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Table of Contents

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Preface

Dear Colleagues,

under this year's motto "partnering with patients: the cornerstone of cancer care and research", oncology experts from around the world gathered at the Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago, USA, and virtually from 2nd–6th June 2023, to discuss the latest data in lung cancer with emphasis on practice-changing new studies, less toxic treatments, precision oncology and new ways to reduce collateral damage.

Surgical resection followed by cisplatin-based platinum-doublet adjuvant chemotherapy has been a long-standing standard of care for patients with early-stage, resectable non-small-cell lung cancer. Since the incorporation of immunotherapy and targeted therapy into the perioperative setting has demonstrated improved disease-free or event-free survival in biomarker-defined subsets of patients, the first chapter provides current insights into perioperative strategies including promising new treatment options.

Small-cell lung cancer with its distinct biological and clinical features is at the center of the second chapter that highlights the feasibility of conducting biomarker-selected trials, the first-in-human results for bispecific T-cell engager therapy, and progression-free survival improvements with first-line pembrolizumab plus etoposide and platinum chemotherapy.

Moreover, the potential of targeted therapies and immunotherapies in non-small-cell lung cancer is outlined, including the newest results for EGFR tyrosine kinase inhibitors either as monotherapy or in combination with chemotherapy or an EGFR-MET bispecific antibody, as well as HER2, $KRAS^{G12C}$, BRAF and ROS1 inhibitors.

Last but not least, this issue looks closely at stage IV lung cancer with Tumor Treating Fields therapy as an innovative, safe and effective option due to the amplification of the effects of immune checkpoint inhibitors and taxanes. Whereas an antibody-drug conjugate and anti-angiogenic treatment plus docetaxel both showed encouraging efficacy, immunotherapeutic treatment after failure of EGFR TKIs only prolonged progression-free survival and overall survival without reaching statistical significance.

Once again, experts gathered at the ASCO annual meeting to shape the future of cancer care and left Chicago feeling inspired for their daily practice. Since making a difference in patients' lives begins with passion and oncology is full of exciting opportunities, feel encouraged to enter the field and increase your knowledge.


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We hope you enjoy reading this special issue!

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Early-stage NSCLC: current insights into perioperative strategies

Overall survival superiority in ADAURA

The randomized phase III ADAURA study was conducted in response to the unmet need of improving 5-year overall survival (OS) rates in patients with completely resected *EGFR*-mutated, stage IB-IIIA non-small cell lung cancer (NSCLC), which are estimated to range between 45 % and 85 % [1-3]. In ADAURA, 682 patients after complete resection of stage IB, II, or IIIA NSCLC with or without adjuvant chemotherapy received either osimertinib 80 mg OD or placebo for 3 years. Adjuvant osimertinib was shown to improve disease-free survival (DFS) vs. placebo in a statistically significant and clinically meaningful manner in both the primary (i.e., stages II-IIIA) and the overall population (stages IB-IIIA) [4-7]. At ASCO 2023, Herbst et al. presented the OS results from the trial [8].

ADAURA is the first global phase III study to demonstrate a statistically significant and clinically meaningful OS benefit with targeted treatment in this patient group. Previously, no phase III trial assessing EGFR tyrosine kinase inhibition (TKI) had demonstrated translation of a DFS advantage into a significant OS benefit [9]. In the primary population, the 5-year OS rates were 85 % vs. 73 % (HR, 0.49; p = 0.0004), and in the overall population, 88 % vs. 78 % (HR, 0.49; p < 0.0001; **Figure 1**). Both of these analyses resulted in risk reductions of 51 % compared to placebo.

