrolizumab (Pem) + chemotherapy (CT) in previously untreated metastatic non-squamous non-small cell lung cancer (NSCLC): Patient (Pt) and disease characteristics subgroup analyses from the PERLA trial

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Background: The randomized, double-blind phase II PERLA trial was the first global head-to-head comparison of 2 programmed death (PD)-1 inhibitors in NSCLC and showed similar efficacy for Dos + CT and Pem + CT with no new safety signals identified. Here, we report overall response rate (ORR) by pt and disease characteristics.

Methods: PERLA evaluated efficacy of Dos + CT and Pem + CT as first-line treatment for pts with metastatic non-squamous NSCLC, no targetable oncogenic drivers, and Eastern Cooperative Oncology Group performance status (ECOG PS) 0–1. Pts, stratified by PD-L1 and smoking status, were randomized 1:1 to Dos 500 mg or Pem 200 mg every 3 weeks (Q3W) for ≤35 cycles, both combined with ≤35 cycles of 500 mg/m^2 pemetrexed and ≤4 cycles of platinum-based chemotherapy (area under curve5 mg/mL/min carboplatin or 75 mg/m^2 cisplatin) Q3W. Disease assessments were at Week (W) 6 and 12, then every 9Ws until W48, then every 12Ws. ORR by pt and disease characteristics were exploratory analyses; point estimates and 95% Clopper–Pearson confidence intervals (CIs) were assessed.

Results: ORR by pt and disease characteristic subgroups are shown in the table. ORR was similar across subgroups and numerically favoured Dos + CT in all but those with ECOG PS 0, in which it was 46% for both treatment groups. ORR remained the same within Dos + CT regardless of age or ECOG PS (46%); however, ORR was lower in patients treated with Pem + CT who had ECOG PS 1 as opposed to 0.

Table: 44P ORR by pt/disease characteristics

ORR,* % (95% CI), n/N	Dos + CT (N = 121)	Pem + CT (N = 122)
Age	-	-
<65 years	46 (33.7–59.0), 30/65	35 (22.9–48.9), 20/57
≥65 years	46 (33.0–60.3), 26/56	38 (26.7–51.4), 25/65
Sex	-	-
Female	42 (25.5–59.2), 15/36	33 (20.0–49.0), 15/45
Male	48 (37.3–59.3), 41/85	39 (28.0–50.8), 30/77
ECOG PS	-	-
0	46 (29.5–63.1), 17/37	46 (31.8–60.7), 23/50
1	46 (35.5–57.6), 39/84	31 (20.2–42.5), 22/72
Brain metastasis	-	-
Yes	50 (28.2–71.8), 11/22	27 (7.8–55.1), 4/15
No	45 (35.4–55.8), 45/99	38 (29.1–48.2), 41/107
Platinum-based chemotherapy	-	-
Cisplatin	41 (20.7–63.6), 9/22	36 (12.8–64.9), 5/14
Carboplatin	47 (37.3–57.8), 47/99	37 (27.9–46.9), 40/108

*by blinded independent central review per RECIST v1.1.

Conclusions: ORR was similar between treatments and subgroups. In addition to the similar efficacy between treatments and tolerable safety profile, reported previously for PERLA, these results support further investigation of Dos in combination with other therapies.

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45P

DCVAC/LuCa with chemotherapy in patients with stage IV, non-squamous NSCLC without EGFR/ALK aberrations: Five-year survival update

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Background: Our study was the first clinical trial showing the safety and efficacy of DCVAC/LuCa (dendritic cell vaccines for lung cancer) combined with chemo in Chinese NSCLC patients (Zhong R, Ling X, et al. ESMO Open 2022). The OS data was not mature in our last report. Here, we present a survival update based on 33 months of additional follow-up.

Methods: Patients with stage IV, non-squamous NSCLC, no known EGFR/ALK aberrations, and who had not received systemic therapy for NSCLC prior to treatment, were enrolled in this study. Patients were treated with carboplatin/pemetrexed for up to 6 cycles, followed by pemetrexed maintenance for up to 21 cycles. Non-progression patients after two cycles of chemotherapy, assessed as mITT population, received DCVAC/LuCa subcutaneously (s.c.) on day 15 of cycle 3, and thereafter q3w (day 15 of chemotherapy cycles) for up to 15 doses. The dose of DCVAC/LuCa s.c. depended on the baseline number of leucocytes of each patient.

Results: A total of 61 patients were enrolled. At the clinical cutoff date (14 Dec 2022), the median follow-up was 64 months. In the mITT population (n = 44), the median OS was 27.4 months (95% CI, 18.1 to 36.7 months), the 3-year OS rate was 37.2% and the 5-year OS rate was 23.4%. Among the 15 patients who completed 15 cycles of DC vaccination, 6 (40%) remained alive at a 5-year follow-up. Patients who received higher-dose DCVAC/LuCa had a better prognosis than patients who received lower-dose DCVAC/LuCa.

Conclusions: The combination of DCVAC/LuCa and chemo continued to provide long-term benefits as a first-line treatment in Chinese patients with stage IV, non-squamous NSCLC without EGFR/ALK aberrations. The long-term benefits and the good safety profile support the conduct of a validation trial in a larger population with greater diversity.

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Multi-center, phase II study of docetaxel (DTX) plus ramucirumab (RAM) following platinum-based chemotherapy plus ICIs in patients with NSCLC: SCORPION study

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Background: Platinum-based chemotherapy plus immune check point inhibitors (ICIs) have become a front-line standard treatment in NSCLC, but no prospective data of DTX plus RAM following front-line chemotherapy plus ICIs are available. Previous research has proven residual ICIs efficacy beyond 20 weeks after termination of ICIs, and VEGF-R2 blockade could enhance antitumor immunity by improving T-cell function. Here, we report the results of multicenter, phase II study of DTX plus RAM following front-line chemotherapy plus ICIs.

Methods: The primary end point of the study was objective response rate (ORR), and secondary endpoints were disease control rate (DCR), progression-free survival (PFS), and safety etc. Patients were treated with 60 mg/m^2 of DTX and 10 mg/kg of RAM on day 1 with strong recommendation of pegfilgrastim on day 2 every 3 weeks. A null and alternative hypothesis of ORR were set as 10% and 30% with α error of 0.1 and β error of 0.1.

Results: Thirty-three patients were recruited from 8 institutions. Patient characteristics were as follows: median age (range): 66 (42–79) y; ECOG-PS 1, n = 13 (39%); interval after last administration of ICIs<6 weeks, n = 21 (64%). In the efficacy analysis population (n = 32), the primary endpoint was met as 11 patients achieved PR with ORR at 34.4% (80% CI, 23.1–47.2%). Another 15 patients achieved SD and the DCR was 81.3% (95%CI, 63.6–92.8%). Median PFS was 6.5 months. Grade≥3 anemia and febrile neutropenia was observed in 2 (6%) and 3 patients (9%). No treatment-related deaths and no new safety signals were observed.

Conclusions: DTX plus RAM demonstrated encouraging antitumor activity with a manageable safety profile in patients who have failed with front-line chemotherapy plus ICIs.

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47P

Timing of radiotherapy affects outcomes of patients with metastatic NSCLC who receive immunotherapy

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Background: Radiotherapy (RT) and immunotherapy (IO) may have synergistic anti-tumor effect for treating metastatic non-small-cell lung cancer (mNSCLC). However, the optimal timing of RT in relevance to IO and whether it affects outcomes is unknown.

Methods: We conducted a retrospective study of all patients with mNSCLC treated with IO at our institution (2011–2022). Patients who received targeted therapy or prior concurrent chemoRT + durvalumab were excluded.

Results: In this cohort of 225 patients, 56% were male, 82% were Caucasian. The median age was 68 (44–95). The histology was predominantly adenocarcinoma (79%). The most common metastatic sites were bone (41%) followed by CNS (25%). 56% patients received RT before or during IO. 27% never received RT. 17% received RT after discontinuation of IO. Pembrolizumab was the most used IO (78%), followed by Nivolumab (14%) and Atezolizumab (12%). Most patients received IO in the frontline (60%). We observed no statistical difference in PFS, OS, or development of immune-related adverse events in patients who received RT before or during IO compared to patients without RT (PFS: 5.9 vs. 5.5 months, p = 0.66; OS: 16.9 vs. 13.1 months, p = 0.84; irAE: 26.2% vs. 34.4%, p = 0.24). Patients with RT were divided into four groups by the timing of RT related to IO: >12 months prior to IO (N = 29), between 1 and 12 months prior to IO (N = 39), <1 month prior to IO (N = 30), after IO initiation (N = 28). The median PFS (months) of the above groups were 4.3, 12.6, 4.2, and 5.1, respectively, and the median OS (months) were 16.5, 25, 13.9, and 16, respectively. We found significantly higher PFS in patients who received RT between 1 and 12 months before IO, compared with those received RT<1 month before IO (12.6 vs. 4.2 months, p = 0.005, HR 0.46, 95% CI 0.26–0.83), or compared with patients without RT (12.6 vs. 5.5 months, p = 0.0197, HR 0.56, 95% CI 0.36–0.89). This trend was sustained in the OS analysis (25 vs. 13.9 months, p = 0.08; 25 vs. 13.1 months, p = 0.18).

Conclusions: We observed statistically significant and clinically meaningful PFS benefits of IO in patients with mNSCLC who received RT between 1 and 12 months prior to IO. There is a positive trend for OS benefit, although not statistically significant. These findings need to be verified in a larger cohort.

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48P

Characteristics and treatment patterns of patients with advanced or metastatic non-small cell lung cancer managed with first-line immuno-oncology strategies in Greece: Interim results of a real-world prospective study (IO-HORIZON)

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Background: IO-HORIZON aims to provide real-world evidence (RWE) on the profile and treatment patterns of patients with advanced/metastatic non-small cell lung cancer (NSCLC) receiving first-line (1L) immuno-oncology (IO) treatment in routine settings in Greece.

Methods: This is an ongoing, non-interventional, prospective study in adults with stage IIIB-IV NSCLC receiving 1L approved IO treatment. Data are collected during routine clinic visits. Baseline results after accrual completion are presented.

Results: From May/2020 to Nov/2021, 240 eligible Caucasian patients (75.4% male, 91.3% ever-smokers) were enrolled by 17 oncology clinics (7 private, 10 public) in Greece. At 1L IO initiation, patients' median age was 69.0 years, with a median of 2.0 months elapsed since advanced/metastatic disease diagnosis. ECOG performance status was 0/1/2 in 62.5/31.3/6.3%. Disease stage was IIIB/IIIC/IV in 5.0/2.1/92.9%; of the latter patients, 78.5% had de novo stage IV, 23.3% ≥3 metastatic sites, while 36.8% had bone, 17.9% brain, and 16.1% liver metastases. Of the tested patients (n = 226), 73.9% had expressing PD-L1. 1L treatment comprised pembrolizumab + chemotherapy (CT) in 79.2%, pembrolizumab monotherapy in 12.1%, nivolumab + ipilimumab + CT in 6.7%, atezolizumab + bevacizumab + CT in 1.7%, and atezolizumab + CT in one patient (table).

Table: 48P Characteristics at 1L immunotherapy initiation

	Pembrolizumab			
	Monotherapy N = 29	+CT N = 190	Nivolumab + ipilimumab + CT N = 16	Atezolizumab + CT ± bevacizumab N = 5
	% of patients			
Age ≥70 years	58.6	43.2	50.0	20.0
Male	65.5	76.8	81.3	60.0
Ever smokers	75.9	93.2	93.8	100.0
Presence of comorbidity	62.1	74.2	50.0	60.0
ECOG Performance Status 0-1	82.8	94.7	100.0	100.0
Stage IV disease	75.9	94.7	100.0	100.0
Adenocarcinoma	62.1	72.1	31.3	100.0
PD-L1 Tumor Proportion Score ≥50%	96.6	21.9	14.3	20.0

CT: chemotherapy.

Conclusions: These results yield novel RWE on the profile and IO treatment patterns of advanced/metastatic NSCLC patients in Greece. Such data help to better understand disease and therapy approaches so as to design informed health policy strategies.

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Patient-reported outcomes (PROs) in patients with advanced non-small cell lung cancer (aNSCLC) with programmed cell death-ligand 1 (PD-L1) ≥50% receiving cemiplimab (CEMI) monotherapy vs chemotherapy (CHEMO): EMPOWER-Lung 1 liver metastases subpopulation

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Background: In subgroup analyses of EMPOWER-Lung 1, a randomised 1:1 open-label phase III study, improvement in overall survival (OS) with CEMI (n = 48) vs CHEMO (n = 47) (median OS: not reached vs 7.4 months; HR: 0.38; 95% confidence interval [CI]: 0.19, 0.75) was observed in patients with aNSCLC with PD-L1 ≥ 50% and baseline liver metastases. In this post hoc analysis, we evaluated PROs.

Methods: PROs were assessed at baseline and Day 1 of each treatment cycle for the first 6 cycles, then on Day 1 of every third cycle using the European Organisation for Research and Treatment of Cancer Quality of Life-Core 30 (QLQ-C30) and Lung Cancer 13 (QLQ-LC13) questionnaires. Higher scores indicate better functioning and global health status (GHS)/quality of life (QoL) or worse symptom severity. Mixed-effects repeated-measures analyses were used to compare overall change from baseline scores between the treatment arms, controlling for baseline scores and other covariates.

Results: Statistically significant difference in overall change from baseline in physical functioning favoured CEMI vs CHEMO (6.24; 95% CI: 0.34, 12.14; P = 0.0384). CEMI also resulted in a statistically significant favourable difference vs CHEMO in overall change from baseline in the symptoms of nausea/vomiting (−3.80; 95% CI: −7.29, −0.31; P = 0.0334), alopecia (−15.75; 95% CI: −24.61, −6.88; P = 0.0007) and pain in arm or shoulder (−9.05; 95% CI:−16.67, −1.43; P = 0.0208). Compared with CHEMO, CEMI had numerically improved scores in GHS/QoL, all functioning scales, and 15 of 18 symptom scales. No analyses yielded statistically significant PRO results favouring CHEMO vs CEMI on any QLQ-C30 or QLQ-LC13 scales.

Conclusions: In patients with aNSCLC with PD-L1 ≥50% and baseline liver metastases, CEMI resulted in significant favourable overall change from baseline in physical functioning, nausea/vomiting, alopecia and pain in arm or shoulder symptoms vs CHEMO. PRO results further support the favourable benefit-risk profile of first-line CEMI vs CHEMO in patients with aNSCLC with PD-L1 ≥50% and baseline liver metastases.

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Interests, Personal, Advisory Role, Honoraria: Roche, Merck Sharp & Dohme, Gen İlaç, Novartis. X. He: Financial Interests, Personal, Full or part-time Employment: Regeneron Pharmaceuticals, Inc.; Financial Interests, Personal, Stocks/Shares: Regeneron Pharmaceuticals, Inc. G. Gullo: Financial Interests, Personal, Full or part-time Employment: Regeneron Pharmaceuticals, Inc.; Financial Interests, Personal, Stocks/Shares: Regeneron Pharmaceuticals, Inc. P. Rietschel: Financial Interests, Personal, Full or part-time Employment: Regeneron Pharmaceuticals, Inc.; Financial Interests, Personal, Stocks/Shares: Regeneron Pharmaceuticals, Inc. R. Quek: Financial Interests, Personal, Full or part-time Employment: Regeneron Pharmaceuticals, Inc.; Financial Interests, Personal, Stocks/Shares: Regeneron Pharmaceuticals, Inc. All other authors have declared no conflicts of interest.

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Patient-reported outcomes in non-small cell lung cancer patients receiving immunotherapy monotherapy: Analysis from enhanced, EHR-facilitated cancer symptom control (E2C2) pragmatic clinical trial

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Background: Immunotherapy has improved or maintained health-related quality of life (QOL) according to patient-reported outcomes (PROs) of non-small cell lung cancer (NSCLC) clinical trials. However, real-world evidence has been limited. Our study describes clinical outcomes and PROs in NSCLC while receiving immunotherapy monotherapy as first-line treatment using real-world data.
Methods: We retrospectively collected clinical data and PROs of adult patients with NSCLC who enrolled in Enhanced, EHR-facilitated Cancer Symptom Control (E2C2) pragmatic trial from 3/2019 to 11/2022. PROs were collected by survey in six domains including sleep disturbance, pain, anxiety, physical dysfunction, fatigue, and distress.
Results: Out of 31225 patients with cancer enrolled in E2C2 trial, one-hundred patients were identified to have received immunotherapy monotherapy as first-line treatment for NSCLC. Eighty-three patients had metastatic disease at initiation of immunotherapy; nine had stage III disease, and eight had recurrent disease. Ninety patients received pembrolizumab. Median length of therapy was 15 months. Sixty patients discontinued treatment by censor date; nineteen patients were on active treatment, and eighteen patients were on treatment holiday and active surveillance. Top reasons for discontinuation of therapy were progression (33.3%), immunotherapy-related adverse event (26.7%), and poor performance status (20%). A total of 999 PRO surveys were analyzed. The most frequent moderate to severe symptoms include physical dysfunction (76%), fatigue (75%), and sleeping disturbance (68%); pain (58%), anxiety (55%), and distress (49%) were less frequently reported. For a subgroup of patients (n = 50) whose baseline symptom measurement was available, there was a trend of moderate to severe symptoms decreasing over time.
Conclusions: Our study demonstrated that patients with NSCLC on immunotherapy monotherapy have significant symptom burden, particularly physical dysfunction, fatigue, and sleeping. Our study highlights the unmet supportive care needs of individuals living with NSCLC receiving immunotherapy.

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51P

Real-word outcomes of immunotherapy in non-small cell lung cancer: A population-based cohort study in Sweden

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Background: In a previous study, we reported real-world PD-L1 testing rates, treatment patterns, and outcomes for patients with advanced non-small cell lung cancer (NSCLC) in the era of immuno-oncology in Sweden. In this follow-up study, with additional patients and 12 more months follow-up, the aim was further investigation with a focus on overall survival (OS) in the Swedish setting.
Methods: Data were extracted from the Swedish National Lung Cancer Registry for patients with unresectable stage IIIB-IV NSCLC and ECOG performance status (PS) 0–2 who initiated first-line (1L) PD-(L)1-based regimen from Apr 1, 2017 to Jun 30, 2021, with data cutoff Jun 30, 2022. Kaplan-Meier analysis was used to assess OS by histology and by PD-(L)1 combination therapy (combo) and monotherapy (mono) in patients with ECOG PS 0–1, where index date was defined as the start of 1L therapy.
Results: Of 1153 eligible patients, 669 (58%) received PD-(L)1 inhibitor combo and the remaining PD-(L)1 mono. The vast majority of patients treated with PD-(L)1 inhibitors initiated a pembrolizumab-based regimen: 294 (96%) and 62 (97%) initiated a pembrolizumab-based combo and 504 (85%) and 147 (76%) initiated pembrolizumab mono, in patients with nonsquamous and squamous histology, respectively. The table presents baseline demographics and OS data by histology and by

Table: 51P Baseline demographics and OS by histology in patients with ECOG PS 0–1

	Nonsquamous		Squamous	
	PD-(L)1 combo N = 305	PD-(L)1 mono N = 590	PD-(L)1 combo N = 64	PD-(L1) mono N = 194
Female, %	57.0	58.0	40.6	39.7
Age, mean (SD), years	68.0 (8.9)	70.3 (8.5)	68.3 (7.6)	71.8 (8.2)
Event, N	124	262	23	90
Median OS (95% CI), months	20.6 (15.9, 26.9)	19.8 (17.6, 24.4)	18.9 (14.1, NE)	15.0 (11.6, 17.2)
OS rate (95% CI), %				
At 12 months	64.9 (58.9, 71.5)	64.2 (59.8, 68.9)	71.3 (59.2, 86.0)	57.8 (49.8, 67.1)
At 24 months	45.4 (38.6, 53.3)	45.9 (41.1, 51.2)	44.6 (30.3, 65.6)	30.6 (22.9, 41.0)
At 36 months	33.1 (25.7, 42.6)	33.1 (28.3, 38.8)	NE (NE, NE)	19.4 (12.6, 30.0)

type of PD-(L)1 regimen in patients with ECOG PS 0–1. For reference, in patients receiving 1L platinum-based combination regimen with ECOG PS 0–1 in this Registry, median OS was 10.2 and 11.7 months and the 12-month OS rate was 43.7% and 49.9% in patients with nonsquamous and squamous histology, respectively.

Conclusions: Updated OS data from this nationally representative patient cohort with advanced NSCLC in Sweden are generally in alignment with OS results reported from PD-(L)1 inhibitor clinical trials, supporting the benefit of PD-(L)1 inhibitors as frontline therapy in clinical practice.

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52P

Real-world versus clinical trial outcomes of pembrolizumab plus chemotherapy in patients with stage IV non-squamous non-small cell lung cancer

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Background: For many systemic treatments in oncology, a divergence between efficacy in clinical trials versus effectiveness in clinical practice has been observed. The present study investigated the real-world outcomes for pembrolizumab plus chemotherapy in patients with stage IV non-squamous non-small cell lung cancer (NSCLC) and compared these with the results of the KEYNOTE-189 trial.

Methods: This retrospective cohort study included all patients diagnosed with stage IV non-squamous NSCLC and treated with first-line pembrolizumab plus pemetrexed-platinum in 2019 and 2020 within a network of seven teaching hospitals (Santeon) in the Netherlands. The overall survival observed in the real-world was compared with the KEYNOTE-189 trial by calculating hazard ratios (HR) with 95% confidence intervals (95%CI) for the total population and PD-L1 subgroups.

Results: A total of 512 patients were included (median age 65 years, 49% males; 9% ECOG-PS 2, and 19% with brain metastasis). The median OS (mOS) was shorter in clinical practice than in the trial (13 vs 22 months) with a HR (95%CI) of 1.50 (1.26–1.79) (table). The divergence from the trial was most pronounced in patients with <1% PD-L1 expression (mOS 10 vs 17 months; HR 1.38, 95%CI 1.06–1.79). Early discontinuation of chemotherapy (<4 cycles platinum) was more frequent in the real-world than the trial (35 vs 18%).

Table: 52P The overall survival for stage IV non-squamous patients treated with pembrolizumab plus chemotherapy (real-world vs KEYNOTE-189)

	Real-world vs KEYNOTE-189	
	mOS in months (n)	HR (95%CI) for OS
Total population	13 (512) vs 22 (410)	1.50 (1.26–1.79)
PD-L1 subgroups		
PD-L1 <1%	10 (269) vs 17 (127)	1.38 (1.06–1.78)
PD-L1 ≥1–49%	20 (158) vs 22 (128)	1.10 (0.80–1.51)
PD-L1 ≥50%	26 (59) vs 28 (132)	1.21 (0.76–1.89)
Unknown	9 (26) vs NA (23)	NA

mOS, median overall survival; HR, Hazard Ratio; 95%CI, 95% confidence interval; NA, not available.

Conclusions: This study showed considerably worse real-world mOS for pembrolizumab plus chemotherapy compared to the corresponding clinical trial. In patients with low PD-L1 expression, the benefit of pembrolizumab added to chemotherapy seems limited.

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53P

Real-world outcomes of first-line pembrolizumab (Pem) for metastatic non-small cell lung cancer (mNSCLC) with ≥50% expression of programmed cell death-ligand 1 (PD-L1): A multicentre retrospective study

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Background: Pem is the standard first-line treatment for mNSCLC patients based on the greater benefit showed in a well-designed phase III trial (Keynote-024). However, these data represent only a part of patients (pts) due to the strict selection criteria. Pts' characteristics in clinical practice are more heterogeneous. The real-world data are useful to validate the trial results and find which patients are suitable for treatment.

Methods: Multicentre retrospective study of pts with mNSCLC and PD-L1 expression in tumour cells ≥50%, without actionable mutations, treated with first-line Pem at 2 hospitals in Valencia, Spain. Baseline factors, efficacy and adverse effects were collected. Statistical analysis was carried out with SPSS v25.0.

Results: From January 2017 to January 2021, 109 pts were treated. Median age 69. Men 81.7%. 19.8% had treated brain metastases, 47% had Performance Status (PS) <2. Median follow-up was 11 months (m). Median number of cycles administered was 8; 10 in pts with PS 0–1 and 5 in PS≥2. 43.5% of PS≥2 pts received less than 4 cycles ($p = 0.007$). Median Overall Survival (mOS) was 12 m (95% Confidence Interval, CI, 8.6–15.4), 16 m in PS 0–1 pts (12.7–19.2) and 10 m (12.6–14.3) in PS≥2 pts ($p = 0.019$). Median Progression Free Survival (mPFS) was 6 m (3.6–8.3), 10 m in PS 0–1 pts (4.6–15.4), and 4 m in PS≥2 (2.6–5.3) ($p < 0.0001$). Overall response rate was 43.7%, with 8.2% of complete responses. Disease control rate was 58.2%. Median time to onset of immune-related adverse events (irAEs) was 4 m. Toxicity of any degree was reported in 52.3%, grade (G) ≥3 in 15.6%. Hepatogastrointestinal (24.8%) and skin (20.2%) toxicities, the most common. mPFS in pts with irAEs was 11 m (7.2–14.8) and mOS 29 m (12–46), while those

without irAEs had a mPFS of 2 m (0.8–3.2) ($p < 0.0001$) and mOS of 4 m (2–6) ($p < 0.0001$).

Conclusions: Real-world data confirm that Pem is an effective, tolerable option for mNSCLC pts with PD-L1 ≥ 50%. PS≥2 pts were not included in the Keynote-024 trial and this subgroup showed significantly shorter mPFS and mOS. The role of Pem in PS≥2 needs to be validated in a prospective phase III trial. Occurrence of irAEs is associated with an increase in mPFS and mOS.

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54P

Real-world efficacy of immunotherapy plus anti-angiogenesis versus immunotherapy monotherapy as second-line or later treatment in advanced non-small cell lung cancer

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Background: Previous clinical research has demonstrated that immunotherapy plus anti-angiogenesis have a synergistic effect and achieved promising clinical outcomes in treating advanced NSCLC patients as first-line therapy. However, there are limited data for immunotherapy plus anti-angiogenesis as second-line or salvage therapy. Herein, we conduct a retrospective study to evaluate the efficacy of immunotherapy in combination with anti-angiogenesis as second-line or later therapy for patients with advanced NSCLC in the real world.

Methods: We retrospectively enrolled eligible patients with advanced NSCLC who were treated with immunotherapy plus anti-angiogenesis (I+A group) or immunotherapy monotherapy (IM group) as second-line or later therapy at Shanghai Chest Hospital from January 1, 2018, to March 30, 2022. The clinical information was collected, and the treatment outcomes and survival data were assessed and compared between the two groups.

Results: A total of 211 patients were included in this study (83 patients in the I+A group and 128 patients in the IM group). The I+A group achieved a higher objective response rate (ORR) compared with the IM group (27.7% VS. 3.9%, $P < 0.001$). The median progression-free survival (PFS) was 6.77 months VS. 4.67 months ($P < 0.001$), and the median overall survival (OS) was 16.73 months VS. 12.63 months ($P = 0.035$), respectively. In the subgroup analysis, patients who received immunotherapy as second-line treatment were more likely to benefit from combination therapy (mPFS: 8.93months VS. 4.03 months, $P < 0.001$). Additionally, multivariate analysis showed that immunotherapy plus anti-angiogenesis had significantly prolonged the PFS and OS ($P = 0.011$ and $P = 0.008$).

Conclusions: Immunotherapy plus anti-angiogenesis achieved longer PFS and OS in patients with advanced NSCLC in the second-line or posterior treatment. Further prospective research should be conducted on larger populations.

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55P

Real-world monitoring of hybrid dosing of pembrolizumab in stage IV non-small cell lung cancer in the Netherlands

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Background: In the Netherlands, pembrolizumab dosing guidelines have been altered from a fixed dose to hybrid dosing. Hybrid dosing reduces costs and helps to maintain a sustainable healthcare system, without compromising the safety and efficacy. Implementation of these new dosing guidelines can be challenging in daily clinical practice. The Dutch Institute for Clinical Auditing (DICA) medicine program was set up to help hospitals overcome these challenges by analyzing real-world drug use and discussing the different policies between hospitals. In this project we aimed to determine to what extent hybrid dosing is being used and aid to further implementation.

Methods: Clinical and claims data of stage IV non-small cell lung cancer patients from 2018–2022 were linked to analyze dosing strategies of pembrolizumab in the 26 Dutch hospitals that participated in the DICA medicine program. Standard dosing was defined as a fixed dose of 200 mg per three weeks or 400 mg per six weeks. Hybrid dosing was defined as 100 mg or 150 mg per three weeks, or 200 mg or 300 mg per six weeks depending on patients' weight. Insights per hospital were discussed in a roundtable session with medical specialists and hospital pharmacists.

Results: Of the 26 hospitals involved, five prescribed pembrolizumab with hybrid dosing. Implementation of hybrid dosing increased between 2020 and 2022. One hospital reduced the dosage using a different dosing strategy. Within the hospitals that fully implemented hybrid dosing, a reduction of costs for pembrolizumab of 25% was observed. In the roundtable session hospital staff shared best practices. Technical limitation was among others mentioned as challenge to overcome by hospitals that did not implement hybrid dosing yet.

Conclusions: The DICA medicine program is a platform to use real-world data to improve quality of care. Clinical and claims data showed that hybrid dosing of pembrolizumab in NSCLC patients was only partially implemented in the Netherlands. Providing insights on implementation across hospitals and sharing best practices may support the implementation of guidelines. Because the DICA medicine program is connected with different clinical registrations, in the future real-world outcome of this new strategy can be assessed.

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56P

Pooled analysis of 4 studies evaluating weekly oral vinorelbine in patients with locally advanced or metastatic non-small cell lung cancer

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Background: Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. Vinorelbine (VNR) is an established treatment for advanced NSCLC, both as a single agent and in combination with platin chemotherapy. Four previous phase II, open-label clinical trials evaluated the efficacy and safety of oral VNR as monotherapy in NSCLC patients. Here, we aim to assess the efficacy and safety of oral VNR using pooled data.

Methods: This analysis included individual data of 4 phase II, open-label trials, focusing only on patients receiving oral VNR as monotherapy administered as standard weekly doses administration. Patients received VNR at the dose of 60 mg/m^2 weekly at cycle 1 (3weeks per cycle), followed by an increase to 80 mg/m^2 weekly for the subsequent cycles, until disease progression or toxicity. Main outcomes were overall response rate [ORR], disease control rate [DCR], progressive free survival [PFS] and overall survival [OS]), and tolerance.

Results: A total of 247 patients were included, and 244 were treated. The patient characteristics were: 75.7% of male patients, 81.4% of them had a stage IV, and 37.2% had squamous histology. The ECOG PS (Eastern Cooperative Oncology Group Performance Status) was 0, 1, ≥2, in respectively 40.9%, 45.7%, and 12.6% of patients. There were 108 patients (43.7%) with ≥ 3 organs involved. Overall, 243 patients received oral VNR for a total of 1176 cycles, representing a median number of 4 cycles per patient, and 73% of patients had dose escalation at cycle 2. ORR was 8.9% (95% confidence intervals [CI]: 5.7; 13.2), DCR was 57.5% (95% CI: 51.1; 63.7), median PFS and OS were 3.3 (95% CI: 2.8; 4.0) and 8.5 (95% CI: 7.6; 10.3) months, respectively.

Conclusions: This pooled analysis showed that weekly oral VNR dosing was a valid option in this population of patients with advanced or metastatic NSCLC, confirming the results from previous studies. Safety analysis will be presented at the meeting.

Clinical trial identification: Two of the studies used in this analysis do not have official designation CT (old studies). TEMPO LUNG, with European trial protocol number EudraCT 2014-003859-61. And the last trial used had European trial protocol number EudraCT 2012-003361-18.

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57P

A study of gemcitabine-cisplatin vs paclitaxel-carboplatin chemotherapy in patients with advanced squamous cell carcinoma of the lung

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Background: Squamous cell carcinoma accounts for about 20% of all lung cancers. Gemcitabine-cisplatin and paclitaxel-carboplatin are the two commonly used combination chemotherapeutic regimens in advanced squamous cell carcinoma of lung where we have no access to the novel therapeutics such as immunotherapy, with proven benefit in terms of response rate, survival, and also they are tolerated by the majority of patients.

Methods: This prospective observational study was conducted in patients diagnosed with stage IV squamous cell carcinoma of lung in the department of Radiation Oncology of Government Medical College, Trivandrum, from April 2018-September 2019. Due to the non-availability of PDL1 testing and novel immunotherapeutics, these patients were started on palliative chemotherapy either with gemcitabine-cisplatin and paclitaxel-carboplatin. After 4 cycles of chemotherapy CT thorax taken was assessed for the tumour response to treatment. The primary outcome was overall response rate (ORR), which was defined as per Response Evaluation Criteria In Solid Tumors (RECIST) criteria, after completion 4 cycles of chemotherapy. Secondary outcome includes the incidence and grade of toxicity of the above two regimens.

Results: 194 patients were taken up for the study. Overall response was 26% in paclitaxel-carboplatin arm and 27% in gemicitabine-cisplatin arm (p value- 0.76) and it was not statistically significant among the 2 regimens. Grade 3 and 4 anemia and neutropenia was seen more with paclitaxel-carboplatin compared to gemcitabine cisplatin (4% vs 0% and 4% vs 0%) (p value < 0.01). Grade 3 and 4 thrombocytopenia was also seen more among paclitaxel-carboplatin than in gemicitabine-cisplatin and it was statistically significant (4% vs 0%; p value < 0.01). Grade 3 and 4 nausea & vomiting was seen more in the gemicitabine-cisplatin arm but it was not statistically significant (8% vs 4%); (pvalue 0.07). There was no grade 3 or 4 renal toxicity, electrolyte abnormality or hearing loss in our study population.

Conclusions: We concluded that the overall response rate was similar in both treatment groups. Therefore both can be viewed as an acceptable option when we have no access to novel immunotherapeutics.

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58P
Treatment combinations in non-driver mutated mNSCLC: A systematic review and Bayesian network meta-analysis

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Background: To compare the relative survival benefits & toxicities among treatments for non-driver mutated metastatic NSCLC (mNSCLC).
Methods: RCTs since inception, to June 1st 2021, were systematically searched from databases, trial registries & annual meeting abstracts. All trials comparing survival & toxicity between at least two of the following treatments were included: chemotherapy (CT) (single/multi-agent); PD1, PDL1 or CTLA4 immune checkpoint inhibitors (ICI) (single/multi-agent) (with/without CT), &; radiotherapy followed by either chemotherapy (RT+CT) or immune checkpoint inhibitors. The primary outcomes were risk of death at 1 year, risk of progression at 6 months & 1 year, & overall grade 3 or higher (G3+) toxicities. A Bayesian network meta-analysis using a random-effects model & empirical Markov Chain Monte Carlo simulation of multiple interventions was used. Results were expressed as risk ratios (RR)[95% Credible Interval (CrI)] & ranked using SUCRA scores. All CT regimens were merged into a single category & ICIs were divided into two categories (PD1 or PDL1; CTLA-4). Local & global consistency and sensitivity analyses were performed on the network (after splitting treatments). All treatments satisfied the transitivity assumption. Risk-of-bias (RoB) & confidence were assessed with Cochrane RoB & CiNeMA tools.
Results: 30 RCTs (n = 14904; 36 possible comparisons; 12 direct comparisons) comparing 9 treatments were included. The combination of RT+PD1/PDL1 was ranked highest & demonstrated the lowest risk of death [RR = 0.47 (0.30–0.72)][SUCRA = 95%], progression [6 m RR = 0.39 (0.23–0.63)[SUCRA = 96%]; 1 yr RR = 0.74 (0.59–0.95)][SUCRA = 87%], & G3+ toxicities [RR = 0.74 (0.57–0.96)][SUCRA = 81%]. Results are shown below [RR (95% CrI)]. All sensitivity analyses favored RT +PD1/PDL1 over other treatments.
Conclusions: The results suggest that combining RT with PD1/PDL1 inhibitors could improve outcomes over other treatments in non-driver mutated metastatic NSCLC.
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59P
Assessment of QoL results and correlation with survival outcomes in phase III clinical trials in metastatic NSCLC

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Background: In addition to improvements of survival outcomes, new oncology treatments should lead to amelioration of patients' quality of life (QoL). In patients with non-small lung cancer (NSCLC), a potential correlation between QoL results with progression-free survival (PFS) and overall survival (OS) outcomes is unknown.
Methods: We examined whether QoL results correlated with PFS and OS outcomes in phase III randomized controlled trials (RCTs) investigating new systemic treatments in metastatic non-small cell lung cancer (NSCLC), published between 2012 and 2021. Our systematic review identified 81 RCTs for further analysis.
Results: Compared to control arms, experimental treatments led to superior QoL in 30 (37.0%) RCTs and inferior QoL in 3 (3.7%) RCTs. In the remaining 48 (59.3%) RCTs, a statistically significant difference between experimental and control arms was not found. QoL results did not positively correlate with OS outcomes ($X^2 = 0.81$, $p = 0.368$). Instead, we found a statistically significant correlation between QoL and PFS improvements ($X^2 = 3.93$, $p = 0.0473$). More in detail, this correlation was not significant in trials testing immunotherapy or chemotherapy. On the contrary, in RCTs testing target therapies QoL results positively correlated with PFS outcomes ($p = 0.0196$). This correlation was stronger in the 32 trials testing EGFR or ALK inhibitors ($p = 0.0077$). Furthermore, we found that experimental treatments led to superior QoL in 27/57 (47.4%) trials with positive results and in 3/24 (12.5%) RCTs with negative results ($p = 0.0028$). Next, we analyzed how QoL data were described in publications of RCTs in which QoL outcomes were not improved (n = 51). We found that a favorable description of QoL results was associated with sponsorship by industries ($p = 0.0232$).
Conclusions: Our study reveals a positive correlation of QoL results with PFS outcomes, but not with OS, in RCTs testing novel treatments in advanced NSCLC, particularly for target therapies. Moreover, inappropriate description of QoL data was more frequent in RCTs funded by pharma companies.
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Table: 58P Results

	Death-1yr	Progression-6m	Progression-1yr	G3+Toxicity
CT (ref)				
CT + RT	0.56 (0.3–0.92)	0.47 (0.26–0.77)	0.77 (0.55–1)	0.77 (0.55–0.99)
CTLA4	0.93 (0.69–1.21)	1.07 (0.84–1.35)	0.97 (0.88–1.05)	0.85 (0.58–1.16)
CTLA4 + CT	0.85 (0.60–1.2)	0.89 (0.65–1.23)	1 (0.93–1.08)	0.82 (0.68–0.96)
PD1/PDL1	0.84 (0.79–0.9)	0.91 (0.85–0.97)	0.9 (0.89–0.92)	0.9 (0.87–0.93)
PD1/PDL1 + CT	0.84 (0.77–0.92)	0.7 (0.63–0.78)	0.83 (0.8–0.86)	0.85 (0.81–0.9)
PD1/PDL1 + CTLA4	0.86 (0.75–0.99)	0.9 (0.78–1.04)	0.86 (0.82–0.9)	0.87 (0.8–0.94)
PD1/PDL1 + CTLA4 + CT	0.7 (0.54–0.9)	0.7 (0.57, 0.97)	0.8 (0.77–0.91)	0.8 (0.73–0.96)
PD1/PDL1 + RT	0.47 (0.3–0.72)	0.39 (0.23–0.63)	0.74 (0.59–0.95)	0.74 (0.57–0.96)

60P

Comparison of metastasis patterns and prognosis of advanced old NSCLC patients by age groups: A SEER database analysis

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Background: We aimed to investigate the different metastatic patterns and corresponding survival outcomes between early age of elderly (aged between 65 to 80 years) and late age of elderly (aged more than 80 years) stage IV NSCLC patients.
Methods: Stage IV old NSCLC patients from the Surveillance, Epidemiology, and End Results (SEER) database between 2010 and 2016 were divided into an early age and late age of elderly group. To reduce the bias of retrospective studies, propensity score matching (PSM) analysis was performed. Baseline characteristics of patients were analyzed by the t test and chi- square test. Overall survival (OS) and lung cancer specific survival (LCSS) were evaluated by Kaplan-Meier curves and Cox proportional hazards models. Univariate and multivariate Cox regression models were used to analyze survival outcomes and other prognostic factors. Finally, a nomogram was constructed and validated to predict patient survival time.
Results: From the SEER database, a total of 47 438 old patients with stage IV NSCLC from 2010 to 2016 were enrolled in this cohort study. X-tile analysis identified the optimal cutoff age for LCSS as 80 years old. In this study, 35 385 patients aged 65–80 years and 12 052 patients aged over 85 years were included. After 1:1 PSM analysis, 10 931 patients aged 65–80 years and 10 931 patients aged over 85 years were ultimately included. Adenocarcinoma was the dominant histological subtype across each age group, particularly in the younger group. With aging, the proportion of patients undergoing treatment, including surgery, radiation, and chemotherapy, progressively declined. Compared with younger NSCLC patients, lung metastases were significantly more frequent in the elderly group, and lung metastases and distant lymph nodes metastases were independent prognostic factors of LCSS [lung metastases: hazard ratio (HR): 0.890; distant lymph nodes metastases: hazard ratio (HR): 0.844, all P values were <0.001]. In each age subgroup, patients with multi-organ metastasis had the worst LCSS.
Conclusions: Various clinicopathological features and prognostic values are associated with different metastatic sites. Understanding these differences may enable targeted pre-treatment assessment of advanced old NSCLC.
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61P

Early palliative care in patients with non-small cell lung cancer: A 36-weeks randomised controlled trial in China

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Background: Effective interventions to improve prognosis in non-small-cell lung cancer (NSCLC) are urgently needed. We assessed the effect of the early integration of interdisciplinary palliative care for patients with NSCLC on the nutritional status, quality of life (QoL), psychological state and cancer pain.
Methods: In this randomised controlled trial, 280 newly diagnosed NSCLC patients were enrolled and randomly assigned (1:1) to the combined early palliative care (CEPC) group integrated with standard oncologic care or standard oncological care (SC) group. QoL and psychological state were assessed at baseline and at 36 weeks by Functional Assessment of Cancer Therapy-Lung (FACT-L) scale, the Hospital Anxiety and Depression Scale (HADS) and Patient Health Questionnaire-9 (PHQ-9), respectively. Cancer nutritional and pain status were assessed with the use of the Patient-Generated Subjective Global Assessment (PG-SGA) and Numerical Rating Scale (NRS), respectively. The primary outcome was the change in the quality of life, psychological state and nutritional status at 36 weeks. Analysis was by intention to treat.
Results: 280 patients were enrolled: 140 in CEPC group (88 completed) and 140 in the SC group (62 completed). Patients in CEPC group had a better nutritional status [severe malnutrition: 10.71% (15/140); mild or moderate malnutrition: 60.71% (85/140); no malnutrition: 26.4% (37/140)] than SC group [severe malnutrition: 35.71% (50/140); mild or moderate malnutrition: 55.0% (77/140); no malnutrition: 7.86% (11/140)] (P = 0.001). Furthermore, CEPC group had a better QoL than SC group (P < 0.05). In addition, fewer patients in the CEPC group than in the SC group had depressive (P = 0.005) symptoms. There was no significant difference in NRS score between CEPC group and SC group.
Conclusions: Among patients with non-small-cell lung cancer, early palliative care led to significant improvements in nutritional status, quality of life and psychological state.
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Predictive value of combined positive score (CPS) and tumor proportion score (TPS) for immunotherapy response in advanced non-small cell lung cancer (NSCLC)

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Background: In advanced stage non-small cell lung cancer (NSCLC), tumor proportion score (TPS) is typically used to predict the efficacy of immune checkpoint inhibitors (ICI). However, in other cancer types, the combined positive score (CPS), which covers PD-L1 expression on both tumor and surrounding immune cells, is used. We investigated the predictive value of CPS in comparison to TPS in advanced NSCLC.
Methods: A monocenter retrospective study was performed in advanced NSCLC patients treated with ICI monotherapy between 2015 and 2021. H&E and PD-L1 were stained on baseline tumor biopsies to score PD-L1 by both TPS and CPS. Positivity for TPS and CPS was defined as a score of 1% or above. Progression-free survival (PFS) and overall survival (OS) were assessed for TPS and CPS scores.
Results: Amongst the 187 included patients, PD-L1 positivity was found in 112 patients (59.9%) by TPS and 135 patients (72.2%) by CPS. In terms of PFS, no significant differences were observed between TPS^- and TPS^+ or CPS^- and CPS^+ patients (HR 0.86, p = 0.37 and HR 0.72, p = 0.065, respectively). There was no significant difference in OS between TPS^- and TPS^+ patients (HR 0.81, 95%CI 0.59–1.12, p = 0.20). However, CPS^+ patients did show a longer OS than CPS^- patients (HR 0.62, 95%CI 0.44–0.87, p = 0.006). OS was superior in both TPS^-/CPS^+ and TPS^+/CPS^+ as compared to TPS^-/CPS^- cases (HR 0.52, p = 0.018 and HR 0.64, p = 0.015, respectively). Cases that were TPS^-/CPS^+ had a comparable OS to TPS^+/CPS^+ cases (11.3 vs 9.7 months, p = 0.016).
Conclusions: To our knowledge, this is the largest real-world population study comparing TPS and CPS in NSCLC. We showed that CPS differentiated OS better than TPS in advanced NSCLC patients with ICI monotherapy. Remarkably, this was driven by the performance of the TPS^-/CPS^+ subgroup, indicating that CPS may be a better predictive biomarker for ICI efficacy. These findings support the notion that ICI also

have an anti-cancer efficacy through inhibiting the immune suppressive immune cells in the tumor microenvironment.

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63P

Inflammatory indexes and treatment response as correlates of pembrolizumab effectiveness in patients with PD-L1≥50%: Data from the real-life practice

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Background: Pembrolizumab is the standard first-line option for patients with metastatic non-small cell lung cancer (NSCLC) with programmed death-ligand 1 (PD-L1) expression of ≥50%. Clinicopathological correlates of effectiveness in real-life populations remain unclear.

Methods: This study is a single-center retrospective analysis of patients (pts) with stage IV NSCLC treated with pembrolizumab in routine practice. Inclusion criteria included good performance status (ECOG 0–1), no active brain metastases, and no EGFR or ALK alterations. The median progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method. The log-rank test and Cox regression model were used for uni- multivariate analysis.

Results: A group of 240 pts was included, of whom 20% were >75 years old, 10% had brain and 14% liver metastases. The ORR was 34%, 23% of pts had progressive disease, while 17% of pts has before the first radiological assessment. Median PFS and OS were 8.4 months (95% CI 4.9–11.8; 153 events) and 13.8 months (95% CI 10.47–17.12; 141 events), respectively. Adverse events (AEs) were reported in 28% of pts, including irAE in 18.8%. AEs led to treatment discontinuation in 10.3% of pts, and resulted in death in 2%. In the univariate analysis, tumor burden <110 mm ($p < 0.04$), neutrophils/lymphocytes ratio (NLR) <2.64 ($p < 0.009$), platelet/lymphocyte ratio (PLR) <256 ($p < 0.024$), monocyte/lymphocyte ratio (MLR) <37 (0.030), and Systemic Inflammatory Index <1309 ($p < 0.003$) and the Lung Immune Prognostic Index (LIPI) of 0 ($p < 0.038$) had a favorable impact on OS. Other pretreatment evaluated factors- age >75 years included- were not relevant. Early PD was a negative prognostic factor, with substantially shorter OS ($p < 0.001$). In multivariate analysis, the trend for a negative impact on OS of larger tumor burden was observed ($p < 0.090$, HR 1.35 95% CI 0.95–1.9).

Conclusions: The results of treatment with pembrolizumab in real-life are not as favorable as those obtained in the clinical trial setting. Taking into account additional factors - such as tumor burden and inflammatory indices - may be helpful in identifying the optimal patient population.

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Pretreatment predictive score for metastatic non-small cell lung cancer patients treated with immunotherapy

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Background: Immune checkpoint inhibitors (ICIs) demonstrated efficacy in NSCLC patients, but only minority of them archive a clinical benefit from the therapy. The aim of the study was to investigate predictive value of the new score based on pretreatment markers in NSCLC patients treated with ICIs.

Methods: The study included 181 patients with EGFR/ALK-negative metastatic NSCLC receiving anti-PD-1/PD-L1 monotherapy in second and subsequent lines. The clinical, morphological and laboratory parameters were obtained before the start of treatment in all patients included in the study. The endpoints were overall survival (OS) and progression-free survival (PFS).

Results: Overall median of OS and PFS was 13,7 and 4,9 months, respectively. Multivariate analysis for OS determined baseline neutrophil-to-lymphocyte ratio (NLR) >4.3 (HR 4.89, 95% CI: 3.16–7.62, $p < 0.0001$), non-smokers (HR 1.80, 95% CI: 1.21–2.68, $p = 0.004$) and ECOG ≥2 (HR 2.02, 95% CI: 1.06–3.91, $p = 0.035$) as negative prognostic factors. The multivariate analysis for PFS also indicated these markers as independent predictors of resistance to ICIs. The three parameters were included in the NSE score (NLR- 2 points, Smoking status- 1, ECOG- 1 point). According to the score patients were classified into 3 groups: good (0 point), intermediate (1–2 points) and poor prognosis (≥3 points). The median of OS for good, intermediate and poor outcomes were 33.7, 12.2 and 7.2 months, respectively ($p < 0.0001$). Also, the NSE score could predict PFS in NSCLC patients: the median was 17.1, 4.3 and 3.2 months for good, intermediate and poor prognostic groups ($p < 0.0001$).

Conclusions: The NSE score including pretreatment clinical and blood markers can help to predict survival in NSCLC patients receiving ICIs in second and subsequent lines.

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Correlation of overall survival and surrogate endpoints in advanced non-small cell lung cancer treated with immune checkpoint inhibitors: A trial-level analysis

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Background: Immune checkpoint inhibitors (ICIs), either alone or in combination with chemotherapy, have radically changed treatment of patients with non-small cell lung cancer (NSCLC). We investigated whether progression-free survival (PFS) and objective response rate (ORR) correlate with overall survival (OS) in phase III randomized controlled trials (RCTs) testing ICIs in advanced NSCLC.