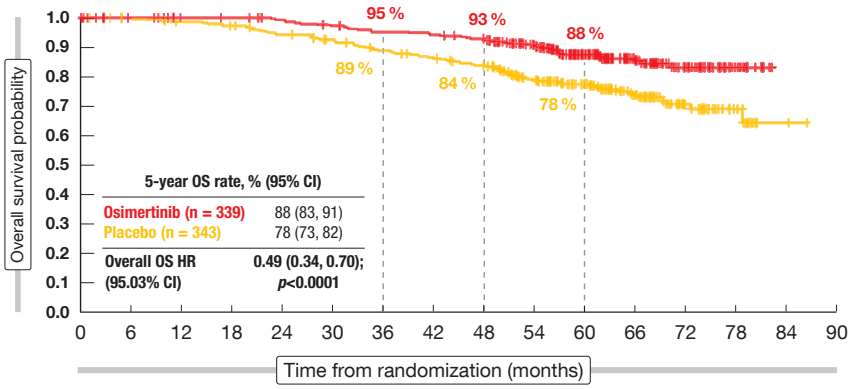

Figure 1: Overall survival advantage of adjuvant osimertinib compared to placebo in the ADAURA trial

The OS advantage was generally consistent across subgroups. Mortality reductions in stages IB, II and IIIA were 56 %, 37 % and 63 %, respectively. Both patients with and without adjuvant chemotherapy derived risk reductions of more than 50 % when treated with osimertinib. Subsequent anti-cancer therapies were administered in 22 % vs. 54 % of patients treated with osimertinib and placebo, respectively, with EGFR TKIs being the most common strategy across both arms. The safety findings observed during the extended follow-up were consistent with the primary ADAURA analysis [4]. No treatment-related deaths occurred in either arm.

In their conclusion, the authors noted that these results reinforce adjuvant osimertinib as the standard of care for patients with resected *EGFR*-mutant, stage IB-IIIA NSCLC. Ongoing osimertinib studies in the setting of resectable *EGFR*-mutated NSCLC include the phase III NeoADAURA study (NCT04351555), the phase III ADAURA2 study (NCT05120349) and the phase II TARGET trial (NCT05526755).

No MPR improvement with neoadjuvant osimertinib

A multicenter phase II trial was initiated to assess the neoadjuvant use of osimertinib in patients with resectable stage I-IIIA, *EGFR*-mutated NSCLC based on the assumption that targeted therapy might improve MPR rates, thus leading to survival prolongation. Twenty-seven individuals received neoadjuvant osimertinib for 1–2 months prior to surgical resection.

With 15 % of patients achieving major pathological responses (MPR), the study did not meet its primary endpoint, which was defined as an MPR rate of 50 % [10]. Pathological responses occurred in 48 %, and lymph node downstaging resulted in 44 %. None of the patients achieved pathological complete response (pCR). The R0 surgical resection rate was 89 %. No surgical complications occurred; serious adverse events (AEs) and perioperative complications were in line with the predicted rates in this population. Median DFS was 32.4 months.

The scientists used exome sequencing, single-cell RNA sequencing and multiplex immunohistochemistry to explore molecular mechanisms of disease persistence, which is an issue in both early-stage and advanced *EGFR*-mutated NSCLC. According to these findings, co-occurring loss-of-function mutations in *RBM10* might limit patient responses. The addition of the Bcl-xL inhibitor navitoclax to osimertinib was shown to induce apoptosis in *RBM10*-deficient preclinical models [11], although this observation needs to be confirmed in clinical trials. Moreover, upregulation of the YAP pathway appeared to drive tumor cell survival, which might provide another target for combination therapies to eliminate residual disease.

KEYNOTE-671: perioperative immunotherapy

Although immune checkpoint inhibition has proven beneficial in phase III trials when administered before or after resection of early-stage NSCLC, recurrence is still common [12-14]. Therefore, it was hypothesized that a perioperative approach including both neoadjuvant and adjuvant PD-(L)1 inhibition might be superior to either approach alone. The randomized, double-blind, phase III KEYNOTE-671 trial assessed neoadjuvant pembrolizumab 200 mg Q3W plus chemotherapy (i.e., cisplatin plus gemcitabine or pemetrexed) vs. placebo plus chemotherapy for up to 4 cycles in patients with resectable stage II, IIIA, or IIIB (N2) NSCLC. After surgery, the patients allocated to the experimental arm went on to receive pembrolizumab 200 Q3W for up to 13 cycles, while placebo was administered to those in the control arm. Event-free survival (EFS) per investigator review and OS were defined as the dual primary endpoints.