Methods: We systematically reviewed literature to select articles of RCTs investigating ICIs in advanced NSCLC, published by December 2022. For each RCT, we collected data about ORR, hazard ratio of OS (HR_{OS}) and PFS (HR_{PFS}). When not reported, odds ratio for ORR (OR_{ORR}) was manually calculated. Spearman's rank correlation coefficient (ρ) was used to evaluate the relationship between: i) HR_{OS} and HR_{PFS}; ii) HR_{OS} and OR_{ORR}. Absolute value of ρ indicated the power of correlation between the two variables (0.9–1.0 very strong, 0.7-<0.9 strong, 0.5-<0.7 moderate, 0.3-<0.5 weak, 0-<0.3 negligible).

Results: We identified 25 RCTs with 2 distinct arms and 5 trials with >2 experimental arms. Overall, 36 experimental arms of ICIs ± chemotherapy (ChT), versus standard ChT, were considered for further investigation. Analysis of trials results revealed a weak positive correlation between HR_{OS}-HR_{PFS} (n = 35, ρ = 0.4562, p = .0059) and a moderate negative correlation between HR_{OS}-OR_{ORR} (n = 36, ρ = -0.6029, p < .001). HR_{OS}-HR_{PFS} had a moderate positive relationship in studies testing ICIs in first-line setting (n = 27, ρ = 0.5681, p = .002), as well as in RCTs testing ICIs alone (n = 18, ρ = 0.5498, p = .018). Next, HR_{OS}-OR_{ORR} showed only a weak negative relationship in RCTs of ICIs alone (n = 18, ρ = -0.4694 p = .049). Finally, we found that PFS and ORR strongly correlated to OS in trials testing ICIs combined with ChT (n = 17, HR_{OS}-HR_{PFS} ρ = 0.7606, p < .001; n = 18, HR_{OS}-OR_{ORR}ρ = -0.8388, p < .001).

Conclusions: Across trials investigating ICIs in advanced NSCLC, PFS and ORR demonstrated plausible relationship with OS, particularly in RCTs testing combination of ICIs+ChT. However, our results show that caution should be taken when novel treatments are approved based on surrogate outcomes.

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Outcome predictors for pembrolizumab alone or with chemotherapy in advanced non-small cell lung cancer (NSCLC)

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Background: Apart from PD-L1 expression, no predictors for choosing between Pembrolizumab (Pembro) or Pembrolizumab-chemotherapy (Pembro-CT) as frontline treatment for advanced NSCLC are validated. Here we explore the potential role of different clinical, radiological, biological factors.

Methods: We retrospectively collected data from 112 and 84 patients, selected for Pembro or Pembro-CT solely based on PD-L1 as per Italian prescribing limitation (combination treatment reserved to PD-L1<50%), at two health facilities, and evaluated progression-free survival (PFS), overall survival (OS), objective response rate (ORR), disease control rate (DCR).

Results: Median follow-up was 12.5 and 10.4 months for Pembro and Pembro-CT groups, respectively. The multiple analyzed sub-groups and their OS data are reported in table. Among females, we found a statistical difference (p = 0.01) in PFS, but not in OS, favoring Pembro-CT over Pembro, although median OS in the former sub-group was not reached (NR). Among patients harboring any KRAS mutations, we observed an advantage of Pembro-CT over Pembro in terms of PFS (p = 0.02), with a trend of benefit in OS. In the Pembro group, patients harboring KRAS wild type tumors achieved longer PFS than patients harboring KRAS mutant tumors (p = 0.04). No statistical difference was found in ORR (p = 0.87) nor DCR (p = 0.07) among the sub-groups. However, a higher number of early deaths occurred in the Pembro compared to Pembro-CT group (6 vs. 13).

Table: 66P

	Pembro	Pembro-CT	P
OS (m)	14.4	13.4	0.6
Male	16.5	12.6	0.09
Female	20.3	NR	0.32
Non squamous	20.3	12.6	0.41
Squamous	15.5	13.4	0.6
Never smokers	23.3	12.6	0.44
Age>70	16.0	12.5	0.35
PS ECOG≥2	2.5	1.5	0.34
KRAS mutant	9.7	16.0	0.33
Tumor burden>62 mm	10.9	10.9	0.91
N# lesions >3	13.9	10.9	0.32
Brain metastases	8.7	9.0	0.6
LIPI intermediate	20.3	16.0	0.8
Poor	5.9	5.5	0.64
Corticosteroids>10 mg/day	2.7	8.6	0.38
Proton pump inhibitors	9.2	10.4	0.93

Conclusions: While no significant differences were found in OS, some patients, notably those harboring KRAS alterations, may benefit from the addition of chemotherapy. The enrichment of Pembro-CT group, together with molecular data revealing potential co-mutations, would provide more robust findings.

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Blood cell gene expression and clinical characteristics in advanced non-small cell lung cancer with immune-related adverse events

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Background: Immune checkpoint inhibitors (ICI) have improved the prognosis of non-small-cell lung cancer (NSCLC) but can also cause immune-related adverse events (irAEs), which can be life-threatening and have a complex management. Currently, there is a need for molecular and clinical markers to predict irAEs occurrence and outcome.
Methods: Clinical characteristics of 762 patients with stage IV NSCLC receiving first- or second-line PD-(L)1 inhibitors were analyzed. Additionally, blood samples of 8 patients with irAEs were analyzed at baseline (BL) and at the time of toxicity (TT) in comparison with 8 matched control samples from patients with similar clinical characteristics and ICI exposure, but no irAEs. The expression of 12 genes involved in the immune response (GATA3, TBX21, MKI67, CD247, FAS, FASLv1, FOXP3, GzmB, IFNγ, PD1, PRF1, RORgt) was absolutely quantified in PAXgene blood RNA samples using RT-PCR and plasmid standards.
Results: IrAEs occurred in 176/762 cases (23%), with a similar frequency for ICI monotherapy or chemoimmunotherapy (24% vs. 22%). CTCAE severity was grade 1 in 11%, grade 2 in 41%, grade 3 in 37%, grade 4 in 10%, and 2 events were lethal (1%). Frequently affected were endocrine glands (21%), lungs (17%), musculoskeletal system (17%), colon (15%) and liver (15%). All other organs were less commonly affected (15%). IrAEs occurrence showed a significant association with a better ECOG performance status (28% vs. 18% for PS 0 vs. 1, p = 0.006), PD-L1 positivity (25% vs. 14%, p = 0.009), and a lower neutrophil-to-lymphocyte ratio (NLR, 28% vs. 19% with the median 6.2 as cut-off, p = 0.004). Blood cell gene expressions in patients with irAEs was slightly higher for 7/12 immunologically relevant genes at TT, and for 11/12 genes at BL, but not significantly different ($p \geq 0.07$). No substantial changes in gene expression were noted between BL and TT in each group (mean fold change for the irAEs group = 0.82, for the controls = 0.84, $p \geq 0.07$).
Conclusions: IrAEs under PD-(L)1 inhibitors occur more frequently in patients with PD-L1-positive NSCLC, a better ECOG PS, and a lower NLR. No relationship between the blood expression of selected immunologically relevant genes and irAEs occurrence was noted.
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OncoMutational ratio on ctDNA: A potential novel biomarker in NSCLC

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Background: Emerging evidence proposed ctDNA as a noninvasive biomarker for multiple cancer-related objectives. NSCLC patients (pts) with negative post-treatment ctDNA have better outcomes compared to positive post-treatment ctDNA. Tumor mutational burden (TMB) has been offered as a predictive marker for immunotherapy (IOT), although its use in the clinical setting remains uncertain due to conflictual RCT data. This study evaluated the impact on survival of the mutation load ratio detected on liquid biopsy in aNSCLC pts.
Methods: We retrospectively calculated "OncoMutational Ratio" (OMR), defined as a fraction between the number of pathogenic mutations and the number of genes analysed of genomic panels, on aNSCLC pts who undergone liquid biopsy at Fondazione IRCCS Istituto Nazionale dei Tumori in Milan and Luigi Vanvitelli Hospital in Naples from April 2017 to September 2022. Guardant360CDx® and Archer® LiquidPlex™ test were utilized. Patients with OMR value above the median value were defined high-OMR (h-OMR).
Results: 456 patients had OMR status available on liquid biopsy, with a median value of 0.04545 (IQR 0.021–0.091). Patients with h-OMR were more frequently smokers and enriched with TP53 mutations. In the total population h-OMR was associated with worse OS (18.7 vs 28.4 m; HR 1.55, CI 95% 1.23–1.95; p < 0.001). OS was not significantly different among pts not treated with IOT (17.4 vs 19.4 m) (non-IOT-cohort), whereas a significant worse OS was observed among IOT-treated patients (18.9 vs 33.8 m, p for interaction <0.001) (IOT-cohort). Among patients treated with any-line IOT (N = 293) a trend for worse PFS was also observed in h-OMR, although without statistical significance (HR 1.24, CI 95% 0.97–1.58, p = 0.082). Notably, a trend to a decreased IOT-DCR was observed in h-OMR patients (69.7% vs 58.3%, p = 0.066), while no differences were observed in terms of ORR.

Conclusions: The present study demonstrated that a higher mutation load ratio detected on liquid biopsy significantly predicted survival in aNSCLC patients treated with standard therapies. This effect was mostly shown in IOT-cohort compared to non-IOT-cohort, suggesting h-OMR as a predictive potential biomarker. These results deserve to be validated in prospective studies to be used in clinical practice.

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69P

The effect of inflammatory-nutritional prognostic scoring system (INPS) on treatment response and prognosis in patients with metastatic NSCLC as second-line treatment with nivolumab

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Background: We aimed to reveal the predictive and prognostic value and biomarker of the novel scoring system, the inflammatory-nutritional prognostic score (INPS), on nutritional and immune status in patients with NSCLC who received second-line nivolumab therapy.

Methods: In this study, patients who were treated in Dokuz Eylul University, Department of Medical Oncology between October 2018 and September 2022, and who were diagnosed with metastatic NSCLC and received nivolumab as a second-line therapy were evaluated retrospectively. Demographic characteristics, blood tests, clinicopathological features of the tumor and information about the treatments they received were recorded. We selected the most valuable biomarkers to develop INPS by the least absolute shrinkage and selection operator (LASSO) Cox regression model. A prognostic nomogram incorporating INPS and other independent clinicopathological factors was developed based on the stepwise multivariate Cox regression method. Then, we evaluate the prognostic performance and predictive accuracy of the predictive nomogram.

Results: Using the LASSO Cox regression model, determining overall survival as primary endpoint, six inflammatory-nutritional biomarkers, namely, SII, NLR, PLR, MLR, PNI, and LAR, out of 8 (eliminated two inflamatory variables AAPR and CAR) have been selected and used to construct the INPS for 67 metastatic NSCLC cancer patients treated with nivolumab. Six of the eight inflammatory markers were shown to have a statistically significant prognostic value on overall survival and were included in the INPS nomogram. Using the cut-off points of these six inflammatory-nutritional biomarkers, the INPS scores (from 0 to 6) have been obtained. As a final step, the INPS scores are used to construct the risk groups (from low to high).

Conclusions: The search for prognostic markers other than PD-L1 and TMB is still ongoing in patients receiving immunotherapy. With this study, for the first time in the literature, the new screening system, INPS, created with various nutritional and inflammatory markers, has shown that it can be used as a prognostic tool in metastatic NSCLC patients receiving immunotherapy.

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70P

Impact of TP53/KRAS mutations on overall survival of metastatic non-small cell lung cancer patients (pts) treated with systemic first-line therapy

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Background: Mutations in TP53 and KRAS are frequent in NSLC pts, particularly in non-squamous histology. Improved biomarkers for treatment selection are needed. We aimed to investigate the impact of TP53 and KRAS mutation on treatment outcome of pts with first-line systemic therapy for mNSCLC.

Methods: Single-institution retrospective cohort of mNSCLC pts treated with ≥1 line of systemic therapy. A targeted NGS panel (Oncomine Precision) including KRAS and TP53 was performed on all pts; actionable EGFR, ALK, ROS-1 alterations were excluded. PDL1 was assessed by IHC (SP263 Ab). The main objective was to study the association between TP53 and/or KRAS mutations and OS (overall population, and in PDL1 ≥ 50% and PDL1 < 50% populations). OS was defined as the time from therapy start to last visit or death. Kaplan-Meier method was used to calculate median OS; associations with OS were assessed through Cox-regression models.

Results: 68 mNSCLC pts were included. Most had non-squamous histology (92.5%), ECOG PS 0–1 (81%) and PDL1 < 50% (81%). TP53 and KRAS mutations were observed in 34.3% and 23.9%, respectively; 3% had co-occurring mutations. 52% received chemo-immunotherapy combinations and 20% immunotherapy. Median OS was 9.8 months

Table: 70P

	TP53 mutation			KRAS mutation		
	Yes	No	HR (95%CI); pval	Yes	No	HR (95%CI); pval
All pts	18.4 m	7.3 m	0.50 (0.24–1.02); p = 0.058	7.3 m	12.4 m	1.5 (0.75–2.9); p = 0.25
PDL1 < 50%	18.4 m	6.9 m	0.44 (0.20–0.97); p = 0.043	8.9 m	12.4 m	1.3 (0.60–2.7); p = 0.49

(95%CI: 6.8-NR). In the overall population, a non-significant trend was observed for higher OS in TP53-mutated pts (HR 0.5; p = 0.058). There was a significant OS benefit in TP53 mutated pts with PDL1 < 50% (HR: 0.44; 95%CI: 0.20–0.98; p = 0.043), but not in PDL1 ≥ 50% (HR 0.89; 95%CI: 0.10–7.7; p = 0.92) pts. No association between KRAS mutations and OS was observed (table).

Conclusions: We observed a statistically significant difference in OS favouring pts with TP53 mutations in the PDL1 < 50% population. No survival impact of KRAS mutations was observed. TP53 mutations could represent a potential biomarker for treatment selection for pts with low PDL1 expression treated with chemo-immunotherapy. Prospective validation is needed.

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71P

Biomarker analysis from phase I/II study of tusamitamab ravtansine (SAR408701) in patients with advanced non-small cell lung cancer (NSCLC)

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Background: Tusamitamab ravtansine is an antibody-drug conjugate of a humanized carcinoembryonic antigen (CEA)-related cell adhesion molecule 5 (CEACAM5)-specific monoclonal antibody linked to DM4. A phase I/II study showed tusamitamab ravtansine antitumor activity in pretreated patients (pts) with advanced nonsquamous NSCLC and high CEACAM5 expression. Here, we explore biomarker associations with tumor CEACAM5 expression by immunohistochemistry (IHC), and whether biomarkers predict objective response rate (ORR).

Methods: We assessed CEACAM5 expression by IHC, RNA sequencing, and whole exome sequencing (WES) on latest archival tumor samples; and circulating CEACAM5 (cCEACAM5) and CEA (cCEA). We enrolled 2 cohorts of pts with IHC CEACAM5 membrane expression at ≥2+ intensity: in ≥50% of tumor cells (high expressors, HEs, n = 64); and in ≥1% to <50% of tumor cells (moderate expressors, MEs, n = 28). Pts received tusamitamab ravtansine 100 mg/m^2 IV every 2 weeks.

Results: cCEA and cCEACAM5 were strongly associated (Spearman rho, 0.9), with weak associations between IHC CEACAM5 and cCEA or cCEACAM5 (Spearman rho, 0.3 and 0.4, respectively). Higher levels of CEACAM5 mRNA were observed in CEACAM5 HEs vs MEs (P = 0.0027). EGFR and KRAS genetic alterations by WES were present in 44.8% and 65.5% of CEACAM5 HEs, respectively, and 21.4% and 78.6% of CEACAM5 MEs, respectively. Confirmed partial responses were seen in 13/64 HEs (ORR 20.3%) and 2/28 MEs (ORR 7.1%). In CEACAM5 HEs with available baseline (BL) cCEA data, 25/62 (40.3%) had a cCEA level ≥100 µg/L, with a median value of 71.6 µg/L (range 1–8809); corresponding values in CEACAM5 MEs were 7/28 (25.0%) and 12.4 µg/L (range 0.5–684). In response evaluable CEACAM5 HEs with available BL cCEA data (n = 61), ORR was 10/24 (41.7%) in pts with high cCEA (≥100 µg/L) and 3/37 (8.1%) in pts with low cCEA (<100 µg/L); corresponding ORRs in CEACAM5 MEs were 0/7 and 2/21 (9.5%).

Conclusions: In CEACAM5 HEs, high cCEA was associated with numerically greater ORR vs low cCEA (41.7% vs 8.1%). Associations were also observed between: cCEA and cCEACAM5; IHC CEACAM5, cCEA, and cCEACAM5; and IHC CEACAM5 and CEACAM5 tumor mRNA levels, but not between IHC CEACAM5 and actionable oncogenic drivers.

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72P

Association of receptor activator of nuclear factor kappa-B ligand (RANKL) and epidermal growth factor receptor (EGFR) gene expression with bone metastases (mets) in patients (pts) with metastatic non-small cell lung cancer (mNSCLC)

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Background: Bone mets are frequent in NSCLC. The receptor activator of Nuclear Factor κB (RANK)/ RANKL/osteoprotegerin (OPG) pathway is important in bone mets development. EGFR signaling promotes osteoclast formation and stimulation. Understanding the biological mechanism of bone mets development might have implications for treatment strategies. We studied the association of EGFR, RANKL, RANK, OPG gene expression in tumor and presence of bone mets in mNSCLC.

Methods: Retrospective multicenter study (2008–2017), included: EGFR mutated (EGFR+), Kirsten rat sarcoma (KRAS+), EGFR/KRAS wildtype mNSCLC. Ribonucleic Acid was isolated from tumor samples and EGFR, RANK, RANKL, OPG gene expressions were determined via quantitative Polymerase Chain Reaction. Data on demographics, molecular subtyping, origin of pathology sample, presence/progression of bone mets, SREs were collected. Primary endpoint: relation between EGFR, RANK, RANKL, OPG gene expression, RANKL:OPG ratio and bone mets.

Results: n 169/335 (50%) pts tumor samples were available, in 73 (43%) gene expression analysis could be performed. 46/73 (63%) pts had bone mets at diagnosis/developed bone mets (table). EGFR+ NSCLC had significantly higher EGFR gene expression compared to other tumors. Pts with bone mets had a significantly higher RANKL gene expression and RANKL:OPG ratio compared to those without, but EGFR gene expression was not different. An increased RANKL:OPG ratio

resulted in a 1.65x increased risk to develop bone mets, especially in the first 450 days after diagnosis of mNSCLC.

Table: 72P Baseline characteristics

Characteristics	Total n = 73
Female n (%)	46 (63)
Never smoker n (%)	8 (11)
Mean age at diagnosis metastatic NSCLC, years (range)	62.8 (32–84)
Molecular subgroup n (%)	
EGFR+	23 (32)
KRAS+	36 (49)
EGFR/KRAS wildtype	14 (19)
Origin of pathology sample n (%)	
Lung (primary tumor)	29 (40)
Bone	9 (12)
Other metastasis	35 (48)
Metastatic disease at diagnosis n (%)	47 (64)
Bone mets at diagnosis stage IV n (%)	27 (37)
Bone mets at diagnosis or during course of disease n (%)	46 (63)
SRE n (% of all pts with bone mets)	26 (57)
Type of SRE n (% of all SREs)	
Radiotherapy	25 (96)
Pathologic fracture	4 (15)
Surgery	6 (23)
Spinal cord compression	2 (8)
BTA use in all pts n (%)	9 (12)
Denosumab	1 (1)
Bisphosphonate	8 (11)

Conclusions: Increased RANKL gene expression and RANKL:OPG ratio, but not EGFR expression, was associated with presence of bone mets. Increased RANKL:OPG gene ratio was associated with a higher incidence of bone mets development.

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73P

Qualitative research to evaluate perceptions around biomarker testing and patient-reported outcomes (PROs) for use in studies of non-small cell lung cancer (NSCLC)

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Background: Exon 19 deletion (19Del) and exon 21 point mutation (L858R) account for 85–90% of EGFR mutations in NSCLC and confer sensitivity to EGFR tyrosine kinase inhibitors. To evaluate the content validity and relevance of 4 PROs (NSCLC-SAQ, EORTC QLQ-C30, PROMIS-PF-8, TASQ) for use in clinical trials of this specific NSCLC population and understand perceptions of biomarker testing (BT), qualitative interviews were conducted.

Methods: ICAN, International Cancer Advocacy Network, helped identify study participants. Participants completed one Zoom interview containing concept elicitation and cognitive debriefing questions, guided by an interview guide, developed for this study. Interviews were recorded, transcribed, and analyzed using qualitative software. Symptoms/impacts were mapped to the PROs, and gap analysis was conducted. IRB approval was obtained.

Results: A total of 36 NSCLC adult patients with a confirmed diagnosis of advanced or metastatic 19Del or L858R NSCLC in the US, UK, Canada, Spain, and India were enrolled (mean age = 56, 81% female, 64% receiving 1st-line treatment, 92% with metastatic disease). Pain in areas other than the chest (69%), cough (67%), fatigue (64%), shortness of breath (58%), difficulty remembering/focusing (58%), and chest pain (33%) were the most common symptoms. Physical (35%), social (40%), and emotional (82%) impacts, and difficulty with daily activities (77%) were common. In general, patients found the PROs to be clear, comprehensive, and relevant. Gap analysis revealed the only concept missing was weight loss. All patients had undergone BT. 68% underwent BT at the time of diagnosis, biopsy, or surgery. 42% were unaware that BT was being done until after it had occurred. 79% reported BT was done to inform the targeted treatment decision, 96% felt results affected the type of treatment received, and 60% reported that they understood at least a little about the results. 78% would consider a timeframe of < 1 week to receive results as acceptable.

Conclusions: Findings provide evidence to support the content validity, clarity, and relevance of the four PROs in a population with EGFR-mutated NSCLC. Patients understand the value of BT.

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74P

Non-small cell lung cancer (NSCLC) predictors of response to immunotherapy (ICI): LIPI index and immune-related toxicity

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Background: ICI is proposed as the standard treatment for metastatic NSCLC in first-line and subsequent indications. It has different adverse effects with respect to traditional antineoplastics, given the stimulation of the immune system. Objective: analyze whether patients with a good prognosis lung cancer immunotherapy prognostic index (LIPI) have a better response to ICI and also to evaluate the relation of immune-related adverse events (irAEs) and response in patients with NSCLC in real clinical practice.

Methods: Observational, retrospective, single-center study. Cohort of stage IV NSCLC patients between 2016 and 2021. Toxicity grade (1–4) according to The Common Terminology Criteria for Adverse Events version 4.0. Response assessment according to RECIST 2.0 and immuno-related criteria. ICI in first (65%) or second (35%) line. Descriptive and survival analysis. Degree of toxicity and response to treatment (overall results and according to treatments and histology). LIPI index and response. LIPI defined as: dNLR (absolute neutrophil count/[white blood cell count − absolute neutrophil count]) ≥3 and lactate dehydrogenase (LDH) greater than the upper limit of normal; stratifies patients in "good" (G), "intermediate" (I) and "poor" (P) prognostic groups.

Results: N = 168 patients (p) (130 men/38 woman). Mean age 64.3 years. Mean dNLR 2.46. Average LDH 244U/L. Response: 15 (9%) complete response (CR), 50 (30%) partial response (PR), 39 (22%) stable disease (SD), 45 (28%) progression disease (PD) and 19 (11%) not evaluated (NE). 114 deaths (56% G, 76% I, 93% P). PFS (G 19 months, I 6, P 2) and OS (G 27 months, I 8, P 3). Adenocarcinoma 116 [77 with irAES G1-4 (13 CR, 31 PR, 21 SD, 8 PD, 4 NE), 39 without (3 PR, 6 SD, 21 PD, 9 NE]. Squamosus 52 [27 with irAES G1-4 (2 CR, 12 PR, 9 SD, 4 PD), 25 without (4 PR, 3 SD, 12 PD, 6 NE).] irAES appearance: longer PFS (19 vs 2 months) and OS (27 vs 4 months) $p < 0.0001$.

Conclusions: Good prognosis LIPI score patients (dNRL<3 and normal LDH) present a better response to ICI. LIPI index is a positive predictor of response to ICI. The presence of irAES is related with a better immune system response. In contrast, the absence of toxicity predicts a worse prognosis.

Legal entity responsible for the study: Medical Oncology Department, Hospital Clínico Universitario Lozano Blesa.

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75TiP

A multicenter, open-label, phase II trial evaluating the safety and efficacy of folate receptor alpha (FRα) antibody-drug conjugate (ADC) farletuzumab ecteribulin (FZEC*) in patients with previously treated, metastatic non-small cell lung cancer (NSCLC) adenocarcinoma (AC)

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Background: There is an unmet therapeutic need for patients with NSCLC who have disease progression after standard of care treatment. FRα is highly expressed on tumor cells in patients with NSCLC AC. FZEC is an ADC comprised of the humanized anti-FRα monoclonal antibody farletuzumab and the microtubule dynamics inhibitor eribulin. A phase I study in Japan (NCT03386942) demonstrated the antitumor activity of FZEC across multiple tumor types, including NSCLC, and identified interstitial lung disease (ILD) as an adverse event of interest (Shimizu 2021). This global, multicenter, phase II trial across 6 countries aims to evaluate the safety, efficacy, and optimal dose of FZEC in patients with previously treated metastatic NSCLC AC.

Trial design: Approximately 60 adults with advanced/metastatic NSCLC either without genetic alterations who have received ≥ 1 line of platinum-doublet chemotherapy and anti–PD-1/PD-L1 therapy or with genetic alternations who have received 1 targeted therapy and ≤ 3 lines of systemic therapy will be enrolled. Patients will be randomized 1:1 to receive FZEC Q3W at doses of 33 mg/m^2 (Arm A) or 25 mg/m^2 (Arm B). A pharmacokinetics model demonstrated that body surface area (BSA)–based dosing is predicted to reduce the risk of exposure-driven ILD (Hayato 2022). The primary objectives are to assess incidence of treatment-related adverse events leading to study discontinuation and investigator-assessed objective response rate by RECIST v1.1. Primary analysis will be performed after ≥ 6 months follow-up. Safety follow-up will occur 30 days after last dose, with survival follow-up every 3 months from safety follow-up visit until last participant has completed 2 years of follow-up. Measures to enhance early detection of ILD have been introduced and steps to potentially reduce the occurrence of severe ILD include implementation of BSA–based dosing, lung-specific eligibility criteria, revised and stringent ILD management criteria, and ILD training for relevant study personnel. *Formerly MORAb-202.

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76TiP

Fecal microbiota transplantation to improve efficacy of immune checkpoint inhibitors in metastatic lung cancer

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Background: Immunotherapy has recently become a main-stream treatment option in cancer care, with improved clinical outcomes in many malignancies, especially that of lung cancer. The long-term benefits of this treatment however are limited. Thus, there is a critical need to distinguish predictive biomarkers of response from those of resistance, and to develop synergistic strategies for improved therapeutic response. Strong emerging evidence indicates that the gut microbiome has the ability to influence response to immunotherapy. Unlike tumor genomics, the gut microbiome is modifiable, and thus, its modulation to enhance response to immunotherapy is an attractive therapeutic strategy. The main objective of this study is to evaluate the safety and efficacy of Fecal Microbiota Transplant (FMT) in altering response to immunotherapy in patients with metastatic lung cancer. The overall goal is to determine microbiome compositional and gene-content changes in patients who respond more efficiently to immunotherapy subsequent to FMT. This understanding may lead to future microbiome-based treatments combined with immunotherapy to significantly increase the efficacy of lung cancer treatment. In this prospective clinical-and molecular study, we will perform an in-depth analysis of the potential role of FMT in the context of immunotherapy.

Trial design: This prospective, stratified, randomized, placebo-controlled, double-blinded, comparative study. The study will assess the feasibility of Fecal microbiome transplant (FMT) when used in conjunction with standard immunotherapy +/- chemotherapy as a first-line treatment for metastatic lung cancer to enhance the disease control rate. Completely respond metastatic patients to immunotherapy will serve as the fecal implant donors. Patients will start receiving placebo/antibiotics then receive placebo/FMT on the first day of the (chemo-)immunotherapy cycle 1 and then every 3 weeks. The FMT capsules and (chemo-)immunotherapy administrations will be repeated until End of Treatment.

Clinical trial identification: NCT05502913.

Legal entity responsible for the study: I. Massalha.

Funding: Israel Cancer Association.

Disclosure: N. Geva-Zatorsky: Financial Interests, Personal, Leadership Role: Biotax Labs LTD. All other authors have declared no conflicts of interest.

77TiP

A phase I/II dose escalation and dose expansion study of ozuriftamab vedotin (BA3021) alone and in combination with nivolumab in patients with advanced solid tumors including non-small cell lung cancer

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Background: Ozuriftamab vedotin (BA3021) is a conditionally active biologic (CAB) anti-receptor tyrosine kinase orphan receptor 2 (ROR2) humanized monoclonal antibody (IgG1) conjugated to monomethyl auristatin E (MMAE) using a cleavable linker (CAB ROR2 ADC). Preclinical data suggest targeting ROR2 may result in antitumor activities in various tumor types, such as NSCLC. Taken together with the proposed mechanism of BA3021 and underlying biology, antitumor activity in NSCLC is anticipated. The upregulation of ROR2 in PD-1 resistant tumor strongly suggests its role in resistance and recurrence in this population.

Trial design: BA3021-001 is a multi-center, open-label, phase I/II study designed to evaluate the safety, tolerability, PK, immunogenicity, and antitumor activity of BA3021 alone and in combination with nivolumab in patients with advanced solid tumors. Phase I will comprise 2 sequential parts—dose escalation and dose expansion—and is designed to evaluate the safety and tolerability of BA3021 in patients with advanced solid tumors and to identify the MTD and/or RP2D for BA3021. Phase II is an open-label study to evaluate the efficacy and safety of BA3021 alone and in combination with nivolumab in patients with ROR2-expressing tumor membrane percent score $\geq 1\%$, metastatic NSCLC, or melanoma who have measurable disease by RECIST version 1.1 criteria and have documented progression according to RECIST v1.1 criteria within the 6 months prior to enrollment. NSCLC patients must have experienced failure, defined as disease progression or discontinuation due to an adverse event, of a PD-1/L-1, epidermal growth factor receptor (EGFR) inhibitor, or anaplastic lymphoma kinase (ALK) inhibitor (either monotherapy or in combination with another therapy such as ipilimumab). Enrollment completion is anticipated in 2023.

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Legal entity responsible for the study: BioAtla, Inc.

Funding: BioAtla, Inc.

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78TiP

Phase Ib/IIa safety and tolerability study of bemcentinib with pembrolizumab/carboplatin/pemetrexed in subjects with untreated advanced or metastatic non-squamous NSCLC with/without STK11 mutations

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Background: The combination of platinum chemotherapy, pemetrexed and pembrolizumab (CIT) has become a standard of care as first-line (1L) treatment in patients with non-squamous NSCLC. Despite improvements in response rates and survival, the emergence of primary or acquired resistance limits its efficacy. Serine/threonine kinase 11 mutations (STK11m) are common (˜20%) in NSCLC and promote immune suppression by activation of AXL signalling. Bemcentinib (BEM), a selective AXL inhibitor, has been shown in preclinical studies to sensitize STK11m NSCLC to pembrolizumab. Therefore, the addition of BEM to CIT has the potential to improve the 1L treatment outcomes of NSCLC, particularly in tumors harboring STK11m.

Trial design: This is an open-label, multi-center, phase Ib/IIa clinical study to assess the safety, tolerability, and preliminary anti-tumor activity of BEM in combination with CIT as 1L treatment in patients with advanced (stage IIIb/IIIc) or metastatic (stage IV) non-squamous NSCLC without actionable mutations. In the phase IIa, patients with a STK11 mutation will be enrolled. All patients will receive BEM orally on Day 1 of each 21-day CIT treatment cycle. After the completion of 4 cycles of CIT + BEM, patients will receive maintenance with BEM + pemetrexed + pembrolizumab. Phase Ib follows a 3+3 design. Patients will receive BEM + CIT at one of 3 daily BEM dose levels: Cohort 1 = 75 mg; Cohort 2 = 100 mg; or Cohort 3 = 150 mg. An independent data safety monitoring board will review the safety data from each cohort at the end of the dose-limiting toxicity assessment period (the first 21 days of cycle 1 for each patient of each cohort) and will recommend the BEM dose for the phase IIa expansion. The study consists of a screening period (up to 28 days), a treatment period (up to 24 months) and overall survival follow up for each subject for at least 2 years. Up to 24 and 40 patients will be enrolled in the phase Ib and IIa, respectively. The trial is currently enrolling patients in the phase Ib in the US; patients' recruitment for the phase IIa is planned to open in Q2 2023 in Europe, UK, and US.

Clinical trial identification: EudraCT 2019-003806-28/NA/124645.

Legal entity responsible for the study: BerGenBio Ltd, UK.

Funding: BerGenBio.

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79TiP

Progress of a phase I trial (TOTEM) of repotrectinib in combination with osimertinib in advanced, metastatic EGFR mutant NSCLC

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Background: Osimertinib has robust efficacy as first-line treatment for advanced EGFR mutant non-small cell lung cancer (NSCLC). Osimertinib with repotrectinib inhibited Src/FAC/Janus kinase 2 (JAK2), STAT3 and YAP1 signaling, abrogating tumor growth, and having efficacy with no substantial toxicity in patients (pts) with EGFR-mut tumors. Based on this evidence, we designed the current trial. The TOTEM trial will evaluate the tolerability/safety, preliminary efficacy, the pharmacokinetic (PK) and pharmacodynamic (PD) profile of repotrectinib and osimertinib.

Trial design: Eligible pts are ≥ 18 years, diagnosed with locally advanced, unresectable or metastatic NSCLC harboring EGFR exon 18, exon 19, exon 21, or T790M mut, ECOG 0-1, either without brain metastasis (BM) or asymptomatic BM, and creatinine clearance >50 mL/min. Treatment with previous chemotherapy, immunotherapy, and tyrosine kinase inhibitors (TKIs), including osimertinib, is allowed. The study includes an initial dose escalation phase following a 3+3 design to determine the recommended phase II dose (RP2D). Pts receive osimertinib monotherapy for 14 days at 80 mg per day (QD), followed by osimertinib in combination with repotrectinib at the assigned dose level (80 mg QD, 160 QD, or 160 mg twice a day [bid]); The expansion phase will enroll 20–30 pts who have progressed to osimertinib or first /second-generation TKIs, who will receive the combination at the RP2D. Treatment will continue until progression, or unacceptable toxicity. Tolerability is evaluated by the incidence of dose-limiting toxicities (DLTs). The RP2D is defined as the dose level with less than 33% of pts experiencing a DLT. Safety is assessed by frequency and severity of adverse events. Secondary endpoints include objective response rate, intracranial response (for pts with BM), PFS, and OS. As of Jan 2023, 11 pts are accrued. No DLT was reported at 80 mg QD of repotrectinib, while 1/6 pts had a DLT consisting of renal toxicity at 160 mg QD. Preliminary PKs results showed no significant interaction that required dose adjustments. The third dose level (160 mg bid repotrectinib/80 mg osimertinib) is currently open to recruitment and 2 pts have already initiated study treatment.

Clinical trial identification: NCT04772235, EudraCT 2020-005151-20.

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80TiP

High-dose aumolertinib versus osimertinib in EGFR T790M+ NSCLC patients with brain metastases (ATTACK)

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Background: Third-generation EGFR-TKIs have demonstrated superior CNS efficacy compared with first-generation EGFR-TKIs or chemotherapy in previous phase III studies (AENEAS, FLAURA, AURA3). However, there is a lack of head-to-head comparison of CNS efficacy between third-generation EGFR-TKIs. Herein, we conduct the ATTACK study to evaluate the efficacy and safety of aumolertinib compared with osimertinib in EGFR T790M+ NSCLC patients with brain metastases.
Trial design: ATTACK is a multicenter, open-label, randomized, controlled trial. Patients with histologic or cytologic confirmation of advanced NSCLC and are known to have progression of radiologic disease on first- or second-generation EGFR-TKIs and harbor an EGFR T790M mutation are eligible. At baseline, patients are required to have at least one measurable intracranial lesion, defined as ≥10 mm. Approximately 232 patients will be randomized (1:1) to receive either 165 mg aumolertinib or 80 mg osimertinib, administered once daily orally, stratified by the type of EGFR mutation (Ex19del or L858R). Treatment continues in 21-day cycles until disease progression, withdrawal of consent, the development of unacceptable side effects, or the fulfillment of other discontinuation criteria. The primary endpoint is intracranial progression free survival (iPFS). Secondary endpoints include PFS, objective response rate (ORR), disease control rate (DCR), intracranial ORR (iORR), intracranial DCR (iDCR), overall survival (OS), and safety. Adverse effects are graded per CTCAE v.5.0. The first patient had been enrolled in November 2022.
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Legal entity responsible for the study: Shanghai Chest Hospital.
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81TiP

NVL-655, a selective anaplastic lymphoma kinase (ALK) inhibitor, in patients with advanced ALK-positive solid tumors: The phase I/II ALKOVE-1 study

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Background: Aberrations of the ALK oncogene drive tumor cell proliferation, survival, and metastasis in multiple adult and pediatric cancers. ALK gene fusions are detected in ~5% of advanced non-small cell lung cancers (NSCLC); among these patients, the incidence of central nervous system (CNS) metastases at diagnosis is ~40%. Although 5 tyrosine kinase inhibitors (TKIs) are approved by the FDA and EMA for ALK-positive NSCLC, therapeutic limitations remain, such as acquired resistance due to secondary and compound ALK mutations and/or neurologic adverse events attributed to off-target inhibition of TRK. NVL-655 is a novel, brain-penetrant ALK-selective TKI that exhibits preclinical activity against diverse ALK fusions and mutations, including G1202R and G1202R compound mutations, while sparing inhibition of TRK. The ALKOVE-1 study is evaluating the safety and preliminary activity of NVL-655 in patients with solid tumors harboring oncogenic ALK alterations, including those with acquired ALK resistance mutations and CNS metastases.
Trial design: ALKOVE-1 consists of a phase I dose escalation followed by a phase II expansion in cohorts defined by tumor type and prior therapies. Phase I includes adult patients with any solid tumor type harboring an oncogenic ALK gene fusion or activating mutation (by local testing), including ALK fusion-positive NSCLC after ≥ 1 prior 2nd or 3rd generation ALK TKI. Prior platinum-based chemotherapy and/or immunotherapy, CNS disease without progressive neurological symptoms or increasing corticosteroid doses, and evaluable but non-measurable disease are allowed. Patients will receive NVL-655 by daily oral administration. Primary phase I objectives are to determine the NVL-655 recommended phase II dose and, if applicable, maximum tolerated dose. Additional objectives include evaluation of safety/tolerability, preliminary activity, and characterization of the pharmacokinetic and pharmacodynamic profiles of NVL-655. Longitudinal analysis of circulating tumor DNA will be performed, including ALK mutation profiling and other relevant biomarkers. The phase I portion of the study is ongoing.
Clinical trial identification: NCT05384626 (May 20, 2022).
Legal entity responsible for the study: Nuvalent, Inc.
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Hoffmann-La Roche Ltd, Merck Sharp & Dohme Corp, AstraZeneca AB, Daiichi Sankyo Inc, Exelixis Inc, Merck KGAA, Janssen-Cilag International NV, GlaxoSmithKline Research & Development Limited, AbbVie Deutschland GmbH & Co KG, Novartis Farmaceutica SA, Bayer Consumer Care AG, Takeda Pharmaceuticals International, Boehringer Ingelheim International GmbH, Pfizer S.L.U., Amgen Inc, Bristol-Myers Squibb International Corporation (BMS), Mirati Therapeutics Inc; Non-Financial Interests, Personal, Leadership Role, President (2021–2023): SEOM (Sociedad Espanola de Oncologia Medica); Non-Financial Interests, Personal, Member, Member of ESMO Nominating Committee and Compliance Committee: ESMO; Non-Financial Interests, Personal, Member, Member of Scientific Committee: ETOP (European Thoracic Oncology Platform). C. 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82TiP

A modular, open-label, phase I/II study to evaluate the safety, tolerability, pharmacokinetics and efficacy of EP0031, a next generation selective RET inhibitor, in patients with advanced RET-altered malignancies

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Background: Addressing resistance to 1st generation (gen) selective RET inhibitors (SRIs) is an area of high unmet need, with a number of RET dependent and independent pathways identified[1,2]. The ideal profile of a next gen SRI has been proposed: broad activity against RET fusions/mutations, inhibition of both V804M/L gatekeeper and G810C/S/R solvent front mutations and penetration of the CNS to address brain metastases[1,2]. This trial is evaluating whether EP0031, an orally available next gen SRI, can address resistance to 1st gen SRIs and improve on their clinical profile.

Trial design: This phase I/II study is recruiting up to 265 patients with NSCLC, thyroid cancer or other solid tumours with RET aberrations. The 1st part of the study is a dose escalation to investigate safety, tolerability, PK and PD and to define the maximum tolerated dose (MTD) and/or Recommended Phase II Dose (RP2D). Dose escalation is based on a rolling 6 design and is expected to recruit up to 40 patients. Once an RP2D is established, expansion cohorts of approximately 25 evaluable patients each will further explore the safety and tolerability of EP0031, and provide preliminary efficacy data in selected patient populations with RET-altered tumours with/without prior 1st gen SRI therapy: Four cohorts of patients with NSCLC and medullary thyroid cancer Two cohorts of patients with other solid tumours, including differentiated thyroid cancer. Key inclusion criteria are as follows: Male or female ≥ 18 years of age, with a diagnosis of an advanced solid tumour with

documented RET altered malignancy ECOG Performance Status of 0 or 1 at screening with no deterioration over the previous 2 weeks. For expansion cohorts patients must have a solid tumour measurable by RECIST v1.1, with/without asymptomatic, stable brain metastases Recruitment was initiated in the US in November 2022 and is expanding to centres across Europe. A parallel phase I/II trial is ongoing in China (A400, NCT05265091, Kelun Biotech).

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83TiP

A phase II study of mecbotamab vedotin (BA3011), a CAB-AXL-ADC, alone and in combination with nivolumab in adult patients with metastatic NSCLC who had prior disease progression on or are intolerant to a PD-1/L1, EGFR, or ALK inhibitor

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Background: Mecbotamab vedotin (BA3011) is a conditionally active biologic (CAB) anti-AXL antibody-drug conjugate being developed as an anticancer therapy for patients with advanced solid tumors. Conditional and reversible binding by CABs is designed to reduce off-tumor toxicity and immunogenicity, avoid tissue-mediated drug disposition, and improve pharmacokinetics. AXL is a cell-surface transmembrane receptor protein tyrosine kinase highly expressed in several tumor types including sarcoma. Increased AXL expression has been associated with tumor resistance to chemotherapy, programmed death-1 (PD-1) inhibitors, molecular targeted therapy, and radiation therapy. The upregulation of AXL in PD-1 resistant tumor strongly suggests its role in resistance and recurrence in this population. Additionally, as patients who have experienced failure of either an epidermal growth factor receptor (EGFR), or anaplastic lymphoma kinase (ALK) inhibitor have been shown to achieve minimal benefit with subsequent exposure to PD-1 monotherapy, there is considerable additional rationale for use of BA3011-based therapy.

Trial design: Study BA3011-002 is an ongoing multi-center, open-label, phase II trial designed to evaluate the efficacy and safety of BA3011 alone or in combination with nivolumab in patients with AXL-expressing (tumor membrane percent score $\geq$ 1%), metastatic NSCLC who have measurable disease by RECIST version 1.1 criteria. To enroll, patients must have experienced failure of an approved programmed death1/ligand-1(PD-1/L1) treatment, epidermal growth factor receptor (EGFR), or anaplastic lymphoma kinase (ALK) inhibitor (either monotherapy or in combination with another therapy such as ipilimumab). Treatment failure is defined as disease progression on a PD-1/L1, EGFR, or ALK inhibitor, or discontinuation of a PD-1/L1, EGFR, or ALK inhibitor due to an adverse event. Enrollment completion is anticipated in 2023.

Clinical trial identification: NCT04681131, EudraCT 2022-000135-23.

Legal entity responsible for the study: BioAtla, Inc.

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EARLY STAGE NSCLC

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Neoadjuvant nivolumab (N) + platinum-doublet chemotherapy (C) for resectable NSCLC: 3-y update from CheckMate 816

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Background: The phase III CheckMate 816 study demonstrated statistically significant and clinically meaningful improvements in event-free survival (EFS) and pathologic complete response (pCR) with neoadjuvant N + C vs C in patients (pts) with resectable NSCLC. Here, we report 3-y efficacy, safety, and exploratory biomarker analyses from CheckMate 816.

Methods: Adults with stage IB (tumors ≥4 cm)–IIIA (per AJCC 7th ed) resectable NSCLC, ECOG PS ≤ 1, and no known EGFR/ALK alterations were randomized to N 360 mg + C Q3W or C alone Q3W for 3 cycles followed by surgery. Primary endpoints were EFS and pCR, both per blinded independent review. Exploratory analyses included EFS by surgical approach and extent/completeness of resection, and EFS and pCR by a 4-gene (CD8A, CD274, STAT-1, LAG-3) inflammatory signature score derived from RNA sequencing of baseline (BL) tumor samples.

Results: At a median follow-up of 41.4 mo (database lock, Oct 14, 2022), continued EFS benefit was observed with N + C vs C (HR, 0.68; 95% CI, 0.49–0.93); 3-y EFS rates were 57% and 43%, respectively. N + C improved EFS vs C in pts who had surgery, regardless of surgical approach or extent of resection, and in pts with R0 resection (table). Recurrence occurred in 28% and 42% of pts who had surgery in the N + C (n = 149) and C arms (n = 135), respectively. In the N + C arm, BL 4-gene inflammatory signature scores were numerically higher in pts with pCR vs pts without, and EFS was improved in pts with high vs low scores (data to be presented). Grade 3–4 treatment-related and surgery-related adverse events occurred in 36% and 11% of pts in the N + C arm, respectively, vs 38% and 15% in the C arm.

Conclusions: Neoadjuvant N + C continues to provide long-term clinical benefit vs C in pts with resectable NSCLC, regardless of surgical approach or extent of resection. Exploratory analyses in pts treated with N + C suggested that high BL tumor inflammation may be associated with improved EFS and pCR.

Clinical trial identification: NCT02998528.

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Table: 840

	N + C			C			N + C vs C
		EFS			EFS		
	n	Median (95% CI), mo	3-y rate, %	n	Median (95% CI), mo	3-y rate, %	HR (95% CI)
All randomized pts	179	NR (31.6–NR)	57	179	21.1 (14.8–42.1)	43	0.68 (0.49–0.93)
Surgical approach							
Minimally invasive	44	NR (30.8–NR)	67	29	NR (9.5–NR)	53	0.61 (0.28–1.29)
Thoracotomy or conversion	105	NR (40.4–NR)	61	106	42.1 (18.2–NR)	51	0.74 (0.48–1.13)
Extent of resection							
Lobectomy	115	NR (44.4–NR)	64	82	34.3 (16.6–NR)	49	0.62 (0.40–0.96)
Pneumonectomy	25	NR (19.4–NR)	67	34	21.1 (13.9–NR)	48	NC[a]
Completeness of resection							
R0	124	NR (44.4–NR)	64	105	42.1 (19.6–NR)	51	0.65 (0.43–0.98)
R1/R2	21	NR (12.6–NR)	53	25	NR (10.8–NR)	57	NC[a]

[a]Too few events (< 10 per arm) to calculate HR.
NC, not calculated; NR, not reached.

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Updated survival, efficacy and safety of adjuvant (adj) atezolizumab (atezo) after neoadjuvant (neoadj) atezo in the phase II LCMC3 study

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Background: Neoadj chemoimmunotherapy (IO) treatment (tx) without adj tx has shown impressive DFS outcomes but the role of adj IO after neoadj IO is unclear. LCMC3, an open-label, single-arm ph II study of neoadj atezo (anti–PD-L1) with optional adj atezo in patients (pts) with early-stage non-small cell lung cancer (NSCLC). Here we report updated DFS, OS and safety in pts who received adj atezo vs pts who did not.

Methods: Eligible pts aged ≥18 y had resectable stage IB-IIIA or select IIIB NSCLC and ECOG PS 0-1. Pts received neoadj atezo 1200 mg IV for ≤2 cycles (Days 1 and 22) followed by surgery (Day 40 ± 10). Pts without progression were offered the option to receive adj atezo every 3 weeks for ≤12 months. The primary endpoint was MPR rate (≤10% viable tumor cells at surgery) in pts without EGFR/ALK mutations. Exploratory endpoints included DFS and OS. Safety was assessed during the adj phase.

Results: Data cutoff was Oct 21, 2022. The primary efficacy population (PEP) was 137 pts without EGFR/ALK alterations who had surgery and MPR assessment. The updated 3-y DFS and OS rate for the entire group was 72% and 82%, for stage I/II was 75% and 82%, and for stage III was 68% and 81%, respectively. In the PEP, 53 pts (39%) received adj atezo and 84 (61%) did not. While not randomized, these groups were clinically well balanced. The 3-y DFS rate was 83% with adj atezo vs 64% without adj atezo (HR, 0.43; 95% CI: 0.21, 0.90; P = 0.025). In pts without MPR (n = 108) 3-y DFS for adj atezo vs without adj atezo was 80% vs 62% (HR, 0.48; 95% CI: 0.20, 1.12; P = 0.088) and 3-y OS was 87% vs 75% (HR, 0.49; 95% CI: 0.17, 1.46; P = 0.202). In the adj atezo safety population (n = 57), there were 11 treatment-related adverse events (19%; Gr 3/4, 16%) leading to discontinuation of adj atezo.

Conclusions: This exploratory analysis revealed that LCMC3 pts with resectable NSCLC who received adj atezo had improved DFS and showed a trend toward improved OS vs pts who did not receive adj atezo. Furthermore, the non-MPR subgroup had the same trend toward improved DFS and OS with adj atezo vs pts who did not receive adj atezo. Adj atezo was well tolerated, with no new safety concerns. These data suggest that adding adj IO to neoadj IO may result in improved outcomes.