The analysis presented at ASCO 2023 after a median follow-up of 25.2 months included 397 and 400 individuals randomized to the experimental and control arms, respectively [15]. Among these, 325 and 317, respectively, had received in-study surgery. R0 resection was performed in 92.0 % and 84.2 %, respectively. Lobectomy represented the most commonly used surgical procedure (78.8 % and 75.1 %, respectively). The study population contained patients with known *EGFR* mutations (3.5 % and 4.8 %, respectively) and *ALK* translocations (3.0 % and 2.3 %, respectively).

Indeed, the perioperative strategy, as compared to neoadjuvant chemotherapy and surgery alone, provided statistically significant and clinically meaningful EFS improvement (median EFS, not reached vs. 17.0 months; HR, 0.58; $p < 0.00001$). At 12 months, the EFS rates were 73.2 % vs. 59.9 %, and at 24 months, 62.4 % vs. 40.6 %. The EFS benefit was generally consistent across all patient and disease characteristics analyzed, which included histology, disease stage and PD-L1 levels. Patients in the pembrolizumab arm experienced significantly higher rates for both MPR and pCR ($p < 0.00001$ for both; **Figure 2**). An exploratory analysis showed that EFS benefits were more likely in the groups that achieved MPR and pCR across the study arms. However, pembrolizumab-treated patients generally fared better than control patients.

Regarding OS, the significance boundary had not been crossed yet, although the curves have started to separate (median OS, not reached vs. 45.5 months; HR, 0.73). The AE profile observed in KEYNOTE-671 was as ex-

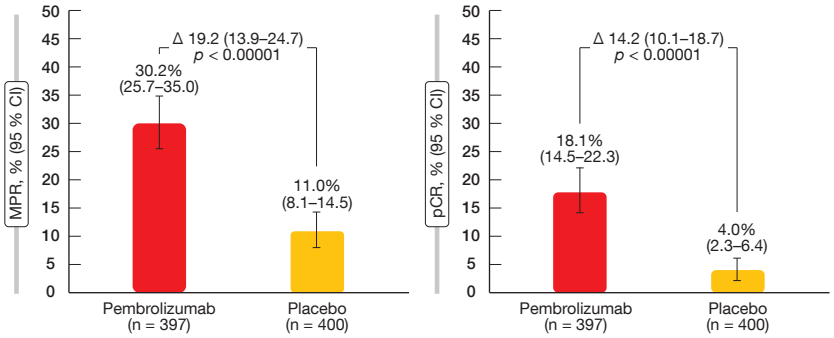

Figure 2: Pathological responses achieved with perioperative pembrolizumab plus chemotherapy vs. neoadjuvant chemotherapy plus surgery alone

pected based on the known profiles of the individual treatment components. Grade 3–5 immune-related AEs and infusion reactions occurred in 5.8 % vs. 1.5 % of patients, with one pneumonitis-related fatality in the pembrolizumab-treated group (0.3 %). Overall, the results from the KEYNOTE-671 trial support perioperative pembrolizumab as a promising new treatment option for patients with resectable stage II, IIIA, or IIIB (N2) NSCLC.

NEOpredict: nivolumab plus relatlimab

Given the demand for novel agents in the curative setting, the randomized, multicenter phase II NEOpredict-Lung study investigated the feasibility, safety and early efficacy of the combined preoperative treatment with nivolumab and the anti-LAG-3 antibody relatlimab. Patients with stage IB, II and selected IIIA NSCLC were randomized to either nivolumab 240 mg plus relatlimab 80 mg on days 1 and 15 (n = 30) or nivolumab alone (n = 30) followed by surgery and standard-of-care adjuvant treatment. Meanwhile, a third study arm has been added to investigate nivolumab plus relatlimab at an increased dose. The feasibility of curatively intended surgery within 43 days of treatment was the primary endpoint.

All patients in both treatment arms met the primary objective [16]. Curative resection was obtained in 98.3 % across the arms. Most patients underwent lobectomy (24 and 23 in the combination and nivolumab monotherapy arms, respectively). Video-assisted thoracoscopic surgery was possible in 63.3 % vs. 60 %; two vs. three patients had to undergo conversion to thoracotomy. Perioperative complications occurred in 26.6 % vs. 33.3 %, which was within the expected range. One patient each (3 %) required intraoperative conversion due to bleeding. Surgical revision was necessary in one individual in the experimental arm (3 %) due to middle lobe torsion and in two patients in the control arm (7 %) because of empyema and prolonged air leak. In the nivolumab-only arm, there was one case of pulmonary embolism. No patient died within 30 days.