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85P

The impact of adjuvant EGFR-TKIs and 14-gene molecular assay on patients with stage I non-small cell lung cancer harboring sensitive EGFR mutations

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Background: Currently, the role of EGFR-TKIs as adjuvant therapy for stage I, especially IA NSCLC, after surgical resection remains unclear. We aimed to compare the effect of EGFR-TKIs versus observation on survival in such patients by incorporating an established 14-gene molecular assay for risk stratification.

Methods: From March 2013 to February 2019, completely resected stage I (8^{th} TNM staging for NSCLC) non-squamous NSCLC patients with sensitive EGFR mutation, who were followed up for at least five years, were included. Patients with eligible samples for molecular risk stratification were subjected to the 14-gene prognostic assay. The 5-year disease-free survival (DFS) rates between patients who underwent EGFR-TKI treatment and observation were compared using Kaplan-Meier analysis and Cox regression with a propensity score matching (PSM). The results of the 14-gene assay were used to further stratify the effect of EGFR-TKIs in different risk groups.

Results: A total of 227 stage I NSCLC patients were enrolled, with 110 in stage IA and 117 in stage IB. After PSM, a matched cohort with 96 (48:48) patients was generated. The median duration of follow-up was 78.9 months. In the overall population, patients with adjuvant EGFR-TKIs had better 5-year DFS rates than those in the observation group (97.9% vs. 81.3%; P = 0.008). For patients with IA NSCLC, those receiving EGFR-TKIs had favorable 5-year DFS rates (100.0% vs. 88.2%; P = 0.485); a same trend was obtained from IB group (96.8% vs. 77.4%; P = 0.053). The 14-gene assay was performed in 71 patients. In the observation group, patients in high-risk group had inferior DFS compared with those with intermediate (HR = 3.48, P = 0.192) and low-risk group (HR = 12.50, P = 0.024). Among intermediate-high-risk patients, EGFR-TKIs were associated with a significant trend in 5-year DFS rate benefit compared to observation (95.2% vs. 68.8%; P = 0.066), while there was no difference among low-risk group (100.0% vs. 89.5%; P = 0.492).

Conclusions: We showed that adjuvant EGFR-TKI might improve DFS of EGFR-mutated stage IA and IB NSCLC, and the 14-gene molecular assay could help enrich those benefits from treatment. This modality merits prospective interventional trials in the future.

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86P

KRAS G12C mutation and risk of disease recurrence in stage I surgically resected lung adenocarcinoma

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Background: KRAS G12C mutations are found in about 12–13% of LUAD samples and it is unclear whether they are associated with worse survival outcomes in resected, early stage LUAD. We evaluated a retrospective, single-center cohort of patients treated with video-assisted thoracoscopic surgery (VATS) or robot-assisted thoracoscopic surgery (RATS) at our institution and leveraged on publicly available cohorts (TCGA LUAD, MSK $LUAD^{604}$) to confirm the findings.

Methods: IRE cohort: retrospective cohort of patients with surgically resected, pathological stage I LUAD whose tumor tissue underwent targeted sequencing. TCGA LUAD cohort: pathologic stage I LUAD; patients who received post-operative radiation therapy and patients exposed to non-curative surgical resection were not included. MSK $LUAD^{604}$ cohort: pathologic stage I LUAD. Clinical and genomic data for the TCGA LUAD and MSK $LUAD^{604}$ cohort were downloaded from cBioPortal. The pooled cohort was made up by merging eligible patients in the IRE stage I cohort, TCGA LUAD stage I cohort and MSK LUAD604 stage I cohort.

Results: In the IRE stage I cohort we found a significant association between KRAS G12C mutations and worse DFS in multivariate analysis (DFS HR 2.47). In the TCGA LUAD stage I cohort we did not find any statistically significant association between the KRAS G12C mutation and survival outcomes. In the MSK LUAD604 stage I cohort we found that KRAS G12C mutated tumors had worse survival outcomes only when compared to KRAS nonG12C mutated tumors in univariate analysis (DFS HR 3.5). In the pooled stage I cohort (IRE stage I, TCGA LUAD stage I and MSK LUAD604 stage I tumors) we found that KRAS G12C mutated tumors had worse DFS when compared to KRAS nonG12C mutated tumors (DFS HR 2.6), to KRAS wild type tumors (DFS HR 1.6) and to any other tumors (DFS HR 1.8) in univariate analysis; in multivariable analysis, the KRAS G12C mutation was associated with worse DFS (DFS HR 1.61).

Conclusions: Our results suggest that patients with resected, stage I LUAD with a KRAS G12C mutation may have inferior survival outcomes

when compared to KRAS nonG12C mutated tumors and to KRAS wild type tumors.
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87P
Prognostic models of recurrence-free survival in non-small cell lung cancer

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Background: Accurate prediction of recurrence-free survival (RFS) in patients undergoing radical surgery for early-stage non-small cell lung cancer (NSCLC) is necessary to improve outcomes. We aimed to develop pre- and post-operative prognostic models based on a range of clinicopathological factors using machine learning.
Methods: Retrospective data was collected from patients treated with radical surgery from 2015 to 2021, and 66 clinicopathological features were extracted. Three regularised Cox models were trialled (Ridge, LASSO and Elastic Net) and features were selected using a 'maximum relevancy-minimum redundancy' approach. Model development and validation were performed using nested cross-validation. Performance was assessed using the Concordance Index (C-index), Cumulative Dynamic Area Under the Receiver Operating Characteristic Curve (AUROC) and Dynamic Brier Score.
Results: 392 patients were included; 145 (37%) patients developed recurrence or died from all causes, and median RFS was 74 months. The Elastic Net model – trained using systemic inflammatory response index [SIRI], eosinophil count, pre-operative nodal stage, weight loss, performance status and maximum standardized uptake value (SUVmax) – and the Ridge model – using performance status, weight loss, SIRI, eosinophil count, lymphovascular invasion, visceral pleural invasion, and pathological stage – proved optimal for pre- and post-operative prognosis, respectively (table).

Table: 87P Prognostic performance of pre- and post-surgical models

Model	Regularisation	N Features	C-Index	Mean AUROC	Mean Brier Score
Pre-surgical	Elastic Net	6	0.70 ± 0.03	0.72 ± 0.02	0.18 ± 0.05
Post-surgical	Ridge	7	0.75 ± 0.04	0.79 ± 0.02	0.16 ± 0.04

Both models had better performance at predicting earlier recurrence or death with a pre-surgical and post-surgical 1-year AUROC of 0.73 ± 0.03 and 0.83 ± 0.08 respectively.
Conclusions: Our prognostic models demonstrate robust prediction of RFS in early-stage NSCLC, and may identify patients who will benefit from peri-operative anti-cancer therapy and/or closer post-operative surveillance. Future work is required to validate these models externally and prospectively.
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88P
Quantitative CT parameters in predicting the degree of risk of solitary pulmonary nodules

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Background: Correctly determining the degree of invasiveness based on histological pattern is markedly important in developing effective treatment strategies. Analyzing the characteristics of SPNs is quite important. The aim of our study, therefore, was to investigate the value of CT parameters in predicting the degree of risk.
Methods: Patients with clinical stage 0 to IB NSCLC who underwent radical surgical resection and were pathologically diagnosed with invasive adenocarcinoma were enrolled. All patients in this study underwent preoperative high-resolution CT scans with three-dimensional reconstruction. The minimum, maximum, and mean HU values were measured and recorded by Dr. Wise Lung Analyser on preoperative CT scans. All pathology specimens were centrally reviewed.
Results: The mean age was 57.4 ± 10.2 years old (median age was 57 years old), and 228 (64.2%) were females. A total of 355 SPNs were evaluated. CT findings revealed 71 pure GGO lesions (20.0%), 206 part-solid GGO lesions (58.0%), and 78 solid lesions (22.0%). In univariate logistic regression analysis, CT value max, CT value min, CT value mean, CT findings, and clinical stage were significantly related to high-risk SPN. The CT value mean and CT findings were independent significant factors on multivariate analysis. The receiver operating characteristic area under the curve used to identify low- or high-risk SPNs was 0.811.
Conclusions: The CT value mean and CT findings were independently correlated with high-risk SPN in multivariate analysis and are likely to be helpful for decisions on the therapeutic regimen, especially the appropriate extent of surgical resection.
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89P

A clinical- and biological-based nomogram to predict unforeseen nodal metastases in clinically node-negative, radically resected lung adenocarcinoma

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Background: Despite an adequate preoperative staging, unexpected nodal metastases after surgery are detected in a relevant number of cases. Given the promising role of novel neoadjuvant treatments, the definition of predictive factors for nodal metastases is critical. In this study we aim to analyze the clinical and molecular factors associated with upstaging in patients with early stage LUAD without evidence of nodal disease in the preoperative staging who underwent lobectomy and radical lymphadenectomy.
Methods: Patients who underwent radical treatment for early stage LUAD without evidence of nodal disease at the preoperative staging with available molecular targets evaluation were evaluated. Univariable and multivariable logistic regression was used to quantify the association between clinical and biological variables and the risk of unforeseen nodal metastasis, in addition to odds ratios and their 95% confidence intervals. A nomogram to predict unexpected nodal metastasis was computed based on the results of the multivariable model.
Results: A total of 359 patients were included. The variables that showed a significant correlation with the upstaging rate at the univariate analysis were the PD-L1 status, ALK rearrangement, number of resected lymph nodes and the tumor diameter. This result was confirmed in the multivariate analysis, with an OR of 8.052 (3.123–20.763, p = 0.00001) for ALK rearrangements, 1.895 (1.093–3.286, p = 0.02) for PD-L1 status, 1.087 (1.048–1.127, p = 0.0001) for the number of resected nodes and 1.817 (1.214–2.719, p = 0.004) for cT status. Using the nomogram, we classified the patients into three classes: the lower risk group with a rate of unexpected nodal metastasis of 13.6% the intermediate group with a rate of 33.6% and the high group with a rate of 81.8%.
Conclusions: Our results showed that in patients with clinical node-negative early stage LUAD the presence of ALK rearrangements, PD-L1 status, number of resected lymph nodes and tumor diameter can predict unforeseen nodal metastasis after surgical resection. The established nomogram could assess the risk of nodal metastases in patients with early stage NSCLC eligible for surgical resection.
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90P

Cell-free DNA as a predictive and prognostic marker in adjuvant-treated non-small cell lung cancer

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Background: There is a correlation of genomic alterations between tumor tissue and circulating cell-free DNA (cfDNA) in blood samples, mostly in advanced stages of cancer. The main objective of this study was the characterization of cfDNA of patients with non-small cell lung cancer (NSCLC) stages I–III before the adjuvant treatment (at the time of surgical intervention) and in those who relapse, with next generation sequencing (NGS). It was expected that the results could determine the changes that occur in cfDNA during treatment, follow-up and relapse.
Methods: Two blood samples were collected from each patient (before surgery and at relapse) and a paraffin tissue sample from the surgical specimen. cfDNA from blood plasma was sequenced using the 50-gene Oncomine Pancancer Assay panel. DNA obtained from tissues was analyzed with the 50-gene Oncomine Focus Assay panel.
Results: This prospective study included 73 patients with NSCLC of whom 22 met inclusion criteria (adjuvant treatment after surgery). The mean age was 63.36 years with a male/female ratio of 2.44. The concentrations of cfDNA were 1.42 ± 0.55, 1.57 ± 1.58 and 1.03 ± 0.45 ng/µl for stages I, II and III respectively with no significant differences. To date, two of the 22 patients have relapsed. The mean ratio of the cfDNA concentration (time of relapse/time of surgery) was 2.96. In the patient 1, no genetic variants were found in the three samples analyzed. The first liquid biopsy of patient 2 carried the p.R249S mutation in the TP53 gene and a 1.5-fold increase in CCND2 gene dosage. At the time of relapse, the allelic frequency of p.R249S alteration augmented from 3 to 40% and a 2.5-fold increase in CCND2 gene dosage was observed.
Conclusions: The use of liquid biopsy in early stages and the follow-up of patients with NSCLC is a potential tool for detecting tumor recurrence, as demonstrated by the increase in cfDNA concentration, mutated allele frequency and gene dosage after relapse. A long-term follow-up is required to assess the consistency and robustness of results.
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91P

Treatment (tx) patterns and outcomes in resectable early-stage non-small cell lung cancer (NSCLC): A global real-world (rw) study

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Background: Complete resection ± adjuvant chemotherapy is recommended for most patients (pts) with early-stage (I–IIIA) NSCLC; however, 5-year overall survival (OS) rates for this regimen decrease with advancing disease stage. Osimertinib is a third-generation, EGFR-tyrosine kinase inhibitor approved as adjuvant tx for resected stage IB–IIIA EGFR mutated (EGFRm) NSCLC, based on the ADAURA trial results. We report final results from a global retrospective chart review of electronic health records (EHRs) for pts with resected stage IA–IIIA NSCLC, to show EGFRm frequency, tx patterns and outcomes prior to osimertinib approval.

Methods: Adults (≥18 yrs) with completely resected stage IA–IIIA NSCLC with available EGFRm results, who were diagnosed between 01Jan2014–31Dec2017, were assessed from diagnosis (Dx) until last follow-up/death. Primary endpoints included EGFRm frequency, tx patterns and OS. Sites of 1st recurrence was a secondary endpoint.

Results: EHRs were collected from 1243 pts in 8 countries. Of 530 pts (43%) with EGFRm NSCLC (pt characteristics, table); 251 (47%) received surgery only (88% were stage I), 32 (6%) received surgery + neoadjuvant tx, and 177 (33%) received surgery + adjuvant tx. Chemotherapy was the most common adjuvant tx (170/177, 95% [n = 14 stage IA, 37 stage 1B, 56 stage II, 63 stage III]). After a median follow-up of 58 months (IQR 46–73) median OS was not reached; 5-year OS probability was 78%. Five-year OS probabilities for stages IA/IB/IIA/IIB/IIIA were 94%/85%/73%/76%/46%. For 113 pts who received (neo)adjuvant tx, the most common sites of 1st recurrence were lung (38%) and brain (28%).

Table: 91P

Characteristic, n (%)	Pts with EGFRm (n = 530)
Median age, yrs (range)	64 (36–85)
Male	183 (35)
Female	347 (65)
Country	
United States	84 (16)
Canada	18 (3)
Taiwan	139 (26)
S. Korea	200 (38)
France	25 (5)
Germany/Austria	45 (8)
United Kingdom	19 (4)
Smoker	
Current every-day	19 (4)
Current some-day	4 (1)
Former	145 (29)
Never	326 (65)
Other	4 (1)
Unknown	32 (6)
Early-stage Histology at Dx in ≥1%	
Adenocarcinoma	513 (98)
Squamous cell carcinoma	5 (1)
Unknown	7 (1)
Stage	
IA	186 (35)
IB	144 (27)
IIA	65 (12)
IIB	29 (5)
IIIA	106 (20)
EGFRm in >2%	
Exon19del	219 (41)
L858R	209 (39)
Exon21 L861Q	16 (3)
PD-L1	
Tested	178/530 (34)
Positive	46/178 (26)
PD-L1 >1% to <50%	32 (18)
PD-L1 >50%	14 (8)
Negative	129 (72)
Inconclusive	3 (2)

Conclusions: In this rw international study of pts with completely resected stage IA–IIIA EGFRm NSCLC, diagnosed between 2014 and 2017, 5-year landmark OS probabilities decreased from 94% to 46% from stage IA to IIIA. Early Dx and EGFR testing to inform optimal tx may improve outcomes in this population.

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92P

Predictors, surrogate and patient-reported outcomes in neoadjuvant immunotherapy for lung cancer: A single-center retrospective study

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Background: Development of immunotherapy/molecular targeted therapy has significantly increased survival/QoL in advanced stages of NSCLC. Aim: to analyze outcome predictors, surrogate outcomes, and PROMs after neoadjuvant immunotherapy for initially unresectable NSCLC.

Methods: Initially unresectable NSCLC (2014–2021) patients who received immunotherapy ± platinum-based chemo and/or radiotherapy evaluated after response (reduction of primary tumor and/or

mediastinal lymphadenopathy/control of distant metastatic disease underwent surgical resection). PROMs were recorded using EORTC QLQ-29.

Results: 19 underwent salvage surgery after ICI. 14 had partial response (73.6%), 5 stable disease. Diagnosis was achieved by endobronchial ultrasound (EBUS) in 8 (42.1%), fine-needle aspiration biopsy (FNAB) in 7 (36.8%), metastasis biopsy in 4 (21.0%). 11 (57.9%) were treated with neoadjuvant platinum-based chemo before or with ICI, 1 (5.2%) pemetrexed before ICI, 5 (26.3%) radiotherapy for metastatic control. 3 (15.7%) had ICI adverse effects. Radiotherapy was never used preoperatively for pulmonary/mediastinal disease. 7 (36.8%) received adjuvant therapy (5 [26.3%] pembrolizumab, 1 [5.2%] pemetrexed, 1 [5.2%] pemetrexed + pembrolizumab). 4 (21.0%) had local relapse (no systemic relapse). Median OS was 19 months (range: 2–57.4). At 2 months, 94.7% were alive (6 months: 89.5%; 31 months: 79.5%). 2 (10.5%) had local recurrence. 2 (10.5%) died due to recurrence, 1 (5.2%) to COVID. 4 (21.0%) relapsed (median DFS: 5.3 months [range: 2.2–13.0]). PROMs were reviewed retrospectively at 30 days/1 year with significant decrease in coughing, side effects of treatment, surgery-related problems.

Table: 92P Data as No (%), median (range), mean ± SD

Age	66 (47–76)		
M/F	8.5		
Adenocarcinoma	11 (57.9)		
Squamous cell	5 (26.3)		
Other	3 (15.6)		
Clinical Stage	Before ICI		After ICI
IA			4 (21.0)
IIB			3 (15.7)
IIIA	3 (15.7)		2 (10.5)
IIIB	4 (21.0)		3 (15.7)
IIIC	3 (15.7)		
IVA	8 (42.1)		7 (36.8)
IVB	1 (5.2)		
Pembrolizumab	14 (73.6)		
Nivolumab	3 (15.7)		
Atezolizumab	2 (10.5)		
Lobectomy	15 (78.9)		
Pneumonectomy	2 (10.5)		
Other	2 (10.5)		
Pathological response			
Complete	7 (36.8)		
Major	3 (15.7)		
EORTC QLQ-29	30 d	1 y	p-value
Coughing	18.8 ± 15.5	5.5 ± 10.2	0.19
Shortness of breath	11.1 ± 11.8	8.1 ± 9.8	0.84
Side effects of treatment	10.5 ± 6.5	7.7 ± 4.4	0.91
Fear of progression	13.3 ± 16.9	6.6 ± 13.8	0.40
Surgery related problems	10.2 ± 9.4	4.0 ± 6.0	0.53

Conclusions: Radical surgical resections following definitive immunotherapy/immune-chemotherapy in selected initially unresectable NSCLC are feasible and safe (low surgical-related mortality and morbidity). Symptoms and surgery-related outcomes were lower with higher QoL due to a selected group of highly motivated patients.

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93P
A phase II study of camrelizumab plus chemotherapy in patients with medically inoperable early-stage non-small cell lung cancer

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Background: For medically inoperable patients (pts) with early-stage non-small-cell lung cancer (NSCLC), stereotactic body radiation therapy is recommended, but long-term outcomes are not satisfactory for this population. At present, chemoimmunotherapy has become the standard of care for untreated advanced NSCLC; however, its benefit in medically inoperable early-stage NSCLC is unclear. Herein, we explored the efficacy and safety of camrelizumab (an anti-PD-1 antibody) plus chemotherapy in pts with medically inoperable stage I–IIA NSCLC.

Methods: In this single-arm, single-center, phase II study, treatment-naïve pts with pathologically confirmed medically inoperable stage I–IIA NSCLC and an ECOG PS of 0 or 1 received camrelizumab (200 mg) plus chemotherapy (pemetrexed [500 mg/m^2] for non-squamous NSCLC or nab-paclitaxel [260 mg/m^2] for squamous NSCLC) intravenously on day 1 of a 21-day cycle. After 4–6 cycles, pts received up to 1 year of camrelizumab (200 mg, day 1, every 21 days) monotherapy as maintenance treatment. The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR) as per RECIST 1.1, disease control rate (DCR), overall survival (OS), PFS and OS rates at 1, 2 and 5 years, and safety.

Results: From October 19, 2020 to July 4, 2022, 18 pts were enrolled. The median age was 75 years (IQR 71–78). Ten pts (55.6%) were male and 11 pts (61.1%) had adenocarcinoma. As of December 15, 2022, the median PFS was not reached (95% CI 11.1-not reached). Of the 18 pts, six pts (33.3%) achieved partial response, 11 pts (61.1%) had stable disease and one pt (5.6%) was not evaluable. The ORR and DCR were 33.3% (95% CI 13.3%-59.0%) and 94.4% (95% CI 72.7%-99.9%), respectively. The median treatment cycle of camrelizumab was 17 (IQR 11–17). Treatment-related adverse events (TRAEs) occurred in 14 pts (77.8%). Four pts (22.2%) had grade 3 TRAEs, with one each of anemia, platelet count decreased, white blood cell count decreased, and pneumonia. No grade 4 or 5 TRAEs were reported.

Conclusions: Camrelizumab plus single-agent chemotherapy showed promising activity with a manageable safety profile in pts with medically inoperable stage I-IIA NSCLC.

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94P
Neoadjuvant tislelizumab combined with (nab)-paclitaxel plus platinum-based chemotherapy for patients with stage IIA-IIIB squamous NSCLC: A real-world retrospective study

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Background: Immunotherapy combined with chemotherapy as neoadjuvant therapy has shown promising efficacy. Tislelizumab is an anti-PD-1 mAb approved in China for the treatment of first-line advanced squamous NSCLC in combination with chemotherapy. This study aimed to evaluate the efficacy of tislelizumab combined chemotherapy as

neoadjuvant therapy in resectable stage IIA–IIIB squamous NSCLC in a real-world setting.

Methods: A retrospective analysis included patients (pts) with resectable IIA–IIIB (AJCC 8th) squamous NSCLC who received neoadjuvant tislelizumab combined with chemotherapy at the Second Affiliated Hospital of Medical School of Zhejiang University between Apr 2020 and Oct 2022. The primary endpoints were major pathological response (MPR) rate and pathological complete response (PCR) rate; secondary endpoints included objective response rate (ORR) by RECIST1.1, down-staging rate and safety outcomes.

Results: 60 pts were included with a median age of 55 (range 41–85) years, and 98% males. 56 pts were administrated with tislelizumab combined with nab-paclitaxel plus platinum-based chemotherapy, and the other 4 pts chemotherapy regime was paclitaxel instead of nab-paclitaxel. All pts received 2–3 cycles neoadjuvant therapy. The MPR rate and PCR rate were 81.67% (95%CI: 69.56-90.48) and 41.67% (95%CI: 29.07-55.12) respectively. The ORR, and down-staging rate were 75% (95%CI: 62.14-85.28), 38.3% (95%CI: 26.07-51.79), As of 1 Oct 2022, the median follow-up time was 20 (range: 4–29) months, 7 pts experienced recurrence, and 5 of them are non-MPR. For the safety information, mild immune-related AEs such as rash and pneumonitis were experienced in this retrospective analysis.

Conclusions: This real-world retrospective study revealed that tislelizumab combined with (nab)-paclitaxel and platinum-based chemotherapy is a promising option as neoadjuvant therapy for resectable stage IIA-IIIB squamous NSCLC.

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95P

Neoadjuvant treatment pattern and association between real-world event-free survival (rwEFS) and overall survival (OS) in patients (pts) with resected early-stage non-small cell lung cancer (eNSCLC)

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Background: This study aimed to describe neoadjuvant treatment patterns, rwEFS, OS and assess association between rwEFS and OS in resected eNSCLC.

Methods: This retrospective study used the US SEER-Medicare data (2007–2019) to select pts with newly diagnosed, resected, stage II-IIIB (N2) NSCLC (AJCC 8th edition) treated with neoadjuvant therapy. Index date was defined as neoadjuvant therapy initiation. rwEFS (time from index date to first recurrence or death, whichever first) and OS (time from index date to death) were described using Kaplan-Meier analysis and correlation was assessed using normal scores rank test. OS was compared between pts with and without recurrence by 1, 2, and 3-year landmarks after index date; hazard ratios were estimated using Cox models adjusted for key baseline factors.

Results: 221 pts (156 with recurrence and 65 without) met eligibility criteria (median follow-up: 32.7 months). Selected pt characteristics are presented in the table. ~97% received platinum-based neoadjuvant therapy and ~49% received neoadjuvant chemoradiation. Carboplatin + paclitaxel, cisplatin + etoposide, and carboplatin + pemetrexed are most frequently used regimens. Median rwEFS was 17.6 months; median OS was 48.5 months. The normal scores rank correlation demonstrated a statistically significant correlation between rwEFS and OS (0.68; P < 0.001). Pts with recurrence by each landmark had significantly shorter OS than those without recurrence (All Ps <0.01). Adjusted Cox models indicated that pts with recurrence had 2.7–3.2 times increased risk of death (All Ps <0.05).

Table: 95P Selected characteristics, rwEFS and OS among patients with early-stage, resected NSCLC who have received neoadjuvant therapy

Patient characteristics	
Age at surgery (years), mean ± SD	72.1 ± 4.9
Male, N (%)	126 (57.0%)
White	191 (86.4%)
Adjuvant chemotherapy, N (%)	67 (30.3%)
Post-operative radiotherapy, N (%)	56 (25.3%)
rwEFS rate	
1-year	61.1%
2-year	42.4%
3-year	33.3%
4-year	26.9%
5-year	20.9%
OS rate	
1-year	91.4%
2-year	72.4%
3-year	60.6%
4-year	50.3%
5-year	44.9%

NSCLC: non-small cell lung cancer; rwEFS: real-world event-free survival; OS: overall survival; SD: standard deviation.

Conclusions: Among pts with resected eNSCLC receiving neoadjuvant therapy, poor survival outcomes were observed. rwEFS is positively and significantly associated with OS. These findings highlight the need for and importance of more effective treatments for this pt population.

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96P

Characteristics of patients with resectable non-metastatic non-small cell lung cancer treated with or without neoadjuvant therapy in Europe and Canada: A real-world survey

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Background: There are limited data on real world usage of neoadjuvant (neo) treatment (tx) in clinical practice in non-metastatic non-small cell lung cancer (nmNSCLC). As immunotherapies (IO) emerge in the

resectable setting, we aimed to describe characteristics and tx patterns of patients (pts) receiving neo tx for resectable nmNSCLC.

Methods: Data were drawn from the Adelphi nmNSCLC Disease Specific Programme™, a point in time survey of 274 oncologists/pulmonologists/surgeons in France (FR), Germany (DE), Italy (IT), Spain (ES), United Kingdom (UK) and Canada (CA) between Apr-Nov 2022. Physicians provided information on their next four consulting pts with resectable nmNSCLC [random] (n = 1074) and an additional four pts receiving/received any neo and/or adjuvant tx [oversample] (n = 1090).

Results: Of 1074 random pts, 208 (19.4%) received neo tx; country splits were 45/203 (22.2%) FR, 36/200 (18.0%) DE, 39/205 (19.0%) IT, 49/200 (24.5%) ES, 30/198 (15.2%) UK and 9/68 (13.2%) CA. Characteristics of pts who did and did not receive neo tx [random and oversample] are shown in the table. Of 739 neo pts, cisplatin + vinorelbine (18.8%), carboplatin + paclitaxel (11.0%) and cisplatin + gemcitabine (9.6%) were the most common txs initially received. Radiotherapy was administered to 22.2% alongside or subsequent to neo tx. Pathological response for pts who concluded neo tx (n = 251) was complete in 12.0%, major in 43.8%, and neither complete nor major in 22.7%. Top three reasons for prescribing neo tx were to; improve overall survival (OS) (64.1%), facilitate surgery of resectable pts (60.5%) and improve event-free survival (42.8%).

Table: 96P

	Received neo tx (n = 739)	Received surgery without neo tx (n = 1425)
Age (mean, years)	63.2	64.9
Male, %	65.2	64.1
Stage at dx, %*		
0–IIB	28.8	77.9
IIIA–C	66.6	16.0
Unknown	4.6	6.1
Histology, %		
Squamous cell	37.8	37.2
Adenocarcinoma	55.9	58.2
Large cell carcinoma	5.0	3.6
Other	0.8	0.5
Unknown	0.5	0.4
ECOG PS at dx, %		
0–1	93.4	93.2
2+	6.0	6.0
Unknown	0.7	0.8
Biomarker testing, %		
PD-L1	62.1	62.9
Driver mutations**	58.9	60.4
PD-L1 expression, %	n = 450	n = 872
<1%	28.7	31.3
1–49%	58.2	54.9
≥50%	13.1	13.8
Driver mutations** results prior to tx, %	n = 435	n = 861
Yes (some/all results)	79.3	76.9

*8th TNM edition.
**EGFR, ALK, ROS1, RET, BRAF, MET, KRAS dx, diagnosis; tx, treatment; ECOG, Eastern Cooperative Oncology Group.

Conclusions: Neo tx was prescribed to one third of nmNSCLC pts, two thirds of whom were stage IIIA–C at diagnosis. Prescribing neo tx aimed to improve OS and facilitate surgery of resectable pts. With recent advances in neo IO tx showing benefits over chemotherapy, neo tx may be a realistic option for more pts.

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97P

Aumolertinib as adjuvant therapy in postoperative EGFR-mutated stage I-III non-small cell lung cancer with high-risk pathological factors

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Background: Pulmonary adenocarcinoma with high-risk pathological factors are known to be associated with poor prognosis in early-stage non-small-cell lung cancer (NSCLC). Aumolertinib is a third-generation EGFR-TKI that has efficacy in EGFR sensitive and resistant NSCLC. The efficacy of aumolertinib as adjuvant therapy in resected stage I–III NSCLC with high-risk pathological factors remains unknown.

Methods: Patients underwent completely resected pathologic stage I–III lung adenocarcinoma with micropapillary/solid component with or without complex glands were enrolled. Patients were assigned to aumolertinib group (group A): patients with EGFR mutation-positive (exon 19 deletion or L858R) received aumolertinib (110 mg daily), group B (EGFR mutation positive) and group C (EGFR mutation negative or unknown). Both group B and C received observation for disease recurrence and no adjuvant therapy was given. The primary endpoint was investigator assessed disease-free survival (DFS) and safety was evaluated.

Results: A total of 115 stage I–III lung adenocarcinoma with micropapillary or solid component patients were enrolled. 70 patients were EGFR mutation-positive (45 in aumolertinib group, 25 in group B). 45 patients were EGFR mutation-negative or unknown and assigned to group C. At data cut-off, all patients in aumolertinib group have no symptoms of tumor recurrence and continued aumolertinib, the 1-year DFS was 100%. In group B, 64% patients were alive and disease-free, 3 of 25 patients had tumor recurrence within 1 year (1-year DFS: 88%). In group C, 89% patients were alive and disease-free, 1-year DFS was 93%. Compared two no EGFR-TKI treatment groups, the recurrent ratio in EGFR mutated patients was higher than EGFR negative or unknown group. There were no grade ≥3 adverse events occurred during aumolertinib treatment, rash (15%), pruritus (27%), diarrhea (11%) and mouth ulceration (11%) were common adverse events.

Conclusions: This is the first report that aumolertinib has efficacy in patients with completely resected stage I-III EGFR mutated NSCLC with high-risk pathological factors. EGFR mutation positive as a poor prognosis factor was associated with higher recurrence than the negative or unknown.

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98P

Adjuvant aumolertinib in resected EGFR-mutated non-small cell lung cancer: A multiple-center real-world experience

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Background: Aumolertinib as a novel third-generation Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitor (TKI) has been shown to be efficacy in EGFR mutations and also in CNS metastasis NSCLC. We aimed to evaluate long-term efficacy and safety of adjuvant aumolertinib in postoperative patients.

Methods: A total of 215 patients who underwent radical lung cancer surgery with EGFR-sensitizing mutations from four different medical centers were enrolled and received aumolertinib 110 mg daily, the medication time (6months-36months) depended on the pathological stage and physical conditions. The disease-free survival (DFS), safety and tolerability were evaluated.

Results: The study retrospectively analyzed 215 patients with pathologically confirmed adenocarcinoma, EGFR mutation-positive, stage Ia2–IIIa NSCLC (132 females, 87 males, ranging in age from 27 to 86 years, with a median age of 63). All patients were followed for at least 6 months, 40 patients have been followed up for over 2 years, and 110 patients have been followed for over 1 year. At data cutoff, all patients were alive, only one patient had bone metastasis, and no patient presented with CNS metastasis. 2-year DFS was 99%. During aumolertinib treatment, 69 patients (69/215, 32.1%) experienced drug-related adverse reactions. Rash (39/215, 18.1%), diarrhea (15/215, 7.0%), abnormal liver and kidney function (12/215, 5.6%), and mouse ulcer (11/215, 5.1%). There was no grade ≥3 adverse events that occurred, and no patients withdrew from treatment due to adverse reactions.

Conclusions: Based on our previous study, we expanded the number of patients and extended the follow-up period. Our study further demonstrates the pronounced efficacy of aumolertinib in the post-operative adjuvant treatment of NSCLC with an excellent safety profile. Long term follow-up of our study is ongoing to investigate further survival outcomes.

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99P

The optimal treatment for patients with stage I non-small cell lung cancer: Minimally invasive lobectomy or stereotactic ablative radiotherapy?

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Background: The standard treatment for operable patients with stage I non-small cell lung cancer (NSCLC) is a minimally invasive lobectomy (MIL). However, stereotactic ablative radiotherapy (SABR) is increasingly being used. The ESLUNG study compares the outcome of MIL and SABR in operable patients.

Methods: In this retrospective cohort study with 38 participating centres, patients with clinical stage I NSCLC (TNM7), treated in 2014–2016 with MIL or SABR, were included. Recurrence rates, 5-year recurrence-free survival (RFS), overall survival (OS) and lung cancer-specific mortality (LCSM) were calculated. RFS and OS were compared after adjusting for confounding by propensity score (PS) weighting.

Results: In total, 2183 patients (1211 MIL and 972 SABR) were included. SABR patients were significantly older, had more comorbidities and poorer lung function and performance status. Postoperative nodal upstaging occurred in 13.0% of operated patients. 30-day mortality was 1.0% after MIL and 0.2% after SABR. SABR patients developed significantly more regional recurrences (18.1 versus 14.2%) and/or distant metastases (26.2 versus 20.2%) with a similar local recurrence rate (13.1 versus 12.1%). Unadjusted 5-year RFS and OS were 58.0 versus 25.1% and 70.2 versus 40.3% after MIL and SABR, respectively. 5-year LCSM was 17.4% after MIL and 24.0% after SABR (HR 0.74, 95% CI 0.61–0.90). PS-weighted analyses showed – in patients considered operable – better RFS after MIL (HR 0.70, 95% CI 0.49–0.99), but no significant difference in OS (HR 0.80, 95% CI 0.53–1.21).

Conclusions: In operable patients with stage I NSCLC, MIL leads to fewer regional recurrences and distant metastases than SABR. However, OS did not differ significantly. Future studies should focus on optimization of patient selection for MIL or SABR to further reduce postoperative mortality after MIL and nodal failures after SABR.

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100P

Effects of U.S. insurance type on 5-year all-cause mortality after robotic-assisted pulmonary lobectomy for lung cancer

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Background: Public insurance type has been correlated with worse overall survival in several cohorts of cancer patients in the United States, but few analyses included combination insurance as a discreet insurance category. The objective of this study is to determine whether public, private, or combination insurance type predicted 5-year mortality after robotic-assisted pulmonary lobectomy (RAPL) for lung cancer.

Methods: We retrospectively analyzed 711 patients who underwent RAPL from September 2010 to March 2022 by one surgeon.

Results: Among our 711 study patients, 367 (52%) patients had combination insurance, 144 (20%) had public insurance, and 200 (28%) patients had private insurance. There were no differences in sex, race, body mass index, or tumor characteristics including stage, grade, pathology, histology, size and nodal status. Patients with combination insurance had a higher mean age ($p < 0.0001$), the largest proportion of former smokers ($p = 0.0003$), higher Charlson comorbidity index scores ($p = 0.0014$), more comorbid conditions, and the least estimated blood loss during surgery ($p = 0.003$). There were no differences in hospital length of stay, discharge disposition, and in-hospital or 30-day mortality. Multivariable regression analysis identified combination insurance type as an independent predictor of 5-year all-cause mortality (hazard ratio, 1.72; 95% CI, 1.08–2.75; $p = 0.02$; table).

Table: 100P Multivariable analysis on predictors of 5-year overall mortality

Variable	Hazard Ratio (95% CI)	p = value
Combination insurance	1.72 (1.08–2.75)	0.02
Public insurance	1.18 (0.72–1.93)	0.51
Former smoker	0.75 (0.45–1.24)	0.26
Never smoker	0.69 (0.38–1.23)	0.21
Charlson Comorbidity Index Score	0.97 (0.76–1.23)	0.81
Preoperative chronic kidney Disease	4.81 (0.60–38.4)	0.14
Preoperative atrial fibrillation	1.17 (0.39–3.50)	0.79
Preoperative hypertension	0.95 (0.62–1.46)	0.82
Preoperative hyperlipidemia	1.36 (0.87–2.12)	0.17
Intraoperative estimated blood loss	1.00 (1.00–1.00)	0.99

Conclusions: Although previous studies identified public health insurance as a predictor of worse 5-year overall survival in the United States, in our present cohort, combination insurance type was associated with the greatest risk for all-cause mortality.

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101P

Evidence base for exercise prehabilitation suggests favourable outcomes for patients undergoing surgery for non-small cell lung cancer despite being of low therapeutic quality: A systematic review and meta-analysis

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Background: The aim of this systematic review was to evaluate whether exercise prehabilitation programs reduce postoperative complications, postoperative mortality, and length of hospital stay (LoS) in patients undergoing surgery for non-small cell lung cancer (NSCLC), thereby accounting for the quality of the physical exercise program.
Methods: Two reviewers independently selected randomized controlled trials (RCTs) and observational studies and assessed them for methodological quality and therapeutic quality of the exercise prehabilitation program (i-CONTENT tool). Eligible studies included patients with NSCLC performing exercise prehabilitation and reported the occurrence of 90-day postoperative complications, postoperative mortality, and LoS. Meta-analyses were performed and the certainty of the evidence was graded (Grading of Recommendations Assessment, Development and Evaluation (GRADE)) for each outcome.
Results: Sixteen studies, comprising 2,096 patients, were included. Pooled analyses of RCTs and observational studies showed that prehabilitation reduces postoperative pulmonary complications (OR 0.45), postoperative severe complications (OR 0.51), and LoS (mean difference −2.46 days), but not postoperative mortality (OR 1.11). The certainty of evidence was very low to moderate for all outcomes. Risk of ineffectiveness of the prehabilitation program was high in half of the studies due to an inadequate reporting of the dosage of the exercise program, inadequate type and timing of the outcome assessment, and low adherence.
Conclusions: Although risk of ineffectiveness was high for half of the prehabilitation programs and certainty of evidence was very low to moderate, prehabilitation seems to result in a reduction of postoperative pulmonary and severe complications, as well as LoS in patients undergoing surgery for NSCLC.

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102P

A qualitative stakeholder analysis of beliefs, facilitators, and barriers for a feasible prehabilitation program before lung cancer surgery

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Background: In order to develop a feasible prehabilitation program before surgery of NSCLC, this study aimed to gain insight into beliefs, facilitators, and barriers of 1) healthcare professionals to refer patients to a prehabilitation program, 2) patients to participate in and adhere to a prehabilitation program, and 3) informal caregivers to support their loved ones.
Methods: Semi-structured interviews were conducted with healthcare professionals, patients who underwent surgery for NSCLC, and their informal caregivers. The capability, opportunity, and motivation for behavior-model (COM-B) guided the development of the interview questions. Results were analyzed thematically.
Results: The interviews were conducted with twelve healthcare professionals, seventeen patients, and sixteen informal caregivers. Healthcare professionals mentioned that multiple professionals should facilitate the referral of patients to prehabilitation within primary and secondary healthcare involved in prehabilitation, considering the short preoperative period. Patients did not know that a better preoperative physical fitness and nutritional status would make a difference in the risk of postoperative complications. Patients indicated that they want to receive information about the aim and possibilities of prehabilitation. Most patients preferred a group-based physical exercise training program organized in their living context in primary care. Informal caregivers could support their loved one when prehabilitation takes place by doing exercises together.
Conclusions: A prehabilitation program should be started as soon as possible after the diagnosis of lung cancer. Receiving information about the purpose and effects of prehabilitation in a consult with a physician seems crucial to patients and informal caregivers to be involved in prehabilitation. Support of loved ones in the patient's own living context is essential for adherence to a prehabilitation program.

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103P

Patient and clinician perspectives on adjuvant treatment in early-stage non-small cell lung cancer (NSCLC): Qualitative results

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Background: Despite advances in treatment options, little is known about patient and clinician perspectives on the benefits of adjuvant treatment in early-stage NSCLC. Qualitative interviews with patients and clinicians explored concepts related to adjuvant treatment benefit, including the value of prolonging survival.
Methods: Patients with fully resected stage IB-IIIA NSCLC who had or had not received adjuvant treatment and treating oncologists, thoracic surgeons, and pulmonologists in 13 countries completed online interviews. Themes investigated were informed by a review of the literature and clinical data for comparator treatments and included NSCLC symptoms, expectations for adjuvant treatment, and desired outcomes.
Results: Fifty-eight patients (Asia Pacific n = 9, Europe n = 29, North America n = 10, South America n = 10) and 109 clinicians (Asia Pacific n = 30, Europe n = 54, Middle East n = 5, North America n = 10, South America n = 10) completed an interview. Mean patient age was 56 years. Most patients were female (n = 34, 59%) and had received adjuvant treatment for NSCLC (n = 32, 55%). Most clinicians were oncologists (n = 69, 63%) and 20% were female (n = 22). The most common desired treatment benefits related to survival. In the patient sample this included cure or remission (n = 27, 47%), avoiding disease spread (n = 11, 19%), and delaying recurrence (n = 6, 10%), while clinicians reported overall survival (OS) (n = 97, 89%), disease-free survival (DFS) (n = 78, 72%), and progression-free survival (n = 21, 19%). For adjuvant treatment-naïve patients, tolerability was an important treatment consideration (n = 7, 27%). Clinician treatment decisions were influenced by treatment tolerability and quality of life (QoL) concerns (both n = 37, 34%), as well as reduced symptom burden (n = 22, 20%).
Conclusions: Survival outcomes including OS and DFS were most frequently mentioned as desired benefits but were described differently by patients and clinicians. Treatment tolerability and QoL on treatment were also important considerations. Results will be used to inform the design of a quantitative study assessing the trade-offs participants are willing to make between OS, DFS and treatment risk.
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104TiP

MRD Evaluation of aumolertinib in EGFR mutation-positive stage IB and stage IA2-3 NSCLC after complete surgical resection: A multicenter, open-label, single-arm study (ASSIST)

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Background: Surgery is the standard treatment for early non-small cell lung cancer (NSCLC). However, even after complete surgical resection, about 20% of stage I patients (pts) are still exposed to early recurrence or metastasis. Epidermal growth factor receptor (EGFR) mutation is often a poor prognostic factor for early recurrence and metastasis. There are few treatment options for pts with EGFR-mutant stage IB and stage IA2-3 NSCLC, and lack of standard adjuvant therapy currently. Aumolertinib is a third-generation EGFR-tyrosine kinase inhibitor (EGFR-TKI) approved in China to treat EGFR-mutant NSCLC, and application for listing permission has been accepted by European Medicines Agency (EMA). Preliminary studies have shown that minimal residual disease (MRD) detection plays an important role in guiding treatment and predicting disease progression. The ASSIST study is designed to assess the efficacy and safety of aumolertinib as adjuvant therapy in pts with EGFR-mutant stage IB and stage IA2-3 NSCLC according to MRD detection.
Trial design: This multicenter, open-label, single-arm study is ongoing and aims to enroll approximately 130 pts with histologically confirmed stage IB or stage IA2-3 invasive NSCLC after standard radical surgery, harboring sensitive EGFR mutations, aged 18–75 years, Eastern Cooperative Oncology Group (ECOG) performance status 0–1, and have not previously received chemotherapy, radiotherapy or targeted therapy for NSCLC. Eligible pts receive aumolertinib 110 mg orally once daily until disease progression or complete the overall treatment for 3 years. Stratified by the results of two postoperative MRD detections. Pts receive aumolertinib as adjuvant therapy regardless of whether MRD positive or negative. Plasma samples are collected at week 12 and 24 after surgery and every 24 weeks at each follow-up time to evaluate MRD status. The primary endpoint is disease-free survival (DFS) rate at 3 years. Secondary endpoints include DFS rate at 4 and 5 years, overall survival (OS) and safety. The first patient in (FPI) was in July 2022, and the estimated study completion date is Q3 2024.
Clinical trial identification: ChiCTR2200063184 (release date: September 1, 2022).
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Disclosure: All authors have declared no conflicts of interest.

IMAGING AND STAGING

105P
Development and assessment of artificial intelligence detection of lung nodules on chest roentgenograms

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Background: Artificial intelligence (AI) based on deep learning and convolutional neural networks (CNN) has been applied to various medical fields. We have started to develop novel AI to support detection of lung cancer, which will enable physicians to efficiently perform interpretation of radiograms and diagnosis.
Methods: We analyzed the image features as teacher data using 853 chest X-ray images (401 normal images and 452 abnormal images) from Fukushima Preservative Service Association of Health, in which lung cancer screening was mainly conducted and more than 100 000 chest roentgenograms from the NIH database. We categorized these data into two groups, according to including NIH datasets (group A) or not (group B). Then we integrated their datasets for deep learning and CNN using ImageNet to develop proprietary AI algorithm, and analyzed the accuracy of interpretation of radiograms statistically. We also demonstrated the abnormal shadow in the form of heat map display on each chest roentgenogram for easy visualization and also showed positive probability score as an index value (from 0.0 to 1.0), which indicated the possibility of lung cancer. The accuracy of our AI system has been improved by using technology that absorbs differences in radiographic apparatus and imaging environments.
Results: Our novel AI showed the accuracy of 0.74 for AUC, 0.75 for sensitivity and 0.74 for specificity in the group A, and 0.80 for AUC, 0.73 for sensitivity and 0.75 for specificity in the group B. These AI systems used the positive probability cutoff value of 0.5. Both groups are superior to the accuracy of radiologists (AUC 0.71) and also compatible to previous study reports (AUC 0.78). We also demonstrated the heat map display on the monitor screen clearly, if each roentgenogram had abnormal shadows.
Conclusions: In this study, we confirmed proprietary AI had a similar accuracy of interpretation of the chest roentgenograms compared with both previous studies and radiologists. However, further research and improvement is needed to verify the accuracy. We are now in the process of performing various types of validation.
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106P
AI negative predictive performance exceeds that of radiologists in volumetric-based risk stratification of lung nodules detected at baseline in a lung cancer screening population

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Background: Lung cancer is the leading cause of cancer-related mortality due to the late stage at which it is diagnosed. When detected at stage 4, 5-year survival is <5%. Whereas lung cancer detected at stage 1, has a 5-year survival >75%. Early detection can be achieved through LDCT lung cancer screening in a high-risk population. Despite being proven effective, widespread implementation remains a challenge for multiple reasons. One of which, the ever-increasing workloads which radiologists face. AI could be crucial in overcoming this challenge.
Methods: Performance of different versions of an AI-prototype (AVIEW LCS; v1.0.34, v1.1.39.14, and v1.1.42.56) was analysed in 283 ultra-LDCT baseline scans. Volumetric nodule measurements from independent reads of the AI-prototypes were compared that of five experienced radiologists, and an independent consensus reference read was performed. Discrepancies between individual reads and consensus were classified as follows; positive misclassifications (nodules classified by the reader/AI as $\geq$100 mm^3, which at the reference consensus read were <100 mm^3) and negative misclassifications (nodules classified as a <100 mm^3 by the reader/AI, which at consensus read were $\geq$100 mm^3).
Results: Using AVIEW LCS v1.0.34, 1149 nodules were detected of which 878 were classified as solid non-calcified. For v1.1.39.14 and v1.1.42.55, 1502 nodules were detected of which 1019 were solid non-calcified. Overall, v1.0.34 had 61 discrepancies (53 positive and 8 negative misclassifications), and v1.1.39.14 and v1.1.42.56 both had 32 discrepancies (28 positive and 4 negative). The improved AI versions (v1.1.39.14 and v1.1.42.56) had a better negative predictive value than 4 radiologists and equivalent negative predictive value to the 5th radiologist.
Conclusions: AI can surpass the negative predictive performance of experienced radiologists, meaning it could provide a solution to reducing radiologists' workload associated with lung cancer screening if used as a first read filter.
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107P
Artificial intelligence-based volumetric classification of pulmonary nodules in Chinese baseline lung cancer screening population (NELCIN-B3)

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Background: Developments in artificial intelligence (AI) systems to assist radiologists in reading low-dose computed tomography (LDCT)

could improve lung cancer screening efficiency by triaging negative screenings. Our aim is to evaluate the performance of an AI system as an independent reader when used to rule-out negative scans (with no nodules/nodules <30 mm^3) in LDCT lung cancer baseline screening in a Chinese population.

Methods: 362 individuals from the Netherlands and China Big 3 (NELCIN-B3) study with at least one non-calcified solid-component nodule were included. Volumetric nodule measurement was performed on all scans by two experienced radiologists and a fully automated AI lung cancer screening software (AVIEW LCS, v1.1.39.14, Coreline Soft) independently. The largest non-calcified solid-component nodule was determined for each scan. Discrepancies between two radiologists or the AI were reviewed by a consensus panel and stratified into two groups based on NELSON-plus/EUPS protocol threshold: PM was indeterminate/positive nodule (≥100 mm^3) classified by radiologists/AI, which at consensus read was negative (<100 mm^3); NM was negative result classified by radiologists/AI (<100 mm^3), which at consensus read were indeterminate/positive (≥100 mm^3).

Results: When looking at the discrepancies for the largest solid-component nodule per participant; 34 (9.4%; 23 PM, 11 NM) discrepancies were reported for AI, compared to 31 (8.6%; 0 PM, 31 NM), and 27 (7.5%; 8 PM, 19 NM) discrepancies for radiologist 1, and 2, respectively. 13 out of 23 PM findings by AI were due to vessel segmentation, 7 were non-nodular morphology, and 3 were incorrect nodule type classification.

Conclusions: In a Chinese baseline lung cancer screening population, the use of an AI system as an independent reader to triage negative scans resulted in the lowest negative-misclassification result compared to radiologists.

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Disclosure: All authors have declared no conflicts of interest.

108P
Optimization of automatic emphysema detection in lung cancer screening dataset

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Background: To improve the detection of early emphysema in a low dose CT (LDCT) lung cancer screening dataset.

Methods: We selected 352 participants from a regional community health center lung cancer screening dataset. Unenhanced low dose CTs were performed using Definition AS (Somatom Definition AS 64), at inspiration, in spiral mode at 120 kVp and 35 mAs. Images were reconstructed with B30f kernel at 2.0/1.0 mm thickness. AI based post-processing software, Aview (Coreline soft, v. 1.0.40), was used to automatically segment the lungs while excluding the pulmonary vessels and bronchus. Emphysema was quantified by voxel counting below a Hounsfield unit (HU) threshold. A wide range of thresholds from −900 to −1024 HU were used. Three readers including one experienced general radiologist (reader A) and two trainees in thoracic radiology (reader B, C) read the CT images by evaluating the emphysema according to the Fleischner criteria. Inter-reader agreement was evaluated using statistical analysis with Cohen's Kappa. Spearman analysis and ROC (Receiver operating characteristic) curve were used to assess the correlation between quantified emphysema under different HU thresholds and reader visual evaluation.

Results: 184 (52.3%), 146 (41.5%), and 185 (52.6%) of the cases were classified respectively by reader A, reader B and reader C as positive for emphysema. All readers showed high agreement in diagnosis of the cases. The p value of Spearman analysis is less than 0.05, demonstrating a statistically significant correlation between emphysema volume and the visual classification under different thresholds. The optimal HU threshold was −1000 UH for all readers. The area under the curve (AUC) was 0.799 (95%CI: 0.751–0.847) for reader A, 0.797 (95%CI: 0.751–0.843) for reader B, and 0.785 for reader C (95%CI: 0.738–0.832).

Conclusions: Threshold of −1000 HU was determined to be optimal for the early detection of emphysema in LDCT lung cancer screening dataset. HU threshold optimization for automatic early emphysema detection by CT is indicated.

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Disclosure: All authors have declared no conflicts of interest.

109P
Setting up 4D-CT based image guided radiotherapy (IGRT) for locally advanced lung cancer: Is it safe to reduce PTV margin for dosimetric benefit?

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Background: 4D-CT based IGRT is currently standard in many developed countries; for radical lung cancer radiotherapy. Here, we aim to assess the volumetric and dosimetric differences of 4D-CT based and Helical free breathing CT (FBCT) based radiotherapy planning for lung cancer patients. We would also evaluate the safety of reduced PTV margin for 4D-CT planning.

Methods: 46 patients decided for radical radiotherapy was planned based on 4D-CT based contouring with 7 mm PTV margin (PTV_4D). FBCT based volume was also generated using PTV margin of 1 cm all around and 1.3 cm cranio-caudally (PTV_3D). Patients had two IMRT plans for PTV_3D and PTV_4D; using similar planning parameters. Patients were treated with plans generated on 4D-CT based volumes. The FBCT based plans were extrapolated onto the 4D-CT volume and vice versa. Two plans were compared for PTV, PTV coverage by 95% of prescribed dose and organ at risk (OAR) dose. Dice Similarity Coefficient (DIC) was calculated to examine the overlap between PTV_3D and PTV_4D. Set-up data of 890 fractions were also analysed. We calculated the systematic error (Σ) and random error (δ) in each of the three axes, i.e. x, y, z and PTV margin using van Herk formula. We also calculated the translational vector of each fraction of individual patients.

Results: PTV was significantly low with 4D-CT based planning (mean PTV 509 cc vs 739 cc); so as OAR doses (Mean heart dose 11.6 Gy vs 14.5 Gy, Mean lung dose 13.5 Gy vs 15.5 Gy, and Spinal cord max dose 35.7 Gy vs 37.5 Gy). Mean DIC of PTV_3D and PTV_4D was 0.8 (80%). Our calculated PTV margin was 0.7 cm, 1.1 cm and 0.5 cm in X, Y and Z axis. PTV margin calculated for translational vector was 0.4 cm. Percentage of shifts >5 mm was 8.3%, 31.4% and 1.1% in X, Y and Z axis. Percentage of shifts >7 mm was 3.8%, 17.7% and 0.2% in X, Y and Z axis. Translational vector shift >5 mm and >7 mm was 23.1% and 0.2% respectively.

Conclusions: 4D-CT based radiotherapy planning for locally advanced lung cancer with reduced PTV margin of 7 mm, can significantly reduce the PTV, OAR doses. However, while using 7 mm PTV daily imaging should be recommended to ensure PTV coverage particularly Y-axis

where shifts more than 7 mm can be higher. Further PTV margin reduction to 5 mm was not found to be safe in our set up.
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110P
Volumetric tumor volume doubling time in lung cancer: A systematic review and meta-analysis

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Background: Tumor growth patterns have important implications for determining screening intervals, making treatment decisions, and predicting prognosis. Our study aimed to characterize tumor volume doubling time (VDT) or growth pattern of primary lung cancer and identify factors associated with rapid and indolent growth patterns.
Methods: We performed a systematic literature review of Medline, EMBASE, and Web of Science databases starting from 2004 until April 2022. We identified studies reporting volumetric measured tumor VDT or growth patterns of pathologically confirmed primary lung cancer without intervention, and abstracted data to calculate pooled VDT and find correlations of growth patterns (rapid defined as VDT ≤400 days, indolent as VDT >400 days, non-growth or shrinkage). Meta-analysis was performed for pooled mean VDT for overall lung cancer and for different histology subtypes. Pooled mean VDT was calculated using a random-effects model.
Results: We have identified 26 studies, including 2275 patients with primary lung cancer (mean age range from 54.6 to 72.0 years), comprising 61.6% men and 38.4% women. For overall lung cancer, median VDT ranged from 139 to 357 days and mean VDT ranged from 151 to 408 days. Pooled overall mean VDT was 213 days (95% CI 171 to 256 days, I^2 = 90.0%). In subgroup analyses, pooled mean VDT of adenocarcinoma, adenocarcinoma (subsolid), squamous cell, small cell, and other lung cancer were 241, 731, 136, 71, and 183 days, respectively. Rapid growth accounted for 64.8% of overall lung cancer and 23.7% of adenocarcinoma. The most consistent correlations of rapid tumor growth included nodule solidity, non-adenocarcinoma histology subtype, and invasiveness in adenocarcinoma.
Conclusions: Median VDT in overall lung cancer is always £400 days (range 139 to 357 days) with around two-thirds being rapid; solidity and histology subtypes demonstrate the most consistent correlations.
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111P
Application of radiomics signatures and unidimensional vs volumetric measurement of early tumor growth dynamics (TGD) to predict first-line treatment outcomes in patients with stage IV non-small cell lung cancer (NSCLC)

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Background: TGD modeling using sum of longest diameters (SLD) is associated with long-term outcomes in NSCLC. Early changes in radiomics features within the tumor may also correlate with survival outcomes. We retrospectively evaluated 3 methods to assess early treatment outcomes: tumor growth rate (g) by SLD, volumetric measurements, and change in radiomics signatures to predict survival outcomes in NSCLC.
Methods: Patients with stage IV NSCLC in CheckMate 9LA treated with first-line nivolumab+ipilimumab+chemotherapy (NIVO+IPI+CHEMO) or CHEMO alone were included. TGD was modeled using radiologically-assessed SLD from ≤5 target lesions or sum of volumes (SVOL) from all measurable lesions >10 mm at baseline, 6, 12, and/or 18 weeks. Measurements were fitted to the TGD model.[1] Overall survival (OS) for each growth quartile was estimated by Kaplan–Meier curves. Changes in radiomic features from all measurable lesions >10 mm were assessed at week 6 and 12.
Results: At week 18, low SVOL- and SLD-derived g values were associated with longer median OS across both treatment arms. SVOL-derived g values were more consistent across timepoints if evaluated at week 12 and 18 than SLD-derived g values. Delta radiomics signatures to predict long-term OS at week 6 (table) and 12 performed better than RECIST 1.1 in the NIVO+IPI+CHEMO arm.

Table: 111P Median OS in groups defined by unidimensional vs volumetric estimates of tumor growth, and by RECIST 1.1 criteria of response vs delta radiomics signature

Median OS, months	SLD measurements[a]		SVOL measurements[a]	
	NIVO +IPI +CHEMO	CHEMO alone	NIVO +IPI +CHEMO	CHEMO alone
g quartile1	25.8	17.9.	26.4	19.1
g quartile4	12.5	9.5.	11.6	8.2
Median OS, months	RECIST response (NIVO IPI+CHEMO)		Delta radiomics-derived response (NIVO+IPI +CHEMO)	
	At 6 weeks		At 6 weeks	
Progressive disease	7.1		7.4	
Stable disease	15.0		14.5	
Partial or complete response	32.5		4	

[a]Four timepoints, week 18. Patients were grouped according to quartiles of g, with quartile 1 representing the subgroup with slowest g.

Conclusions: SVOL-derived g values correlate with longer OS and are more consistent across timepoints than SLD-derived g values at 18 weeks of treatment. Delta radiomics signatures as early as 6 weeks on-treatment were better than RECIST in identifying patients with NSCLC deriving long-term OS benefit. Both findings can potentially inform early decision making in clinical trials and real-world use.
1. Fojo AT et al. J Clin Oncol. 2022;40(16_suppl):Abst 9063.

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112P
Retrospective analysis of the use of immunohistochemistry for the diagnosis of adenosquamous carcinoma of the lung in a Dutch national cohort

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Background: Adenosquamous carcinoma (ASC) is a subtype of NSCLC, which can be diagnosed if the tumor meets three criteria: (1) a combination of an adenocarcinoma and squamous cell carcinoma component, (2) the adenocarcinoma part must constitute at least 10% of the tumor, and (3) the squamous cell carcinoma component also has to cover at least 10%. The goal of this study is to determine to which extent immunohistochemistry (IHC) alone is used to diagnose ASC.
Methods: A query was performed through the Dutch National Pathology Archive. All excerpts with a possible ASC were included. Subsequently the excerpts were categorized. Excerpts were included in the 'certain' group if ASC was the working diagnosis. Afterwards, this group was subdivided: (1) only IHC for the diagnosis of ASC and (2) all other methods to diagnose ASC. With this distinction the percentages of patients diagnosed with IHC only can be determined.
Results: The query resulted in 1468 excerpts. After categorization and removing duplicates 651 patients remained in the certain group, 267 patients were diagnosed with ASC based on IHC only.
As seen in the table, the diagnosis of ASC slightly increases over time. This might be explained by the introduction of molecular diagnostics (MD). Over time, the guidelines for the performance of MD for systemic therapy of NSCLC changed from 'adenocarcinoma only' to all non-squamous carcinomas. Patients with inconclusive IHC were therefore amenable for MD, possibly leading to an increase in ASC diagnosis. Moreover, IHC-only diagnoses appear to have increased over this time period. This might show that IHC is a useful tool in the primary diagnosis of ASC, particularly with the advent of MD.

Table: 112P Number of patients diagnosed with ASC each year with the method used for diagnosis

Year	Total number ASC	ASC diagnosed with IHC only
2004	26	2 (7.7)
2005	31	6 (19.4)
2006	22	5 (22.7)
2007	31	8 (25.8)
2008	37	11 (29.7)
2009	35	12 (34.3)
2010	37	14 (37.8).
2011	28	14 (50.0)
2012	38	18 (47.4)
2013	27	13 (48.1)
2014	36	19 (52.8)
2015	33	16 (48.5)
2016	32	16 (50.0)
2017	46	20 (43.5)
2018	42	20 (47.6)
2019	46	22 (47.8)
2020	36	19 (52.8)
2021	42	15 (35.7)
2022	26	17 (65.4)

Conclusions: IHC is increasingly being used for the initial diagnosis of ASC. Furthermore, the use of molecular diagnostics may have led to a pragmatic increase in the diagnosis of ASC.
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113P
Clinical overstaging in pathologic stage I non-small cell lung cancer: Prognostic implications

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Background: Surgery serves a key role in curative therapy for early-stage non-small cell lung cancer (NSCLC), and operative decision-making is heavily dictated by clinical stage. Multiple patient- and disease-specific factors can influence stage assignment in the therapy-naïve patient. As such, discordant clinical and pathological staging may occur, and clinical overstaging may indicate risk of worse outcomes for patients with features that are not otherwise captured in our staging paradigm. Thus, we sought to evaluate the impact of clinical overstaging on overall survival (OS) in patients with pathologic stage I NSCLC who underwent upfront surgery.
Methods: A single-center database was queried for patients who underwent resection of pathologic stage I NSCLC 1998–2021 in the absence of neoadjuvant therapy. Clinicopathologic, circulomic, and operative details were collected. Patients were grouped by clinical-to-pathologic stage concordance to evaluate impact of clinical overstaging on outcomes. Kaplan-Meier and multivariable analyses were performed to assess impact on OS.
Results: 2318 patients met inclusion criteria, among whom 151 (6.5%) were clinically overstaged. Slightly over half were women (1355, 58.4%), most were smokers (1649, 71.0%), and median age was 67.0 years (interquartile range [IQR]: 60.1–73.3). In clinically overstaged patients, clinical tumor (T) and nodal (N) statuses were significantly discordant from pathologic T and N status ($p < 0.001$ for both). Moreover, clinically

overstaged patients had shorter median OS (115.4 months) than those with stage-concordance (156.7 months, $p < 0.001$). After controlling for confounders, we found that clinically overstaged patients experienced greater mortality (hazard ratio 1.34, CI 1.04–1.73).

Conclusions: Clinical overstaging of patients with pathologic stage I NSCLC was associated with worse survival compared concordant staging. This finding may be attributable nto patient and disease factors that prompted assignment of higher clinical stage, and further investigation is needed to better elucidate and ameliorate such factors. Moreover, heightened postoperative cancer surveillance may be indicated for patients found to be clinically overstaged.

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LOCALLY ADVANCED NSCLC

114MO

First-line cemiplimab for locally advanced non-small cell lung cancer: Updated subgroup analyses from EMPOWER-Lung 1 and EMPOWER-Lung 3

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Background: Patients (pts) with unresectable locally advanced non-small cell lung cancer (laNSCLC) who are not candidates for concurrent chemoradiation have often been excluded from immunotherapy trials, and their care represent an unmet medical need. We report post hoc analyses of pts with laNSCLC who received cemiplimab (anti–programmed cell death-1) from two phase III clinical trials with long-term data.

Methods: EMPOWER-Lung 1 and EMPOWER-Lung 3 included pts with squamous or non-squamous NSCLC that was metastatic or locally advanced (not suitable for definitive concurrent chemoradiation) without EGFR, ALK or ROS1 genomic aberrations. In EMPOWER-Lung 1 pts were randomised 1:1 to first-line (1L) cemiplimab monotherapy or chemo for NSCLC with ≥50% programmed cell death-ligand 1 (PD-L1) expression. In EMPOWER-Lung 3 pts were randomised 2:1 to 1L cemiplimab + chemo or placebo + chemo regardless of PD-L1 expression level.

Results: In each trial, 15% of pts were treated for laNSCLC. In EMPOWER-Lung 1, at ~3-year follow-up of pts with laNSCLC, 1L cemiplimab monotherapy led to a median overall survival (OS) of 26.1 vs 13.9 mo with chemo (HR: 0.67; 0.38–1.17; p = 0.1532). Progression-free survival (PFS) was 8.1 vs 6.2 mo (HR: 0.56; 0.34–0.95; p = 0.0286). Objective response rate (ORR) was 49% vs 31%. Median duration of response (DOR) was 18.8 vs 6.2 mo. In EMPOWER-Lung 3, at ~2-year follow-up of pts with laNSCLC, greater efficacy was observed with 1L cemiplimab + chemo vs placebo + chemo. Median OS was 24.1 vs 13.8 mo (HR: 0.50; 0.27–0.95; p = 0.0293) and median PFS was 12.5 vs 6.2 mo (HR: 0.34; 0.19–0.61; p = 0.0002). ORR was 58% vs 29%. Median DOR was 27.8 vs 4.2 mo.

Table: 114MO

	EMPOWER-Lung 1[†] (n = 565)	EMPOWER-Lung 3 Part 2 (n = 466)
Subgroup with laNSCLC	Cemiplimab (n = 45) vs chemo (n = 42)	Cemiplimab + chemo (n = 45) vs placebo + chemo (n = 24)
Study follow-up duration,[‡] median (range), mo	36.2 (24.4–53.7) vs 35.6 (24.3–53.6)	28.7 (21.0–35.9) vs 29.3 (22.6–35.4)
OS median, mo	26.1 vs 13.9	24.1 vs 13.8
OS HR (95% CI)	0.67 (0.38–1.17); p = 0.1532	0.50 (0.27–0.95); p = 0.0293
PFS median, mo	8.1 vs 6.2	12.5 vs 6.2
PFS HR (95% CI)	0.56 (0.34–0.95); p = 0.0286	0.34 (0.19–0.61); p = 0.0002
ORR, %	49 vs 31	58 vs 29
Kaplan-Meier estimated DOR, median (95% CI), mo	18.8 (6.4–NE) vs 6.2 (3.4–8.5)	27.8 (13.1–27.8) vs 4.2 (3.0–10.3)

[†]PD-L1 ≥50% population. [‡]From randomization to data cutoff.

Conclusions: Long-term follow-up data from EMPOWER-Lung studies continue to suggest clinical benefit of 1L cemiplimab as monotherapy or in combination with platinum-based chemo in pts with unresectable laNSCLC who are not candidates for definitive concurrent chemoradiation.

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115P

Salvage surgery in patients with locally advanced or metastatic non-small cell lung cancer

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Background: In patients with stage IIIB, IIIC and IV non-small cell lung cancer (NSCLC), current guidelines recommend systemic therapy with

or without radiotherapy. Despite this treatment, complete response in these stages is rare and median overall survival (mOS) ranges between 6 and 48 months. However, in a selected group of patients with either residual disease after partial response to first-line systemic treatment, or oligo-recurrence, surgical resection within a salvage concept is under evaluation as an additional treatment option. Currently, clinical data on the outcome of this approach are scarce and candidate selection remains challenging. We therefore aimed to assess short- and long-term outcomes of salvage surgery in advanced NSCLC.

Methods: We retrospectively identified 35 patients with initial stage IIIB, IIIC, or IV NSCLC who underwent anatomical lung resection to treat local relapse or residual disease between 2001–2023. All patients had initially received systemic treatment with or without radiotherapy. Patients were only included if surgical resection had not been part of the first-line treatment approach.

Results: Among 35 patients (54% male, mean age 60.2 ± 10.9 years), the initial clinical UICC NSCLC stage was IIIB in 4, IIIC in 4, IVA in 22, and IVB in 5 cases. 17 patients (48.6%) were treated with curative intent and had received radiochemotherapy. The indication for salvage resection was residual disease after first-line treatment in 21 cases (60%) and local relapse in 14 cases (40%). Lung resections included 22 lobectomies (6 sleeve-resections), 11 pneumonectomies, 1 bilobectomy and 1 segmentectomy. R0-resection was achieved in 94.3% and pathological complete response was found in 22.9% of all resections. 30 and 90-day mortality were 0% and 11.4%, respectively. mOS and progression-free survival (calculated from the date of salvage surgery) were 69 months [95% CI 37–101 months] and 22 months [95% CI: 0–45months] respectively.

Conclusions: In selected patients with advanced stage NSCLC presenting with local relapse or residual disease after systemic treatment, anatomical salvage lung resections are associated with a favorable short- and long-term outcome. However, further prospective evaluation of this treatment approach is required.

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116P

Survival outcome of chemotherapy in stage IIIA and IIIB non-small cell lung cancer

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Background: About 80% of all lung cancers are non-small cell lung cancer (NSCLC). The early stages are asymptomatic which lead to a late diagnosis. Surgery is the preferred option for stages I and II but the best treatment modality for stages III and IV are chemotherapy and radiotherapy. However, some studies have shown that NSCLC is chemotherapy resistant, which leaves some debates. So, this study aimed to assess the outcome of chemotherapy in stage III cancers.

Methods: Data of 2368 patients was extracted from Surveillance, Epidemiological, and End Results (SEER) database. All of them had stage III non-small cell lung cancer diagnosed from 2000–2019. The classification of stage III was according to eighth edition of AJCC. We divided the patients into four groups; groups who received chemotherapy and groups who had no systemic therapy for stages IIIA and IIIB each. For each group, we calculated relative 5-year survival, and using SPSS 25, we performed Kaplan-Meier curve and log rank test for survival analysis.

Results: The 5-year relative survival for the groups who received chemotherapy for stages IIIA and IIIB and the groups who had no systemic therapy for stages IIIA and IIIB were (23.8%, 18.1%, 7.6%, 6.6% respectively; P < 0.001). The overall survival of sex for stage III was 9.2% for males, and 10.7% for females (P < 0.02). Performing Cox regression model revealed, sex was associated with poor survival outcomes as IIIA (P < 0.001, HR: 1.12, 95%CI: 0.995–1.261) and IIIB (P < 0.001, HR: 1.1, 95%CI: 0.964–1.234,).

Conclusions: Non-small cell lung cancer patients who received chemotherapy showed threefold higher 5-year relative survival compared to the groups who had no systemic therapy. These results also showed that sex is associated with poor survival outcome. So, we recommend chemotherapy to be the first line of treatment for stages IIIA and IIIB for better survival outcome.

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Survival outcomes of surgery-based treatment or definitive chemoradiation with immunotherapy consolidation in stage IIIA NSCLC in the immune therapy era: An NCDB analysis

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Background: Stage IIIA non-small cell lung cancer (NSCLC) is a heterogeneous disease treated by a surgery-based approach or definitive chemoradiation (CRT). Surgery is thought to have superior outcomes despite an upfront mortality disadvantage. However, there is no real-world data on outcomes of stage IIIA NSCLC receiving definitive CRT and durvalumab (ICI) consolidation in comparison to surgery-based treatment since durvalumab was introduced.

Methods: We used National Cancer Database (NCDB) to identify 23,110 patients with clinical stage IIIA NSCLC treated with either surgery-based treatment or definitive CRT followed by ICI during 2017–2019, and surgery-based treatment or CRT during 2014–2016. The primary outcome analyzed was overall survival (OS). Kaplan-Meier (KM) plots were used to examine survival curves and Cox regression analysis was used to identify factors associated with OS.

Results: During 2017–2019, surgery consistently had a survival advantage (HR 0.81, 95%CI 0.75–0.88, p < 0.001) across all T and N groups compared to CRT-ICI. Consolidation ICI has improved 3-year OS from 39.1% during 2014–2016 to 56.5% during 2017–2019. A delay of 6+ weeks in initiating ICI after radiation did not confer a negative impact on survival. Lobectomy patients had better OS compared to pneumonectomy. On multivariate analysis, younger age (ages 19–39; HR 0.47, 0.35–0.64); (ages 40–64; HR 0.71, 0.67–0.75); (ages 65–74; HR 0.79, 0.76–0.83); (ages 75+ as HR 1.0), female sex (male sex; HR 1.24, 1.20–1.29; female sex as HR 1.0), non-squamous histology (adenocarcinoma; HR 0.90, 0.86–0.93; squamous histology as HR 1.0) and lower Charlson Comorbidity Index (CCI) (CCI 0; HR 0.81, 0.77–0.85), CCI 1 (HR 0.87, 0.83–0.92); (CCI 2 as HR 1.0), were associated with better OS (p < 0.001).

Conclusions: For stage IIIA NSCLC patients, surgery-based treatment is recommended if operable/resectable. In the first year, surgery has a small survival disadvantage, reflecting the upfront surgical mortality. Using CRT+ICI is slightly inferior to surgery but confers an impressive survival advantage compared with no ICI. Interestingly, delay in ICI did not cause a loss in efficacy.

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118P

High dose chemo-radio-immunotherapy for NSCLC III: ESR/ATS thresholds for DLCO correlate with radiation dosimetry and predict pneumonitis

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Background: Durvalumab following chemoradiotherapy for non-small cell lung cancer (NSCLC) UICC stage III has become the standard of care in the past few years. With this treatment approach 5-year overall survival has risen to 50% for PD/PDL-1-positive patients. Therefore pulmonary function (PF) after treatment is of high importance in long term survivors. In this respect carbon monoxide diffusing capacity (DL_{CO}), which represents the alveolar compartment, was found to be a suitable measure for residual pulmonary capacity. The aim of the current analysis was to correlate pre-treatment DL_{CO} with the occurrence of pneumonitis and to model DL_{CO} decline after therapy to the total radiation dose within a defined lung volume.
Methods: Eighty-five patients with histologically confirmed NSCLC III treated between 2015/10 and 2020/10 were eligible for this study. Patients received two cycles of platinum-based induction chemotherapy followed by high dose radiotherapy and Durvalumab maintenance for one year. The clinical endpoints were based on the thresholds published by the European Respiratory Society. Pre-treatment DL_{CO} of 60% was correlated to the incidence of pneumonitis and DL_{CO} decline of 10% within three months after treatment was related to radiation dose.
Results: Patients with a pre-treatment DL_{CO} below 60% had a higher probability for pneumonitis grade 2 or higher (N = 71, one-sided Pearson correlation coefficient −0.183, p-value 0.063), which became significant in the subgroup of patients without Durvalumab (N = 40, one-sided Pearson correlation coefficient −0.306, p-value 0.027). The decline in DL_{CO} > 10% after the end of radiotherapy depended on the size of the lung volume receiving 45% to 65% ($V_{65\%-45\%}$) of the total radiation dose (one-sided Pearson correlation coefficient = 0.264, p-value = 0.019).
Conclusions: The current analysis revealed that DL_{CO} is a predictor for clinically relevant pneumonitis and a monitoring tool for post-treatment lung function as it correlates with radiation dose. This underlines the importance of peri-treatment lung function testing.
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Disclosure: All authors have declared no conflicts of interest.

119P

Prospective trial of immuno-(chemo)therapy (IO) prior to resection, definitive chemo-radiotherapy, or palliative therapy in patients with borderline resectable non-small cell lung cancer (NSCLC) including oligometastatic disease (KOMPASSneo)

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Background: Recent trials of IO prior to resection in locally advanced NSCLC report high rates of pathological response. However, primarily irresectable patients were excluded from most studies. Moreover, there is no data on chemo-radiotherapy (CRT) after IO in patients who are primarily not amenable to CRT. We hypothesized that induction IO may enable more NSCLC patients to receive curative treatment.
Methods: We enrolled 78 patients with borderline resectable NSCLC including oligometastatic disease into a prospective real-world trial of induction IO followed by morphologic and metabolic reassessment and multidisciplinary board-guided curative treatment (resection [preferred] or CRT) or palliative therapy. 1° endpoint was the proportion of patients completing curative treatment. 2° endpoints included response and survival. Furthermore, pathological response was assessed in resected patients. Exploratory endpoints included the predictive role of PD-L1-TPS and the TP53-mutation status.
Results: 73 patients (94%) received curative treatment (32 complete resections, 41 CRT). 18 (56%) of resected patients had a major pathological response including 13 (41%) with pathological complete response. In curatively treated patients, there were 23 recurrences (32%) and 15 tumor-related deaths (21%): 5 recurrences (16%) and no deaths in resected patients, and 18 recurrences (44%) and 15 (37%) deaths in CRT-patients (median follow-up 18 months). There were two treatment-related deaths (one postoperative due to sepsis, one after CRT due to pneumonitis). Patients with high PD-L1-TPS had deeper pathological response and longer survival. Resected patients with TP53-mutation had poorer pathological response and numerically more recurrences than those without TP53-mutation.
Conclusions: In patients with borderline resectable NSCLC including oligometastatic disease, induction IO resulted in a high rate of curative treatment with promising survival. Resected patients achieved a high rate of prognostically favorable pathological response.
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120P

Neoadjuvant immunochemotherapy of pembrolizumab plus chemotherapy in resectable non-small cell lung cancer

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Background: Neoadjuvant immunotherapy, as the focus of current research and treatment means for long-term survival, has become one of the options in supporting primary treatment intervention in early NSCLC.
Methods: This was a retrospective analysis of patients with locally resectable NSCLC, who received the neoadjuvant drug pembrolizumab plus chemotherapy and underwent surgical resection. The pathology responses and the PFS and OS in the total sample and subgroups were determined and analyzed. Additionally, artificial intelligence was utilized to incorporate multiple factors for developing a high-performance prediction model.
Results: Of the 61 patients included in the retrospective analysis, 31 (50.82%) patients achieved a pCR, and 38 (62.30%) patients obtained an MPR. For the OS, patients with a pCR were significantly better than the patients with non-pCR (HR, 0.093; P = 0.0227); patients with an MPR performed significantly better than the patients with non-MPR (HR, 0.05357; P = 0.0169). Patients with lymph node metastasis after

surgery had significantly worse OS and PFS than those without lymph node metastasis (HR, 0.01607; p = 0.0004; HR, 0.08757; p = 0.0004). The PFS of patients with SCC was better than the patients with non-SCC (HR, 0.3939; p = 0.0340). No significant differences in OS and PFS were found between 2 cycles vs. 3 cycles of neoadjuvant therapy before the surgery; ≤5 cycles vs. >5 cycles of adjuvant therapy post-surgery; TPS of <50% vs. ≥50% (P > 0.05). After model training and optimization, and 5-fold cross-validation, KNC (K-Neighbors Classifier) algorithm was able to predict the pCR with an 85.71% accuracy.

Conclusions: Neoadjuvant immunochemotherapy of pembrolizumab plus chemotherapy for non-small cell lung cancer is safe and tolerable. Both pCR and MPR were closely related to OS and PFS, reflecting the good response of tumor tissues to drug therapy. Lymph node metastasis after surgery was a poor prognostic factor, causing worse OS and PFS. Artificial intelligence constructed a prediction model for assessing treatment efficacy.

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121P

Neoadjuvant sintilimab and anlotinib combined with chemotherapy for resectable NSCLC: A prospective, single arm, multicenter study

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Background: To explore the efficacy and safety of neoadjuvant Sintilimab and Anlotinib combined with chemotherapy for resectable NSCLC.

Methods: Before operation, the patients were treated with Sintilimab (200 mg) and Anlotinib (10 mg, po, day 1–14) combined with chemotherapy for 3 cycles, and surgery was performed 4 weeks after the last chemotherapy. After operation, patients were treated with Q3W of Sintilimab (200 mg) for 1 year. Primary end point: Complete pathological response (pCR). Secondary end point: Major pathological response (MPR), safety.

Results: 39 patents were included in the study group, including 35 males and 4 females; 30 people with smoking index > 400, 9 people with smoking index < 400; There were 9 cases of adenocarcinoma and 30 cases of squamous cell carcinoma. In addition, 4, 6, 12 and 17 patients in this group were in stages IIA, IIB, IIIA, and IIIB, respectively. Thirty-five patients finally received surgical treatment, one patient refused any treatment due to grade 3 liver damage, and three patients refused surgery after completing neoadjuvant treatment. The pCR of intention to treat (ITT) population is 21 (53.8%), the MPR is 25 (64.1%). The pCR of Per-protocol (PP) population is 60%, and the MPR is 71.4%. According to RECIST 1.1, there was 1 case of progress disease, 9 cases of SD, 27 cases of PR and 2 cases of CR in ITT population. The pCR and ORR of squamous cell carcinoma is much higher than those of adenocarcinoma in ITT or PP population. There were three patients with EGFR mutation (included Exon 19 and L858R) in adenocarcinoma. The incidence rate of AE events above grade 3 related to treatment was 20 (51.3%).

Table: 121P

Patient characteristics (N,%)	
Age	
≥60	24 (61.5)
<60	15 (38.5)
Sex	
Male	35 (89.7)
Female	4 (10.3)
Smoking Index	
≥400	30 (76.9)
<400	9 (23.1)
Pathological type	
Squamous cell carcinoma	30 (76.9)
Adenocarcinoma	9 (23.1)
Clinical stage	
IIA	4 (10.3)
IIB	6 (15.4)
IIIA	12 (30.8)
IIIB	17 (43.5)
Pathological response	
PCR(ITT)	21 (53.8)
MPR(ITT)	25 (64.1)
PCR(PP)	21 (60.0)
MPR(PP)	25 (71.4)
Squamous cell carcinoma (PCR-PP, N = 26)	19(73.1)
Squamous cell carcinoma (MPR-PP, N = 26)	23(88.5)
Adenocarcinoma (PCR-PP, N = 9)	3 (33.3)
Adenocarcinoma (MPR-PP, N = 9)	3 (33.3)
RECIST 1.1	
ORR(ITT)	29 (74.4)
ORR(PP)	25 (71.4)
Squamous cell carcinoma (ORR-PP, N = 26)	21 (80.8)
Adenocarcinoma (ORR-PP, N = 9)	5 (55.6)

Conclusions: The neoadjuvant treatment of Sintilimab and Anlotinib combined with chemotherapy can significantly increase the pCR of resectable NSCLC, which is an effective treatment method. However, the perioperative AE events should be paid attention to.

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Disclosure: All authors have declared no conflicts of interest.

122P

Comparison of the efficacy of neoadjuvant pembrolizumab vs sintilimab combination with chemotherapy in resectable lung cancer: A multicenter propensity score matching study

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Background: This study aims to evaluate the effectiveness of using Pembrolizumab or Sintilimab combined with chemotherapy in NSCLC treatment using the Propensity Score Matching (PSM) analysis.

Methods: The NSCLC patients were treated with neoadjuvent Pembrolizumab or Sintilimab combined with chemotherapy in two hospitals since June 2018. The objective response rate (ORR), pathological complete response (pCR), and operation-related information of the two groups were analyzed by PSM analysis.

Results: Here, 116 patients were enrolled in the study, where 61 were classified into the Sintilimab group while 55 were included in the

Pembrolizumab group. The results indicated that 28 patients (45.9%) in the Sintilimab group achieved pCR while 30 patients (54.5%) in the Pembrolizumab group showed pCR(P = 0.353). No significant differences were noted in MPR between the Sintilimab and Pembrolizumab groups (39, 63.9% vs 36, 65.5%, P = 0.861). Furthermore, the ORR values showed no statistically significant differences between the groups when compared to the assessment of the effects by the Sintilimab and the Pembrolizumab groups (46, 75.4% vs. 44, 80.0%, P = 0.554). There was no discernible difference in ORR and pCR values between the two groups after the first and second PSM analyses. After a Logistic analysis, before and after PSM, treatment with ≥3 cycles were still regarded as the promoting factor of pCR.

Table: 122P

	Sintilimab (n = 61)	Pembrolizumab (n = 55)	P
Sex			0.493
Male	53(86.9)	50(90.9)	
Female	8(13.1)	5(9.1)	
Age			0.864
≥60	39(63.9)	36(65.5)	
<60	22(36.1)	19(34.5)	
BMI			0.001
≥24	12(19.7)	26(47.3)	
<24	49(80.3)	29(52.7)	
Smoking Index			0.07
≥400	48(78.7)	40(72.7)	
<400	13(21.3)	15(27.3)	
Pathological type			0.069
Squamous cell cancer	45(73.8)	48(87.3)	
Adenocarcinoma	16(26.2)	79(12.7)	
Cycles of neoadjuvant therapy			0.002
≤2	30(49.2)	12(21.8)	
≥3	31(50.8)	43(78.2)	
Clinical stage			0.670
I, II	14(22.9)	11(20.0)	
III	47(77.1)	44(80.0)	
RECIST 1.1 evaluation			0.554
ORR	46(75.4)	44(80.0)	
NON-ORR	15(25.6)	11(20.0)	
Pathlogical evaluation			0.353
pCR	28(45.9)	30(54.5)	
NON-pCR	33(54.1)	25(45.5)	

Conclusions: Sintilimab or Pembrolizumab combined with chemotherapy display a similar pCR to the neoadjuvant treatment of resectable NSCLC. So these both PD-1 inhibitors could show similar effects in NSCLC treatment.

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123P

Second progression-free survival (PFS2) after first progression in patients receiving PACIFIC regimen: An exploratory analysis of the Blue Sky observational study

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Background: The Blue Sky Radiomic trial is a multicenter, observational, retrospective, and prospective study started in 2020, with a target sample size of 100 patients with unresectable stage III A-C NSCLC treated with the PACIFIC regimen (clinicaltrial.gov identifier: NCT04364776, active, recruiting). We here report an exploratory analysis of PFS2 after the first progression.

Methods: All patients were deemed unresectable by MTB and had PD-L1-positive (>1%) tumors, with at least stable disease, and receiving one durvalumab dose after CRT; 93/100 pts were evaluable, with 56 recorded events (6 deaths and 50 progressions). PFS2 was calculated for these 50 pts from the date of first to second progression or death (Kaplan-Meier).

Results: At a median follow-up time of 18 months, the median PFS of the entire cohort was 23.2 months (2.10–47.63). Median OS was not reached. Among patients experiencing a first PD (n = 50), 9 pts (18%) relapsed within the first 3 months from durvalumab start, 10 (20%) between 3 and 6, and 31 (62%) after 6 months. The pattern of relapse was as follows: 16 local recurrences (32%), 17 distant progressions (34%), and 17 both (34%), respectively. Forty-one/50 (82%) patients did receive an active treatment at the first progression: 22 pts systemic therapy (53.6%, 9 pts a platinum-based doublet, 11 mono-CT, 1 IO, and 1 TKI); 10 RT alone (24.4%); 6 CT plus local treatment (14.6%), and 3 metastasectomies alone (7.4%). With a median follow-up of 5.33 months (1.07–32.43) from the first PD, we recorded 29 deaths. Ten pts are alive without progression, and 11 are alive with progressive disease. Median PFS2 was 7.23 months (1.03–42), and median OS was 15.5 months (1.07–46.17), respectively.

Conclusions: This exploratory analysis suggests that most progressing patients can receive subsequent therapy at the time of first progression following CRT plus durvalumab in a real-world setting. The median PFS2 of around 7 months could be used as a reference for the design of future trials.

Clinical trial identification: NCT04364776.

Legal entity responsible for the study: Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.

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124P

SPOTLIGHT real-world study: Outcomes with or without consolidation durvalumab (D) after chemoradiotherapy (CRT) in patients with unresectable stage III NSCLC

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Background: PACIFIC established D as the standard of care for patients (pts) with unresectable Stage III NSCLC and no progression after CRT. In retrospective observational studies, such as PACIFIC-R (Girard, 2022), outcomes in pts who receive D after CRT have been consistent with PACIFIC, demonstrating the real-world (RW) effectiveness of this regimen. We report exploratory analyses comparing outcomes in pts who did or did not receive D after concurrent CRT (cCRT) in the retrospective observational SPOTLIGHT study.

Methods: A US oncology database (Flatiron Health) was used to collect de-identified pt-level data from a sample of unresectable Stage III NSCLC pts treated with CRT. Two prespecified cohorts were curated: pts who did or did not receive D. The exploratory endpoints of RW progression-free survival (rwPFS) and overall survival (OS), both defined from the end of CRT, were analyzed by Kaplan–Meier method in pts who completed cCRT and did not progress or die before D start, for the D cohort, or within 42 days from the end of CRT, for the non-D cohort. Cox regression was used to assess the association of D with outcomes, adjusting for available pt characteristics.

Results: The D and non-D cohorts included 332 and 137 pts, respectively; 299 and 77 pts met the above-mentioned criteria for inclusion in the analyses. Pt characteristics were similar between the two groups. Median rwPFS (95% CI), defined from the end of CRT, was 20.0 mo (16.2–not estimable [NE]) in the D group and 10.2 mo (6.7–12.4) in the non-D group. In the Cox regression analysis for rwPFS (adjusting for pt characteristics), pts in the D group had a lower risk of progression or death versus pts in the non-D group (HR 0.36; 95% CI 0.26–0.52). Median OS (95% CI) was not reached in the D group and 24.8 mo (13.4–NE) in the non-D group. In the Cox regression analysis for OS, pts in the D group had a lower risk of death versus pts in the non-D group (HR 0.30; 95% CI 0.19–0.48).

Conclusions: In the RW SPOTLIGHT study, pts who received D after CRT had better outcomes versus pts who did not (e.g. median rwPFS 20.0 vs 10.2 mo). There were no apparent differences in pt characteristics to explain why pts had not received D. Further investigation of factors that led to this is warranted.

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125P

Real-world treatment patterns in stage III NSCLC patients: Interim results of a prospective, multicenter, non-interventional study (MOOREA)

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Background: Stage III non-small cell lung cancer (NSCLC) is highly heterogeneous and often warrants multidisciplinary collaboration. Thus, there is a huge unmet need to understand real-world treatment patterns, and relationship to survival outcomes in stage III NSCLC patients.

Methods: MOOREA study is a prospective, non-interventional study to assess the real-world treatment patterns and outcomes of Chinese patients with stage III NSCLC. Treatment naïve stage III NSCLC patients were enrolled and assigned to cohort 1 (unresectable) and cohort 2 (resectable). The primary endpoint is treatment pattern, secondary endpoints are progression-free survival, overall survival, and EGFR/ALK/PD-L1 testing rate. Due to the immaturity of survival endpoints, they will not be reported here.

Results: Between July 2019 and February 2022, 437 eligible patients enrolled from 19 centers in China were included in interim analysis (median age 63 years, 32.3% adenocarcinoma). The testing rates for EGFR, ALK, and PD-L1 were 18.1%, 13.3%, and 10.3%, respectively. In Cohort 1, 41.3% (142/344) patients have received chemoradiotherapy (CRT), including 62.7% (89/142) concurrent CRT (cCRT) and 37.3% (53/142) sequential CRT (sCRT). Of patients after cCRT, 52.8% (47/89) further received consolidation therapy, among which 59.6% (28/47) was immunotherapy. For sCRT patients, 34.0% (18/53) received consolidation therapy, with chemotherapy as the majority (44.4%, 8/18). In Cohort 2, all 93 patients have received surgery and 42.4% (39/92) received neoadjuvant therapy (table).

Table: 125P Treatment patterns in two cohorts

Cohort 1 (344 pts)	
Treatment	
CRT	142/344 (41.3)
cCRT	89/142 (62.7)
Consolidation therapy	47/89 (52.8)
sCRT	53/142 (37.3)
Consolidation therapy	18/53 (34.0)
Cohort 2 (93 pts)	
Neoadjuvant treatment	
Yes	39/92 (42.4)
No	53/92 (57.6)
Missing, n	1

Note: data are presented as n/N (%) except specifically notified.

Conclusions: MOOREA study presents the real-world treatment pattern for stage III NSCLC in China, showing that treatment options for this subset are varied in clinical practice due to disease heterogeneity. Further survival correlations with different treatment patterns are ongoing.
Clinical trial identification: NCT04023812.
Legal entity responsible for the study: The authors.
Funding: AstraZeneca China.
Disclosure: All authors have declared no conflicts of interest.

126P

Chemotherapy and stereotactic ablative radiotherapy in newly diagnosed and recurrent locally advanced non-small cell lung cancer patients unfit for concurrent radio-chemotherapy: Sub-analysis and update of START-NEW-ERA non-randomised phase II trial

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Background: Early analysis[1] of a single arm phase II trial assessed local control (LC) and safety of SAbR in unresectable LA-NSCLC patients unfit for concurrent chemo-radiotherapy (ChT-RT). Here we report outcomes of LA-NSCLC patients submitted to ChT and SAbR.
Methods: Between December 31, 2015 and June 30, 2022 71 LA-NSCLC patients were enrolled. 40 (56%) and 31 (44%) received neoadjuvant ChT+SAbR and SAbR, respectively. Among patients receiving ChT, 15 (37%) received Durvalumab. The tumor volume included primary tumor (T) and any regionally positive node/s (N). The co-primary study endpoints were LC and safety.
Results: The median age was 71 years (range, 52–85). 36 (90%) and 4 (10%) patients had PS 0–1 and 2, respectively. Histology was squamous cell carcinoma (SCC) and adenocarcinoma (ADC) in 52% and 48%, respectively. The stage was IIB, IIIA, IIIB and IIIC in 4 (10%),13 (33%), 17 (42%) and 6 (15%) patients, respectively. Median prescribed dose was 45 Gy (range, 35–55) and 40 Gy (35–45) in 5 daily fractions to T and N, respectively. After a median follow-up of 26 months (range, 6–66), 14 (35%) patients had experienced local recurrence (LR). The median LR-free survival (FS) was not reached (95% CI, 28 to not reached). The 1-, 2- and 4- year LR-FS rates were 86 ± 6%, 67 ± 8% and 50 ± 10%, respectively. At last follow-up, 23 (58%) patients were alive. Median overall survival (OS) was 50 months (95% CI, 31–55). The 1, 2, and 4-year OS rates were 92 ± 5%, 70 ± 8% and 51 ± 9%, respectively. 14 (35%) patients developed distant progression (dP). The median dP-FS was not reached (95% CI, 16 to not reached). The 1, 2, and 4-year dP-FS rates were 86 ± 6%, 56 ± 9% and 56 ± 9%, respectively. 2 (5%) patients developed grade (G) ≥3 esophageal and lung toxicity.
Conclusions: LA-NSCLC patients treated with ChT and SAbR had optimal LC and promising OS with low rate of G3 toxicity. Our early outcomes would suggest the feasibility of using this approach in LA-NSCLC patients unfit for concurrent ChT-RT.
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127P

Stereotactic ablative radiotherapy and durvalumab: The backbone of unresectable locally advanced non-small cell lung cancer patients unfit to concurrent chemo-radiotherapy - Rib of START-NEW-ERA trial

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Background: Several real-world experiences have been reported safety and effectiveness of Durvalumab after concurrent or sequential chemo-radiotherapy (ChT-RT) in lLA-NSCLC patients. There is a lack of data after sequential ChT-hypofractionated RT. In single arm phase II trial (NCT05291780) we assessed local control (LC) and safety of stereotactic ablative radiotherapy (SAbR) in unresectable LA-NSCLC patients unfit for concurrent ChT-RT (1). Here we report clinical outcomes of SAbR in LA-NSCLC patients treated with radical-intent based on PACIFIC trial.
Methods: Between December 31, 2015 and June 30, 2022 71 LA-NSCLC patients were enrolled. 40 (56%) fit patients received neoadjuvant ChT and 15 (37%) received Durvalumab. The tumor volume included primary tumor (T) and any regionally positive node/s (N). The co-primary study endpoints were LC and safety.
Results: The median age was 71 years (range, 52–78). Histology was adenocarcinoma (ADC) and squamous cell carcinoma (SCC) and in 9 (60%) and 6 (40%), respectively. The stage was IIIA, IIIB and IIIC in 7 (47%), 5 (33%) and 3 (20%) patients, respectively. Median prescribed dose was 45 Gy (range, 40–50) and 40 Gy (35–50) in 5 daily fractions to T and N, respectively. After a median follow-up of 16 months (range, 6–62), 4 (27%) patients had experienced local recurrence (LR) at a median time of 13 months (range, 7–34). The median LR-free survival (FS) was 34 months (95% CI, 14 to 34). The 1-, 2- and 4-year LR-FS rates were 92 ± 8%, 72 ± 14% and 48 ± 22%, respectively. At last follow-up, 23 (58%) patients were alive. Median overall survival (OS) was 50 months (95% CI, 31–55). The 1, 2, and 4-year OS rates were 92 ± 5%, 70 ± 8% and 51 ± 9%, respectively. 7 patients had disease recurrence, 4 and 3 during and after completion of Durvalumab. 2(13%) discontinued Durvalumab due to G3 toxicity.
Conclusions: SABR and immunotherapy can be the backbone of patients unfit to concurrent ChT-RT. Our early outcomes would suggest the feasibility of using this approach in LA-NSCLC patients unfit for concurrent ChT-RT.
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Stereotactic ablative radiotherapy in locally-advanced non-small cell lung cancer patients: Little palliation or big cure? Sub-analysis of START-NEW-ERA phase II trial

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Background: Early analysis[1] of a single arm phase II trial assessed local control (LC) and safety of stereotactic ablative radiotherapy (SAbR) unresectable locally advanced non-small cell lung cancer (LA-NSCLC) patients unfit for concurrent chemo-radiotherapy (ChT-RT). Here we report clinical outcomes of LA-NSCLC patients submitted to exclusive SAbR.
Methods: Between December 31, 2015 and June 30, 2022 71 LA-NSCLC patients were enrolled. 40 (56%) and 31 (44%) received neoadjuvant ChT+SAbR and exclusive SAbR, respectively. The tumor volume included primary tumor (T) and any regionally positive node/s (N). The co-primary study endpoints were LC and safety.
Results: The median age was 80 years (range, 45–88). Twenty (64%) and eleven (36%) patients had PS 0–1 and 2, respectively. Histology was adenocarcinoma (ADC) and squamous cell carcinoma (SCC) in 71% and 29%, respectively. 27 (87%) patients had ultra-central tumor. Median prescribed dose was 45 Gy (range, 35–55) and 40 Gy (35–45) in 5 daily fractions to T and N, respectively. After a median follow-up of 27 months (range, 6–92), 9 (29%) patients had experienced local recurrence (LR) at a median time of 13 months (range, 7–34). The median LR-free survival (FS) was not reached (95% CI, 28 to not reached). The 1-, 2- and 4- year LR-FS rates were 81 ± 7%, 66 ± 9% and 66 ± 9%, respectively. At last follow-up, 23 (74%) patients were alive. Median overall survival (OS) was not reached. The 1, 2, and 4-year OS rates were 97 ± 3%, 74 ± 8% and 70 ± 9%, respectively. Eight (26%) patients developed distant progression (dP). The median dP-FS was not reached (95% CI, 26 to not reached). The 1, 2, and 4-year dP-FS rates were 82 ± 7%, 72 ± 9% and 66 ± 10%, respectively.
Conclusions: LA-NSCLC patients treated with exclusive SAbR had optimal local control and promising overall survival with excellent treatment compliance and absence of ≥G3 toxicity. Our preliminary prospective clinical outcomes provide an attraction to evaluate this approach in patients unfit to ChT, to obtain a "big" cure beyond "little" palliation.
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129P

Adjuvant therapy for T3 non-small cell lung cancer with additional intrapulmonary nodules

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Background: The recommended treatment for T3 non-small cell lung cancer (NSCLC) presenting with separate tumor nodule(s) in the same lobe as the primary ("T3-Add") includes surgical resection followed by adjuvant chemotherapy. This study sought to assess long-term survival of patients receiving adjuvant chemotherapy for T3-Add tumors across different tumor histologies.
Methods: Patients with T3-Add, N0-2, M0 NSCLC, after restaging based on AJCC 8th Edition TNM staging guidelines, in the National Cancer Database (NCDB) from 2010 to 2015 who underwent lobectomy with complete (R0) resection, without neoadjuvant therapy were included. Long-term overall survival was evaluated stratified by adjuvant chemotherapy status and histology (lung adenocarcinoma vs lung squamous cell carcinoma), using Kaplan-Meier analysis, Cox proportional hazards modeling, and propensity score matching on 11 common prognostic variables including comorbidities and clinical N status.
Results: Of the 2,069 patients with T3-Add tumors who satisfied the study's inclusion criteria, 842 (40.7%) received adjuvant chemotherapy. Lung squamous cell histology was associated with significantly worse overall survival than lung adenocarcinoma histology (HR: 1.30, 95% CI: 1.09–1.56, p = 0.003). 41.7% (677/1,624) patients with adenocarcinoma and 37.1% (165/445) patients with squamous cell carcinoma received adjuvant chemotherapy. Individual propensity score-matched analyses stratified by histology were conducted comparing patients that did or did not receive adjuvant therapy. In the adenocarcinoma cohort (466 in each arm), use of adjuvant chemotherapy was not significantly associated with overall survival (66.3% [95% CI: 61.2–70.9] vs 63.8% [95% CI: 58.6–68.5], p = 0.24). However, for patients with lung squamous cell carcinoma (100 in each arm), adjuvant chemotherapy was associated with better 5-year overall survival (56.9% [95% CI: 44.0–67.8] vs 45.1% [95% CI: 33.5–56.1]).
Conclusions: The results of this national analysis support current guidelines that recommend adjuvant chemotherapy following surgery for T3 NSCLC presenting as a primary tumor with additional intrapulmonary nodule(s) in the same lobe for lung squamous cell carcinoma but not for lung adenocarcinoma.
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130TiP

Adjuvant osimertinib in patients with completely resected, stage IB-IIIB non-small cell lung cancer with uncommon EGFR mutations: A phase II, open-label, single arm, multicenter, exploratory study

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Background: Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) show decreased sensitivity and suboptimal treatment outcomes in non-small cell lung cancer (NSCLC) patients (pts) with uncommon EGFR mutations (EGFRm) compared to pts with common EGFRm. 2022 'ESMO expert consensus statements on the management of EGFR mutant non-small-cell lung cancer' recommends osimertinib as the preferred first-line treatment for late-stage NSCLC pts with major uncommon EGFRm (G719X/L861Q/S768I). ADAURA study showed osimertinib adjuvant treatment has overwhelming DFS benefit among IB to IIIA NSCLC pts with complete tumor resection and optional, standard post-operative adjuvant chemotherapy. Data on adjuvant osimertinib treatment in NSCLC with uncommon EGFRm is not available. Hence, this study has been planned to evaluate the efficacy and safety of adjuvant osimertinib in completely resected NSCLC pts with uncommon EGFRm.
Trial design: This is a phase II, open-label, single-arm, multicenter, exploratory study conducting at 10 hospitals in China. 50 completely resected, histologically confirmed stage IB-IIIB non-squamous NSCLC pts with any uncommon EGFRm (G719X/L861Q/S768I/de novo T790M) but without EGFR Ex19del/L858R/exon 20 insertion, will be enrolled. Pts who have received prior neoadjuvant or adjuvant EGFR-TKI/radiotherapy/chemotherapy (except adjuvant platinum doublet

chemotherapy) will be excluded. Pts will receive 80 mg osimertinib QD orally for a maximum of 3 years or until the discontinuation criterion is met. The primary endpoint is 3-year DFS rate by investigator assessment. Secondary endpoints include DFS rates at 2, 4, and 5 years and overall survival (OS) rates at 2, 3, 4, and 5 years. Safety assessments include adverse events, physical examinations, vitals, electrocardiogram, echocardiogram and clinical laboratory assessments. Exploratory analysis of tumor and blood samples will be performed in a retrospective manner to investigate the molecular mechanism of recurrence. Trial recruitment is ongoing and the first patient is anticipated to be enrolled in Feb 2023.