Regarding histopathological response, the regimens gave rise to similar pCR (16.7 % vs. 13.3 %) and MPR (30 % vs. 27 %) rates. Deeper responses were observed in patients with higher PD-L1 expression. Adjuvant therapy was indicated in 14 patients in each group and could be safely administered in all cases. Across both groups, the 12-month OS rate was 96 %, and the 12-month DFS rate was 91 %. Grade ≥ 3 immunotherapy-related AEs occurred in one patient in the combination arm and three in the monotherapy arm.

In their conclusion, the authors noted that perioperative course, morbidity and mortality rates observed in this study were comparable to those observed with other neoadjuvant regimens. Both minimally invasive and open surgical techniques were safe, and there appeared to be no increased risk of complications in bronchial and/or vascular sleeve resections. Comprehensive correlative studies and biomarker analyses are ongoing.

Toripalimab plus chemotherapy

More than 400 patients with resectable stage II and III NSCLC have been enrolled into the randomized, double-blind, phase III NeoTORCH trial that is investigating the perioperative use of the anti–PD-1 monoclonal antibody toripalimab. In the experimental arm, toripalimab 240 mg Q3W is being administered in addition to neoadjuvant chemotherapy for 3 cycles; after surgery, patients receive 1 adjuvant cycle of the same regimen and go on to maintenance treatment with toripalimab Q3W for up to 13 cycles. In the control arm, placebo is used instead of the PD-1 inhibitor. EFS according to investigator in stages III and II/III as well as MPR according to blinded independent pathologic review in stages III and II/III are defined as the primary objective. At ASCO 2023, Lu et al. presented the results of the interim EFS analysis that related to 202 patients in each study arm [17].

In the combination and chemotherapy-alone arms, 87.1 % and 91.6 % of patients, respectively, completed 3 neoadjuvant cycles. Surgery was performed in 82.2 % vs. 73.3 %. Adjuvant treatment was administered in 71.3 % and 64.9 %, respectively, and similar percentages of patients received maintenance. Thirteen cycles of maintenance treatment were completed by 43.6 % and 32.7 %, respectively. R0 resection resulted in 95.8 % vs. 92.6 %.

With respect to the primary endpoint of EFS by investigator in patients with stage III disease, the analysis revealed superiority of the immunotherapy-based approach, translating into a 60 % risk reduction (not reached vs. 15.1 months; HR, 0.40; two-sided p < 0.0001; **Figure 3**). The EFS rates at 24 months were 64.7 % vs. 38.7 %. Improvement in EFS was consistent across all key subgroups including the PD-L1 cohorts, with HRs of 0.59, 0.31 and 0.31 for the PD-L1 < 1 %, 1-49 % and ≥ 50 % subgroups, respectively. Benefits were seen in both non-squamous (HR, 0.54) and squamous (HR, 0.35) subtypes.

Considerable differences favoring the toripalimab combination were observed regarding the pCR rate (24.8 % vs. 1 %; p < 0.0001) and the MPR rate (48.5 % vs. 8.4 %; p < 0.0001). Patients who had achieved MPR or pCR showed longer EFS with both treatments than those who had not. The OS analysis revealed a trend in favor of the combined strategy (2-year OS rates, 81.2 % vs. 74.3 %; HR, 0.62). Toripalimab plus chemotherapy