Clinical trial identification: NCT05546866.

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131TiP

A phase I–III platform study evaluating the safety and efficacy of multiple therapies in patients (pts) with biomarker-defined locally advanced, unresectable stage III non-small cell lung cancer (NSCLC)

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Background: Durvalumab following chemoradiation (CRT) is a standard of care for stage III unresectable NSCLC, but there remains an unmet need for improved therapeutic options among pts with driver mutated tumours that are unresponsive to immunotherapy. As targeting of specific driver mutations (e.g., ALK, RET, ROS1) has proven effective in the metastatic setting, it is hypothesised that outcomes could also be improved for pts with driver-mutated stage III NSCLC.

Trial design: BO42777 is a phase I–III platform study evaluating the safety and efficacy of multiple targeted therapies vs durvalumab following CRT in pts with locally advanced, unresectable, Stage III NSCLC. Biomarker eligibility is determined via local tissue testing or central testing within the BX43361 master screening study. Biomarker-eligible pts are enrolled into the relevant cohort and randomised 1:1 to receive durvalumab or targeted therapy (alectinib [ALK+], entrectinib [ROS1+], or pralsetinib [RET fusion+]). New cohorts may be added in the future. Key inclusion criteria: locally advanced, unresectable Stage III NSCLC, age ≥18 years, ≥2 prior cycles of concurrent or sequential CRT (cCRT or sCRT), ECOG PS 0–2. Pts are stratified based on staging (IIIA vs IIIB or IIIC), CRT type (cCRT vs sCRT), and PD-L1 status (tumour cell score <1% vs ≥1% vs unknown) and will receive investigational treatment for 3 years or durvalumab for 1 year, until progression or maximum duration of treatment, unacceptable toxicity, consent withdrawal, or death. Primary endpoint: progression-free survival (RECIST v1.1) by blinded independent central review. Key secondary endpoints: distant metastasis-free survival, time to CNS progression, objective response rate, duration of response, overall survival, and safety (adverse events). Time to confirmed deterioration and patient-reported outcomes will be assessed through questionnaires. Tumour response will be assessed by CT/MRI imaging at regular intervals. Enrolment is ongoing (target of 320 pts) across 200 sites in 11 countries. As of 6 Jan 2023, 2 pts have been randomised.

Clinical trial identification: NCT05419375 & NCT05170204.

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132TiP

Boosting immune response with copanlisib in locally advanced unresectable non-small cell lung cancer starting durvalumab consolidation: A phase Ib study

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Background: Unresectable stage 3 non-small cell lung cancer is treated with chemoradiation followed by consolidation durvalumab since early 2018. However, the updated 5-year survival from the PACIFIC study showed a OS of 42.9% vs 33.4% and PFS of 33.1% vs 19% when compared with the placebo. Patients treated with durvalumab had 28% less chance to die within 5 years. There is still a lot of room to improve.

Tregs participate in anti-tumor immunity leading to immune evasion. We hypothesize that Tregs contributes to immune checkpoint inhibitor resistance and copanlisib boosts immune response in stage III NSCLC on durvalumab.

Trial design: This is a phase Ib clinical trial with a dose finding phase and a dose expansion phase. Primary objective of the study is the safety and tolerability adding copanlisib to durvalumab. The secondary objective includes PFS. Initially 3 patients appropriate for durvalumab consolidation will be enrolled and treated with copanlisib 60 mg intravenously once every two weeks along with durvalumab 1500 mg IV every 4 weeks. If no more than one dose limiting toxicity is observed in 28 days, another 3 will be treated. If 2 or less out of 6 patients experience DLT, the trial will proceed with the above dosing schedule in the dose expansion phase enrolling 6–12 patients. Treatment with both drugs will continue until disease progression, intolerance or at the end of one year whichever comes first. Patients aged 18–80 year will be enrolled when they do not have disease progression following concurrent chemoradiation for stage 3 disease appropriate for durvalumab consolidation. Patients need minimal organ functional reserve for bone marrow, liver and kidney function. Hepatitis or HIV infection patients are eligible if the infection is under control. Heart function cut off is NYHA class IIb or better. Known driver mutation-positive patients (EGFR, ALK) are excluded so is autoimmune disease on active immunosuppressant, organ transplant status. Hypertension not controlled well (above 150/90) or poorly controlled diabetes (HbA1c.8.5) are excluded. Patients are not allowed to take strong CYP3A4/5 inhibitor or QT prolongation agents. Currently, 4 patients are enrolled.

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133TiP

Neoadjuvant osimertinib followed by sequential definitive radiotherapy and/or surgery in stage III EGFR-mutant NSCLC: An open-label, single-arm, phase II study

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Background: The treatment of unresectable, locally advanced stage III non-small cell lung cancer (NSCLC) is concurrent chemoradiation therapy (CRT), followed by consolidation durvalumab. This study aims to evaluate the benefit of neoadjuvant osimertinib as an alternative therapy to this approach with the aim of reducing the radiation field.

Trial design: This investigation was a nonrandomized, open-label, single-arm, phase II prospective, proof-of-concept study. Eligible patients were treatment-naïve, nonoperable, stage III EGFR-mutant NSCLC patients. Patients received 80 mg oral osimertinib daily for 12 weeks prior to definitive radiotherapy (RT) and/or surgery. The response was assessed at week 6 and week 12. For responders, sequential definitive RT and/or surgery were planned. Nonresponders were started on standard CRT. After RT ± surgery or CRT, patients were followed for two years without adjuvant therapy. The primary endpoint was the objective response rate (ORR), with September 20, 2022 set as the cut-off for data collection. Secondary endpoints were safety and the gross tumour volume (GTV), planned tumour volume (PTV) and the percentage of total lung volume exceeding 20 Gy (V20%) before vs. after osimertinib. Exploratory analyses included assessments of the presence of plasma circulating tumour-free DNA (cfDNA) before osimertinib treatment, at weeks 6 and 12, at the end of RT, and 6 weeks post-RT.

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MESOTHELIOMA

134P
Clinical and epidemiological patterns of pleural mesothelioma in the United States: Long-term data from SEER database

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Background: Malignant pleural mesothelioma is a rare and aggressive cancer type with a rising global incidence over the past decade. In this study, we aimed to assess the clinical and epidemiological patterns of pleural mesothelioma in the United States. Moreover, we tracked the changing trend of overall survival and disease distribution of the different histological subtypes.
Methods: We used Surveillance, Epidemiology, and End Results Program (SEER) database to extract data of cases diagnosed with microscopically confirmed malignant pleural mesothelioma between 2004 and 2019 [17 reg; Nov 2021 sub]. Cases with unknown/unreported stage were excluded.
Results: We analyzed data from 9,511 malignant pleural mesothelioma patients. Most cases were males (77.6%, n = 7384), of white race (90.8%, n = 8635), ≥70 years at diagnosis (65.3%, n = 6215), and presented with distant disease (70.5%, n = 6703). The overall incidence rate of pleural mesothelioma was 7.2 per million and decreased from 7.7 per million in 2004 to 6.1 per million in 2019 with a marginal increase in the median overall survival (Table). Moreover, patients became more likely to present with localized and regional stages. Longitudinal tracking of cases with different histological subtypes showed an increase in the epithelioid mesothelioma which had a statistically significant longer median overall survival compared with fibrous mesothelioma and biphasic mesothelioma (12 months vs. 4 and 8 months, respectively; P = 0.001).
Conclusions: The incidence of pleural mesothelioma decreased between 2004 and 2019 with a marginal improvement in the median overall survival. However, there is a substantial increase in the proportion of patients presenting with epithelioid mesothelioma and those presenting with localized stage.

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135P
Macroscopic complete resection versus non-surgical management for malignant pleural mesothelioma

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Background: Malignant pleural mesothelioma is a rare aggressive tumor originating from the pleural mesothelial cells with average survival of 12 months. Primary chemoradiotherpy, surgery with or without adjuvant chemo(radio)therapy are different treatment modalities. However, there is only one small randomized controlled trial discussed the role of surgery versus non-surgical management for malignant pleural mesothelioma. So this study aims to evaluate the impact of macroscopic complete resection versus non-surgical management on survival outcome to provide additional evidence for better management for pleural mesothelioma.
Methods: Data of 4233 patient was extracted with Surveillance, Epidemiology and End Results (SEER) program software, all of them had malignant pleural mesothelioma and diagnosed from 2000 to 2019. They were divided into two subgroups; a group had macroscopic complete surgical resection and a group had non-surgical management with further stratification for both groups by the systemic therapy received. We used SPSS 23 for data analysis. Kaplan-Meier curve, Log-rank test for survival analysis.
Results: The 3-year and 5-year overall relative survival for malignant pleural mesothelioma was 13.7% and 7.4%. The 5-year overall survival for macroscopic surgical resection with and without adjuvant therapy was 16.8% and 8% while for non-surgical management with and without systemic therapy was 5.3% and 5.7%; P > 0.0001. Performing COX-regression model; Sex, stage, age and systemic chemo(radio) therapy are significant survival predictors (P > 0.0001).
Conclusions: Malignant pleural mesothelioma had a very poor survival outcome. However, macroscopic complete resection increased the survival about three folds than non-surgical management. Systemic chemo(radio)therapy improved the overall survival after surgical resection while it had no survival benefit in the non-surgical management. Among all treatment modalities, adjuvant radiotherapy had survival benefit of 17% over surgery without systemic therapy. These results highlight surgical resection with adjuvant radiotherapy as

Table: 134P Distribution and overall survival of pleural mesothelioma cases between 2004 and 2019

ICD-O-3	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
9050/3 Mesothelioma (NOS)	54.2%	52.6%	52%	48.7%	46.2%	46.9%	41.5%	38.4%	37.6%	39.2	39%	34.8%	32.7%	27%	31.1%	37.3%
9051/3 Fibrous mesothelioma	10%	11%	11.7%	10.9%	12.3%	10.8%	13.7%	13.5%	14.3%	11.3%	10%	11.2%	9.6%	11.7%	11%	12.4%
9052/3 Epithelioid mesothelioma	28.8%	30.7%	32.6%	31.8%	35.9%	35.3%	36.8%	38.8%	38.6%	41.4%	40.2%	44.2%	48.2%	50.2%	45.1%	42.7%
9053/3 Biphasic mesothelioma	7%	5.8%	3.8%	8.7%	5.5%	7%	8%	9.3%	9.6%	8.1%	10.7%	9.8%	9.6%	11%	12.8%	7.7%
Overall survival (months)	7	7	8	7	8	8	8	9	8	8	9	9	10	10	10	Not reached

the modality of choice after consideration of the age, sex and stage in final evaluation.

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136P
Germline testing in a cohort of malignant mesothelioma (G-MESO)

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Background: Malignant mesothelioma (MM) is associated with asbestos exposure and about 10–15% of patients are carriers of germline pathogenic or likely pathogenic variants (GPV/GLPV) in genes associated with cancer predisposition. The prevalence of GPV/GLPV in patients diagnosed with MM in our country is unknown.
Methods: All patients signed the informed consent and were prospectively tested using a custom NGS panel covering 164 cancer-predisposing genes. We present preliminary results from a cohort of 66 patients diagnosed with pleural and peritoneal malignant mesothelioma (MM) at the Catalan Institute of Oncology.
Results: Median age was 70.5 (46–88) and 70% were males. 60 patients had pleural and 6 peritoneal MM and most patients had epithelioid MM (86%). Most patients had history or probable exposure to asbestos (44% and 23%, respectively). Nine patients had personal history of cancer and 44 (67%) had family history of cancer (first degree relative). Eight patients (12.1%) harbored GPV/GLPV in 6 genes: BAP1 (n = 2), BARD1 (n = 2), FANCA (n = 1), RECQL4 (n = 1), SBDS (n = 1), SDHC (n = 1). Five patients (7.5%) were referred to Genetic Counselling. Patients with GPV/GLPV compared to their counterparts were more likely to have personal and family history of cancer, lack of asbestos exposure, however these differences were not statistically significant probably due to the limited statistical power (table). We will present updated results of this study at the ELCC 2023.

Table: 136P Clinicopathological and epidemiological features of carriers of GPV/GLPV with their counterparts

	GPV/GLPV (n = 8)	No GPV/GLPV (n = 58)	P-value
Age, median (range)	69 (46–86)	70.5 (52–88)	0.302
Gender, n (%)			0.418
Male	7 (87.5%)	39 (67%)	
Female	1 (12.5%)	19 (33%)	
Asbestos exposure, n (%)			0.111
Yes	1 (12.5%)	28 (48.3%)	
Probable	2 (25%)	13 (22.4%)	
No	5 (62.5%)	17 (29.3%)	
Personal history of cancer, n (%)			0.305
Yes	2 (25%)	7 (12%)	
No	6 (75%)	50 (88%)	
Family history of cancer, n (%)			0.417
Yes	7 (87.5%)	37 (67%)	
No	1 (12.5%)	18 (33%)	
Mesothelioma location, n (%)			0.151
Pleural	6 (75%)	54 (93%)	
Peritoneal	2 (25%)	4 (7%)	
Histological subtype, n (%)			0.702
Epithelioid	7 (87.5%)	50 (86%)	
Non-epithelioid	1 (12.5%)	8 (14%)	

Conclusions: In this series, 12.1% of patients with malignant mesothelioma harbored GPV/GLPV and 7.5% were candidates to be referred to Genetic Counselling. Germline molecular testing should be considered in patients diagnosed with MM.

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137P
Repurposing drug screen of patient-derived malignant pleural mesothelioma cells reveals potential anti-cancer activity

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Background: Malignant pleural mesothelioma (MPM) has a very poor prognosis: 50% of the patients die within 12 months after starting first-line treatment and no improvement of survival has been reached with second-line treatment. To date, data available on drug screening for mesothelioma is very limited and was only performed using established cell lines. We previously showed that these cell lines have a highly different transcriptomic profile when compared to fresh tumors while patient-derived cell lines most closely resemble the profile of the corresponding cancers.
Methods: Patient-derived cell lines were generated from digested fresh tumor specimens and characterised by RNA sequencing, whole exome sequencing and histological analysis. A cell viability assay was established for four patient-derived cell lines and a healthy control. A drug screen using a set of 6'500 chemical compounds including Food

and Drug Administration (FDA)-approved drugs and candidates in clinical development was performed. Approximately 1000 molecules were considered as hits during the primary screen and dose response curves were performed using 120 selected hits based on viability inhibition potential, previous data on inactivity in mesothelioma and approval status of drugs. A final selection of promising drugs was made after this screen for testing on additional cell lines to understand their mode of action.

Results: Calculating dose response curves revealed 11 promising drugs to be repurposed in mesothelioma including anthelmintics, antibiotics, statins, CDC-, HDAC- and NF-kB inhibitors with IC50 s being significantly lower in malignant cell lines compared to healthy cells. To validate the viability inhibiting potential of these drugs, 21 additional MPM cell lines were screened and revealed Regorafenib, Rigosertinib and NSC663284 as most potent candidates for further inVitro and inVivo analysis.

Conclusions: Here, we could demonstrate that a high-throughput drug repurposing screen can be an effective tool to find new treatment candidates for MPM. Currently, further validation of the three promising drug candidates is ongoing and will reveal the full potential of repurposing drugs in mesothelioma.

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138P

Cost-effectiveness of nivolumab and ipilimumab versus chemotherapy (with and without bevacizumab) in patients with unresectable malignant pleural mesothelioma in Switzerland

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Background: Malignant pleural mesotheliomas (MPMs) are aggressive and often unresectable. In the past, chemotherapy was the standard for palliation. Recently, immunotherapy with nivolumab and ipilimumab (nivo+ipi) was approved. This study evaluated the cost-effectiveness of nivo+ipi versus chemotherapy (with and without bevacizumab) for Swiss patients with unresectable MPM, overall and by histological subtype.

Methods: We developed a three-state Markov cohort model with a cycle length of one month, a 30-year time horizon, and a discount rate of 3% for costs and benefits. The model included the updated survival and treatment-dependent utility results from the Checkmate-743 and MAPS registration trials. A Swiss statutory health insurance perspective was considered with unit costs for 2022 from both publicly available and real-world sources. We assumed a willingness-to-pay (WTP) threshold of CHF100'000. Model robustness was explored in sensitivity analyses.

Results: Compared with chemotherapy, nivo+ipi incurred additional costs of CHF104'100 and 0.48 additional quality-adjusted life years (QALYs), yielding an incremental cost-effectiveness ratio (ICER) of CHF217'288/QALY gained. Chemotherapy+bevacizumab was a dominated strategy. Preference of cisplatin over carboplatin led to an ICER of CHF175'057. For the non-epithelioid subtype, the ICER decreased to CHF124'612. Nivo+ipi may be cost-effective if priced at 43% for all histologies and at 79% for non-epithelioid MPM of their 2022 list price.

Conclusions: Substantial discounts for nivo+ipi would be necessary to achieve cost-effectiveness at the Swiss list prices. Accepting a higher WTP threshold, cost-effectiveness would be more likely for non-epithelioid MPM than for all histologies. Chemotherapy+bevacizumab is unlikely to be a cost-effective alternative. [Grant support: SUVA, Lucerne, Switzerland].

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139P

Gemcitabine as maintenance treatment of malignant pleural mesothelioma (GEMO): Randomized phase II study

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Background: Patients with malignant pleural mesothelioma have a median overall survival of approximately 1 year, and the feasibility of maintenance treatment is debatable in this setting. Unresectable malignant pleural mesothelioma has limited therapeutic options, with controversial data being present on the role of gemcitabine maintenance. We assessed the efficacy of gemcitabine maintenance versus best supportive care in patients with unresectable disease.

Methods: This open-label, randomized phase II study included patients with histologically confirmed unresectable pleural mesothelioma who responded to 4–6 cycles of first-line chemotherapy (platinum+gemcitabine or platinum+pemetrexed). Group 1 received gemcitabine 1000 mg/m^2 IV in Days 1, 8 of a 21-day-long cycle until disease progression or unacceptable toxicity, and group 2 received best supportive care. Progression-free survival (PFS) at 6 months and overall survival (OS) at 18 months were evaluated using SPSS Statistics, version 22.0.

Results: A total of 64 patients were included (32 in each group). There was no difference in response rate to first-line chemotherapy between the groups ($p = 0.209$). PFS was better in group 1 than in group 2 (median 6.2 (95% CI, 4.7–7.6) vs 2.8 (1.8–3.9), $p < 0.001$). Among the clinical variables, only ECOG PS I status was associated with longer PFS (5.5 (95% CI, 4.6–6.4) vs 3.1 (2.4–3.7) for PS II, $p < 0.001$). OS did not differ significantly between the groups (23.3 (95% CI, 15.7–30.8) vs 13.4 (9.5–17.3, $p = 0.155$)). Patients who had a baseline prognostic nutritional index of >35 ($p = 0.010$), baseline PS I ($p = 0.002$), epithelioid vs non-epithelioid histology ($p = 0.001$), received pemetrexed in the first-line ($p = 0.040$), underwent not less than 6 cycles of chemotherapy ($p = 0.006$), received second-line treatment ($p = 0.025$) demonstrated better OS.

Conclusions: Maintenance treatment with gemcitabine after first-line chemotherapy prolongs progression-free, but not overall survival in patients with malignant pleural mesothelioma.

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METASTASES TO AND FROM THE LUNG

140P
Stereotactic radiotherapy improves disease control in oligoprogressive patients included in early clinical trials, with focus on NSCLC

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Background: Patients included in phase I trials are often heavily pre-treated and display strong treatment expectations. In some cases, oligoprogressive disease may occur but with pursued clinical benefit. In such scenarios, local ablative stereotactic radiotherapy (SRT) could allow disease control with prolonged use of current systemic treatment.
Methods: We retrospectively analysed data from patients included in early clinical trials who received SRT for oligo-acquired resistance (≤3 lesions of disease progression; OAR) between 01/2014 and 12/2021. OS, PFS1 (trial entry to OAR), PFS2 (SRT to subsequent relapse), time to next treatment (TTNT) were assessed. Subsequent patterns of relapse were distinguished as OAR2 or systemic AR (SAR).
Results: 39 patients with 48 oligoprogressive lesions were included. Most frequent primary tumor histology was NSCLC (33%). Median age was 59 years, median baseline RMH score was 1 and 93% patients had an ECOG-PS<1. Early clinical trials mostly included ICI (64%) and molecular targeted therapies (MTT) (46%). SRT was mainly delivered to brain (38%) and lymph nodes (26%) at a median dose of 30 Gy. Median follow-up was 19 months. Median OS, PFS1, PFS2, and TTNT were respectively 16, 11, 7 and 9 months, while in NSCLC subgroup analysis they were respectively 14, 6, 3 and 5 months. PFS2 included 44% OAR2 and 56% SAR. No SRT-related grade 3–5 toxicity was observed. Increased OS was associated with primary tumor local control, higher baseline lymphocytes count, lower baseline RMH score, lower post-SRT tumor burden and absence of SAR. Increased TTNT was associated with primary tumor local control, absence of baseline polymetastatic disease, lower baseline RMH score, OAR2, OAR2-local treatment, and both lower baseline/post-SRT tumor burden. OAR2 was more often observed in MTT trials and SAR was associated with absence of primary tumor local control, short PFS1 and higher baseline tumor burden.
Conclusions: In pre-treated patients with NSCLC included in phase I trials, OAR managed with SRT led to durable benefit and prolonged continuation of investigational treatments. Predictive factors could be used for patient selection by distinguishing subsequent OAR2 from SAR.
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Disclosure: All authors have declared no conflicts of interest.

141P
Unveiling the likely pharmacological mechanisms of brigatinib on brain metastasis in ALK+ patients with non-small cell lung cancer: A systems biology and artificial intelligence-based approach

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Background: Brain metastasis occurs in 10% of patients with non-small cell lung cancer (NSCLC) and it is more frequent in ALK+ NSCLC, with a frequency of around 20–30% at the time of diagnosis [doi 10.18632/oncotarget.26073]. In a multinational, phase III study (ALTA-1L), brigatinib significantly improved progression-free survival, the confirmed objective response rate (ORR) and the confirmed intracranial ORR compared with crizotinib in ALK+ NSCLC patients. Interestingly, in silico studies unveiled the potential of brigatinib in modulating proteins associated with metastasis [doi 10.18632/oncotarget.27875], however the molecular mechanisms still need to be elucidated. The aim of the present study was the creation of in silico systems biology and artificial intelligence-based models to unveil brigatinib's effects on metastatic processes both in the primary tumor (PT) and established brain metastases (BM) of ALK+ NSCLC.
Methods: We used Therapeutic Performance Mapping System technology, based on bibliographical molecular characterization of PT with metastatic capability and BM in NSCLC cohorts, and machine learning for mathematically modelling of the pharmacological mechanisms of brigatinib in the PT and already established BM. Models were constrained with publicly available gene expression data (GSE31210 and GSE128309).
Results: The results suggest that brigatinib has the potential to successfully modulate a wide array of metastasis-involved proteins both in the PM and in BM, acting mainly through IGFR1, EGFR, FLT3, ALK and ROS1. Brigatinib modulation of the effectors of PT with metastatic capability seems to be derived from a downregulation of STAT5 and 3, CXCR4, ETS1, AKT3, CTNB1, ERBB2 and MAPK and an activation of CADH1, whereas its action on the effectors of BM seems to be derived from a downregulation of YAP1, FGFR1, ABL1, CTNB1, NFKB1 and PI3 K/AKT/mTOR pathway.
Conclusions: In silico models have revealed the potential of brigatinib to successfully modulate a wide array of metastasis-involved proteins both in the PT and in the BM. Further clinical studies are needed to validate these potential results before translation into clinical practice.
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142P

Patients with ECOG status 2 should not receive whole brain radiotherapy (WBRT): A prospective cohort study of 294 non-small cell lung cancer (NSCLC) patients with brain metastases (BM)

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Background: For NSCLC patients with BM were RT is considered, both WBRT and stereotactic RT (SRT) are established options. As the evidence for potential benefits of RT in patients with BM and poor performance status is meager, the risk for overtreatment is high. The aim of our study was to analyze overall survival (OS) after radiotherapy for patients with first-time BM in relation to ECOG performance status.

Methods: In a prospective cohort study, 294 consecutive NSCLC patients (pts) with newly diagnosed BM with RT as initial treatment, were included from November 2017 to March 2021. Clinical and treatment related data were collected every 3 months for up to 2 years. Median OS (mOS) was calculated from start of RT to death or last follow up (October 2022).

Results: At time of analysis, 42 pts (22%) were still alive. Median OS was 4.0 months (mo), 2.0 mo after WBRT (n = 141); 7.0 mo after SRT (n = 153). After WBRT, pts with ECOG 2 and pts with ECOG 3-4 had equal mOS (1.0 mo). After SRT, mOS was 4.0 mo and 1.0 mo for ECOG 2 and ECOG 3-4, respectively. In multivariate analysis age ≥70, WBRT and ECOG ≥2 were associated with short survival.

Table: 142P

	ECOG status			
	ECOG 0-1	ECOG 2	ECOG 3-4	Unknown
WBRT N 141 (%)	62 (44)	46 (33)	29 (20)	4 (3)
mOS WBRT months	4.0 (2.1–5.9)	1.0 (0.5–1.5)	1.0 (0.4–1.6)	
SRT N 153 (%)	96 (63)	39 (25)	18 (12)	
mOS SRT months	11.0 (6.6–15.3)	4.0 (2.0–6.0)	1.0 (0.0–2.4)	

Conclusions: After WBRT, pts with ECOG 2 has equally poor mOS (1.0 month) as patients with ECOG 3-4.

Consequently, we suggest that WBRT should not be given to patients with ECOG 2 or worse. Although other clinical factors (i.e. targeted treatment options) and the patient's opinion must be included in treatment decision, most of these patients seem to be at risk of experiencing only the side effects of WBRT with little or no benefit on symptoms or survival. Instead, they should rather be considered for best supportive care alone to improve quality of life at the end of life.

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Disclosure: All authors have declared no conflicts of interest.

PREVENTION, EARLY DETECTION, EPIDEMIOLOGY, TOBACCO CONTROL

143MO

Risk of lung cancer among current smokers by pack-year smoking: A cohort study with 23 years of follow-up

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Background: We have recently demonstrated that current heavy smokers with >20 pack-year (PY) smoking history (median, 48.8, IQR, 31.6–57.0 PY) and non-heavy smokers (<20 PY; median, 11.4; IQR, 7.3–14.4 PY) have about 40- and 10-times higher risk of lung cancer, respectively (JAMA-Oncol. 2022; 8:1428–1437). In the current study, we examined the magnitude of the graded risk increase associated with PY of smoking among current smokers.
Methods: Of the 2505 community-dwelling older current smokers (mean age, 73 ± 5.7 years, 69% women, 17% African American) in the Cardiovascular Health Study (CHS), 1973 were never-smokers. The 532 current smokers were categorized based on PY smoking into: <20 (n = 95), 20–39 (n = 157), 40–59 (n = 181) and ≥60 (n = 94). Cause-specific HR (95% CI) for incident lung during 23 years of follow-up were estimated for the 4 groups (reference: never-smokers) based on Cox regression model, adjusting age, sex, race and competing risk of death.
Results: Incident lung cancer occurred in 0.5% of never smokers, and 5.0%, 14.6%, 17.7% and 16.0% of those with <20, 20–39, 40–59, and ≥60 PY smoking history, respectively. Compared with never smokers, cause-specific HRs (95% CIs) for incident lung cancer in the 4 groups with <20, 20–39, 40–59, and ≥60 PY smoking history were 9.73 (3.27–28.99), 30.33 (14.25–64.53), 42.97 (20.76–88.94), and 46.02 (20.08–105.48), respectively.
Conclusions: The risk of lung cancer among current smokers with <20 PY smoking for whom low-dose computed tomography screening is not recommended is high, but the risk was 3 and 4 times higher in those 20–39 and 40–59 PY, but plateaued for those with ≥60 PY. This study underscores the importance of smoking abstinence and early cessation.
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144P

Exposure-lag response of surface net solar radiation on lung cancer incidence: A worldwide interdisciplinary and time-series study

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Background: Recently, solar radiation (RAD) has attracted increasing attention in the effects on diseases globally. This study is the first global interdisciplinary study investigating the lag exposure-response between RAD measured by satellite and lung cancer.
Methods: The data of RAD was obtained from Google Earth Engine, which was post-processed by European Centre for Medium-Range Weather Forecasts (ECMWF). The data of lung cancer incidence, smoking prevalence and socio-demographic index (SDI) were collected from Global Burden of Disease (GBD) project. The Spearman's rank correlation tests and linear regression were conducted to explore the correlation between RAD and lung cancer incidence. A distributed lag non-linear model (DLNM) was applied to reveal the lag effects of RAD on lung cancer incidence.
Results: 186 countries from 1992 to 2019 were included in this study. Lung cancer incidence ranging from 4.735 to 104.156 cases per 100,000, while RAD exposure ranging from 1291606.49 to 18440775.92 Joule per square meter monthly. After adjusted for smoking and SDI, the Spearman's correlation coefficient ranged between −0.630 and −0.581. In the DLNM for lung cancer adjusted for smoking and SDI, the maximum RR was 1.013 [95% CI (confidence interval): 1.011–1.014], occurring at RAD exposure of 12760000 with 5.8 lag years, while the minimum RR (relative risk) was 0.973 [95% CI: 0.947–0.992] occurring at RAD exposure of 12845000 with 8.0 lag years.
Conclusions: Low exposure to RAD turned out to be significant for the increment of lung cancer incidence in global population. And the protective effects of sunlight on lung cancer had a hysteresis. This study provides a potential approach to the prevention of lung cancer and is significant in epidemiological studies because it provides a new pattern to investigate more potential risk factors for diseases.
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146P

The changing landscape of stage-at-presentation in lung cancer in the United States: Long-term data from SEER database

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Background: Lung cancer is a global problem with an increasing incidence worldwide. Efforts have been made to adopt screening programs that can lead to earlier diagnosis. However, little is known about the resulting changes in disease distribution.
Methods: Small and non-small cell lung cancer cases between 2004 and 2019 were extracted using the SEER database [17 reg; Nov 2021 sub]. We excluded patients with unknown/unreported stages in stage trend analysis. We further performed an exploratory analysis using the year 2013, when the American Cancer Society issued its first recommendation for lung cancer CT screening with patients, to explore potential associations between screening and change in stage at presentation.
Results: We analyzed data from 660 532 lung cancer patients (non-small cell lung cancer [86.8%, n = 573 139]; small cell lung cancer

[13.2%, n = 87 393]). Most cases were presented with the distant disease at initial presentation (54.9%, n = 362 733). Longitudinal tracking of the distribution of cases among different disease stages showed an increase in the proportion of patients diagnosed with the localized disease compared to patients diagnosed with a regional disease or those with distant spread with an increased median overall survival over time (table). Compared to patients diagnosed before 2013, patients diagnosed after 2013 had a statistically significant higher likelihood of presenting with a localized disease stage (24.1% vs. 19.2%, p = 0.001) and longer median overall survival (14 months vs. 10 months, p = 0.001).

Conclusions: There is an increase in the proportion of lung cancer cases presenting with localized disease stages with improved overall survival. This can probably be partially attributed to efforts made to implement wide screening programs.

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147P

Changes in demographic and smoking history trends in patients referred to a London thoracic malignancy specialist centre between 2010–2021: The Guy's Cancer Centre experience

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Background: In the UK it is estimated that 10–15% of lung cancer cases occur in never-smokers. This study demonstrates the changes of the demographic characteristics, including the smoking status, of all the patients referred to the thoracic malignancy unit at Guy's Cancer Centre, South East London, between 2010 and 2021.

Methods: We included patients with a documented ICD10 diagnosis of bronchus and lung malignancy who were referred to Guy's thoracic malignancy unit from 2010 until 2021. A total of 6861 patients with a diagnosis of lung cancer were identified. We collected baseline demographic and clinical characteristics, including smoking status and socio-economic status for all the patients. Descriptive statistics were utilised to highlight the dynamic changes over the years of the referred patients.

Results: The number of referrals per year remained overall stable from 2010 until 2019, with a decrease in the number of referrals in 2020 and 2021, most likely due to the COVID-19 pandemic. We observed a gradual increase in the percentage of never smokers among the lung cancer patients: 5%, 8%, 10% and 13% of the referred patients were never smokers in the years 2010, 2015, 2018 and 2021 respectively. Median age remained stable across the years (range 68–71 years). Male percentage was 56%, 55%, 53% and 53% in 2010, 2015, 2018 and 2021 respectively. From the patients that we had a documented ethnic background the proportion of White/Black/Asian/Other or Mixed ethnicity remained stable across the years with a median 87%, 7%, 3%, and 3% respectively. The most common histological diagnosis was adenocarcinoma, followed by squamous cell carcinoma and small cell lung carcinoma.

Conclusions: The proportion of never-smoking to smoking related lung cancer has gradually increased between 2010 and 2021. There was little variability in age, sex and ethnic background. Never-smoking lung cancer is a distinct biological entity, therefore, further research should focus on the understanding of the aetiology and the risk factors leading to the development of lung cancer, in the absence of a history of tobacco exposure.

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148P

Education level of lung cancer patients and matched controls in Denmark: Development over time in a nationwide study 1994–2018

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Background: Inequality in lung cancer is a major problem. An inverse relationship between risk of lung cancer and education level has previously been shown in cohort and small registry-based studies. This nationwide epidemiological study covering 1994–2018 evaluates education level in lung cancer patients and matched controls.

Methods: Using the nationwide Danish Cancer Registry and Danish Statistics Education Registry, all lung cancer patients in Denmark in the period 1994–2018 were identified. The patients were divided into a period I cohort (1994–2007) and a period II cohort (2008–2018). Lung cancer patients were matched with controls at a 1:4 ratio by age, gender, marital status, and municipality at time of diagnosis. A multinomial logistic regression was performed to assess odds ratio of lung cancer.

Results: Education levels were divided into primary school, secondary school, vocational school, and college. Lung cancer patients were more likely to be primary school graduates compared to matched controls, and this tendency increased from period I to period II (47.3% vs. 41.1% in 1994–2007; 46.2% vs. 38.0% in 2008–2018; $p < 0.01$). Contrary, control subjects were more likely to have a college degree compared to lung cancer patients (8.7% vs. 13.7% in 1994–2007; 13.2% vs. 21.0% in 2008–2018; $p < 0.01$). When comparing lung cancer patients and matched controls, there was no difference regarding secondary school and vocational school. The education levels: Secondary school, vocational school, and college were all significantly less associated

Table: 146P Distribution and overall survival of lung cancer cases among different disease stages

	Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Stages	Localized	18%	18.2%	18.5%	19.4%	19.6%	20.1%	19.2%	19.9%	19.8%	20.4%	20.9%	21.9%	24.4%	25.9%	27.8%	27.2%
	Regional	25.4%	24.8%	24.4%	24.3%	24.2%	23.5%	24.3%	24.6%	23.9%	23.8%	23.4%	23.5%	23.7%	23.1%	21%	22%
	Distant	56.7%	57%	57.1%	56.4%	56.2%	56.3%	56.6%	55.6%	56.3%	55.8%	55.7%	54.5%	51.9%	51%	51.2%	50.8%
Overall survival																	
(Months)	Localized	47	48	53	51	52	51	57	54	59	60	62	*	*	*	*	*
	Regional	17	17	18	19	20	20	21	22	21	22	24	25	24	25	*	*
	Distant	5	5	5	5	5	5	5	5	5	5	6	6	5	6	6	7
	All stages (combined)	9	9	10	10	10	10	11	11	11	11	12	13	14	15	17	*

*Not Reached.

with lung cancer compared to primary school; odds ratio 0.59 (95% CI: 0.54–0.63); 0.82 (0.80–0.84) and 0.52 (0.50–0.53), respectively.
Conclusions: In a nationwide study covering 1994–2018, lung cancer patients were more likely to have primary school as education level and less likely to have a college degree. Study subjects with education levels: Secondary school, vocational school, and college were all less likely to have lung cancer compared with primary school. Special attention regarding prevention and early detection of lung cancer should be aimed at people with primary school as education level. Information from this study could be of great importance in a lung cancer screening setting.
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149P
Gender differences in non-small cell lung cancer: A comparative analysis of European and Asian patients

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Background: Lung cancer is the leading cause of cancer-related deaths in both males and females. The demographic landscape has shifted dramatically in recent decades. The increasing interest in personalized medicine and the recognition of sex as a major influencing factor in disease behavior, has resulted in a greater emphasis on understanding gender differences. This study aims to analyze the different aspects of gender in lung cancer care in Europe and Asia.
Methods: This study was conducted using a web-based physician questionnaire. In Q1 2022, IQVIA engaged 2583 investigators from Europe and Asia. Gender, age, clinical stage, oncogenic driver status, location of metastases, ECOG, and comorbidities were analyzed.
Results: A total of 18 217 cases were analyzed; 7006 (38.5%) were females (F) and 11 211 (61.5%) males (M). The prevalence of NSCLC in females was slightly higher in Asia (40%) compared to Europe (38.5%). Females were younger and had more adenocarcinoma cases than males on both continents. The percentage of non-smokers was substantially higher in Asian females (87%) compared to males (20%) and the European population (F: 40%, M: 15%). Asia had more asymptomatic (ECOG 0) patients than Europe, possibly because most Asian patients had fewer pulmonary comorbidities. Most patients had metastatic disease at diagnosis. However, in Asia there was a higher proportion of localized disease (34.4%) compared to Europe (19.1%) regardless the sex; and early-stage disease was more frequent in males than in females in both regions. The frequency of brain metastases in Asian females was significantly higher (20%) than in Asian males (14%) and the European population (F: 16%, M: 10%). EGFR mutation was the most common oncogenic driver in both genders, but its prevalence was higher in Asian females. We found that the deletion in exon 19 was the most prevalent across both continents and genders. However, we also report a high occurrence of L858R mutation among Asian subjects (F: 38.9%, M: 41.8%).
Conclusions: This research highlights the differences in cancer staging between Asian and European patients and the importance of gender-based differences suggesting that lung cancer may be increasingly considered a distinct disease in females.
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Disclosure: All authors have declared no conflicts of interest.

150P
Sex differences in inoperable lung cancer risk and prognosis: Evidence from low-income population setting

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Background: Recent decades have seen a dramatic shift in the demographics of lung cancer. Despite a decrease in overall lung cancer incidence relative to men, women now appear at greater risk of developing the disease, suggesting distinct risk profiles and disease processes between men and women. The study aimed to explore the sex-based differences in lung cancer risk and prognosis in low-resource settings.
Methods: We included 1868 (1580 men, 288 women) newly diagnosed and histologically confirmed primary lung cancer patients admitted to the National Institute of Cancer Research and Hospital (NICRH), Bangladesh in 2018 and 2019. Patients were follow-up until June 30, 2020, or the event of death, whichever came first. Sex differences in risk factor profile and survival were assessed using Cox proportional hazard models.
Results: On average, women (55.3 ± 12.9) were younger than men (60.4 ± 10.3), More men were smokers (P = 0.001), more women used smokeless tobacco (P = 0.35), and at diagnosis had more comorbidities ($p < 0.001$). Adenocarcinoma (46.3%) was the predominant histological type in women, and squamous cell carcinoma (43.2%) was in men. In Men age ≥60 years, <18.5 Kg/m^2, with No-formal schooling and having comorbidity, and in women, Tobacco use appeared as a predictor of poor survival. Irrespective of performance status and treatment—women with adenocarcinoma [HR-0.64 (95% CI; 0.44–0.91)] tend to survive longer than men. The trend is reversed in squamous cell carcinoma [HR-1.31 (95%CI; 1.04–1.63)]. Women who received no treatment (HR; 0.65, 95%CI; 0.44–0.96) or received CT only (HR; 0.54, 95%CI; 0.34–0.85) were less likely to die in comparison to their men counterparts, after adjusting for age, education, smoking habit, performance status, and comorbidity.
Conclusions: Women lung cancer patients are a distinct subgroup and have differences from their male counterparts in terms of risk factors, histological types, and prognosis. The risk factors, histopathology, and prognosis associated with inoperable lung cancer differ based on the gender and further research is needed in this area.
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151P

Molecular epidemiology and real-world outcomes of genomically-matched non-squamous non-small cell lung cancer (nsNSCLC) patients in a diverse Brazilian population

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Background: The prevalence of actionable drivers in nsNSCLC may vary according to ancestry and performance of the next-generation sequencing (NGS) assay. In Brazil, comprehensive genomic profiling of nsNSCLC is sponsored by pharma support programs with tests performed in-house (Oncoclínicas Precision Medicine – OCPM) or abroad. We aimed to assess prevalence of actionable drivers in a real-world clinico-genomics cohort with linked survival outcomes under genomically-matched therapies.
Methods: All patients prospectively recruited in the OCPM Lung Mapping consortium from January 2020 to December 2022 were assessed for driver prevalence. Archived formalin-fixed paraffin-embedded (FFPE) tumor material underwent sequencing with GS180 panel (Archer Dx DNA/RNA assay). We calculated median overall survival (mOS) of nsNSCLC patients that received targeted therapies at Oncoclínicas during the same period with Kaplan-Meier method (from diagnosis date of metastatic disease until the last follow-up or death).
Results: In total, 592 patients had informative GS180 results for driver mutations and/or fusions, with 313 cases (52.9%) harboring actionable alterations: EGFR mutations in 25.5% (exon 20 insertion in 3.5%), KRAS G12C in 7.9%, MET exon 14 skip in 5.4%, ALK fusion in 5.2%, ERBB2 mutations in 3.2%, ROS1 fusion in 2%, BRAF V600E in 1.5%. RET/NTRK1-3/NRG1 fusions in <1%. We identified 373 patients with exposure to genomically matched targeted agents at Oncoclínicas when considering all metastatic nsNSCLC population, irrespective of the laboratory used for molecular diagnosis. With median follow-up of 13 months, 62% received targeted therapy in first-line, and mOS was 30.6 months (95% CI, 26–43).
Conclusions: Molecular epidemiology of nsNSCLC in Brazilian patients is unique when compared to published literature in European and North American cohorts, with numerically higher prevalence of EGFR mutations, MET exon 14 skip and ALK fusions. These results may be in part explained by fusion sensitivity with RNA sequencing. Survival outcomes for those treated with targeted agents are promising, but a large proportion of the patients still receive non-matched therapies in the first-line.
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152P

Role of occupation in patients with non-small cell lung cancer (NSCLC) in Spain: Data from the SCAN study

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Background: Cancer is the primary cause of work-related death in Europe (52%). Lung cancer (LC) is one of the most common tumors linked to occupational exposure, although the real prevalence and its clinical profile remains unknown. We aim to study the occupations and patient's profile in a real-world data cohort of NSCLC.
Methods: Prospective study of patients (pts) with all-stages NSCLC treated at Hospital Clinic (Spain) between 2020-present. A personal interview was performed to collect demographic, smoking habit, environmental, cancer history and occupation data. Clinical data was collected from medical reports. Up to 4 jobs were collected for each patient, according to the Spanish National Classification (CNO11), including duration/workplace and occupational exposure.
Results: In the first 168 pts enrolled, median age was 67 years (yrs), 60% male, 87% smokers; 62% had stage IV with mainly adenocarcinoma histology (70%); 60% with a driver alteration. Two out of 3 had high education level; 50% were retired at diagnosis. In our area (city center) the main occupations were: commerce [15%] (60% males; 96% smokers), public services [11%] (44% males; 28% smokers) and mechanical engineering [11%] (83% males; all smokers). Diagnosis before 65 yrs was observed in 75% of construction (6) and 100% of agriculture workers (2) vs. 14% in the tourism sector or none in housekeepers. Occupations related to potential carcinogens exposure were exclusively seen in males (construction, industries), with high smoking rates (75–100%). In contrast, health workers were mainly females (71%) and all housekeepers were females, with lower smoking rates (33%-88%). Regardless of the occupation, adenocarcinoma was the predominant histology; with higher ratio of squamous seen in textile, mechanical, metal/chemical sectors (20–37%).
Conclusions: In our preliminary data, differences on occupational profile were identified in NSCLC. Male smokers were observed in occupations with potential exposure to carcinogens. Deeper characterization of occupation and its clinical impact could improve the work-related LC prevention.
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153P

Molecular epidemiology of EGFR mutations in NSCLC: A single-center experience from India

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Background: EGFR (Epidermal growth factor receptor) is a key driver mutation frequently isolated in lung cancers and anti-EGFR TKIs (tyrosine kinase inhibitors) have demonstrated significant improvements in patient outcomes in comparison to conventional chemotherapy. This study assessed the prevalence and clinical outcomes of EGFR mutations among Indian NSCLC cohort.
Methods: Retrospective analysis of 2548 NSCLC patients who underwent EGFR mutational analysis from 2013 to 2021 using amplified refractory mutation system (ARMS)/Scorpion® real time polymerase chain reaction. Clinical data for 141 patients was obtained and significance assessed using Kaplan-Meier and chi-square method.
Results: EGFR sensitizing mutations were detected in 40.4% (1029/2548) cases with compound mutations detected in 7.8% (81/1029) cases. EGFR mutations were detected at a higher prevalence in females ($p = 0.002$) and never-smokers ($p < 0.001$) in the cohort. Uncommon EGFR mutations demonstrated a locoregional variation with Exon 18 G719X (7.2%) been the most frequently isolated in comparison to TKI resistant exon 20 T790M (3.98%) in other NSCLC cohorts. Exon 20 Insertions (1.8%) which received approval for targeted therapies was observed in 19 cases. EGFR mutation demonstrated a significant relationship with regard to brain metastasis ($p = 0.011$). Patient follow-up and treatment response (mutational load) was monitored using ctDNA (liquid biopsy) on ddPCR platform. EGFR mutated individuals had significantly longer median overall survival compared to EGFR wild type (26 months vs 12 months, p −0.044).
Conclusions: The study provides significant insights into the molecular epidemiology of EGFR TKD mutational spectrum from India, reiterating its role as a key predictive marker in NSCLC. Mutational analysis of EGFR is a pre-requisite test employed to identify subcategories of patients who would benefit from the therapy in addition to identification of EGFR resistance in patients already on TKI therapy.
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154P
Why is the screening rate in lung cancer still low? A 7-country analysis on the factors impacting adoption

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Background: Strong evidence of lung cancer screening's effectiveness in mortality reduction, for example as demonstrated in the National Lung Screening Trial (NLST) in the US and the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) has prompted countries to implement formal lung cancer screening programs. However, participation level remains largely low. This study aims to understand how lung cancer screening programs are currently performing. It also identifies the barriers and enablers contributing to adoption of lung cancer screening across seven case study countries which may be relevant for the recently adopted Council Recommendations on Cancer Screening in the EU.
Methods: A literature review about lung cancer screening programs in Canada, China, Croatia, Japan, Poland, South Korea and the United States was conducted covering academic articles, governmental official reports, non-governmental organization (NGO) reports and media reports. Findings were distilled into key themes which impact adoption. The research was validated with local experts, representing payer, policy advisor, patient, and the private sector perspectives.
Results: Adoption rates of formal lung cancer screening programs (the percentage of the target population screened) vary significantly from 4% to 53% across studied countries. The analysis finds five main factors impacting adoption: (1) political prioritization of lung cancer (2) financial incentives/cost sharing and hidden ancillary costs (3) infrastructure to support provision of screening services (4) awareness around lung cancer screening and risk factors and (5) cultural views and stigma around lung cancer. Although common across most countries, the weighting of each factor on driving or hindering adoption varies by country.
Conclusions: The variation in adoption of lung cancer screening requires heightened focus. The five areas set out by this research need to be factored into policy making to maximize effectiveness of lung cancer screening programs, such as country implementation of the Council Recommendation on Cancer Screening in Europe.
Legal entity responsible for the study: Merck & Co., Inc.
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Disclosure: All authors have declared no conflicts of interest.

155P
Eligibility for lung cancer screening among patients diagnosed with lung cancer in Greece

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Background: Implementation of lung cancer screening with annual low-dose computed tomography (CT) scans has resulted in significant improvement in disease-specific and overall survival in large prospective studies. Little is known about the proportion of patients with lung cancer that would be eligible for participation in screening programs in the real world.
Methods: We performed a retrospective chart review of patients with lung cancer diagnosed at Sotiria General Hospital for Chest Diseases, Athens, Greece, between January 2016 and December 2018. Descriptive statistics were utilized to calculate the proportion of patients that would be eligible for lung cancer screening and chi-squared test to assess for associations between baseline patient characteristics and lung cancer screening criteria. All hypothesis testing was conducted at a two-sided significance level of $\alpha = 0.05$.
Results: 898 patients were screened; 750 patients were eligible for study inclusion. The median age at diagnosis was 67 years (range 34–93). Among study participants, 73.2%, 21.5%, and 5.3% were current, former, and never smokers, respectively. Histotypes were distributed as follows: adenocarcinoma, 42.7%; squamous cell carcinoma, 30.8%; small cell lung cancer, 14.7%; large cell neuroendocrine carcinoma, 3.6%; not otherwise specified, 4.1%; other, 4.0%%. Targetable driver alterations were identified in 16.9% of patients (39/231). The proportion of patients eligible for lung cancer screening at the time of diagnosis ranged according to screening criteria applied (NLST: 60.3%, USPSTF: 78.7%, NELSON: 64.4%). Baseline characteristics associated with qualification for screening according to the NLST criteria were squamous (OR, 2.23; 95% CI, 1.57–3.19; $p < 0.00001$) and small cell (OR, 2.10; 95% CI, 1.34–3.34; $p = 0.001$) histology and lack of targetable driver alterations (OR, 3.39; 95% CI, 1.49–8.54; $p = 0.003$).
Conclusions: Most patients with lung cancer qualify for screening at the time of diagnosis; baseline characteristics directly linked with smoking appear significantly associated with screening eligibility. This underlines the need for more personalized screening approaches in the absence of substantial smoking history.
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Disclosure: All authors have declared no conflicts of interest.

156P

Development of a predictive model for early detection of lung cancer: SREAL-eLUNG study

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Background: Lung Cancer (LC) diagnosis is highly complex due to non-specific initial symptoms and lack of routine screening. Machine Learning (ML) based cancer risk-assessment tools can ease earlier diagnosis by enhancing referrals for cancer investigations. We present an age and sex matched case-control study aimed at the development of a ML predictive model to identify individuals at high risk of LC, estimating a potential decrease of death risk by 10% per anticipated month.
Methods: Electronic Health Records from a digital cohort of 4332 citizens (722 LC cases & 3610 controls) ≥18 years old having a pathology-confirmed LC and assigned to the Department of Health Valencia La Fe were analysed to identify early risk factors. Initial variable selection was based on structured and semi-structured information, related to laboratory tests, cancer history, use of health-care resources, symptoms and smoking history. The final selection of variables and prediction time was determined by feature selection methods, clinical suitability of predictions and model performance. Four ML classifiers were used (table). The dataset was randomly split into a training (70%) and a test (30%) set. Fivefold cross-validation was used for model selection with the final performance evaluated on the unseen test set.

Table: 156P Performances of ML classifiers on test set

Classifier	AUC	Sensitivity (%)	Specificity (%)
Logistic Regression	0.79	77.9	68.6
Decision Tree	0.77	77.9	68.1
Random Forest	0.80	79.3	68.3
Neural Network	0.79	80	68.3

Results: Using just nine input variables within 60 days prior to diagnosis [ALT, GPT and creatinine levels, platelets, lymphocytes and monocytes counts, smoking status, general malaise, prior emphysema history and number of outpatient visits in the previous year], all techniques displayed similar performances with areas under curves (AUCs).
Conclusions: The developed models could help to identify a greater number of patients for either initiate the diagnostic process or to establish a close monitoring at primary care level with a potential decrease of patients' death risk by around 20%. However, additional clinical validation of models' performance will be imperative to gauge usefulness in a real-world scenario.
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Building a global evidence map of low-dose CT lung cancer screening implementation: Approach and data analysis opportunities

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Background: The Lung Cancer Policy Network, a global multi-stakeholder initiative of experts in lung cancer, has developed a global interactive map of low-dose CT (LDCT) lung cancer screening implementation research. The map aims to visualise the evidence on how LDCT screening is being implemented around the world, including all relevant ongoing and recently completed implementation studies, national/regional organised programmes, and clinical trials.
Methods: A structured search of peer-reviewed and grey literature identified a preliminary list of ongoing LDCT screening programmes and studies completed since 2015. Findings were used to develop a comprehensive research methodology to guide the development of a framework for data extraction of over 70 variables (e.g. inclusion criteria, integration with smoking cessation programmes, quality control protocols). Members of the Network provided ongoing guidance of the development of the map, and a draft of each entry is sent to the lead of each study/programme for validation. The data set will be updated on a biannual basis.
Results: To date, 133 entries have been included. The first edition of the data set was made publicly available online in November 2022. Ongoing research for the second edition will expand the dataset to include organised programmes in the US and studies that ended since 2010. When complete, contents will be visualised as data dashboards with filters to enable analysis of how implementation has been achieved. Interrogation of the map will provide evidence from real-world implementation on how to: model lung cancer risk; embed smoking cessation interventions into the screening pathway; mitigate barriers to participation; or optimise quality assurance. Outcome data (e.g. proportion of participants diagnosed with stage I/II lung cancer) are also collected and can be assessed for how they concord with clinical trial evidence.
Conclusions: This is, to our knowledge, the first global database of LDCT screening implementation. Findings may provide a valuable resource to those implementing LDCT screening programmes, and offer insights to policymakers on how to ensure the feasibility, cost-effectiveness, equity, and quality of screening within their populations.
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Lung cancer detection using smoking status and standard blood test analysis

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Background: Lung cancer (LC) is the leading cause of cancer death due to late-stage diagnosis, which often results in poor prognosis. Therefore, new strategies for the early detection of LC are of outmost importance. Artificial intelligence has shown prominent results in health science during the last decade, using pattern recognition to predict outcomes. Several risk models have been presented to refine LC screening criteria, but most are based on unrepresentative populations or it is challenging to obtain data from different resources. This study presents a risk model based on standard blood sample analysis as well as smoking history from a population at risk.

Methods: All patients examined due to a risk of LC in the Region of Southern Denmark within 2008–2019, were included. Exclusion criteria were patients with missing information on smoking status or results from less than 17 of 20 selected blood sample analysis taken at the time of examination. Several models were tested on a subset of patients with complete results. To obtain a gold standard for comparison, five LC specialists provided their diagnoses on 200 samples.

Results: Among 38,944 patients, data on smoking and blood sample results from at least 17 analyses were available for 9,940 patients. This includes 2505 (25%) LC patients and 7435 (75%) non-LC patients. The best performance was obtained using a light gradient-boosting machine with an accuracy and ROC-AUC of 72% and 80%, respectively. The model performed better than the LC specialists with a sensitivity of 76% compared to 67% for the specialists, at a matched specificity of 70%. The most important predictors of LC were active/former smoking status, high age, and an elevation of neutrophils, LDH and calcium, accordingly.

Conclusions: This study presents a risk-model based on smoking status and regular blood sample analysis, generated on a relevant population at risk. The model demonstrates moderate performance, and outperforms LC specialists presented with the same information. This emphasizes the relevance to consider both clinical and laboratory data in future risk assessment models. A high performing risk model able to provide decision support to the general practitioner would be of great value to the patient, facilitating earlier referral of potential LC-patients.

Legal entity responsible for the study: M.B. Henriksen.

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Optimization and validation of a circulating microRNA biomarker panel for early detection of lung cancer in a Japanese population

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Background: Screening for lung cancer using imaging modalities such as low-dose CT (LDCT) is currently recommended only for high-risk populations. However, the proportion of lung cancer in never-smokers in East Asia, including Japan, is comparatively higher. This study aims to develop and validate a minimally invasive blood test for identifying high-risk individuals who should undergo further diagnostic tests to improve early detection of lung cancer in a Japanese population comprising smokers and never-smokers.

Methods: We conducted a multi-centre case-control study in Japan to prospectively collect plasma samples from a total of 287 lung cancer patients, of which more than 70% had stage I disease, and 327 matched healthy controls. The samples from three centres were divided into two cohorts for optimization and validation of a 12-microRNA (miRNA) plasma biomarker panel developed for early detection of lung cancer. Both cohorts included at least 40% never-smokers. The miRNA quantities were measured using RT-qPCR and performance for detection of lung cancer was assessed using the area under ROC curve (AUC).

Results: The circulating miRNA biomarker panel achieved a maximum AUC of 0.83 for detection of lung cancer in the optimization cohort. The diagnostic performance of the 12-miRNA panel was then further validated in an independent cohort with AUC of 0.76 for detecting all stages of lung cancer. The AUC for detecting stage I lung cancer was 0.75 while AUC for stage II-IV lung cancers was 0.79. Performance was robust across gender and smoking status and was enhanced when the miRNA panel was used in combination with carcinoembryonic antigen (CEA) expression level by ECLIA.

Conclusions: We optimized and validated a circulating miRNA biomarker panel for use as a minimally invasive blood test to aid in the early detection of lung cancer in a Japanese population. This plasma 12-miRNA panel has the potential to complement existing image-based methods currently used for lung cancer screening and diagnosis and improve detection of early stage (stage I) lung cancer, especially when used in combination with biomarkers like CEA. This research was supported by MiRXES.

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Non-invasive analysis of VOCs in exhaled air can distinguish healthy controls from lung cancer patients and may improve the effectiveness of lung cancer screening

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Background: Lung cancer (LC) screening has been shown to be effective to reduce specific mortality in at-risk populations but its performances could be improved by using non-invasive biomarkers such as the analysis of volatile organic compounds (VOCs) in exhaled air from screened subjects. Some limited studies suggest that VOCs could be used to detect LC patients (LCP). Our project aims at determining which VOCs profile could be used to differentiate LCP from healthy controls (HC) in a much larger series of cases.

Methods: We planned to recruit LCP (n = 750) in 7 different thoracic oncology departments, and HC (n = 750) from a preventive health centre. Subjects' exposure was not monitored before VOC collection in order to reproduce real-life conditions. VOCs were collected using the Reciva® mask (Owlstone Medical Ltd.) in sorbents. VOCs were determined using GC-MS analysis. Classification of VOCs was performed using white box auto-ML methods adapted for unbalanced data (Scikit learn + Ripper).

Results: Preliminary analyses on the first 295 LCP and 713 HC found that 2 VOCs rulesets are able to differentiate LCP from HC with 67.8% sensitivity associated with 100% confidence (or for a sensitivity of 84.7%, confidence decreased to 92.6%).

Conclusions: This largest series to date in the literature showed that non-invasive analysis of VOCs in exhaled air could distinguish LCP from HC, and may improve the effectiveness of LC screening. A larger study to validate this new "fingerprint" in a LC screening routine process is planned.

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SCLC

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RESILIENT part 2: A randomized, open-label phase III study of liposomal irinotecan versus topotecan in adults with relapsed small cell lung cancer (SCLC)

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Background: Most patients with SCLC relapse within 1 year of receiving first-line (1L) platinum therapy; second-line treatment options are limited. We report the results of RESILIENT, a randomized, open-label phase III trial of liposomal irinotecan versus topotecan in patients with SCLC that had progressed on or after 1L platinum-based therapy.

Methods: Eligible patients with histologically or cytologically confirmed SCLC and radiologically confirmed disease progression despite 1L platinum-based chemotherapy were randomized (1:1) to receive intravenous liposomal irinotecan (70 mg/m^2, every 2 weeks in a 6-week cycle) or topotecan (1.5 mg/m^2/day for 5 days, every 3 weeks in a 6-week cycle). The primary endpoint of overall survival (OS) was evaluated by log-rank test (stratified by region and platinum sensitivity) with 1-sided significance of 0.023. Secondary endpoints included progression-free survival (PFS) and objective response rate (ORR) per blinded independent central review (BICR).

Results: Overall, 461 patients (median [range] age, 62.0 [28.0–82.0] years; 67.9% men; 74.2% ECOG performance status 1) were randomized to receive liposomal irinotecan (n = 229) or topotecan (n = 232); median follow-up was 18.4 months. Median OS and PFS were 7.9 months and 4.0 months, respectively, with liposomal irinotecan versus 8.3 months and 3.3 months with topotecan. Hazard ratios (HRs) and 95% confidence intervals (CIs) for death, and for disease progression or death, are shown in the table together with ORR and grade >3 treatment-related treatment-emergent adverse events (TEAEs) occurring in >10% of either treatment group.

Table: 1610

	Liposomal irinotecan (n = 229)	Topotecan (n = 232)
OS, median (95% CI) months	7.9 (6.9–9.2)	8.3 (7.3–9.1)
HR for death (95% CI)	1.11 (0.90–1.37), p = 0.3094	
PFS per BICR, median (95% CI) months	4.0 (3.0–4.2)	3.3 (2.8–4.1)
HR for disease progression or death (95% CI)	0.96 (0.77–1.20), nominal p = 0.7053	
ORR per BICR, % (95% CI)	44.1 (37.6–50.8)	21.6 (16.4–27.4)
Patients with a grade >3 treatment-related TEAE, %	42.0	83.4
Grade >3 treatment-related TEAEs occurring in >10% of patients, %		
Diarrhea	13.7	1.3
Neutropenia	8.0	51.6
Neutrophil count decreased	4.4	17.5
Leukopenia	4.0	29.1
White blood cell count decreased	4.0	10.8
Anemia	2.7	30.9
Platelet count decreased	1.3	17.5
Thrombocytopenia	0.4	29.1

Conclusions: The primary endpoint of OS for was not met for liposomal irinotecan versus topotecan; however, a doubling of ORR was observed. The safety profile of liposomal irinotecan was consistent with its known safety profile and no new safety concerns emerged.

Clinical trial identification: NCT03088813.

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Targeting mitogenic addiction as a therapeutic vulnerability in neuroendocrine subtype of small cell lung cancer

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Background: Small cell lung cancer (SCLC) is a high grade neuroendocrine tumor accounting for ~15% of all lung cancers. Whilst MAPK mutations can be found in roughly 30% of human cancers including non-small cell lung cancer (NSCLC), genomic and proteomic analyses have indicated suppression of MAPK pathway activity in SCLC. This striking difference is not well understood and previous attempts to determine whether this might be therapeutically important have had conflicting conclusions. SCLC has recently been defined by the relative expression of four major transcriptional regulators (ASCL1, NeuroD1, POU2F3, YAP1). In this study, we aimed to elucidate the effect of MAPK activation in these different SCLC subtypes and explore its therapeutic vulnerability.
Methods: We used a doxycycline-inducible vector for expression of $MEKDD^{S217D/S221D}$ (MEK1) in a cohort of ASCL1-, NEUROD1, POU2F3- and YAP1-driven cell lines and mouse models.
Results: Activation through MEK1in ASCL1-driven SCLC cell lines resulted in a significant decrease in cell growth over 9 days. This was associated with a decrease in neuroendocrine markers ASCL1 and INSM1, and a G2 cell cycle arrest. Remarkably, athymic mice injected with a MEK1-expressing ASCL1-driven cell line showed significantly slower tumor formation and longer survival than the ASCL1-driven cell line not expressing MEK1. We observed strong upregulation of DUSP6, SPRY2, but not ETV5 upon MAPK activation. Phosphokinase array in all four subtype cell lines after MEK1 activation demonstrated that, almost exclusively, the STAT pathways, in particular, STAT3 through phosphorylation at S727 were strongly upregulated in the ASCL1-driven subtype. Upon treatment with a STAT3 inhibitor, Stattic (1μM), ASCL1-driven SCLC cells reached their IC50 after 3–5 days in comparison to 9 days for other SCLC subtypes. NSCLC cell line was resistant to STAT3 inhibition.
Conclusions: We show that ASCL1-driven SCLC in vitro and in vivo is sensitive to activation of MAPK signaling in comparison to other SCLC subtypes. Whilst activation of the MAPK pathway might seem counterintuitive to current treatment strategies that aim to inhibit oncogenic signaling, we propose the use of a STAT3 inhibitor that has shown to be effective in vitro.
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Integrative analysis of small cell lung cancer patient-derived xenograft models reveals subtype-specific pathway alterations and therapeutic targets

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Background: Small cell lung cancer (SCLC) accounts for 14% of lung cancer diagnoses and is characterized by rapid onset of chemoresistance and poor clinical outcomes. SCLC has four major subtypes driven by transcription factors ASCL1, NEUROD1, POU2F3, and YAP1. Recent studies have also shown intratumoral heterogeneity with respect to ASCL1/NEUROD1 balance and MYC amplification – which are potential mechanisms underlying SCLC's aggressive and refractory biology. Unfortunately, patient-derived models of SCLC with which to better characterize the molecular profiles of refractory SCLC are scarce.
Methods: We generated 46 patient-derived (PDX)/circulating tumor cell-derived xenograft (CDX) models derived from 33 patients with treatment-naïve or relapsed SCLC. We performed multi-omic analyses to deconvolute the mutational landscapes, global expression profiles, and molecular subtypes of these SCLC models.
Results: Our models revealed mutations typical of SCLC (e.g. TP53, RB1), which were maintained in vivo over multiple passages. Consistent with the known distribution of subtypes, most of our samples express ASCL1 or both ASCL1 and NEUROD1. We looked into an inflamed gene signature, including immune checkpoint genes and human leukocyte antigens (HLAs). Seven models showed high expression of HLAs and related antigen presentation genes such as HLA-DRA or HLA-DBP1. To date, there are no reports of an animal model representing POU2F3 subtype. Our cohort included 10 POU2F3-driven models from primary and metastatic tumors from a patient with ES-SCLC. These novel models include high POU2F3 and MYC expression by IHC and RNA-seq; low expression of neuroendocrine (NE) markers; notably high expression of mitochondrial genes such as MT-RNR2 or MT-CO3/1; high expression of REST and BACH2; low expression of DLL3 and ATOH1; and high expression of metabolic genes in comparison to the non-SCLC-P samples such as ABCB6, PGD, or G6PD, highlighting metabolic heterogeneity in our SCLC samples.
Conclusions: Our PDX/CDX models and the multi-omic characterization of these models provide a unique system and resource to characterize SCLC biology and inform clinical research treatment strategies for patients with SCLC.
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Immune cells distribution and spatial relationship within microenvironment as predictive biomarkers of benefit in extended stage small cell lung cancer patients receiving atezolizumab plus carboplatin and etoposide as first-line treatment

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Background: Atezolizumab plus carboplatin-etoposide (ACE) represents the new first-line (1L) standard of care for extended stage (ES) Small Cell Lung Cancer (SCLC) patients (pts).
Methods: This is a single-center retrospective-prospective translational study aiming at investigating the correlation of immune cell distribution and their spatial metrics in tumor samples of ES SCLC pts receiving ACE as 1L treatment, with response rate (RR), progression-free survival (PFS), time to treatment failure (TTF) and overall survival (OS). A 9-color multiplex immunofluorescence panel including primary antibodies (Abs) against CD68, CD163, CD8, FoxP3, CD4, CD20 and HLA-I and a mix of Abs against tumor markers has been performed.
Results: Preliminary data on the first 39 pts are reported. After a median follow-up of 7.2 months (mos), the estimated median PFS, TTF and OS were 5.4 (95% CI 4.5–6.3), 5.8 (95% CI 3.5–8.1), and 7.8 mos (95% CI 1.9–13.7), respectively. Lower CD163+ M2-polarized macrophages density and ratio on CD8+ cells in the total and tumoral areas were favorably associated with RR, PFS, TTF and OS ($p < 0.05$). High intratumoral CD4+FoxP3+ density correlated with better PFS ($p = 0.004$), TTF ($p = 0.011$) and OS ($p = 0.026$). CD8+ and CD20+ B lymphocyte infiltration in the total and tumoral areas correlated with longer OS. A positive role of CD20+ interaction with CD8+ on PFS ($p = 0.038$), TTF (intra-tumoral, $p = 0.036$) and OS ($p = 0.032$) has been observed. High percentage (%) of stromal CD163+ close to CD8+ cells and a low % of CD163+ cells close to tumor cells were correlated with longer PFS ($p = 0.045$) and TTF($p = 0.034$). High % of CD4+ closed to CD8+ cells in the total area ($p = 0.025$) and in the stroma ($p = 0.002$), intra and peritumoral interaction between CD163+ ($p = 0.020$) and CD8+ cells ($p = 0.008$), CD8+ and tumor cells interaction ($p = 0.012$), correlated with longer OS.
Conclusions: We identified that immune cell populations and cell-to-cell spatial metrics in ES-SCLC pts receiving ACE significantly correlated with outcome, highlighting the importance of tumor immune microenvironment and cell-to-cell interaction for tumor response and survival.
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165P
SCLC subtypes are associated with distinct clinicopathological features and outcomes: A biomarker analysis from the CANTABRICO study

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Background: Small cell lung cancer (SCLC) subtypes are driven by dominant transcriptional programs. Preclinical work suggests that transcriptomic subtyping (ASCL1, NEUROD1, POU2F3 and Inflamed) could inform potential tumor vulnerabilities and support therapeutic decisions. Here we explore the association of SCLC subtypes with clinicopathological and EMT characteristics.
Methods: We performed IHC for ASCL1, NEUROD1, POU2F3, E-cadherin and Vimentin in 42 SCLC samples from a phase IIIB clinical trial of durvalumab+platinum-etoposide as first-line treatment of patients with extensive-stage SCLC (CANTABRICO). IHC evaluation was performed using H-score. Cases expressing more than one marker were classified based on the predominant marker with the higher H-score. We evaluated associations between IHC markers and other clinicopathological and outcome variables with GraphPad®.
Results: Forty-two cases were evaluated, 20 classifieds as ASCL1 (47.6%), 11 as NEUROD1 (26.2%), 4 as POU2F3 (9.5%), and 7 as non-A/N/P (16.7%). Of note, consecutive staining of ASCL1, NEUROD1 and POU2F3 revealed that concomitant expression of these markers was observed in the same tumor in non-overlapping areas. The majority (85.4%) of tumors expressed E-cadherin and 45.2% vimentin. ASCL1 expression in tumor cells was positively correlated with tumoral E-cadherin expression (rho = 0.47, $p = 0.0022$). No correlation between subtypes and vimentin expression was observed. Baseline lactate dehydrogenase (LDH) was higher in the POU2F3-positive tumors (median = 541 range (379–1102)) compared with the other subtypes ($p < 0.0001$). Patients with non-A/N/P tumors had no liver or brain metastasis ($p < 0.0001$). With a median follow-up of 12.4 months, median OS was 8.95 months. Notably, 5 out of 7 patients with non-A/N/P tumors are still alive ($p < 0.0001$).
Conclusions: Clinical and biological differences are observed among different molecular subgroups in SCLC. In our study, the non-A/N/P tumors (encompassing the inflamed subtype) showed favorable prognostic features and better outcomes with chemoimmunotherapy.
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166P
Investigating the correlation between circulating tumor cell (CTC) detection and immune checkpoint expression in the peripheral blood of patients with small cell lung cancer (SCLC)

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Background: CTC detection is a marker of metastatic dissemination in SCLC. Tumor spread has been linked to impaired anti-tumor immune surveillance. The expression of immune checkpoints, such as TIGIT and CTLA4, on tumor-infiltrated immune cells (TILs) holds promising prognostic and therapeutic implications in SCLC, however their role in the peripheral blood (PB) is largely unexplored. We herein assessed CTC

detection coupled with CTLA4 and TIGIT expression on peripheral blood mononuclear cells (PBMCs) of SCLC patients.
Methods: PB was obtained from 63 SCLC patients prior to first-line treatment, and PBMC cytospins were prepared. Two distinct immunofluorescence stainings were performed for the detection of CTCs (cytokeratins/CD45) and the immune phenotyping of PBMCs (TIGIT/CTLA4), and samples were analyzed via fluorescence microscopy.
Results: CTCs were identified in 27/63 (42.9%) patients. CTLA4 and TIGIT were frequently expressed on PBMCs (median percentage per patient: 24.8% and 31%, respectively). An increased percentage of CTLA4+ PBMCs and TIGIT+ PBMCs was demonstrated in CTC-positive as compared to CTC-negative patients (Mean Rank: 38.9% versus 26.8%, p = 0.009, and 41.6% vs 24.8%, p = 0.000, respectively, Mann-Whitney U test). A positive correlation was confirmed between the number of CTCs, and the proportion of CTLA4+ PBMCs (p = 0.005) and TIGIT+ PBMCs (p = 0.000). Increased levels of CTLA4+ PBMCs (above median) were more frequently observed in patients with metastatic dissemination to multiple organs (>3 vs 1–2 systems affected: 61.8% vs 36.7%, p = 0.045, Fisher's exact test). The prognostic value of these findings is currently being investigated and will be presented.
Conclusions: CTLA4 and TIGIT expression on PBMCs is frequently observed in SCLC patients and is associated with CTC detection. The analysis of the peripheral blood holds a promising role for the understanding of the metastatic process and immune-surveillance mechanisms in SCLC. The study was partially funded by HESMO (Hellenic Society of Medical Oncology) and ARSA (Anticancer Research Support Association), Heraklion, Greece.
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167P
Five-years incidence of SCLC and analysis of PM2.5 air pollution in the province of Brescia: Preliminary results

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Background: Air particulate matter with diameter less than 2.5 μm (PM2.5) has been advocated as a lung cancer (LC) carcinogen. From recent data, the city of Brescia in Northern Italy has one of the highest PM2.5 concentration among European cities. The incidence of Small Cell Lung Cancer (SCLC) is decreasing in Western countries. However, data on SCLC incidence and its relationship with air pollution are lacking in the province of Brescia.
Methods: We analyzed data of patients (pts) with a new diagnosis of SCLC or high-grade neuroendocrine lung cancer observed from January 2017 to December 2021 at the Spedali Civili of Brescia, the major community hospital in the province. The Brescia province was segmented in 7 geographical areas and incidence of SCLC was calculated on the 2021 population of 1 253 545 individuals. Associations between clinical variables including smoking habits, toxic exposure risk activity, PM2.5 concentrations and SCLC incidence were studied in the same timeframe and areas.
Results: We identified 188 new cases of SCLC (24% limited disease, 76% extensive disease) representing 12% of all new LCs. Sites with higher incidence were the Brescia city or hinterland (62 pts) and the South Brescia area (38 pts). Median age was 69.3 years. More than 92% of pts were current or former smokers with a median of 45 pack/years, >20% of pts had toxic exposure risk activity and 45.2% of pts had both risk factors. Median overall survival from diagnosis was 8.5 months. The median annual incidence rate was 2.87 new cases/100 000 people (range 2.55–3.51) with an incremental rate of 0.24 cases/year from 2017 to 2021. In the same period PM2.5 concentrations in the whole province dropped from 27 to 21 $\mu g/m^3$. SCLC incidence was higher in areas with the highest PM2.5 concentrations.
Conclusions: This study is the first report of specific SCLC incidence, trend and association with air pollution in the highly industrialized Brescia province. In the 5 years of observation, concentrations of PM2.5 decreased below the limit value of 25 $\mu g/m^3$ according to the Italian regulations but above the WHO recommended value of 10 mg/m^3. Correlation of SCLC incidence and PM2.5 concentrations is a preliminary result of concern that requires extensive validation.
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168P
Demographics, clinical characteristics, treatment (tx) patterns and clinical outcomes for patients (pts) with limited-stage SCLC (LS-SCLC)

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Background: Understanding real-world tx patterns for LS-SCLC may provide insights on current practice and inform future tx strategies. We report results of a retrospective, observational study of pts with LS-SCLC.
Methods: Data were included from 1552 pts diagnosed with LS-SCLC from 1 Jan 2015 to 31 Dec 2020 who had received at least 1 tx and were recorded in the US Flatiron Enhanced Datamart database. Primary objectives were to describe demographics, clinical characteristics and tx patterns. Real-world OS was a secondary endpoint.
Results: Median age was 67 yrs and 61.1% of pts were >65 yrs. 57.3% were female; most were Caucasian (74.9%) and 6.2% were Black. 99.1% had a history of smoking. While all were confirmed LS-SCLC at diagnosis, 48.6% had AJCC Stage III disease and stage was not documented in 29.2%; 63.2% had WHO PS 0/1 and 23.1% missing PS. Most pts (73.6%) received chemoradiotherapy (CRT) in line with major guidelines; 7.3% had surgery (± other tx). The majority of pts received platinum-etoposide chemotherapy (CT): 88.0% (carboplatin 49.0% and cisplatin 39.0%). Among 1276 CRT or CT only pts with CT cycle information, 45.7% received 4 cycles of CT and 23.1% had >6 cycles. 38.5% of pts additionally received prophylactic cranial irradiation (PCI), including 52.8% of 305 CRT or CT only pts who had PS 0 and completed >4 CT cycles. Most Stage III pts received CRT (81.3%); surgery (± other tx) and radiotherapy (RT) alone were more common for Stage I pts (table). Overall, 2.8% of pts received immunotherapy (± other tx). Median OS in all pts was 20.3 months (95% CI 19.2–21.7); 5-yr OS rate was 21.7% (95% CI 18.9–24.7). More advanced disease stage was associated with shorter OS (table).

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		Stage			
	Overall N = 1552	I n = 172	II n = 173	III n = 754	Unknown n = 453
*Tx received, %**					
CRT	73.6	47.7	71.1	81.3	71.5
CT only	9.7	4.7	6.4	9.5	13.2
RT only	6.4	8.7	3.5	4.0	10.6
Any surgery	7.3	38.4	15.6	2.1	0.9
PCI	38.5	30.8	48.0	41.8	32.5
OS (all txs)					
Median, months	20.3	48.9	33.5	18.5	17.0
95% CI	19.2–21.7†	36.5–58.4	26.5–50.8	16.8–20.3	14.3–19.5
5-yr, %	21.7	37.6	33.0	20.3	13.9
95% CI	18.9–24.7	25.9–49.3	23.5–42.9	16.4–24.5	10.0–18.5

*Other: CRT + IO (1.0%), CT + IO (0.7%), other systemic tx ± RT (1.4%).
†Median OS (95% CI) was 20.6 (19.4–21.9), 7.5 (6.4–10.0), 25.8 (18.5–46.4) and 67.2 (48.9–not estimable) for pts who received CRT, CT, RT or surgery; and 32.9 (29.0–38.6) and 14.6 (13.4–16.2) for pts who did or did not receive PCI.

Conclusions: Demographics and clinical characteristics were consistent with the known epidemiology of LS-SCLC; survival outcomes with established tx approaches in these pts remain unchanged. These outcomes demonstrate a clear unmet need, and new therapeutic strategies in LS-SCLC are warranted.

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169P

Phase I dose escalation trial combining olaparib and thoracic radiation therapy in extensive-stage small cell lung cancer

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Background: A standard for extensive-stage small cell lung cancer (ES-SCLC) is induction therapy followed by thoracic radiation therapy (TRT). PARP inhibitors including olaparib have demonstrated radiosensitization in preclinical lung cancer models. We performed an investigator-initiated, multi-institutional, single-arm, open label phase I study on concurrent olaparib with TRT.

Methods: Patients with progression-free ES-SCLC after 4 to 6 cycles of platinum/etoposide ± atezolizumab, were treated with olaparib for 3 weeks with concurrent low-dose TRT (30 Gy/10 fractions) in weeks 2 and 3. Olaparib dose escalation using the continuous reassessment method started at 50 mg twice daily, escalating at 50 mg/dose level. Patients were permitted to continue atezolizumab maintenance after completion of TRT per standard of care. The primary objective was the safety and MTD of olaparib+TRT. Secondary objectives were in-field local recurrence rate and progression-free (PFS) and overall survival (OS).

Results: Between 10/2018 and 03/2022, 24 patients were treated (median follow-up: 11.4 months [range: 2 to 48 months]). Median age was 68 years (range: 49 to 79 years); ECOG status was 0–1 for 13 and 2 for 11 patients, respectively. All patients were treated with platinum/etoposide; 10 patients also received atezolizumab. All patients received 30 Gy/10 fractions TRT. The MTD of olaparib+TRT was 200 mg twice daily. There were 4 grade 3 (G3) dose-limiting adverse events (AEs), including pneumonitis, lung infection, esophagitis, and abdominal pain (each n = 1). Olaparib-related G2+ AEs included cough, dyspnea, dehydration, anorexia, dysgeusia, alopecia, and diarrhea (each n = 1). The most common G2+ TRT or olaparib+TRT-related AEs were esophagitis (n = 7), pneumonitis (n = 2), vomiting, dehydration, dyspepsia, maculo-papular rash, fever, and weight loss (each n = 1). There were no G4 or 5 AEs. No significant additional AEs were observed with atezolizumab maintenance. The 12-month cumulative incidence of local recurrence was 27%, median PFS was 3.6 months, and median OS was 17.7 months.

Conclusions: This is the first report on the safety and MTD of olaparib with concurrent low-dose TRT. The MTD of olaparib was identified as 200 mg twice daily.

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Preliminary results from LUMINANCE: A phase IIIb, single-arm study of 1L durvalumab (D) + platinum-etoposide (EP) for patients with extensive-stage SCLC (ES-SCLC)

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Background: The phase III CASPIAN study (NCT03043872) established D + EP as standard of care for 1L treatment (tx) of ES-SCLC; however, like most phase III registrational studies, the study population did not fully represent that found in real-world practice. The phase IIIb LUMINANCE study (NCT04774380) is evaluating D + up to 6 cycles of EP in pts with ES-SCLC, including those with WHO performance status (PS) 2. We report preliminary safety and efficacy results.

Methods: Pts from Europe and Turkey with tx-naïve ES-SCLC and WHO PS ≤2 received D 1500 mg + EP Q3W for 4–6 cycles (investigator's choice), followed by D Q4W until disease progression. Primary endpoints were the incidence of grade >3 AEs and of immune-mediated AEs (imAEs); secondary endpoints included ORR, PFS and OS.

Results: At the data cutoff (19 Aug 2022), median follow-up was 20.6 weeks; 51 pts had received tx and 70.6% of those were still receiving D. Median no. of D doses during the D + EP period was 5.0 (range 1–6); 47.1% of pts received 6 cycles of EP (table). Median age was 64.0 yrs, 58.8% of pts were male and 100% were white; 43.1%, 52.9% and 3.9% had WHO PS 0, 1 and 2, respectively. Grade >3 AEs occurred in 64.7% of pts (table); most common were neutropenia (37.3%), neutrophil count decreased (15.7%) and anaemia (9.8%). Grade >3 AEs occurred in 17/20 (85.0%) and 14/29 (48.3%) pts who received ≤4 or >4 cycles of EP, respectively (no. of EP cycles missing in 2 pts). imAEs occurred in 13.7% of pts; most common was hypothyroidism (5.9%). AEs leading to death occurred in 3 pts: 2 possibly related to EP and none to D. Confirmed ORR was 58.8% (table). PFS and OS will be assessed after longer follow-up.

Table: 170P

	Total (N = 51)
MEDIAN (RANGE) DOSES OF D DURING D + EP PERIOD	5.0 (1–6)
EP CYCLES*	
Median (range)	5.0 (1–6)
>4, n (%)	43 (84.3)
>5, n (%)	29 (56.9)
6, n (%)	24 (47.1)
ANY-CAUSE AE, n (%)	48 (94.1)
Grade >3	33 (64.7)
Serious	14 (27.5)
Immune-mediated	7 (13.7)
Leading to death†	3 (5.9)
CONFIRMED ORR, n (%)	30 (58.8)
95% CI	(44.2–72.4)
BEST OBJECTIVE RESPONSE, n (%)	
Partial response	30 (58.8)
Stable disease for >6 wks	13 (25.5)
Progressive disease	4 (7.8)
Not evaluable	4 (7.8)

*Based on etoposide exposure.
†Causes of death: acute kidney injury, pneumonia/cerebrovascular accident, pneumonia/sepsis.

Conclusions: Preliminary safety and efficacy findings from LUMINANCE, including pts receiving >4 cycles of induction chemo-IO, were consistent with those observed in CASPIAN. The most common grade >3 AEs were those typically associated with chemotherapy. The results further support the use of D+EP as 1L tx for pts with ES-SCLC.

Clinical trial identification: NCT04774380.

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171P

Comparison of etoposide/cisplatin and irinotecan/cisplatin for extensive-stage small cell lung cancer in Koreans: A real-world retrospective observational study

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Background: This study compared irinotecan/cisplatin (IP) with etoposide/cisplatin (EP) in patients with untreated extensive-stage small-cell lung cancer (ES-SCLC). The efficacy of the two regimens in 208 patients with ES-SCLC was retrospectively compared.

Methods: A total of 301 patients were diagnosed with ES-SCLC at Kyungpook National University Hospital in Daegu, Korea, from April 2001 to November 2017. Of these patients, 84 were not included in this study; So, a total of 208 patients were treated with either EP or IP regimen as first-line chemotherapy and analyzed through medical records review. The EP regimen consisted of cisplatin 60 mg/m^2 on day 1 and etoposide 100 mg/m^2 on day 1, 2, and 3 every 3 weeks. The IP regimen consisted of cisplatin 60 mg/m^2 on day 1 and irinotecan 60 mg/m^2 on day 1, 8, and 15 every 4 weeks.

Results: More patients received subsequent chemotherapy after the first-line chemotherapy in the EP group than in the IP group (P = 0.03) The response rate was statistically higher in the IP regimen than in the EP regimen (79.6% vs. 66.7%, respectively, P = 0.04).Patients treated with IP regimen showed significantly longer PFS than EP regimen (PFS for EP = 5.3 months and IP = 6.5 months, Log-Rank P = 0.02; HR = 0.71, 95% CI = 0.52–0.97, P = 0.03, table). However, the first-line chemotherapy regimens did not affect OS with adjustment age, gender, smoking status, stage, ECOG performance status, weight loss, second-line chemotherapy, and thoracic radiation therapy (median survival time [MST] for EP = 10.0 months and IP = 9.8 months, Log-Rank P = 0.72; HR = 0.86, 95% CI = 0.65–1.25, P = 0.31). There was no difference in treatment-related death between the two regimens. There were two treatment-related deaths in the EP regimen and two in the IP regimen.

Table: 171P Overall survival and progression-free survival according to regimens

	Progression-free survival				Overall survival			
Regimen	Median TTP (95% CI, month)	Log-Rank P	HR (95% CI)[a]	P-value[a]	MST (95% CI, month)	Log-Rank P	HR (95% CI)[a]	P-value[a]
EP (n = 110)	5.3 (4.4–5.8)	0.02	1.00		10.0 (8.1–11.7)	0.72	1.00	
IP (n = 98)	6.5 (5.6–7.0)		0.71 (0.52–0.97)	0.03	9.8 (7.9–11.5)		0.86 (0.65–1.15)	0.31

Conclusions: IP regimen together with EP regimen can be considered as the first-line treatment for ES-SCLC in the Asian population.
Legal entity responsible for the study: The authors.
Funding: National Research Foundation of Korea (NRF) funded by the Ministry of Education.
Disclosure: All authors have declared no conflicts of interest.

172P
A Chinese multicenter, real-world study of PD-L1 inhibitors in extensive stage small cell lung cancer

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Background: Based on two randomized phase III studies, IMPOWER133 and CASPIAN, immune checkpoint inhibitors combined with chemotherapy have shown improved clinical efficacy as first-line treatment for extensive-stage small cell lung cancer (ES-SCLC). This study will describe the real-world characteristics and outcomes of patients with ES-SCLC treated with standard chemotherapy with or without PD-L1 inhibitors.
Methods: Treatment-naïve ES-SCLC patients treated with standard platinum-based chemotherapy with or without PD-L1 inhibitors (atezolizumab and durvalumab) were enrolled from 12 sites in China between Jan 2019 and Dec 2021. Analyses of baseline characteristics, survival, treatment-related adverse effects (TRAEs), and subgroups were conducted. The primary end point was progression-free survival (PFS) and overall survival (OS).
Results: 414 ES-SCLC patients were enrolled, of those 208 patients received durvalumab (66.3%) or atezolizumab (33.7%) combined with chemotherapy and 206 patients only received chemotherapy. In this study, 60.1% of patients had a history of smoking and 24.6% had brain metastases. Of 414 patients, 256 (61.8%) received six or more cycles of chemotherapy (median, 6) and 213 (61.8%) received radiotherapy to any site. Median PFS in PD-L1 inhibitors plus chemotherapy group or chemotherapy group was 7.2 months (95% CI 6.6–7.8) and 6.4 months (95% CI 5.8–7.0), respectively (P = 0.001), and HR for disease progression was 0.72 (95% CI 0.59–0.89; P = 0.002). The median OS was 20.6 months and 15.9 months, respectively (HR = 0.74, P = 0.020). TRAEs were similar in the two groups, with AE-related withdrawal rates from 1L therapy of 6.3% in the PD-L1 inhibitors plus chemotherapy group and 3.4% in the chemotherapy group, including one death from immune-related pneumonia in the former group.
Conclusions: In this real-world study, PD-L1 inhibitors combined with chemotherapy demonstrated good efficacy and tolerable safety profiles. The clinical characteristics and treatment patterns were markedly different from those in the two RCTs, including receipt of thoracic radiotherapy (tRT) or prophylactic cranial irradiation (PCI). The OS benefit and radiotherapy subgroup analysis of ES-SCLC patients need to be further followed up.
Legal entity responsible for the study: The authors.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

173P
Extended-stage SCLC (ES-SCLC) patients treated with first-line chemotherapy plus atezolizumab in Spain: Characteristics and outcomes

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Background: Therapy with PD1/PDL1 inhibitors of the immune checkpoints (ICI) has been the only significant advance for the treatment of ES-SCLC reaching the clinical practice within the past decades. Not every patient with this condition may be a candidate for these therapies due to clinical or regulatory reasons, so its impact in real-life patients may be limited.
Methods: We present a series of consecutive patients with ES-SCLC recently diagnosed in several hospitals of a north-eastern area of Spain and that received ICI (Atezolizumab, being the only IT reimbursed by the Spanish Health System at the present time for that indication).
Results: Between Jun/21 and Oct/22 206 patients (p) with ES-SCLC were treated in 8 hospitals. Of them, 61p received A (33.5%). Characteristics: Median age 61.0 years (39–81). Males 59.0%, PS 0/1/2: 36.1/49.2/14.7%, stage IV 98.4%. Median number of metastatic sites 2 (1–6) and the most common organs affected were: liver 52.5%, bone 52.5%, lung 26.2%, adrenal 26.2% and CNS 11.5%. LDH values were elevated in 58.5%, LIPI index was good in 23.8, intermediate 45.2 and poor in 31.0%. Compared to p not receiving IT, had better PS (0, 36.1 vs 17.6%, p = 0.004), were more female (NS) and had more liver metastasis (NS). No differences existed in other characteristics. Accompanying CT scheme was mostly Carboplatin-Etoposide (96.7%), Cisplatin-Etoposide given only to 2p. Median number of CT courses was 4 (1–6) and of IT 6 (1–17). Objective responses (52 evaluable p): complete 1.9%, partial 84.6%, stable ndisease 1.9%, progressive disease 11.6%. 25 p have already progressed (40.9%) and median time to progression was 20 weeks (w) (18–21 w). Second-line therapy was given to 17p (27.9%), mostly topotecan 9p (paclitaxel 5p, other 3p). RT was given to 22p: SNC 10p, bone 8p, subcutaneous metastases 1p, plus 5p receiving PCI. Survival tended to be worse in CNS metastases (18 vs 21 w), worse LIPI index (poor vs good: 20 vs 31 weeks), but no differences were found according to sex, PS, LDH or NSE levels. Median Overall Survival was 38w (29–46 w) with 43% of patients still censored.

Conclusions: These results, albeit early, may replicate those of clinical trials with IT in ES-SCLC, both in terms of patients' characteristics and outcomes.

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Disclosure: A. Artal-Cortes: Financial Interests, Personal, Invited Speaker: Roche, MSD, BMS, AstraZeneca. All other authors have declared no conflicts of interest.

174TiP

PRIMALung (EORTC-1901): Prophylactic cerebral irradiation or active brain magnetic resonance imaging surveillance in small cell lung cancer patients

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Background: PRIMALung is an EORTC-sponsored study. Primary objective is to show that overall survival with brain MRI surveillance alone is non-inferior to brain MRI surveillance combined with PCI in patients with SCLC. PCI is currently SOC in most institutions, but can be associated with neurocognitive toxicity and impact quality of life. 600 patients will be recruited from 50 EORTC centres in 10 countries. This study is currently recruiting and will play an important role in clarifying whether MRI surveillance is a viable strategy in SCLC. Furthermore, it will answer important questions about the role of PCI in the era of immunotherapy, particularly in ES-SCLC.

Trial design: Key eligibility: ECOG performance status ≤2 patients with SCLC (Limited or Extensive-Stage, stage I–IV) who did not progress after (≤16 weeks from day 1 of last cycle of chemotherapy to randomisation) completed standard therapy. Absence of progression, brain metastases or leptomeningeal disease after completing therapy. Trial Interventions: Patients will be randomised 1:1 to receive brain MRI surveillance with or without PCI (25 Gy in 10 fractions). Primary objective - to show that overall survival with brain MRI surveillance alone is non-inferior to brain MRI surveillance combined with PCI. Secondary objectives - cognitive failure-free survival, quality of life and acute/late toxicities according to CTCAE v5.0. The trial was open to recruitment on 27/10/2022. Three countries open to date (Belgium, Switzerland, UK). Further sites in France, Poland and Austria will be open to recruitment Q1 2023. The first patient has been randomized on the 4th of January 2023.

Clinical trial identification: NCT04790253.

Legal entity responsible for the study: EORTC.

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Disclosure: A. Levy: Financial Interests, Institutional, Funding: AstraZeneca, BeiGene, Roche, Amgen. All other authors have declared no conflicts of interest.

TRANSLATIONAL RESEARCH

175MO

HLA-I evolutionary divergence confers response to PD-1 blockade plus chemotherapy in untreated advanced non-small cell lung cancer

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Background: Despite the huge success observed in clinical trials evaluating first-line PD-1 blockade plus chemotherapy in advanced NSCLC, nearly half of patients do not respond. This highlights a critical need to identify the robust predictive biomarkers. Given the potential mechanism of synergistic antitumor effect of PD-1 blockade plus chemotherapy builds upon the increased tumor-related antigen release by some chemotherapeutic drugs and presentation, this study investigated the predictive significance of HLA-I evolutionary divergence (HED), a measurable parameter of HLA-I evolution associated with diverse immunopeptidomes presentation, for PD-1 blockade plus chemotherapy in untreated advanced NSCLC from two phase III trials.
Methods: Here, we integrated clinical and HLA-I genotype data of 427 NSCLC patients treated with first-line PD-1 blockade plus chemotherapy or chemotherapy from two phase III trials and investigated the predictive value of HED. Molecular and immune profiles of tumors with distinct HEDs were analyzed by using whole-exome sequencing, multiplex immunofluorescence staining and single-cell RNA sequencing.
Results: Our results showed that HED^{high} was associated with significantly better treatment response, survival and 2-year PFS probability in NSCLC patients treated with first-line PD-1 blockade plus chemotherapy, especially in these with fully heterozygous HLA-I genotypes, but not in the chemotherapy group. Its predictive value held in multivariate analysis when adjusted for PD-L1 expression and tumor mutation burden. Moreover, we found that combination of mean HED and PD-L1 expression showed better predictive performance. Using scRNA-seq of untreated NSCLC, we found that patients with HED^{high} was associated with improved antigen presentation and antitumor immunity, further supporting HED^{high} as a predictive biomarker in this setting.
Conclusions: HED^{high} represents a potential biomarker to predict the response and survival outcomes of patients with untreated advanced NSCLC received PD-1 blockade plus chemotherapy, especially in those with fully heterozygous HLA-I genotypes.
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Disclosure: All authors have declared no conflicts of interest.