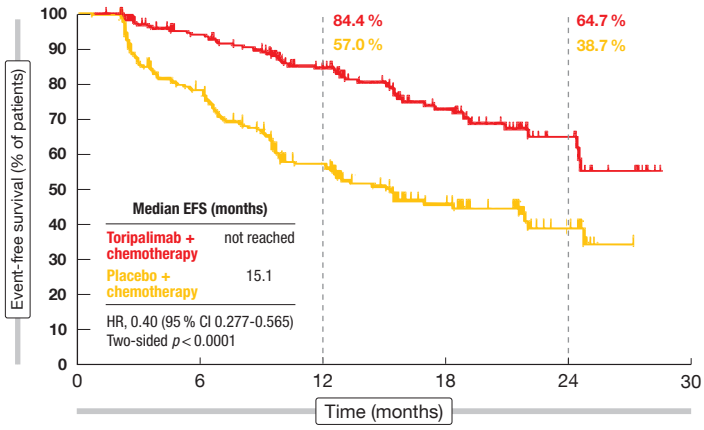

Figure 3: NeoTORCH: event-free survival in the intent-to-treat stage III population according to investigator

was well tolerated. Treatment-emergent AEs leading to interruption of the PD-1 inhibitor were reported in 28.2 % (vs. interruption of placebo in 14.4 %), and discontinuation was necessary in 9.4 % (vs. 7.4 %). One fatal treatment-related event occurred in the experimental arm (0.5 % vs. 0.0 %). Grade ≥ 3 immune-related AEs were seen in 11.9 % vs. 3.0 %, and any-grade infusion-related reactions in 3.5 % vs. 6.4 %. Surgery-related postoperative AEs necessitated interruption of toripalimab in 6.6 % (vs. interruption of placebo in 1.4 %) and discontinuation in 1.8 % (vs. 2.7 %). As the authors emphasized, the results from NeoTORCH are in keeping with those from other studies suggesting that perioperative immunotherapy plus chemotherapy should be a standard of care for patients with stage III NSCLC.

CheckMate 816: 3-year findings according to surgery status

Neoadjuvant nivolumab in addition to chemotherapy for 3 cycles is being assessed in patients with resectable stage IB-IIIA NSCLC included in the phase III CheckMate 816 trial. Compared to neoadjuvant chemotherapy only, the combination significantly improved EFS and pCR, with continued EFS benefit observed at 3 years [12, 18]. At ASCO 2023, Spicer et al. reported an exploratory analysis of the 3-year outcomes in patients who underwent definitive surgery (149 and 135 for nivolumab plus chemotherapy and chemotherapy only, respectively) versus those who did not (30 and 44, respectively) [19].

In addition to the proportion of patients who had surgery being numerically higher in the experimental arm compared to the control arm, the combination gave rise to improved outcomes independent of surgery status, although patients without definitive surgery only showed numerical benefits. In the operated group, median EFS had not been reached with nivolumab plus chemotherapy and was 31.8 months with chemotherapy alone (HR, 0.67). In the cohort without surgery, this was 6.7 vs. 4.1 months (HR, 0.75). Time to distant metastasis was prolonged with the addition of nivolumab both in the resected cohort (not reached vs. 46.8 months; HR, 0.55) and the non-resected group (24.8 vs. 15.6 months; HR, 0.63). EFS2, which was defined as the time from randomization to objectively documented progression after the next line of therapy or to death from any cause, again favored the immunotherapy-based regimen both in the cohort with definitive surgery (36-month rates, 80 % vs. 69 %) and the one without (33 % vs. 24 %). Patients who could not undergo tumor resection mostly received subsequent chemotherapy and/or radiotherapy.

Neither the incidence nor the severity of AEs was increased by the addition of nivolumab to chemotherapy regardless of surgery status. In patients without definitive surgery, grade 3-4 treatment-related AEs were less common with the combination than with chemotherapy alone (26 % vs. 46 %). The authors noted that these long-term results from CheckMate 816 continue to corroborate neoadjuvant nivolumab plus chemotherapy as a standard treatment option for patients with resectable NSCLC.

Pembrolizumab after adjuvant chemotherapy

Pembrolizumab 200 mg Q3W for ≤ 18 administrations was tested against placebo after complete resection of stage IB-IIIA NSCLC in the randomized, triple-blind, phase III PEARLS/KEYNOTE-091 study. Adjuvant chemotherapy for up to 4 cycles was administered prior to pembrolizumab as indicated. In the overall population (n = 1,177), DFS was significantly improved in the experimental arm (53.6 vs. 42.0 months; HR, 0.76; p = 0.0014) [20]. Oselin et al. presented the findings in the group that had received 1–4 cycles of adjuvant chemotherapy per protocol; these constituted 86 % (n = 1,010) of the randomized patients [21].