176P

Multi-omic analyses of lung cancer tumors show role of AKT and MYC as regulators of lung adenocarcinoma to squamous cell lung cancer transdifferentiation

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Background: Lineage plasticity, the ability to transdifferentiate among distinct phenotypic identities, facilitates therapeutic resistance in multiple cancers. In lung adenocarcinomas (LUADs), this phenomenon includes small cell and squamous cell (LUSC) histologic transdifferentiation in the context of acquired resistance to targeted inhibition of driver mutations. The incidence of transdifferentiation into squamous carcinoma in EGFR mutant tumors occurs in up to 9% of cases relapsed on osimertinib and has been associated with poor prognosis. The paucity of well-annotated pre- and post-transdifferentiation clinical samples has precluded the performance of informative molecular analyses: little is known about the molecular mechanisms leading to this histological transition.
Methods: We performed detailed genomic (whole-exome sequencing), epigenomic, transcriptomic (RNAseq), proteomic (antibody arrays), and single-cell RNAseq and ATACseq characterization. Clinical findings were validated in preclinical models including cell lines and patient-derived xenograft treatments.
Results: Our results suggest that LUSC transdifferentiation is primarily driven by transcriptional reprogramming rather than mutational events, and indicate that the resulting squamous tumors retain transcriptomic and methylation profiles of their previous LUAD state. We observed coordinated upregulation of PI3 K/AKT, MYC, and PRC2 pathway genes in the LUSC component of mixed histology tumors. Concurrent activation of PI3 K/AKT and MYC-induced squamous features in EGFR-mutant LUAD preclinical models, further augmented under the selective pressure of osimertinib. Pharmacologic inhibition of EZH1/2 in combination with osimertinib prevented relapse and squamous transdifferentiation in an EGFR-mutant PDX model, and inhibition of EZH1/2 or PI3 K/AKT signaling re-sensitized resistant transdifferentiated LUSC tumors to osimertinib.
Conclusions: Our findings provide the first comprehensive molecular characterization of LUSC transdifferentiation, suggesting putative drivers and promising therapeutic targets to constrain or prevent lineage plasticity in this setting.
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Disclosure: The author has declared no conflicts of interest.

177P

Dissecting the molecular landscape of resistance to ROS1 tyrosine kinase inhibitors with improved NSCLC pre-clinical models

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Background: ROS1+ NSCLC can be targeted with tyrosine kinase inhibitors (TKIs). However, point mutations affecting kinase domain that impair drug binding are a therapeutical challenge to address. Thus, unraveling the impact of mutations like ROS1 G2032R, L2026M, S1986Y in representative pre-clinical models is needed.
Methods: The ROS1+ cell line HCC78 was edited using CRISPR/Cas9 to knock-in the mutations G2032R, L2026M and S1986Y. Mutant lines were treated with crizotinib, lorlatinib, ceritinib, crizotinib and repotrectinib in a monolayer (2D) and spheroids (3D) using the OrBITS platform to track cell viability. Western-blotting was performed to assess MAP kinase pathway. In parallel, ROS1 kinase models for WT and mutants were investigated for conformational landscape using molecular dynamics suite GROMACS. Protein-drug interactions via molecular docking were studied with SMINA.
Results: G2032R line showed in 2D the strongest resistance towards crizotinib, entrectinib and ceritinib, having all a weak activity (IC50 s around 1,1 μM), opposed to repotrectinib (93,25 nM) and lorlatinib (317,17 nM). L2026M clone is more sensitive to TKIs, being repotrectinib (5,9 nM) and lorlatinib (6,85 nM) more effective. S1986Y clone showed a similar response as the WT line. 3D spheroids confirmed these results. p-ROS1 levels were maintained across mutants. The kinase active state, selected as the starting conformation for computational

simulations did not shift from active to inactive mode. DFG and HRD motif interactions are conserved while some change is observed in loop regions that define ATP binding pocket. Mutations distant from the active have less impact on drug binding. Surface area and volumetric changes observed are less informative for such mutants.
Conclusions: We conclude that G2032R is the most aggressive mutation, being partially inhibited by lorlatinib. This TKI showed remarkable activity against L2026M and S1986Y likewise, however both mutants were refractory to entrectinib, crizotinib, repotrectinib and ceritinib. These results were confirmed by western blot. Our approach allows the generation of patient-derived mutant cell lines and screened for TKI sensitivity guided by the in silico modelling of ROS1 variants.
Legal entity responsible for the study: The authors.
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Disclosure: All authors have declared no conflicts of interest.

178P
Targeting XPO1-dependent nuclear export of HMGB1 in non-small cell lung cancer

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Background: We looked at whether high-mobility group box 1 protein (HMGB1) is subject to exportin 1 (XPO1)-dependent nuclear export and whether HMGB1 mRNA levels predict response to immune checkpoint inhibitors (ICI) in NSCLC.
Methods: RNA was isolated from NSCLC tumor patients. Gene expression analysis was conducted using NanoString Counter analysis system (PanCancer Immune Profiling Panel, capturing read counts of 784 genes). Western blotting analysis and cell viability assays in EGFR and KRAS-mutant cell lines were carried out. Evaluation of antitumoral effect of ICI in combination with selinexor and trametinib was determined in murine Lewis lung carcinoma model.
Results: High levels of HMGB1 mRNA in NSCLC patients receiving ICI were associated with progression-free survival (PFS) in exploratory (median PFS 9.0 versus 18.0 months, P = 0.008, hazard ratio = 0.30 in high versus low HMGB1) and validation (median PFS 18.1 versus 35.5 months, P = 0.029, hazard ratio = 0.39) cohorts. The combinations of erlotinib and osimertinib with selinexor in EGFR-mutant NSCLC cell lines (PC9 and H1975), and trametinib plus selinexor in KRAS-mutant NSCLC cell lines (A549, H460) were highly synergistic abolishing tumor cell proliferation. Consistent with this effect, the combination of trametinib with selinexor and/or PD-1 inhibitor highly inhibited tumor growth in the immune-resistant murine Lewis lung cancer model harbor KRAS G12C mutation.
Conclusions: Our results suggest that the addition of selinexor as a blocker of HMGB1 nuclear export could overcome resistance to immunotherapy. The predictive value of HMGB1 mRNA was confirmed in metastatic NSCLC pretreatment samples treated with ICI. Overall, the pattern of reduced tumor growth induced by triple combination therapy (ICI, trametinib and/or selinexor) in the Lewis lung carcinoma model warrants further assessment in a clinical trial.
Legal entity responsible for the study: The authors.
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Disclosure: All authors have declared no conflicts of interest.

179P
Integrative analysis revealed the signature of cancer stem cells and its immunosuppressive role in lung adenocarcinoma

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Background: Cancer stem cells (CSCs) could induce immunosuppression to promote tumor progression and therapy resistance. Due to the absence of specific markers, CSCs and their phenotypes remain unexplored in lung adenocarcinoma (LUAD).
Methods: In the single-cell level, CytoTRACE package was employed to calculate CytoTRACE score representing the level of stemness. Malignant cells with top 25% CytoTRACE score were defined as CSCs. Then, we developed a strict procedure involving weighted gene co-expression network analysis (WGCNA) and metacell algorithm to identify tumor-specific CSC-related genes. Our in-house serum proteomics data was used for screening CSC-related genes for biomarkers of immunotherapy.
Results: Based on over 20 000 single cells from five datasets, we identified a group of CSCs with highest CytoTRACE score. CSCs exhibited enhanced proliferating activities, such as cell cycle, G2M checkpoint and MYC targets. In the WGCNA analysis, a module (correlation = 0.9, $p < 0.0001$) was identified as having a significant association with CytoTRACE Score. A total of 91 genes overlapping between this module and tumor specific genes were exploited to construct the Stemness Score. In bulk transcriptomics level, Stemness Score was positively associated with immunosuppressive cells (correlation >0.3), including the T cells regulatory (Treg) and myeloid-derived suppressor cells (MDSC). Checkpoints PDCD1, CD274, CTLA4 and TIM3 were also observed to have positive association with Stemness Score (correlation >0.3). Stemness Score also linked to undesirable prognosis (HR = 1.68, $p = 0.0004$) in the cohort TCGA LUAD. In our in-house cohort of 57 samples from 17 non-small cell lung cancer (NSCLC) patients treated with immunotherapy, the serum proteomics data revealed that ENO1 was significantly higher in non-responders ($p = 0.0023$) and its level increased as disease progressed ($p = 0.005$).
Conclusions: This study characterized and thoroughly elucidated CSCs, through integrative analyses of multi-omics data, identifying ENO1 as a novel serum biomarker for predicting immunotherapeutic outcome in NSCLC.
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Comprehensive analysis on proteasome-related genes and their correlation with immunity and immunotherapy in squamous cell lung cancer

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Background: Recently, results of many studies suggested that patients with squamous cell lung cancer (SqCLC) could benefit from immune checkpoint inhibitors (ICIs). However, not all patients receiving ICIs could respond well and many biomarkers were selected and employed to identify the subset of patients most likely to derive clinical benefits. Some studies investigated components of proteasome in melanoma, which showed a superior value than PD-L1, TMB and CD8+ T cell on predicting ICIs' effect. Here, we performed a comprehensive analysis on proteasome-related genes and their correlation with immunity and immunotherapy in SqCLC.
Methods: An integrated analysis of transcriptomic data from TCGA and GEO database was performed. Gene set variation analysis (GSEA) was employed to investigate the relative activity of signal pathways. CIBERSORT, quanTIseq and single-sample GSEA were used for evaluating tumor immune microenvironment (TIME). Survival analysis and receiver operating characteristic were used to estimate the value of each proteasome-related gene on predicting ICIs' effect.
Results: A total of 1870 SqCLC patients from 21 cohorts were analyzed in this study. In the result of pathway enrichment analysis, PSMB10, PSMB9, PSMB8, PSME1 and PSMC3IP were shown high correlation with immunity-related pathways, and there were 16, 13, 13, 9 and 8 cohorts that enriched more than 50% of all immunity-related pathways for the five genes, respectively. In terms of TIME analysis, PSMB10, PSMB9, PSMB8 and PSME1 has 47, 46, 41 and 41 statistically significant results, respectively, from totally 63 CD8+ T cell calculated by three algorithms in 21 cohorts, and all of these four genes were positively correlated with high infiltration of CD8+ T cell. As for the evaluation of predictive value on immunotherapy, only PSMB10 was statistically significant (mPFS: 7.33 months vs 0.70 month, p = 0.03; AUC: 0.89, 95%CI 0.65–1).
Conclusions: Among 54 proteasome-related genes, PSMB8, PSMB9 and PSMB10, three important catalytic subunits of immunoproteasome, can distinguish TIME and have high activity of immune-related pathways in SqCLC, in which PSMB10 has the potential as a biomarker of ICIs' effect.
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Disclosure: All authors have declared no conflicts of interest.

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CD27-IgD- B cells might portray an exhausted B cell phenotype resulting in lack of response to checkpoint inhibitor treatment in NSCLC

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Background: Checkpoint inhibitor (CI) therapy has revolutionized the therapy landscape of NSCLC. However, why some patients do not respond to CI therapy remains unknown. The correlation between intra-tumoral B cell follicles and response to CI therapy has been established. B cell follicles within the lymph node become more dispersed with age and CD27-IgD- B cells (DNBc) are described to be age-associated. Moreover, DNBc are abundant in chronic infection, elderly, long COVID and auto-immunity and are described to be anergic and exhausted and often lack expression of CD21. DNBc are expanded in NSCLC tumors compared to healthy lung tissue and inversely correlate to switched memory B cells in the tumor. In this study we explored if there is a correlation between this B cell subtype in peripheral blood of NSCLC patients and response to CI therapy.
Methods: Patients treated with CIs within the Erasmus Medical Center were included in a prospective observational immunomonitoring study. Nineteen NSCLC patients treated with either Pembrolizumab (Pem) or Nivolumab and 5 healthy controls (HC) were selected. Pem was given in 6/11 responding patients (R) and 5/8 non-responding patients (NR). Peripheral blood mononuclear cells (PBMC) were collected before start of treatment and characterized by multicolor flow cytometry.
Results: HC and R showed a similar pattern in most B cell subsets. NR had significantly lower proportion of B cells within the PBMC fraction than R and HC (R: 7.14%, NR: 2.91%, HC: 10.60%). In addition, NR had a significantly higher frequency of DNBc than R and HC (R: 9.43%, NR: 23.78%, HC: 7.19%) and there was no correlation between age and DNBc. The frequency of DNBc correlated positively with lack of CD21 expression (r^2: 0.83) and expression of Ki67 (r^2: 0.54) both in NR, R and HC. The frequency of Ki67+CD21-DNBc within the B cell fraction was higher in NR than in R and HC (NR: 18.34%, R: 3.51%, HC: 0.67%).
Conclusions: We are the first to describe that frequencies of DNBc are higher in NR compared to R and HC. Specifically, Ki67+CD21-DNBc are increased in NR and might reflect an anergic, exhausted B cell phenotype. The absence of a correlation between age and DNBc could suggest that the increase in DNBc is induced by the tumor.
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Identification of an antigen-presenting cells/T/NK cells-related gene signature to predict prognosis and gene marker CTSL to predict immunotherapeutic response for lung adenocarcinoma: An integrated analysis of bulk and single cell RNA sequencing

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Background: Antigen-presenting cells (APC)/T/NK cells are key immune cells that play crucial roles in fighting against malignancies including lung adenocarcinoma (LUAD). In this study, we aimed to identify an APC/T/NK cell-related gene signature (ATNKGS) and potential immune marker genes (IMGs) to realize risk stratification, prognosis and immunotherapeutic response prediction for LUAD patients.
Methods: Based on 196 antigen-presenting cells (APC)/T/NK cells-related genes collected from three pathways in the Kyoko encyclopedia of genes and genomes (KEGG) database, we determined the final genes and established the ATNKGS-related risk model via univariate Cox regression and LASSO Cox regression. Then we correlated ATNKGS with overall survival (OS), clinical characteristics, immune cell infiltration, and functional enrichment analysis of LUAD patients. The single cell RNA sequencing data was applied for identification of key IMGs and investigate their value in immunotherapeutic response prediction.
Results: In this study, 8 independent public datasets including 1089 patients were enrolled. An ATNKGS containing 16 genes was constructed for prognostic prediction of overall survival in the TCGA discovery dataset. Its prognostic capability was verified by TCGA validation dataset and four other GEO datasets. A nomogram combining ATNKGS risk score and clinical TNM stage maximized the survival prediction of LUAD. The single cell RNA sequencing analysis revealed CTSL and HSPA6 as the key IMGs for monocyte and dendritic cells, respectively. Moreover, though CTSL was an indicator for poor prognosis of LUAD patients, CTSL high expression group was associated with higher ESTIMATEScore, immune checkpoints expression, and lower TIDE score. Several immunotherapeutic cohorts have confirmed the response-predicting significance of CTSL in patients receiving ICI treatment.
Conclusions: In conclusion, our study provided an insight into the significant role of APC/T/NK cells-related genes in survival risk stratification and CTSL in response prediction of immunotherapy in patients with LUAD.
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Disclosure: All authors have declared no conflicts of interest.

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INHA acts as a novel and potential biomarker in lung adenocarcinoma and shapes the immune-suppressive tumor microenvironment

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Background: Immune-related subgroup classification in immune checkpoint blockade (ICB) therapy is largely inconclusive in lung adenocarcinoma (LUAD).
Methods: First, the single sample Gene set Enrichment Analysis (ssGSEA) algorithm and K-means algorithm were used to identify immune-based subtypes for LUAD cohort based on the immunogenomic profiling of 29 immune signatures from the Cancer Genome Atlas (TCGA) database (n = 535). Second, we conducted a bioinformatics analysis on data to examine the prognostic and predictive value of immune-based subtypes. The survival analysis and further cox proportional hazards regression analysis were conducted in LUAD. Then, immune score, tumor-infiltrating immune cells (TIICs) and immune checkpoint expression of the three subtypes were analyzed respectively. In the end, GO and KEGG of the differentially expressed genes (DEGs) between 3 immune-based subtypes were analyzed for functional enrichment pathways.
Results: A total of 3 immune-based subtypes with different immune signatures were identified for LUAD. We identified three LUAD subtypes named cluster 1 (C1), cluster 2 (C2) and cluster 3 (C3). Patients in cluster 3 had higher stromal, immune, and ESTIMATE scores, while cluster 1 was the opposite. Cases in cluster 1 showed an enrichment of macrophages M0 and activation of dendritic cells, while in cluster 3 tumors were enriched in $CD8^+$ T cell, activation of CD memory T cells and macrophages M1. Cluster 3 was characterized by greater immune cell infiltration, as well as better survival prognosis compared to the other subtypes. In addition, patients in cluster 3 had higher expression levels of immune checkpoint such as PD-L1, PD1, CTLA4, LAG3, IDO1 and HAVCR2. TMB scores of clusters showed no significantly statistical differences. Furthermore, we identified that immune-related pathways were enriched in cluster 3.
Conclusions: Based on this study, combined-biomarkers were identified to predict outcomes following immune checkpoint inhibitor (ICI) treatment. Furthermore, our findings have enormous potential for assisting in the identification of immunological biomarkers and serving as a starting point for novel combination-based therapy strategies.
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Disclosure: All authors have declared no conflicts of interest.

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Influence of corticosteroids and antibiotics on the microbiota and the efficacy of immunotherapy in patients with non-small cell lung cancer (NSCLC)

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Background: Treatment of NSCLC has undergone important changes in recent years. The availability of immune checkpoints inhibitors (ICI) is the most relevant. It has been suggested that response to these drugs is conditioned by some host-related factors, mainly the microbiome, and the exposure to disruptive treatments, such as antibiotics or corticosteroids.

Methods: Observational and prospective study, involving 55 patients (p) diagnosed with unresectable stage III or IV NSCLC receiving ICI, with at least one year follow-up and recruited between April 2019 and October 2020. Clinicopathological data, as well as faecal, saliva and blood samples were collected previous to ICI treatment. Bacterial composition of faeces and saliva was determined by 16S rDNA massive sequencing using SILVA 132 for taxonomic assignation and QIIME pipeline for statistical comparisons.
Results: Median age was 65 years.70.9% male. 65.5% ECOG 0. 50.9% of patients needed antibiotics and 58.2% used corticosteroids. Median overall survival (OS) was 19 months (m), being lower when patients received antibiotics (12 vs 23 m), but without statistical significance. By contrast, significant differences were observed in OS according to the use of corticosteroids ($p = 0.011$), but was not maintained in subgroups (time of use/indication). While relevant results were not found in faecal microbiota, both alfa- and beta-diversity indexes of saliva were significantly higher in patients with higher OS and ICI response. Streptococcus abundance had a negative correlation for OS, while the differential genera for those patients with optimal response to ICI was Fusobacteria and Porphyromonas. Corticosteroid exposition was associated with more Actinomyces in saliva. Regarding lymphocyte populations (CD8, CD4, CD57…) in blood samples, with a $p = 0.047$, we concluded that the percentage of CD8 T lymphocytes is higher in the group without antibiotics.
Conclusions: According to our data, corticosteroids and antibiotics intake is associated with poorer ICI treatment outcomes for NSCLC patients Interestingly, the differential bacterial composition of saliva could be used as a predictive marker of response to ICI, in particular the abundance of streptococci is significantly related to worse response and survival.
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Elevated CXCL10:IL-8 ratio in bronchoalveolar lavage fluid of immune checkpoint inhibitor-related pneumonitis

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Background: Immune checkpoint inhibitor (ICI) pneumonitis is the most common fatal immune-related adverse event (irAE) from PD-1/PD-L1 blockade, and a diagnosis of exclusion. Based on single-cell transcriptomics, we identified pathogenic T-helper 17.1 cells in ICI-pneumonitis bronchoalveolar lavage fluid (BALF), putatively engaging with pro-inflammatory "M1-like" monocytes, as a key pathophysiologic mechanism. Herein, we present the cytokine profile of ICI-pneumonitis BALF, aiming to identify further mechanistic insights and diagnostic biomarkers.
Methods: Levels of 22 cytokines (GM-CSF, Granzyme B, IFN-γ, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-13, IL-15, IL-17A, IP-10, MCP-1, MIP-1α, MIP-1β, Perforin, sCD137, TNF-α, TNF-β) were measured in BALF supernatant of 17 ICI-pneumonitis and 6 controls from 23 independent patients at UZ Leuven (discovery), using Isoplexis' CodePlex platform. Validation was performed in a published cohort of 13 ICI-pneumonitis and 6 controls from independent patients at Johns Hopkins University. Mann-Whitney U test (Benjamini-Hochberg corrected) was used to compare cytokine levels between groups.
Results: In the discovery cohort, we observed significantly lower levels of IL-8, IL-9, IL-10, IL-17A, CCL2, and sCD137 in ICI-pneumonitis BALF vs. controls. There was a trend towards higher levels of TNF-α and CXCL10 ($p = 0.11$; $p = 0.16$ respectively). Next, we investigated the biomarker potential of ratios of differentially abundant proteins, arguing that disbalance rather than absolute cytokine values provides a more meaningful readout for inflammation, while correcting for technical variability in BALF-derived data. We identified that a high CXCL10: IL-8 ratio distinguishes ICI-pneumonitis from control patients in the discovery cohort (ROC AUC 0.92) and in the validation cohort (ROC AUC 0.82).
Conclusions: Bulk cytokine profiling identifies a high CXCL10: IL-8 ratio as a reproducible characteristic of ICI-pneumonitis BALF, in line with immunophenotypic data suggesting an interferon-γ driven immune response and absence of neutrophilic inflammation, respectively. The diagnostic utility of the CXCL10: IL-8 ratio in BALF to identify ICI-pneumonitis should be further investigated.
Clinical trial identification: NCT04807127.
Legal entity responsible for the study: University Hospitals Leuven.
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Disclosure: All authors have declared no conflicts of interest.

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Tissue B-cell receptor repertoire as biomarker of complete pathological response in NSCLC patients treated with neoadjuvant chemoimmunotherapy (NADIM trials)

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Background: Neoadjuvant chemoimmunotherapy (CI) for potentially resectable stage IIIA NSCLC yields high percentages of complete pathological responses (CPR). However, not all patients achieve CPR, and current biomarkers (PD-L1 and TMB) have limited sensitivity for predicting clinical outcomes. On the other hand, the presence of tertiary lymphoid structures has been associated with better responses to immunotherapy, but the role of B-cells and B-Cell Receptor (BCR) repertoire is largely unknown. Here, using tissue samples from NADIM I and II trials, we analyze the tumoral BCR repertoire and its association with CPR.

Methods: RNAs extracted from pre- and post-neoadjuvant treatment 59 tumor samples of 43 patients enrolled in NADIM I (n = 33) and II (n = 10) trials were sequenced using the Oncomine® BCR IGH SR Assay (ThermoFisher). BCR clones and lineages metrics (count, Shannon diversity, evenness and convergence) were analysed, as well as clonal/lineage space, defined as the summed frequency of clones/lineages belonging to a frequency group (top <1%, 1–2%, 2–5% and >5%) relative to the total BCR repertoire. Results were correlated with pathological response groups: CPR (n = 23) and non-CPR (n = 20).

Results: In pre-treatment samples (n = 19), CPR tumors (n = 8) showed significantly lower BCR diversity and evenness than non-CPR tumors (n = 11) in both clones and lineages ($p = 0.051$ and $p = 0.026$ for clonal and lineage diversity; $p = 0.020$ and $p = 0.026$ for clonal and lineage evenness). Additionally, pre-treatment samples showed higher clonal and lineage space occupied by the top 1% clones/lineages in patients who achieved CPR vs those that did not ($p = 0.021$ and $p = 0.012$). No significant differences were found in total clone count and convergence. In post-treatment samples (n = 40), no differences were observed in any clonal/lineage derived metrics between CPR (n = 22) and non-CPR tumors (n = 18).

Conclusions: Our results support the association between an uneven and less diverse distribution of B cell clones and lineages proportions at diagnosis with complete pathological response after neoadjuvant CI.

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Legal entity responsible for the study: Spanish Lung Cancer Group.

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Disclosure: All authors have declared no conflicts of interest.

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SAKK 16/14: Immune profiling of pre-operative biopsies correlates with survival and immune activation in stage IIIA (N2) NSCLC after neoadjuvant immunotherapy

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Background: The composition and functional state of the tumor immune-environment (TIME) is a critical factor for response to immune checkpoint inhibitors (ICI) in non-small cell lung cancer (NSCLC). In the neoadjuvant setting, the composition of the TIME and the spatial distribution of immune effector cells are captured in the pre-operative biopsy (IB). It remains unknown how (a) TIME changes during neoadjuvant ICI treatment and (b) how immune phenotyping of the IB is predictive for response to ICI therapy.

Methods: We performed digital pathology analysis of tumor tissue obtained from patients with stage IIIA(N2) NSCLC undergoing sequential neoadjuvant chemo-immunotherapy including durvalumab in the phase II trial SAKK 16/14. 14 cases with matched IB and resection specimens were included and analyzed by immunostaining for CD3, CD8 and CD20. Two pathologists consensus-reviewed all cases and assigned global immune phenotypes for each case as excluded ("cold tumors") or inflamed ("hot tumors"). A machine-learning classifier was trained to segment invasive tumor regions and quantify immune cell infiltrates in epithelial and stromal compartments. CD20 stains were used for digital morphometry of tertiary lymphoid structure (TLS) in TIME. Correlations of TIME parameters with event-free survival (EFS) were analyzed by Mann-Whitney-Wilcox test.

Results: Analysis of CD8+ T-cell density in the IB (n = 14) classified TIME as excluded (n = 10) or inflamed (n = 4). Presence of TLS in IB and TLS size strongly correlated with long term EFS ($p < 0.001$). In cases with mature TLS in the IB, a trend towards increased CD8+ T-cell density and increased infiltration into the tumor epithelial compartment was observed. In analysis of matched IB and resections at individual patient level, an activated TIME was found after neoadjuvant anti-PD-L1 treatment. Specifically, we observed a trend towards increased T-cell density and increasing TLS size in the matched resection specimen after ICI, with the highest fold increase found in patients with long term EFS.

Conclusions: In the trial SAKK16/14, presence of TLS and TLS size in the IB correlate with EFS and a signature of immune activation in the matched resection specimen.

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The parallel interrogation of tissue and peripheral blood immune features unveils a bidirectional crosstalk with clinical impact on resected NSCLC

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Background: The cancer-immune interplay and its role on the evolution of NSCLC might be disclosed through the detection of local and systemic cues. Aim: To determine whether peripheral blood (PB) immune profiles may mirror clinically relevant tumor immune microenvironmental (TIME) features in resected NSCLC patients.

Methods: Tissue and PB samples were prospectively collected at surgery from 80 consecutive stage I-IIIA NSCLC cases. The immunohistochemical evaluation of TIME involved PD-L1 status and spatial distribution of CD3+, CD4+, CD8+, PD1+ Tumor Infiltrating Lymphocytes (TILs), defined as immune efficient (IEff) when in contact with cancer cells or immune excluded (IEx) when trapped in fibrosis. TILs clustering was also considered. PB CD3+, CD4+ and CD8+ lymphocytes, NKs, and Tregs together with the expression of PD1, Granzyme B (GnZ) and Perforin (Perf) were assessed by flowcytometry. TIME-PB relationships and their clinico-pathological correlates were statistically examined.

Results: Compared to stage II and III, TIME from stage I revealed increased CD3, CD8 and CD4 clusters (P = 0.03) coupled with higher PB CD8+ and CD4+ lymphocytes (P = 0.02). Females displayed greater IEff and clustered CD3 and CD8 TILs and higher PB CD4, while males exhibited more distally located TILs and predominant PB GnZ+ CD8+ (P < 0.05). Blood from PD-L1^{pos} NSCLC showed a significant immune switch favoring CD8 (P = 0.007), while PD-L1^{neg} cases presented higher PB CD4 (P = 0.02) with predominant Tregs (P = 0.05) phenotype. Tissue CD4-to-CD8 ratio and CD8 TILs density were directly correlated with blood CD4/CD8 (P = 0.002) and CD8 number (P = 0.05), whereas an opposite trend between IEff CD8 TILs and PB Tregs was detected. Tissue PD1-to-CD8 ratio was inversely related to the fraction of CD8+PD1+ in PB. Intriguingly, early recurrent NSCLC patients were characterized by TIME carrying 1.5-fold higher PD1-to-CD8 ratio and lower CD8+PD1+ cells in PB, supporting the double edge sword of PD1 receptor.

Conclusions: Blood shares relevant immune features with TIME, providing an exploitable noninvasive tool to intercept the cancer immunity cycle and its targetable pathways.

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EORTC-SPECTA Arcagen project: Results of the prospective rare thoracic tumors cohort

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Background: Rare cancers are usually under-represented in clinical research including genomic profiling. Arcagen is a European study aiming at defining the molecular landscape of rare cancers for treatment guiding. We present data from the prospective cohort of rare thoracic tumors.

Methods: Patients with malignant pleural mesothelioma (MPM) or thymic tumors (TT) at advanced stage underwent genomic profiling by FoundationOne CDx on FFPE blocks, or alternatively by FoundationOne Liquid CDx on newly collected plasma samples. Molecular tumor boards (MTB) discussed patients' molecular and clinical profile to advise for possible biomarker-guided treatments, including clinical trial options.

Results: Overall, 102 patients recruited from 8 different countries between July 2019–May 2022 were evaluable: 56 patients with MPM, 46 with TT (23 thymomas, 23 thymic carcinomas). One third were female (21% for MPM, 54% for TT), the median age at diagnosis was 70 (IQR 55–74), 29% of the patients were first managed with a curative intent (9% MPM, 54% TT). Molecular profiling was performed on 70 FFPE samples (42 MPM, 28 TT), while in 32 cases the analysis was done on cfDNA (14 MPM, 18 TT), within a median turnaround time of 8 days. We detected relevant molecular alterations in 64 out of 102 patients (63%; 77% MPM, 46% TT), specifically in 49 of 70 FFPE samples (70%; 88% MPM and 32% TT) and 15 of 32 plasma samples (47%; 43% MPM and 50% TT). The most frequently altered genes were CDKN2A/B, BAP1, MTAP in MPM, while TP53, CDKN2A/B, SETD2 in TT. The tumor mutational burden was low across all tumor types (mean 3.2 Muts/MB), 2 tumors had MSI-high status. MTB advised for potential treatment options in 39 situations (including non-biomarker driven trials in 8 cases), for 17 MPM and 22 TT patients, and gave indication to genetic or hematologic counseling for 7 patients (mostly due to the detection of germline pathogenic variants in BAP1 or clonal hematopoiesis).

Conclusions: We found relevant genomic alterations in 63% of rare thoracic tumors, allowing broadening the treatment options for at least 30% of the patients according to MTB recommendation. cfDNA analysis efficiently recovered cases that had inadequate tumor material. Molecular testing and drug accessibility should be implemented for these patients.

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ROS1 fusions in resected stage I-III adenocarcinoma (ADC): A Lungscape ETOP study

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Background: ROS1 fusion is a relatively low prevalence (1–2%) but targetable driver in non-small cell carcinoma (NSCLC). Therefore, robust and low-cost tests are desirable in order to identify patients harboring this fusion. ROS1 immunohistochemistry (IHC) using monoclonal antibody clone D4D6 is widely used for screening patients for a potential ROS1 fusion. However, due to relatively low specificity, confirmation using an orthogonal test (FISH or NGS) has been reported as necessary. We investigated the performance of a novel IHC clone SP384 in a retrospective, stage I-III, lung ADC cohort.
Methods: FFPE sections of resected ADC from the ETOP Lungscape multicenter cohort, constructed in tissue microarrays, were prospectively stained for ROS1 protein expression using the SP384 clone in a ready-to-use kit and Ventana immunostainers. After passing an external quality control, scoring was performed locally by trained pathologists using the H-score. Staining intensity of 2+ (any %) was considered IHC positive (IHC 2/3+). Subsequently, IHC 2/3+ cases were 1:1:1 matched with IHC 0/1+ cases, and subjected to FISH and NGS analyses.
Results: Valid immunostaining results were available in 866 pts with 35 (4%) IHC 2/3. Nineteen had an average H-score of <100, eleven of 100–199 and five of 200–300. Seven IHC 2/3+ cases were not further tested (5 with an EGFR mutation (1 with H-score >200), 1 with an ALK fusion, and 1 with no material left). Of the remaining 28 IHC 2/3+ cases, only 2 (50% of 4 tested with H-score ≥200) were confirmed to have a ROS1 rearrangement, leading to an overall prevalence of 0.23%. Of the ROS1 IHC 2/3+ cases not confirmed by FISH or NGS, 7 harbored a KRAS mutation and 1 a MET mutation. All matched IHC 0/1+ cases were negative by FISH/NGS. Thus, ROS1 positivity and negativity by FISH-NGS were correctly predicted 100% by IHC 2/3+, and 96% by IHC 0/1+, respectively.
Conclusions: The prevalence of ROS1 fusion in an ADC cohort screened by IHC using SP384 clone was relatively low compared to literature. No additional ROS1 fusion was identified by FISH or NGS among IHC 0/1+. Thus, this method is useful for preselection of patients with a potential ROS1 fusion, followed by confirmatory FISH and/or NGS.
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ddPCR versus plasma NGS in detecting clearance of plasma EGFR mutations

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Background: Clearance of plasma epidermal growth factor receptor mutations (pEGFR) post-tyrosine kinase inhibitors (TKI) correlates with improved survival. While droplet digital polymerase chain reaction (ddPCR) and plasma next generation sequencing (NGS) are widely used for diagnosis, head-to-head comparisons are scarce. We sought to compare the performance of ddPCR and Oncomine Pan-Cancer Cell-Free Assay®, a 52-gene NGS panel, in detecting clearance of pEGFR as a predictor of response to EGFR TKI.

Methods: Treatment-naïve advanced EGFR-mutated lung cancer patients treated with first-line TKI at National Cancer Centre Singapore were included. pEGFR were measured at baseline and first response assessment using both ddPCR and NGS. Clearance of pEGFR was defined as undetectable levels after a positive baseline result. Results were correlated with time to treatment failure (TTTF). In exploratory analysis, corresponding change in CEA levels was evaluated.

Results: 27 patients were recruited over 1/1/2020–31/12/2021. Median age at diagnosis was 63, 19 (70%) were males and 17 (63%) were never-smokers. Ex19del comprised 74% (20/27) and L858R 26% (7/27). Osimertinib was used in 59% (16/27), Dacomitinib in 4% (1/27) and Gefitinib/Erlotinib in 37% (10/27). Sensitivity of ddPCR and NGS in detecting pEGFR mutation at baseline was 70% (19/27) and 78% (21/27) respectively (p = 0.16). All patients with detectable pEGFR by ddPCR were detected by NGS. At median 8 weeks (range 3–24) post-TKI initiation, clearance of pEGFR was achieved in 68% (13/19) and 71% (15/21) using ddPCR and NGS respectively. The concordance between ddPCR and NGS was 79% (kappa = 0.513, p = 0.013). Clearance of pEGFR was associated with longer median TTTF (not reached versus 6 months, log-rank p = 0.01). Paired CEA results were available for 14 (52%) patients. Clearance of pEGFR was associated with median decrease in CEA levels by 70% from baseline.

Conclusions: Plasma NGS trended towards higher sensitivity than ddPCR in detecting pEGFR at baseline, although both had similar concordance in detecting clearance of pEGFR. Clearance of pEGFR was predictive of improved TTTF. Our results support using NGS at diagnosis and ddPCR for monitoring response, whereas decrease in CEA levels could be explored as a surrogate for pEGFR clearance.

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Differences in response to immunotherapy between KRAS G12C and KRAS non-G12C mutated NSCLC

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Background: Distinct KRAS mutations subtypes can be found in NSCLC (Non-small cell lung cancer). Targeted therapy has become a treatment choice for patients with KRAS G12C NSCLC although immunotherapy (ICI) is widely used in these patients with good outcomes in a subset of patients. Response to immunotherapy of non-KRAS G12C NSCL is less characterized. Here we aimed to assess the outcomes on immunotherapy

for patients with tumors harboring KRAS G12C mutation compared to other KRAS mutations.

Methods: Patients with KRAS mutant NSCLC treated with immunotherapy between January 2017 and November 2022 were included in this study. Clinicopathological, molecular and clinical outcome data were collected and interrogated to evaluate associations between patients' characteristics, treatment response and survival outcomes from the beginning of ICI.

Results: A total of 71 patients with NSCLC patients with KRAS mutation were included. KRASG12C mutation was detected in 33 patients, representing 46.5% of all KRAS mutations. With a median follow-up for the overall population of 33.82 months, survival analysis showed an improved overall survival (OS) in KRAS G12C tumors compared with tumors harboring KRAS non-G12C mutations (16.9 vs 5.4 months, respectively, p = 0.02). Overall response rate (ORR) to immunotherapy was 66.7% for KRAS G12C mutated patients, compared with 42.1% (p = 0.41) in patients with other KRAS mutations. No differences in median OS were seen between KRAS G12C with and without TP53 co-mutation (17.8 vs 16.9 months, respectively, p = 0.8), neither in KRAS non-G12C (6 vs 5.2 months, respectively, p = 0.52). No significant statistically differences in PD-L1 expression were observed between KRAS G12C and KRAS non-G12C groups (p = 0.14).

Table: 193P

Characteristics	KRAS G12C (n = 33)	KRAS non-G12C (n = 38)
Age median (range)	62 (41–73)	61 (55–83)
Sex (%)		
Male	22 (66.6)	31 (81.6)
Female	11 (33.3)	7 (18.4)
Tobacco (%)		
Never smoker	1 (2.8)	1 (2.6)
Former smoker	11 (43.7)	20 (52.6)
Current smoker	21 (53.5)	17 (44.7)
Tumor stage (8th Edition) (%)		
I	2 (6)	3 (7.9)
II	2 (6)	1 (2.6)
III	7 (21.21)	6 (15.8)
IV	22 (66.6)	28 (73.7)
Co mutations (%)		
TP53	10 (30.3)	15 (39.5)
STK11	1 (3)	2 (5.3)
BRAF G469 V	1 (3)	0 (0)
PI3 K	0 (0)	1 (2.6)
CTNNB1	0 (0)	1 (2.6)
ERBB4	0 (0)	1 (2.6)
FBXW7	0 (0)	1 (2.6)
SMAD4	0 (0)	1 (2.6)
Treatment line (ICI)		
1	16 (48.5)	27 (71.1)
2	15 (45.5)	11 (28.9)
3	1 (3.0)	0 (0)
NA	1 (3.0)	0 (0)

Conclusions: Although a better overall survival in patients harboring KRAS G12C tumors was observed in our study, more biomarkers might be helpful to predict more accurately the response to immunotherapy and select the best treatment for each patient.

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194P

Motion of lymph nodes and the effect on the dose coverage in proton therapy of lung cancer

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Background: Proton therapy is sensitive to density changes, which occur in patients with large tumor motion. Individual margins, or internal target volumes (ITV) to account for motion, are used for the primary tumor (GTVp), while the nodes (GTVn) are treated with a fixed margin. The aim of this study was to evaluate the effect of nodal motion on the dose coverage in proton therapy.

Methods: The study included 58 lung cancer patients with at least an involved upper mediastinal lymph node (4), infracarinal lymph node (7), and/or hilar lymph node (10). All patients had a 4DCT. The total GTVn was delineated on the planning phase and expanded with 5 mm to the clinical target volume (CTVn). The treatment plan was robustly optimized to ensure a coverage (V95%) of at least 95%. The total GTVn was divided into separate structures for GTVn4, GTVn7 and GTVn10 and propagated to the other phases of the 4DCT. For each GTVn, the amplitude was determined using the center of mass method. To evaluate the effect of the nodal motion on the planned dose, the treatment plan was evaluated on all phases of the 4DCT. For each lymph node station, the V95% of their respective CTV was compared using the 3D and 4D evaluation doses.

Results: The motion amplitude was highest in the superior-inferior direction (table). The largest average amplitudes were 1.9 mm (left-right), 1.7 mm (anterior-posterior) and 5.7 mm (superior-inferior). V95% in the 3D-evaluation was >95% for the total GTVn, but ranged from 88–93% for the individual node stations. Loss of coverage due to breathing motion (4D-3D) was at most 1.8% (CTVn7). V95% for the hilar node stations was 93% (10L and 10R), and remained >92% in the 4D evaluation.

Conclusions: The average effect of nodal motion on the proton dose coverage was minimal. Although the superior-inferior amplitude of the

Table: 194P Amplitude in three directions and dose coverage (3D and 4D) of each lymph node station

Lymph node stations		Number of patients	Average amplitude ± SD (mm)			Dose coverage V95% (%)		
			left-right	anterior-posterior	superior-inferior	3D evaluation	4D evaluation	Difference 4D - 3D
Mediastinal	4L	15	1.6 ± 1.5	1.0 ± 0.7	2.6 ± 2.2	88.3 ± 14.1	87.5 ± 16.6	−0.8
	4R	41	1.9 ± 1.6	1.7 ± 1.0	3.4 ± 2.7	92.0 ± 6.7	91.4 ± 7.0	−0.6
	7	37	1.0 ± 0.8	1.2 ± 1.0	4.5 ± 2.9	88.3 ± 16.3	86.5 ± 17.4	−1.8
Hilar	10L	20	1.5 ± 1.8	1.0 ± 0.8	4.5 ± 3.2	92.9 ± 4.7	92.1 ± 4.9	−0.8
	10R	36	1.7 ± 1.6	1.4 ± 1.2	5.7 ± 3.2	93.2 ± 5.6	92.3 ± 5.7	−0.9
All lymph nodes		58	-	-	-	95.2 ± 1.1	94.6 ± 1.5	−0.6

hilar node stations was higher compared to the mediastinal nodes, the dose coverage of the hilar lymph nodes (V95%) remained adequate.
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195P
Efficacy of mobile health intervention on quality of life and symptom burden in lung cancer

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Background: Lung cancer and its therapy related adverse effects carry high symptom burden.[2] The primary goal of clinical management is to reduce symptom burden in order to improve quality of life.[3] Treatment adherence is a top priority for all health-care systems. A key area of innovation that may assist patients manage their health on a daily basis is the use of digital health applications. However, the effectiveness of the apps for this purpose has not been evaluated. The aim of this study is to assess the effectiveness of app based patient support program based on mobile health interventions on symptom burden, quality of life, and emotional well-being in lung cancer patients.
Methods: An interventional trial was conducted over a period of 16 weeks with participants recruited through a convenience sampling method. This was a mobile app based patient support program which included Patients diagnosed with both NSCLC or SCLC (82% patients on stage 4 and 17.39% on stage 3). Interventions included CBT (cognitive behavioral therapy), physiotherapy, onco-nutrition counseling, and tracking of symptoms and activities. FACT-LCS questionnaire, WHO-5 Well-Being Scale was used to assess symptom burden and quality of life.
Results: The current trial enrolled 30 patients (mean aged 51.87 years, SD 14.37 years) on the Wellthy Care DTx platform. The mean logs and interactions per user during the study were 29.09, 34.95 respectively. The trial witnessed an overall improvement in symptom burden and quality of life by 54.55%, 47.83% respectively. The average LCS scores of patients at baseline was 15.33 and at endline was 20.5. Paired T test witnessed a significant improvement in scores from baseline to follow up in symptoms like Shortness of breath, Cough, appetite, Tightness in chest with a significant $p < 0.05$.
Conclusions: High symptom burden is a predictive indicator of poor clinical outcome and is a significant problem for cancer patients, HCPs, and caregivers. This program seems to be an effective, feasible approach for improving quality of life, symptom management in patients with lung cancer. Digital solutions provide growing evidence in improving patient's clinical, health economic end goals and symptom management and have a revolutionary impact on Lung Cancer patient's outcomes.
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196P
A causal Bayesian network structure for predicting dyspnea in lung cancer patients

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Background: Radiation-induced lung diseases (RILD) such as dyspnea, cough, and fever can have a significant impact on the quality of life of a patient and, in rare situations, be fatal. Severe RILD is observed in about 15% of lung cancer patients treated with (chemo-) radiotherapy within the first 6 months after radiation. This study aims to develop a causal Bayesian network (BN) structure based on expert knowledge to predict dyspnea in lung cancer patients receiving (chemo-) radiation treatment.
Methods: Social, clinical, and dosimetric parameters of 730 NSCLC patients treated with (chemo) radiation at Maastro Clinic, Netherlands, from 2009–2014 were used to develop the structure. To develop the structure, eight lung cancer experts determined the causal relationship between the available variables independently. Only causal relationships that more than 50% of the expert agreed on were used to build the final structure. Structure performance was evaluated based on the Area Under the Curve (AUC) and calibration.
Results: The resulting structure included 'chemotherapy', 'Post-RT Dyspnea', 'Baseline Dyspnea', 'Mean Lung Dose, 'FEV', 'Smoking Status', and gtv1as nodes. However, gtv1 was removed from the final structure because it had too much missing information. The structure had an AUC value of 0.86 (95% CI 0.83–0.88) with a sensitivity and specificity of 0.91 and 0.73 respectively.
Conclusions: We developed a BN structure based on experts' opinions to predict if a NSCLC patient will have difficulty breathing after treatment. Our model accurately predicted post-radiation therapy dyspnea. However, the performance of the structure is still not optimal even after using a 50% concordance threshold between experts which suggests further research to choose the optimal threshold to improve structural performance. We also observed that the association between smoking status and baseline dyspnea was much stronger in the data than the number of experts agreeing that this relationship is important. This shows that clinical structures built by experts for clinical plausibility should be complemented by data evidence for optimal performance.
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197P
Combining stereotactic body radiation and low-dose radiation (EclipseRT) with PD-1 inhibitor in mice models and patients with bulky tumor

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Background: Bulky tumors remain challenging to treat. Stereotactic body radiation therapy (SBRT) can induce immunogenic cell death (ICD), thus causing T-cell-mediated antitumor effects. Low-dose radiation (LDRT) can inflame the tumor microenvironment (TME) by recruiting T cells. We designed a new radiotherapeutic method (Eclipse RT, E-RT) that combines partial SBRT and LDRT to the same large tumor with αPD-1 and examined it in mice with bulky colon CT26 or Lewis lung carcinoma. The safety and efficacy of ERT/αPD-1 in patients with bulky tumors were also retrospectively analyzed.
Methods: In mice with bulky tumors (about 400 cm^3), the whole tumor was irradiated by LDRT (2 Gy × 3 fractions) and/or the tumor center was irradiated by SBRT (10 Gy × 3); αPD1 was given weekly. The dependence of therapeutic effects on $CD8^+$ T cells was determined using depleting antibodies. Frequencies of $CD8^+$ T cells and M1 macrophages (Mφ) were determined by FACS. Multiplex IHC was applied to analyze $CD8^+$ T cells and p-eIF2α (ICD marker) in TME. Kaplan-Meier method was applied to estimate the patients' progression-free survival (PFS) and overall survival (OS).
Results: ERT/αPD-1 is superior to SBRT/αPD-1 or LDRT/αPD-1 in controlling bulky tumors in both mouse models and it depended on $CD8^+$ T cells. In the CT26 model, ERT/αPD-1 cured 3 of 11 mice and induced more $CD8^+$ T cells and M1 Mφ compared to other groups. Multiplex IHC analysis showed that ERT/αPD-1 induced higher

infiltration of $CD8^+$ T cells into the tumor center and periphery compared to other groups, and ERT/αPD-1 induced stronger ICD in the tumor center compared to LDRT/αPD-1. In 39 patients with bulky tumors treated with ERT/αPD-1, 30 patients were diagnosed with stage IV NSCLC and failed lines of therapy. Radiation-induced pneumonitis occurred in 1 of 26 patients receiving thoracic ERT. The overall response rate and the median estimated PFS are 46.9% and 5.6 months, respectively. The minimum estimated OS is 16.8 months and the median estimated OS does not reach yet.

Conclusions: ERT/αPD-1 showed superior efficacy in controlling bulky tumor in two mouse models. ERT/αPD-1 was safe and effective in patients with bulky tumors and it might become a new strategy to treat these patients.

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198TiP

Immuno-PET in predicting immune checkpoint inhibitor response in non-small cell lung cancer

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Background: Non-small cell lung cancer (NSCLC) accounts for 80–90% of all lung cancer cases, the leading cause of death by cancer worldwide. Fortunately, great advances in therapy have been achieved over those last years. Immune checkpoint inhibitors (ICI) are an example, having significantly changed prognosis in these patients, however not for all. Multiple biomarkers have been studied to stratify responders from non-responders. Detection of programmed cell death ligand-1 (PD-L1) expression in tissue biopsy is until now the most predictive. Even though, patients with the same value of PD-L1, even if high, may have different response to ICI which is a critical aspect in clinical approach. As tumoral heterogeneity is a known and determinant factor for therapy response, its accurate evaluation by immuno-PET may represent a valid and clinically useful strategy to help predict response to ICI. It may represent the first step to improve global NSCLC treatment strategy including overcoming of ineffective treatments in a disease that is known to be very aggressive and where the unique opportunity to best treat cannot be missed.

Trial design: This multicenter study will include the development of 89Zr-pembrolizumab PET at Nuclear Institute-ICNAS and usual care and imaging follow-up of patients with locally advanced or metastatic NSCLC with PD-L1 expression on tumor biopsy of ≥50% eligible for first-line pembrolizumab at Leiria Hospital Center and Coimbra Hospital and University Center. At baseline patients will be submitted to [18F] FDG-PET and immuno-PET. They will receive the combined dose of 2.5 mg pembrolizumab labeled with 37 MBq 89Zr-oxalate and 2.5 mg of unlabeled pembrolizumab and imaging will be carried out on day 7 after tracer injection. Neutrophil-lymphocyte ratio (NLR) will also be calculated. Treatment with pembrolizumab will be started within two weeks and usual care and imaging follow-up will be performed. Tumor response to pembrolizumab will be measured by objective response rate (iRECIST criteria). To determine whether immunoPET can help identify responders analyse will be performed by SUV lesion determination, [18F] FDG and 89Zr-pembrolizumab PET paired positive lesion determination and combination with NLR.

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Disclosure: All authors have declared no conflicts of interest.