In this group, consistent with the results in the ITT population, pembrolizumab gave rise to improved DFS compared to placebo, resulting in a 27 % risk reduction (58.7 vs. 34.9 months; HR, 0.73). At 18 months, 73.8 % vs. 63.1 % of patients were disease-free. Similar risk reductions were obtained in patients after 1 or 2 (HR, 0.59) and 3 chemotherapy cycles (HR, 0.56). Patients with *EGFR*-mutant disease benefited greatly from pembrolizumab treatment (HR, 0.39). Across the stages, stage IB was associated with the greatest risk reduction (HR, 0.54).

Results from IMpower010 by *KRAS* mutational status

Atezolizumab after adjuvant chemotherapy for completely resected stage IB-IIIA NSCLC was compared with best supportive care (BSC) in the randomized, open-label, phase III IMpower010 trial that met its primary DFS endpoint [13]. As *KRAS* mutations are prevalent in metastatic NSCLC and may be a poor prognostic factor [22, 23], Reck et al. assessed baseline characteristics and DFS outcomes in IMpower010 according to *KRAS* mutational status [24].

The prevalence of *KRAS* mutations in this early-stage setting was similar to that reported for metastatic NSCLC [23]. In the biomarker-evaluable population according to whole exome sequencing (n = 603), *KRAS* mutations were found

TABLE **Baseline characteristics by *KRAS* mutation status in the IMpower010 study**

Baseline characteristic	Biomarker-evaluable population (n = 603)	*KRAS* wildtype (n = 475)	*KRAS* mutation (n = 128)
Median age, years	62 (26-82)	62 (26-82)	63 (40-81)
Male, n (%)	414 (69)	328 (69)	86 (67)
Asian, n (%) White, n (%)	144 (24) 446 (74)	125 (26) 339 (71)	19 (15) 107 (84)
ECOG PS 0, n (%)	382 (63)	299 (63)	83 (65)
Non-squamous, n (%) Squamous, n (%)	399 (66) 204 (34)	278 (59) 197 (41)	121 (95) 7 (5)
Current/previous smoker, n (%) Never smoker, n (%)	480 (80) 123 (20)	364 (77) 111 (23)	116 (91) 12 (9)
MRD (ctDNA) positivity, n (%)	117 (20)	91 (19)	26 (20)
Median CRP, mg/L (range)	2.32 (0.2-166)	2.51 (0.2-166)	1.75 (0.2-48.9)

in 21 % (n = 128). The mutation rates were higher in white vs. Asian patients and in non-squamous vs. squamous tumors **(Table)**. Almost all *KRAS* mutation carriers were current or previous smokers. In the biomarker-evaluable group with stage II-IIIA disease (n = 536), atezolizumab improved DFS vs. BSC irrespective of *KRAS* mutational status. Patients with *KRAS* wildtype derived a 26 % risk reduction (median DFS, 42.3 vs. 31.4 months; HR, 0.74), while this was 44 % in those with *KRAS* mutation (not reached vs. 25.2 months; HR, 0.56). Moreover, PD-L1 positivity did not affect the outcomes in the *KRAS*-mutated subgroup with stage II-IIIA disease. PD-L1–positive samples were present in 59 % in the *KRAS*-mutated subgroup and in 53 % in the *KRAS* wildtype subgroup. Atezolizumab treatment improved DFS compared to BSC for both PD-L1–negative (median DFS, not reached vs. 31.6 months) and PD-L1–positive (not reached vs. 21.7 months) patients. However, the authors cautioned that this analysis is limited by the small sample sizes. ■

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Small-cell lung cancer: novel agents & biomarkers

Atezolizumab plus talazoparib as maintenance

As is known, patients with extensive-stage small-cell lung cancer (ES-SCLC) tend to respond well to systemic induction therapy but frequently experience rapid disease progression. Subsequent treatment success remains a challenge; therefore, improving outcomes in the first line appears critical. Poly (ADP-ribose) polymerase (PARP) 1 has emerged as a potential therapeutic target in neuroendocrine tumors such as SCLC. Also, expression of the Schlafen family member 11 (SLFN11) protein was shown to predict improved overall survival (OS) and progression-free survival (PFS) with the PARP inhibitor veliparib plus temozolomide in SCLC patients [1].