TUMOUR BIOLOGY AND PATHOLOGY

199P
Suppression of mutant Kirsten-RAS (KRAS G12C) non-small cell lung cancer (NSCLC) resistance to KRAS G12C inhibitors by dual inhibition of hepatocyte growth factor receptor (MET) and V-ATPase

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Background: Rapid reactivation of KRAS guanosine triphosphate (GTP) resistance to covalent KRAS G12C inhibitors in NSCLC cells is possibly associated with lower expression of regulator RGS3 GTPase-activating protein. Enhanced MET expression is essential for anchorage-independent growth of KRAS-mutant NSCLC cells. Increased MET levels have been reported in sotorasib resistant cells.
Methods: Establishment of sotorasib and trametinib resistant H358, H23, A549, H460 NSCLC cells lines were performed. In vitro growth inhibitory assays determined cell viability after 3-day treatment with omeprazole, tepotinib or combination. Western blotting was carried out with antibodies specific for phospho-AKT, phospho-ERK1/2, phospho-MET, enolase 1 (ENO1), RGS3, and actin. In vivo tumor growth inhibitory assay was performed with H358 in female BALB/c-Nude mice.
Results: Pretreatment with omeprazole + tepotinib shows broad-spectrum tumor shrinkage in KRAS G12C sensitive and resistant to sotorasib (H358, H23) and in KRAS non-G12C cell lines (A549, H460). Synergism was sustained with HGF stimulation in H358 resistant cell line (CI = 0.790). Colony formation assay shows similar growth inhibition in KRAS G12C and non G12C parental and resistant. In H358 xenograft mice model tumors were efficiently suppressed with omeprazole+tepotinib combination. Cell signaling analysis revealed that the combination shut down crosstalk between MET and Wnt signaling by downregulating enolase 1 and lipoprotein receptor-related protein (LRP5/6), enhancing RGS3 expression.
Conclusions: Co-treatment with v-ATPase and MET inhibitors is active in KRAS-mutant G12C and non-G12C NSCLC parental and resistant to covalent KRAS G12C inhibitors and MEK inhibitors. Intracellular signaling identifies interplay within MET and Wnt pathway and glycolysis inhibition. A clinical protocol was set up to test ex-vivo (patient derived lung tumor organoid fresh biopsy collection) in KRAS-mutant NSCLC patients.
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200P
Dissecting mechanisms of resistance to new generation selective RET inhibitors in NSCLC

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Background: Non-small cell lung cancer (NSCLC), the most common cause of cancer-related deaths, harbors RET rearrangements in up to 2% of cases. Novel selective RET inhibitors, BLU-667 and LOXO-292, showed promising anti-tumor activity. Despite the positive clinical outcomes, not all patients benefit from RET inhibitors and a significant fraction eventually progress, underscoring the need to discover novel therapeutic approaches.
Methods: We chronically exposed CCDC6/RET Lc-2/AD NSCLC cells to increasing doses of BLU-667 and LOXO-292 to generate cells resistant to the drugs (BluR and LoxoR, respectively). RNA-Seq analysis was used to define transcriptional profiles sustaining resistance. SiRNA-mediated knock-down and pharmacological treatment were used to re-sensitize resistant cells, while stable over-expression of candidate gene to induce resistant phenotype in sensitive cells. We further tested combination therapies in vivo.
Results: RNA-Seq studies revealed (i) a significant enrichment of Epidermal Growth Factor Receptor (EGFR) signaling pathway in BluR and LoxoR cells compared to sensitive parental cells, and (ii) AP1 complex members hyper-activation in resistant models. We hypothesized that, under AP1 regulation, EGFR could prompt compensatory mechanisms to RET inhibition, in turn pushing signalling pathways (MAPK) responsible for cell proliferation. siEGFR, as well as AP1 complex members siRNAs, led to a drastic reduction of cell viability and a significant decrease of MAPK activation in BluR/LoxoR cells, overcoming the resistant phenotype. On the other hand, we verified that EGFR overexpression reduced sensitivity of NSCLC cells to RET inhibitors. Since combination study revealed a synergistic effect of BLU-667 and anti-EGFR (afatinib) in vitro, we injected Lc-2/AD-BluR xenografts in Balb/c mice and we verified that tumor growth resulted impaired by combination of afatinib and BLU-667. These data strongly support our hypothesis of a pivotal role for EGFR in anti-RET resistance.
Conclusions: Our findings suggested that targeting EGFR signaling pathway in combination with RET inhibitors therapy may provide a novel treatment strategy for patients unresponsive to RET inhibitors in NSCLC.
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201P

RNA-based plus DNA-based analysis of METexon 14 skipping in a non-small cell lung cancer increases diagnostic performance

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Background: MET exon 14 skipping mutations (METex14 skip) are found in approximately 3–5% of non-small cell lung cancer (NSCLC) and typically occur in the absence of other driver mutations. The recent approvals of MET-tyrosine kinase inhibitors (TKIs) capmatinib and tepotinib have significantly changed clinical outcomes in this subgroup of patients. Consequently, reliable molecular diagnostic approaches that detect these variants are vital for patient care. This study assessed the potential advantages of running an RNA-sequencing assay on top of DNA-based next-generation sequencing (NGS) for METex14 skip detection.

Methods: All NSCLC samples tested at Oncoclínicas Precison Mecidine (OCPM) from March 2020 to December 2022 were retrospectively evaluated. Archived formalin-fixed paraffin-embedded (FFPE) tumor material underwent DNA/RNA extraction followed by NGS with in-house developed GS180 panel (Anchored Multiplex PCR [AMP™] DNA and RNA assay, Archer Dx).

Results: From 548 samples, RNA seq failed in 142 cases (26%). Prevalence of METex14 skip in samples tested with DNA seq only was 4.9% and in the entire cohort with DNA and/or RNA seq was 7%. Out of the 28 cases with METex 14 skip DNA alterations, in 7 cases (25%) we found deep intronic events outside the canonical splice site. In 12 out of 37 cases (32%) the diagnosis of METex14 skip was contingent on RNA sequencing results (DNA failure or hidden deep intronic event). From 26 cases with informative DNA plus RNA sequencing results, the discordance rate was 46%, with METex 14 skip being detected by DNA only in 7 cases (27%) and RNA only in 5 cases (19%).

Conclusions: The prevalence of METex14 skip in Brazilian patients with nsNSCLC is slightly higher than published literature. Unlike other oncogenic drivers, METex14 skip present unique analytical challenges due to variant complexity that require high-quality NGS and optimized bioinformatics pipelines for accurate detection. RNA-based assays increase sensitivity for METex14 skip and support the interpretation of complex intronic events detected by DNA seq. However, RNA-based assays are highly reliant on RNA quality, which can be suboptimal in some clinical samples.

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202P

Molecular kaleidoscope of EGFR mutant NSCLC: Be as precise as possible

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Background: EGFR mutant NSCLC has shown remarkable response since the approval of osimertinib in the first-line. However, despite initial response, many patients do not show sustained clinical benefit. This is attributed to other intrinsic mechanisms owing to concurrently occurring genomic alterations along with EGFR, both clonal and/or subclonal. This is one of the largest cohorts depicting the effect of these mutations on TKI treatment.

Methods: 192 patients of advanced EGFR mutant NSCLC treated with first-line EGFR TKI were included. Next generation sequencing was performed on the diagnostic tumor blocks using a customized lung panel comprising 34 genes. Clinical and genomic features were correlated with outcomes like PFS, OS and objective response rates.

Results: Of the 192 patients included, at least 1 additional genomic alteration was encountered in 91 cases (47.6%). Median number of additional mutations was 2 per patient. EGFR exon 19 mutations were more commonly associated with concurrent alterations when compared to the L858R group (68.6% vs 41.1%, p = 0.05). Uncommon EGFR subgroup showed no additional alterations. Most frequent co-mutation was in the TP53 gene seen in 91 (47.5%) cases, followed by PI3KCA in 41 (21.4%) cases. Other alterations seen included PTEN (9.8%), RB1 (7.2%), KRAS (6.9%), KDR (3.2%) mutations, and FGFR1 and MET amplification. Exon 19 subgroup showed a higher occurrence of PTEN and RB1, contrary to L858R which showed higher TP53 and PIK3CA alterations. Patients with co-occurring PIK3CA showed a shorter PFS (7.8 months vs. 11.3 months p < 0.05) and OS (23.4 months vs. 34.3 months, p = 0.06) after adjustment for use of osimertinib. Similar trend was seen with TP53 concurrent mutations (HR for PFS: 1.78 95%CI = 0.9–2.1). There was no significant correlation of survival measures with the mutant allele burden or type of TKI used.

Conclusions: EGFR mutations in NSCLC show a higher prevalence in this part of the world, and this study also proves that the heterogeneity and molecular landscape of this molecular subgroup is distinct from that of the West. Impact on survival outcomes warrants panel based NGS testing at baseline in all EGFR mutant cases in order to optimise sequencing of TKIs.

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203P

MET gene copy number heterogeneity in non-small cell lung cancer patients resistant to EGFR-TKIs

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Background: Accumulated evidences have demonstrated that mesenchymal epithelial transition (MET) amplification is one of the main mechanisms of epidermal growth factor receptor–tyrosine kinase inhibitors (EGFR-TKIs) resistance in non-small cell lung cancer (NSCLC). Thus, accurate detection of MET gene copy number (GCN) is essential for the treatment of advanced NSCLC patients resistant to EGFR-TKIs. Herein, we analyzed MET GCN variants including amplification and polysomy in NSCLC patients with resistance to EGFR-TKIs.

Methods: Sixty-nine NSCLC patients resistant to first/second-generation EGFR-TKIs and 63 patients resistant to third-generation EGFR-TKIs were enrolled in this study. MET GCN was detected by FISH using MET and centromere (CEP7) probes in all cases, and by NGS in 38 patients resistant to third-generation EGFR-TKIs.

Results: Compared with NSCLC patients resistant to first/second-generation EGFR-TKIs, both incidences of GCN variants [amplification +polysomy, 11.6% (8/69) vs. 42.9% (27/63), P < 0.001] and amplification [5.8% (4/69) vs. 27.0% (17/63), P = 0.001] were significantly increased in patients resistant to third-generation EGFR-TKIs by FISH. Interestingly, heterogeneity of MET GCN variants, including 7 cases with

MET amplification and 1 case with polysomy, was observed only in patients resistant to third-generation EGFR-TKIs, but not in patients resistant to first/second-generation EGFR-TKIs (8/27 vs. 0/8, P = 0.156), although the difference was not statistically significant due to the limited cases. Of 38 cases detected by NGS, 100% (7/7) of patients with FISH homogeneous MET amplification was identified as positivity for MET copy number gain, while only 33.3% (2/6) of heterogeneous amplification and 20.0% (1/5) of polysomy were MET positive.
Conclusions: Higher incidence and heterogeneity of MET GCN variants were demonstrated in NSCLC patients resistant to third-generation EGFR-TKIs than patients resistant to first/second-generation EGFR-TKIs. In technology, FISH showed advantages in detection of MET GCN as compared with NGS. Collectively, these results may provide a guiding role in the accurate detection of MET GCN and subsequent treatments.
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204P
Dysbiosis of the gut microbiome impairs EGFR-tyrosine kinase inhibitors responses in H1975 xenografts mice models

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Background: Proton Pump Inhibitor-Induced Gut Dysbiosis has been demonstrated in previous studies and was associated with poor prognosis in patients received immunotherapies and chemotherapies. However, little is known about the influence of Proton Pump Inhibitor-Induced dysbiosis on efficacies of target therapies like epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs). We conduct a study to elucidate the role of PPI related dysbiosis on EGFR-TKIs efficacies.
Methods: Female BALB/c Mice were raised in specific pathogen-free (SPF) conditions and treated for 14 days proton pump inhibitor, lansoprazole (5 mg/kg) or control. Microbial was tested using NGS with the computational analysis of targeted (16S rRNA hypervariable regions). BALB/c mice were implanted with 5×10^6 H1975 NSCLC subcutaneously and treated orally when tumors reached 20 to 35 mm^2 in size with EGFR-TKIs, Osimertinib (1 mg/kg/day). Feces were cultured on 5% sheep blood enriched Columbia Agar for aerobic and anaerobic conditions, respectively.
Results: Our study revealed PPI impaired TKI effectiveness in H1975 xenografts mice models (tumor fold change, with vs. without PPI: 28.1 vs. 7.4, p = 0.043). The feces culturomic analyses revealed Clostridiales vadin BB60 group was more abundances in xenogeneic EGFR-TKIs mice treated with PPI than without. The optimal cut-off point of relative abondance of operational taxonomic units (OTU) for Clostridiales vadin BB60 group determined by the ROC curve was 10.9%, p = 0.046. Mice with high abundance of Clostridiales vadin BB60 group had higher D17 tumor volume fold change (high vs low abundance of Clostridiales vadin BB60 group: 34.0 vs. 8.1, p = 0.025). Another taxa lactobacillus was more abundances in xenogeneic EGFR-TKIs treated mice with PPI than without. The optimal cut-off point of relative abondance of operational taxonomic units (OTU) for lactobacillus determined by the ROC was 0.3%, p < 0.001. Mice with high abundance of lactobacillus had higher D17 tumor volume fold change than mice with low abundance (tumor fold change 43.6 vs. 9.1, p = 0.04) by Mann-Whitney test.
Conclusions: Our study revealed PPI related dysbiosis are associated with poor EGFR-TKIs response in H1975 xenografts Mice.
Clinical trial identification: The Institutional Animal Care and Use Committee approved animal operative and experimental processes in Kaohsiung Chang Gung Memorial Hospital (Affidavit No. 2020030503).
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Disclosure: All authors have declared no conflicts of interest.

205P
Modelling of NSCLC aPD1 responses in bronchoscopic biopsies on chip (bronchoBOCs)

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Background: Eligibility for aPD1 therapy is based on PD-L1 expression, but few patients experience durable responses. Tumours cultured in microfluidic devices (tumour-on-chip) recapitulate the in vivo micro-environment and are being developed as drug screening platforms. Their application to advanced NSCLC is hampered by the unavailability of surgical tumour resection specimens in these patients. To overcome this, we aimed to develop a methodological approach that will allow culture of bronchoscopic tumour biopsies on chips to model drug responses.
Methods: Bronchoscopic biopsies from 25 NSCLC patients were dissected and filtered to obtain tumour spheroids of 40–100 μm in size (3×10^5 spheroids/biopsy). AIM biotech chips consisting of a central channel and 2 lateral channels were used. Tumour spheroids were dispersed in matrigel and split in the central channels of 2 chips. Endothelial cells were cultured at the lateral channels to mimic vasculature. Pembrolizumab (aPD1) vs isotype control was administered in the lateral channels (10 μg/mL). After 48 h effluents were analysed by cytometric bead array (CBA) for cytokines and cytotoxic molecules. Spheroids, along with effluents, were analysed by mass spectrometry (LC MS/MS).
Results: CBA analysis showed a robust increase in the release of granzyme B and granulysin, used by T cytotoxic cells to kill cancer cells, in pembrolizumab-exposed effluents. LC MS/MS identified 122 differentially abundant proteins in pembrolizumab-treated vs control spheroids and 71 differentially abundant proteins in effluents. Pathway enrichment analysis suggested that pembrolizumab activated innate and adaptive immune responses and signal transduction pathways in bronchoBOCs.
Conclusions: We developed the first bronchoBOCs that develop physiologically-relevant responses to aPD1. We envisage to use bronchoBOCs for biomarker identification, as drug screening platform and to increase our mechanistic understanding of human tumour immunity.
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206P

Synchronous brain metastases and paired lung adenocarcinomas show similar methylation patterns

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Background: Brain metastasis (BM) is a frequent event in patients with lung adenocarcinoma (LUAD) and BM can respond discordantly to systemic therapy compared to extracranial disease resulting in often dismal prognosis. Therefore, there has been an increasing interest to better understand the biology of BM. However, most publications focused on the genomic differences between the primary tumor and its metastases and data on changes on the transcriptional and especially epigenetic level is scarce. In this study, we investigated the methylation changes between primary LUAD and paired BM.
Methods: We conducted a retrospective single center study including all treatment naïve patients with sufficient tissue from paired synchronous LUAD and BM resected between 2000–2019. DNA was extracted from archived formalin-fixed paraffin-embedded sections after macrodissection of the region of interest. Methylation profiling was done with the Infinium MethylationEPIC v1.0®.
Results: Methylation profiling was possible for 24 patients. Five patients were excluded due to low DNA quality. The principal component analysis depicted a high similarity between primary LUAD and paired BM, whereas normal control tissue clustered separately and by organ (lung respectively brain). Unsupervised hierarchical clustering confirmed these results with the most discriminatory feature being the patient and not the origin of tissue. Most sites were hypomethylated in the BM as compared to the LUAD. These hypomethylated sites were often not associated to islands and located in the gene body. However, hypermethylated sites were associated to islands and more often located in potential promotor regions. The MAPK signaling pathway was the most differentially methylated pathway.
Conclusions: Only subtle differences are present when comparing LUAD and paired BM on the methylome level. These differences are primarily characterized by hypomethylation in the gene bodies and hypermethylation in promotor regions. Our results confirm the importance of the MAPK pathway (including EGFR and KRAS) at the epigenetic level which has also been described on the genomic level.
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Disclosure: S. Berezowska: Financial Interests, Institutional, Advisory Board: Daiichi-Sankyo, Eli Lilly, Merck; Financial Interests, Institutional, Other, active participation in webinar: BMS. All other authors have declared no conflicts of interest.

207P

Does age affect PD-L1 expression? Results of a single-center analysis of a large cohort of patients

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Background: Tumor-programmed death ligand 1 (PD-L1) expression is a key biomarker analyzed in patients diagnosed with advanced non-small cell lung cancer (NSCLC). It is important to determine the real-world prevalence of PD-L1 expression and indicate differences in clinically relevant patient subgroups-including the elderly population.
Methods: Samples of patients (pts) who qualified for the first-line treatment of advanced NSCLC in 2017–2022 were analyzed. Immunohistochemistry was performed using the PD-L1 kit (PD-L1 IHC 22C3 pharmDX; Dako). Descriptive analysis, applying chi-square test to compare PD-L1 categories between groups, and logistic regression to calculate odds ratios were performed.
Results: A samples of 1710 pts were analyzed. The median age was 68 years, 34.5% of pts were <65 while 17.3% were >75 years old. The prevalence of squamous-cell carcinoma in the entire population was 35.7%, adenocarcinoma 51.5%, NOS 2.7% and other types 10.1%. PD-L1 expression ≥50% was found in 33.3% of pts, while 1–49% and <1% in 23.8% and 42.8% of pts, respectively. In 5% of the cases, no reliable test result was obtained due to insufficient cellularity of specimens (<100). PD-L1 expression <1% was observed more frequently in patients with non-squamous carcinoma (46.3% vs 37.1%; p = 0.001). Other variables - gender and type of sample (excisional biopsy, thick needle biopsy) - of the entire population, had no impact on the prevalence of PD-L1 expression. Additional analysis was performed in subgroups in relation to age. In the group of patients >65 years of age, no differences were observed for expression levels >1% (p = 0.280) and >50% (p = 0.368), similarly in the group of patients >75 years of age – p = 0.169 and p = 0.882, respectively. However, subgroup analysis indicated a higher probability of <1% expression in patients >65 years of age with a diagnosis of non-squamous carcinoma (OR 0.65, p = 0.00; 95% CI 0.49–0.85).
Conclusions: Analysis of a large cohort of patients indicated an association between non-squamous cancer type in elderly pts and a higher incidence of PD-L1 <1% expression. In 5% of analyzed pts, tests were not feasible. Alternative diagnostic methods for PD-L1, including soluble forms of biomarkers, are needed.
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208P

Lung cancer: Precise prediction

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Background: 5-survival (5YS) and life span after radical surgery for non-small cell lung cancer (LC) patients (LCP) (T1-4N0-2M0) was analyzed.
Methods: We analyzed data of 771 consecutive LCP (age = 57.6 ± 8.3 years) radically operated and monitored in 1985–2022 (m = 662, f = 109; lobectomies = 516, pneumonectomies = 255; combined procedures = 194; only surgery-S = 620, adjuvant chemoimmunoradiotherapy-AT = 151: CAV/gemcitabine+cisplatin+thymalin/taktivin+radiotherapy 45–50 Gy; T1 = 322, T2 = 255, T3 = 133, T4 = 61; N0 = 518, N1 = 131, N2 = 122, M0 = 771; squamous = 418, adenocarcinoma = 303, large cell = 50; early LC = 215, invasive LC = 556. Variables selected for study were input levels of 45 blood parameters, sex, age, TNMG, cell type, tumor size. Regression, clustering, SEPATH, Monte Carlo, bootstrap, neural networks were used to determine significant dependence.
Results: Overall life span (LS) was 2240.9 ± 1748.8 days and 5-year survival (5YS) reached 73%, 10 years – 64.2%, 20 years – 43%. 503 LCP lived more than 5 years (LS = 3126.6 ± 1536 days), 145 LCP – more than

10 years (LS = 5068.5 ± 1513.2 days).199 LCP died because of LC (LS = 562.7 ± 374.5 days). 5YS of LCP after lobectomies was significantly superior in comparison with LCP after pneumonectomies (77.7% vs. 63.4%, P = 0.00001). AT significantly improved 5YS (64.4% vs. 34.8%) (P = 0.00003 by log-rank test) only for LCP with N1-2. Cox modeling displayed that 5YS of LCP significantly depended on: phase transition (PT) early-invasive LC, PT N0—N12, cell ratio factors (ratio between cancer cells- CC and blood cells subpopulations), G1-3, histology, glucose, AT, blood cell circuit, prothrombin index, heparin tolerance, recalcification time (P = 0.000–0.035). Neural networks, bootstrap simulation revealed relationships between 5YS and PT early-invasive LC (rank = 1), PT N0–N12 (rank = 2), thrombocytes/CC, eosinophils/CC, erythrocytes/CC, healthy cells/CC, segmented neutrophils/CC, lymphocytes, stick neutrophils/CC, monocytes/CC; leucocytes/CC. Correct prediction of 5YS was 100% by neural networks computing.

Conclusions: 5YS of LCP after radical procedures significantly depended on: PT early-invasive cancer; PT N0–N12; cell ratio factors; blood cell circuit; biochemical factors; hemostasis system; AT; LC characteristics; surgery type; LC cell dynamics; anthropometric data.

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209P
Clinicopathological features and survival outcome of keratinizing versus non-keratinizing squamous cell lung cancer

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Background: Non-small cell lung cancer represents 85% of all lung cancers. Recently, the histologic subtypes play critical role in patient management and gained importance because of the therapeutic implications of each subtype. Squamous cell subtype accounts for 25% of non-small cell lung cancer with poor prognosis compared to adenocarcinoma. This study aims to assess the impact of keratinization of squamous cell lung cancer on survival outcome with further stratification of the age, grade and stage to fill a gap in the current literature for this subtype.

Methods: We obtained the data of 12 229 patients from Surveillance, Epidemiology and End Results (SEER) software, all of them had pathologically confirmed squamous cell lung cancer; keratinizing (n = 8387) and non-keratinizing (n = 3842). They were diagnosed from 2000 to 2019. We used SPSS 23 IBM for data analysis. Kaplan-Meier curve, Log-rank test for survival analysis.

Results: The age standardized 3-year and 5-year survival for squamous cell lung cancer was 30.7% and 22.8% while the 5-year overall relative survival for keratinizing and non-keratinizing squamous cell lung cancer was 21.1% and 28.6%; P > 0.0001. Non-keratinizing type had improved survival outcome in both age groups: 65+ years and less than 65 years (27.9% and 30.0%; P > 0.0001). Performing COX-regression model revealed age, gender, stage and grade were associated with poor survival outcome (P > 0.05).

Conclusions: The non-keratinizing type had slight improved overall survival outcome and survival benefit across all age groups, localized stage, grade I and grade II compared to the keratinizing type. We encourage more studies to evaluate treatment regimens specific to squamous cell lung cancer putting keratinization feature into consideration in addition to the other risk factors.

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210P
Expression of cancer stem cell markers SOX-2 and OCT-4 and their regulation by nicotine in non-small cell lung carcinoma

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Background: Lung cancer remains one of the leading causes of cancer-related death worldwide and approximately 80% of lung cancers are non-small cell lung carcinomas (NSCLC). The incidence of lung cancer is highly correlated with cigarette smoking and nicotine is the addictive component of tobacco smoke. Nicotine can promote proliferation, migration, and invasion of cells in vitro and promote tumor growth and metastasis in vivo through activation of nicotine acetylcholine receptors. Recently, nicotine is implicated in promoting self-renewal of cancer stem cells in lung cancer. Cancer stem cells (CSC) are a subset of tumor cells that has the ability to self-renew and generate tumor heterogeneity leading to tumor progression and invasion. This study was done to evaluate the expression of CSC markers SOX-2 and OCT-4 in NSCLC and their regulation by nicotine.

Methods: Tissue samples were collected from 40 histopathologically confirmed cases of NSCLC and expression of SOX-2 and OCT-4 was evaluated using immunohistochemistry. The mean immunoreactive score (staining intensity x proportion of positive cells) was calculated and compared between tumor tissue and adjacent normal lung tissue. The immunohistochemical expressions of SOX-2 and OCT-4 were also correlated with clinicopathological parameters such as age, gender, tobacco habit and histopathological grade of the tumor. Experiments were conducted using A549 human lung adenocarcinoma cell lines, where cells were serum starved for 24 hrs and stimulated with 2 μM nicotine. The induction of SOX-2 was examined using immunofluroscence microscopy.

Results: The mean immunoreactive score of SOX-2 and OCT-4 was higher in tumor tissues compared to adjacent normal tissue in patients with NSCLC Higher expression of CSC markers was noticed in tobacco habituates (p = 0.001) and in poorly differentiated tumors (p = 0.01). SOX-2 was found to be induced after 21 hours of nicotine stimulation in A549 lung cancer cells.

Conclusions: Our findings shed light on novel molecular mechanisms underlying the pathophysiology of smoking- related lung cancer in the context of cancer stem cell populations, and reveal new pathways involved that could potentially be exploited therapeutically.

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GENERAL INTEREST

211P

The impact of the COVID-19 pandemic on lung cancer stage shift and the delivery of surgical lung cancer care in the United States

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Background: To investigate whether there was a shift towards later stages of lung cancer diagnosed and worse lung cancer care nationally in the U.S. during the first year of the COVID-19 pandemic.
Methods: Patients diagnosed with stage I-IV non-small cell lung cancer from January 1st, 2015 to December 31st, 2020 in the U.S. National Cancer Database were identified for analysis. Changes in the odds of being diagnosed with one lung cancer stage higher in 2020 vs. 2015–2019 ("pre-pandemic period") were assessed using multivariable ordinal logistic regression. Of patients diagnosed with stage I NSCLC, changes in the (1) odds of undergoing surgery; (2) odds of receiving delayed surgery (surgery >3 months after diagnosis); and (3) odds of receiving anatomic resection (as opposed to wedge resection) were evaluated using multivariable logistic regression. All multivariable models were adjusted for clinically relevant variables and linear time trends.
Results: A total of 622,983 patients met study inclusion criteria. Compared to the pre-pandemic period, there was a 9% increase in the odds of being diagnosed with one lung cancer stage higher in 2020 (aOR: 1.09, 95% CI: 1.06–1.12, P < 0.001). However, among patients diagnosed with stage I NSCLC, there were no significant changes in the odds of undergoing surgery (aOR: 0.99, 95% CI: 0.94–1.04, P < 0.001) in 2020 compared to the pre-pandemic period. Furthermore, among patients who underwent surgery for stage I NSCLC, there were no significant changes in the odds of receiving delayed surgery (aOR: 1.02, 95% CI: 0.94–1.12, P = 0.62) or odds of receiving an anatomic lung resection (aOR: 0.98, 95% CI: 0.89–1.07, P = 0.61) in 2020 compared to the pre-pandemic period.
Conclusions: In this national analysis, during the first year of the COVID-19 pandemic, surgical lung cancer care delivered by thoracic surgeons was not compromised. However, there was a significant increase in the percentage of patients diagnosed with stage IV NSCLC when compared to the pre-pandemic period. With future COVID-19 surges imminent, the study findings illustrate the urgency of implementing policies that ensure high-risk individuals continue to receive timely lung cancer screening.
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212P

Impact of COVID-19 on the timeliness to care in a rapid access lung lesions clinic in a large Australian cancer centre

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Background: Despite being the fifth most diagnosed cancer, lung cancer has the highest mortality rate in Australia. The Rapid Access Lung Lesion Clinic (RALLC) was developed in our health service in 2017 to streamline assessment, diagnosis and management of patients with a suspected or new diagnosis of lung cancer.
Methods: A retrospective review of patients referred to RALLC between 2017 and 2021 was undertaken to assess the impact that the COVID-19 pandemic had on timeliness to care. During this time, 285 patients were referred through RALLC. 19 patients were excluded from analysis as they did not undergo biopsy or were investigated externally. Of the remaining 266, 138 were referred between 2017–2019 (pre-COVID) and 128 between 2020–2021 (during COVID).
Results: In terms of cancer stage at diagnosis, the two groups were similar with 60 (43.5%) and 54 (42.2%) patients presenting with stage 1 or 2 disease, 30 (21.7%) and 27 (21.1%) with stage 3 cancer, and 48 (34.8%) and 47 (36.7%) with stage 4 cancer for the pre-COVID and during COVID cohorts respectively. A higher percentage of patients presented with metastatic disease during COVID compared with pre-COVID. The median time from referral to first RALLC appointment was 7 days, referral to diagnosis was 18.5 days, and referral to treatment was 41.5 days in the pre-COVID cohort, compared with 10, 21 and 47.5 days respectively during COVID. These results showed longer median wait times between each point of care during COVID compared with pre-COVID.

Table: 212P Timeliness to care

	Median time (days)	
	Pre-COVID 2017–2019	During COVID 2020–2021
Referral to first RALLC appointment	7	10
Referral to diagnosis	18.5	21
Referral to treatment	41.5	47.5
First RALLC appointment to diagnosis	9	11
First RALLC appointment to treatment	33	37
Diagnosis to treatment	20	26.5

Conclusions: This review demonstrated that across all timepoints assessed, the median time between each timepoint through RALLC was delayed during the COVID-19 pandemic compared with pre-pandemic wait times. Whether the delays in timeliness to care due to the COVID-19 pandemic resulted in poorer outcomes is currently being investigated at our institution.
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213P

Development of an explainable clinical decision support tool for advanced lung cancer patients

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Background: Pulmonologists have the complex task to select the optimal treatment for patients with advanced lung cancer to extend survival duration while minimizing side-effects. They do this mainly based on patient's demographic and clinical data, patient preferences and guidelines. Digitalization of healthcare makes it possible to support this treatment selection process, aiming at more personalized and precise medicine. This study introduces a clinical decision support tool, based on prediction models for survival and burden of treatment, explainable machine learning (ML) and a Graphical User Interface (GUI) for physicians.
Methods: ML models were trained on cohorts ranging in size of 89–405 lung cancer patients with stage IIIB and IV, to predict the survival probability for different treatment options, 6 weeks, 3 months, 6 months

and 1 year after the start of the first treatment. Additional models were trained on the evolution of two symptom scales, dysphagia and alopecia, of the EORTC-QLQ-LC13 questionnaire to forecast the burden of treatment. Patient demographics, laboratory results, comorbidities, tumour characteristics and treatment regimens were used as features. All models combined allow the pulmonary oncologist to simulate different therapy responses via an in-house developed GUI.

Results: The classification prediction models achieved good performance results with area under the curve values ranging from 0.78 to 0.86. In practice, a physician enters a patient identifier in the GUI. Then, the tool automatically collects all required features of the patient, flagging divergent values. After selecting a treatment schedule, the model probability outcomes are depicted, as well as the importance of each feature (based on Shapley scores) which enables the pulmonologist to understand the rationale behind the ML model's predictions.

Conclusions: We have proven that models trained on real world hospital data are capable of making reliable outcome predictions. This GUI can be used in clinical practice, provided that extra data is collected and an extensive validation procedure takes place. This will enable physicians to use data-driven predictions based on patient and disease characteristics as support in their treatment decision process.

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214P
Development of a nomogram to predict the progression-free survival in lung cancer patients

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Background: Evidences over decades made clear that lung cancer is the most aggressive cancer worldwide causing a high probability of progression and death. The aim of this study, is to build and validate internally a nomogram to predict the progression-free survival (PFS) in Moroccan patients diagnosed with lung cancer.

Methods: Data of 1200 lung cancer patients diagnosed between 2013 and 2021 in the Medical Oncology Department at Mohammed VI University Hospital of Marrakech were extracted manually from patient medical record, and filtered by applying exclusion criteria. The cohort was then split into training and test cohorts with a ratio 2:1. In the training cohort, the independent prognostic factors were determined using Cox Proportional Hazards Regression through univariate and multivariate analyses. We then constructed a nomogram to predict 6-, and 12- months PFS of LC patients, calibrate it and checking the discriminative ability of nomogram. Finally, the model was validated internally based on test cohort.

Results: A total of 342 patients fitted with inclusion criteria, were split and interred into the analysis. From 29 selected factors, five have been independent to predict SSP including performance status, surgery, radiotherapy, number of cures of the first-line chemotherapy, and thrombocytopenia and therefore integrated to establish the nomogram. The calibration and receiver operating characteristics curves also shows that the clinical prediction model performed satisfactorily in predicting the outcome. The area under the ROC curve (AUC) value of the nomogram predicting 6-, and 12-months PFS rates were 0.8, and 0.83 for the training cohort, 0.8 and 0.78 for the validation cohort respectively. The median PFS time was 209 days (95% CI, 185 to 227 days).

Conclusions: We tried to established a novel medical tool to predict the PFS based on a purely well-defined African cohort taking into account demographic, clinic-pathologic, oncogenic drivers, treatments related patients including chemotherapy drugs, alcohol and tabaco status as parameters for analyses.

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215P
Assessment of patient and clinician awareness and clinical outcomes of changes in lifestyle habits during lung cancer treatment

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Background: Exercise and eating habits play a fundamental role in patients with lung cancer, having an impact on mortality, duration of hospitalizations, post-surgical complications, sarcopenia, quality of life and even in overall survival. There are studies which also show how physical exercise can improve the response to immunotherapy. However, we are unaware of the lifestyle habits of our patients, a knowledge gap in our therapeutic approach which we seek to address with this study.

Methods: Cross-sectional observational study featuring patients diagnosed with lung cancer at the Medical Oncology Service of the Nuestra Señora de Candelaria University Hospital, Santa Cruz de Tenerife. We tested the statistical significance of lifestyle habit changes as measured by a form and IPAQ, MUST, and SARC-F surveys using chi-squared tests.

Results: We involved 43 patients with a mean age of 65 years. 84% had stage-four cancer, 77% were receiving first-line treatment and 60% were being treated with immunotherapy. 100% of individuals considered their diet as an important pillar in their cancer disease. However, we found that only 50% had discussed aspects of their nutrition with their oncologist. 77% considered that a healthy lifestyle could help reduce the adverse effects of the treatment, and 21% did not know whether it could help. The validated test results showed that 56% had an intermediate-high risk of malnutrition according to the MUST test and 19% had risk of sarcopenia according to the SARC-F test. Patients receiving treatment via immunotherapy or targeted therapy had a lower risk of malnutrition than those receiving other treatments (43.8% vs 63%), although this result did not reach statistical significance ($p = 0.220$). 49% were sedentary according to the IPAQ test and 83% who did not perform physical activity would start an adapted exercise program if it were available.

Conclusions: The results show that most patients have a general awareness about the importance of the lifestyle during treatment, and the need to invest time and resources to improve their clinical outcomes. However, they could benefit from more clarity about the specific nutritional and fitness initiatives they could undertake, and their ranked impact on their health.

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216P
Differences in immune checkpoint inhibitor (ICI) approvals made by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for thoracic malignancies

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Background: Given the paradigm-shifting impact of ICIs on the treatment of lung cancer, prompt approval of therapies is crucial for patients. In this study, we analyzed differences in approval timing, regulatory review speed and biomarker requirements for ICI approvals by the FDA and EMA. For indications with differing biomarker requirements, we further examined perceived differences in levels of evidence.
Methods: A cross-sectional analysis of approved indications for ICIs from each regulatory database was conducted by tumor type: NSCLC, SCLC and Mesothelioma. The median review speed (Time from regulatory submission to approval) and differences in biomarker requirements (primarily PD-L1 expression) were evaluated. Levels of evidence for indications was determined by NCCN evidence blocks and ESMO MCBS scoring systems.
Results: We identified 7 ICIs approved for thoracic malignancies. For NSCLC, the FDA approved 19 anti-PD1/PD-L1 and 3 anti-CTLA-4 indications while the EMA approved 14 anti-PD1/PD-L1 and 1 anti-CTLA-4 indications. For SCLC, the FDA approved 4 anti-PD1/PD-L1 indications (1 was later withdrawn), while EMA approved 2 anti-PD1/PD-L1 indications. The median review times for ICI approval was shorter for FDA compared to EMA across all thoracic malignancies (NSCLC: 242 vs 272 days, SCLC: 179 vs 308 days, Mesothelioma: 39 vs 280 days). Analysis of biomarker requirements revealed 2 indications for which FDA had a broader label compared to EMA. Although both ESMO MCBS and NCCN rank these indications as being effective and beneficial, the biomarker requirements differ between both regulators for unclear reasons.

Table: 216P

Indication	Biomarker requirement difference	ESMO MCBS score	NCCN evidence blocks
Atezolizumab in adjuvant NSCLC (Approvals based on IMPower010)	FDA: PDL1 ≥1 % EMA: PDL1 ≥50 %	A (Substantial Benefit)	4 (Very Effective)
Durvalumab in unresectable NSCLC (Approvals based on PACIFIC)	FDA: None EMA: PDL1 ≥1 %	A (Substantial Benefit)	3 (Moderately Effective)

Conclusions: More ICIs, and total overall indications, have been approved for thoracic malignancies by the FDA with shorter median review times compared to EMA. There is some discordance in biomarker-based approvals between both agencies, although evaluation of evidence scores are fairly consistent.
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217P
Robotic-assisted navigation system for preoperative percutaneous lung nodule localization: A pilot study

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Background: Computed tomography (CT)-guided percutaneous pre-operative localization of pulmonary nodules is a key step in diagnosing and treating early-stage lung cancer, but traditional manual localization still lacks accuracy. Therefore, the novel robotic-assisted navigation system was developed for the precise localization of small lung nodules. This study aimed to investigate its accuracy and safety in clinical applications.
Methods: Patients with peripheral solitary pulmonary nodules (<2 cm) were enrolled. The robotic-assisted navigation system reconstructed a 3-dimensional (3D) model and calculated the desired path based on the CT image of the patient. The robotic arm then located the lung nodule according to the planned path, with the photoelectric system tracking the patient's position and respiratory motion in real time. The primary outcome was the accuracy of pulmonary nodule localization. Secondary outcomes included complication rate, procedural duration, and total radiation exposure.
Results: A total of 33 nodules were localized through the robotic-assisted navigation system. First-pass success rate was 100%, with a median deviation of 6.1 mm (range, 2.5–7.2 mm) between the localizer and the nodule center. The median localization time was 26.0 minutes, (range, 19.5 to 28.5 minutes), and the received radiation doses and dose-length product (DLP) were 1491.0 mAs (range, 1210.0–1781.5 mAs) and 534.0 mAs·cm (range, 374.0–645.0 mAs·cm), respectively. In our study, no observable complications occurred.
Conclusions: The novel robotic-assisted navigation system could optimize the process of percutaneous lung nodule localization. The method might be a safe and feasible alternative to traditional manual localization.
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218P
Implications of the eighth edition of TNM staging system for thymoma, a single-center retrospective study

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Background: Thymic epithelial tumors are rare malignancies that arise in the prevascular mediastinum. The Masaoka-Koga (MK) staging system is traditionally used for staging. In 2017 the 8th edition of TNM classification was published and is gaining acceptance.
Methods: A retrospective study of all patients who underwent surgery for thymoma between 2011 and 2022 at our institute. Kaplan-Meier survival analysis was used to calculate overall survival.
Results: Among 125 patients identified, 62 were men (50%). Median age was 52.8 years. 45 patients (36%) were diagnosed with myasthenia gravis during the course of the disease. Frequency of B2 thymoma was much higher in our cohort compared to previous studies (N = 65, 52%). According to MK staging system there were 50 stage I (40%), 47 stage IIa/b (~37%), 21 stage III (~16%) and seven stage IVa/b (5.5%). After re-staging according to the 8th edition TNM staging classification, all MK

stage II patients were down staged to stage I. Eight patients were down staged from stage III – six to stage II and two to stage I. Both MK and TNM staging systems were associated with overall survival. 5-year survival was 94% and 10-year survival was 89%. Tumor size, histology and myasthenia gravis were not correlated with survival. Recurrences were seen as late as 8 years following surgery.

Conclusions: This is the first Israeli surgical series of patients with thymoma in recent years. Re-staging according to the 8th edition TNM staging caused significant down staging of tumors.

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219P

Clinical outcomes for advanced thymoma patients receiving platinum-based chemotherapy as first-line treatment

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Background: The rate of incidence for advanced thymoma is low. Reports on the promising efficacy and low toxicity of platinum-based chemotherapy in advanced thymoma are lacking. In addition, correlation for chemotherapy efficacy and safety among different subtypes of thymoma remains unexplored.

Methods: We analyzed the efficacy and safety of platinum-based chemotherapy as the first-line treatment for different types of thymoma patients. The objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and treatment-related adverse event results were obtained. Cox proportional hazards regression was analyzed to determine the factors independently associated with PFS.

Results: The study evaluated 71 thymoma patients treated at the Zhejiang Cancer Hospital between January 2009 and March 2022. The ORR for advanced thymoma patients was 36.6%. PFS and OS for the whole cohort were 17.7 and 59.8 months, respectively. The difference in PFS between A-B2 (including A, AB, B1, and B2 subtypes) and B3 thymoma patients was significant (28.2 vs. 10.7 months, P = 0.015). Cox analysis results indicated that thymoma patient subtype was the only factor influencing the PFS.

Conclusions: Advanced thymoma patients can benefit from platinum-based chemotherapy. B3 thymoma patients demonstrated inferior efficacy of platinum-based chemotherapy used as the first-line treatment compared to A-B2 patients.

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220P

Comparison of efficacy and safety of platinum-based chemotherapy as first-line therapy between B3 thymoma and thymic carcinoma

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Background: B3 type thymoma is defined as a well-differentiated thymic carcinoma and is similar to a thymic carcinoma. However, the differences between them are not well defined. In addition, the data to compare the efficacy and safety of platinum-based chemotherapy as first-line therapy between B3 thymoma and thymic carcinoma are lacking.

Methods: The efficacy and safety of platinum-based chemotherapy as first-line therapy was retrospectively compared between a group of 36 patients with type B3 thymoma and a group of 127 patients with thymic carcinoma treated between January 2009 and March 2022 at the Zhejiang Cancer Hospital. Objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and treatment-related adverse events were analyzed.

Results: The ORRs for B3 thymoma and thymic carcinoma were 36.1% and 28.3%, respectively (P = 0.370). Among all patients, the difference in PFS between B3 thymoma and thymic carcinoma was not significant (11.3 vs. 10.1 months, P = 0.118). The squamous carcinoma subgroup did not exhibit any differences in PFS compared to B3 thymoma (11.7 vs. 11.3 months, P = 0.161). The result for non-squamous carcinoma subgroup was similar (6.5 vs. 11.3 months, P = 0.128). Furthermore, the OS values for B3 thymoma and thymic carcinoma were not significantly different (58.3 vs. 35.1 months, P = 0.067). However, there were differences in OS between B3 thymoma and non-squamous carcinoma (58.3 vs. 30.6 months, P = 0.031).

Conclusions: B3 thymoma and especially squamous carcinoma patients may be treated using a similar therapy scheme as that utilized for thymic carcinoma.

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221P

Comparison of efficacy and safety of carboplatin combined with nab-paclitaxel or paclitaxel as first-line therapy for advanced thymic epithelial tumors

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Background: Paclitaxel/carboplatin (PC) is the standard first-line chemotherapy for advanced thymoma and thymic carcinoma. However, although nanoparticle albumin-bound (nab)-PC and PC have exhibited efficacy in various solid tumors, data for thymic epithelial tumors are lacking, including a comparison of the efficacies of nab-PC and PC.

Methods: We conducted a retrospective study to compare the efficacy and safety of nab-PC with PC in previously untreated patients with advanced thymoma and thymic carcinoma. We analyzed the objective response rate (ORR), progression-free survival (PFS), overall survival

(OS), and treatment-related adverse events (AEs). Cox proportional hazards regression analyses were carried out to determine the factors independently associated with survival.
Results: Ninety-one patients were enrolled from October 2006 to September 2021. The ORRs in patients treated with nab-PC and PC were 48.8% vs 36%, respectively (P = 0.219). Among patients with thymic carcinoma, PFS differed between the nab-PC and PC groups (10.5 vs 6.3 months, P = 0.0049); however, no such difference occurred in the thymoma group (13.8 vs 12.3 months, P = 0.6948). The median OS was 27.4 months in 54 patients in thymic carcinoma, but was not reached for thymoma patients (P = 0.0024).
Conclusions: Nab-PC may be more effective than PC as first-line therapy in patients with advanced thymic epithelial tumors. Nab-PC could thus become an alternative regimen in patients with thymic epithelial tumors, especially thymic carcinoma.
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222P
Thoracic neuroendocrine tumors: Experience in a third level hospital in Mexico

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Background: Frontline treatment with somatostatin analogs (SSA) in advanced low-intermediate grade neuroendocrine tumors (NET) of digestive origin were extensively evaluated; nevertheless, there is a lack of information about this management in lung NETs, which represent less than 1% of all thoracic malignancies. Higher grade tumors, including large-cell neuroendocrine carcinomas (LCNEC) are usually treated with platinum-based chemotherapy combos.
Methods: Patients with advanced thoracic NETs who started treatment between 2012–2021 at Hospital de Oncología, Centro Médico Nacional Siglo XXI, at Mexico City were retrospectively evaluated. The outcome measure was progression-free survival (PFS). We also explored the outcomes according to site of origin (lung vs mediastinal NET).
Results: 41 patients were evaluated; those with typical carcinoid (n = 15) and atypical carcinoid diagnosis (n = 21) were treated with first-line SSAs: 23 patients with octreotide LAR and 11 with lanreotide. Subjects with LCNEC diagnosis (n = 6) were treated with first-line platinum/etoposide chemotherapy during 4–6 cycles. 27 patients had ECOG score of 1 (65.8%) and only in one of the cases the ECOG score was 3. Seventeen patients had locally advanced/unresectable tumors at diagnosis, six with liver metastases, five had lung metastases, three patients with CNS metastases and also three had lymph node involvement. At this time, only 15 patients had disease progression. 20% of them (n = 3) had LCNEC. Median Progression-Free Survivals were calculated on these patients with 12.0 months (9.22–14.77) for lung NETs and 29.0 months (8.26–17.73) for mediastinal NET. No statistical significance was reached despite the site of origin (HR for PFS of lung origin = 2.75; p = 0.097).
Conclusions: SSAs are an effective option as frontline treatment in patients with advanced lung typical and atypical carcinoid tumors. Patients with LCNEC remain with a poorer prognosis.
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223P
Surgery versus bronchoscopic cryotherapy for the treatment of lung carcinoid tumors: An overview of 5-year experience

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Background: Lung carcinoid (LC) tumors are uncommon neuroendocrine epithelial neoplasms that account for less than 1% of all lung cancers. They are divided into two subcategories: typical carcinoids and atypical carcinoids. About 80% of LC occurs centrally. Patients with LC are treated with surgical resection even though several authors are promoting the role of bronchoscopic procedures as avant-garde. Because of this discussion we undertake such a study to decide on the treatment of choice.
Methods: We retrospectively investigated the medical records of 32 patients with LC treated in our clinic in the last five years, of which 21 (80.1%) were treated surgically from the first moment, 11 were initially treated with bronchoscopic cryotherapy of which 6 subsequently treated definitively with surgery. Of the patients, 51.4% were male and 48.6% female, with a mean age of 40 years. Data were statistically analyzed using Anova and Chisquare tests.
Results: There were no cases of complications among the primary or secondary surgically treated patients. The mean number of days of postoperative hospitalization for all surgical cases was 6.2 ± 1.73. As regards the patients treated with bronchoscopic cryotherapy, only in one case was the procedure performed in two stages. In the other cases, at least 4 procedures were performed, but it was not possible to estimate the days of hospitalization because they were sometimes treated on an outpatient basis. In 6 cases the bronchoscopic procedure failed to treat the carcinoid and subsequently the patients were referred for surgical treatment. There was no statistically significant association between surgical method and postoperative hospitalization. In 93.7% of cases the carcinoid was typical while in 2 cases the carcinoid was accompanied by Cushing's syndrome. Regarding the surgically treated patients, 2 of them had a wedge resection, 18 of them had a lobectomy, 3 of them had a broncho-sleeve lobectomy, and 3 of them had a bilobectomy.
Conclusions: We concluded that surgical treatment is a safer procedure with better patient outcomes and a reasonable treatment cost. Lobectomy is the surgical technique of choice. A wedge resection is preferred in peripheral carcinoids and is often sufficient.
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224P
Genetic landscape, PD-L1 expression, and CD8+ infiltration in Chinese pulmonary carcinoids

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Background: Pulmonary carcinoids (PCs), including atypical carcinoids (ACs) and typical carcinoids (TCs), are a rare type of lung cancer with low or moderate malignancy. The genomic and immune features of PCs are poorly understood worldwide.

Methods: A total of 126 PC patients (ACs = 44, TCs = 82) were included in this study. Next-generation sequencing with a 578-gene panel was performed on 90 patients, and the tumor mutation burden (TMB) was further calculated. Moreover, immunohistochemistry staining of PD-L1 (n = 108) and CD8 (n = 94) was performed to explore the characteristics of the tumor microenvironment in PCs.

Results: The most commonly altered genes in PCs included EGFR (n = 16, 18%), KMT2C (n = 11, 12%), LRP1B (n = 10, 11%), MEN1 (n = 10, 11%) and NOTCH2 (n = 9, 10%). Compared to sequencing data from non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), MEN1, GATA2, MST1, and IDH1 were the specific altered genes in PCs. The genetic alteration of TP53, ARID1A, and CUL3 occurred more frequently in ACs in comparison with TCs in further research. However, TMB, PD-L1 expression, and CD8+ infiltration, were all low and exhibited no difference between ACs and TCs.

Conclusions: Our study indicated, for the first time, the genetic landscape and immune features of Chinese PCs. We identified EGFR mutation (including 21L858R and 19Del) and amplification in Chinese PCs, which were totally different from the previously reports of other ethnic population. Overall, our study revealed potentially important mechanisms for PCs, and may provide helpful information for developing potential therapeutic strategies for Chinese PCs.

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