The phase II SWOG S1929 study evaluated maintenance with atezolizumab plus the PARP inhibitor talazoparib in patients with *SLFN11*-positive ES-SCLC. After 4 cycles of induction chemotherapy and atezolizumab, patients who had *SLFN11*-positive and non-progressive disease were randomized to either the combination or atezolizumab alone. PFS was defined as the primary objective. According to the results reported at ASCO 2023 by Abdel Karim et al., central SLFN11 testing of archival tissue using immunohistochemistry revealed positivity in 79 % [2]. The analysis included 54 and 52 patients randomized into the combination and monotherapy arms, respectively. SWOG S1929 met its primary endpoint. Atezolizumab plus talazoparib improved PFS compared to atezolizumab alone, resulting in a 30 % risk reduction (median PFS, 4.2 vs. 2.8 months; HR, 0.70; p = 0.056). Patients with prior thoracic radiotherapy and brain metastases represented the groups deriving the most pronounced PFS benefits, with HRs of 0.54 and 0.42, respectively. The response rates after maintenance did not differ across the arms (12 % vs. 16 %). Disease control was achieved in 59 % vs. 69 %.

As expected, the addition of the PARP inhibitor increased hematologic toxicity, which was mainly reflected by higher rates of grade 3 anemia (37 % vs. 2 %). Grade 3 decreases in platelet counts occurred in 17 % vs. 0 %. With respect to non-hematological toxicity, which mainly included transaminitis and hyperglycemia, grade ≥ 3 treatment-related adverse events (AEs) did not differ across the treatment arms (15 % vs. 13 %). Only three patients overall discontinued treatment due to toxicity.

In their conclusion, the authors noted that the SWOG S1929 study demonstrated the feasibility of conducting biomarker-selected trials in the setting of SCLC, thus paving the way for future evaluation of novel therapies in selected SCLC populations. The association between SLFN11 expression levels and clinical outcomes is currently being explored.

First-in-human results for bispecific T-cell engager

BI 764532 has been developed as a delta-like ligand 3(DLL3)/CD3 IgG-like bispecific T-cell engager with the aim to redirect T cells to tumor sites and induce lysis of DLL3-expressing cancer cells such as SCLC cells. In DLL3-positive cells and xenograft models, BI 764532 has shown potent preclinical anti-tumor activity [3]. Wermke et al. presented the results of the first-in-human dose-escalation trial in patients with DLL3-positive advanced SCLC (n = 57), extrapulmonary neuroendocrine carcinoma (epNEC; n = 41), or large-cell neuroendocrine lung carcinoma (LCNEC; n = 9) at ASCO 2023 [4]. These patients had failed available standard therapies or were ineligible for them. Two thirds had previously received one or two treatment lines, while one third had been treated with ≥ 3 lines. Asymptomatic and stable brain metastases were allowed; therefore, brain lesions were present in 38 % of the study population. Almost half had received prior PD-(L)1 inhibitor therapy. BI 764532 was administered at different dose levels and schedules for a maximum of 36 months.

The compound showed promising efficacy with an overall objective response rate (ORR) of 25 % at doses ≥ 90 µg/kg. Tumor shrinkage was observed across all three entities. For SCLC, epNEC and LCNEC, the ORRs were 26 %, 19 % and 60 % **(Table)**. Responses appeared durable as they were ongoing in 14 out of 18 responders at data cutoff, with a few exceeding already 12 months. Median duration of response had not been reached yet.

Moreover, the AE profile of BI 764532 at clinically efficacious dose levels was acceptable and manageable. Cytokine release syndrome (CRS) occurred as the most common side effect (all grades, 59 %), followed by decreased lymphocyte counts (20 %), dysgeusia (20 %), and asthenia (19 %). Almost all CRS events were graded as 1 or 2, emerged during the initial drug administrations, and were manageable with supportive care, corticosteroids and/or anti-IL-6R antibodies. Treatment-related AEs led to discontinuation in 4 % only. Dose-limiting toxicity events including CRS grade 3-4, infusion-related reaction and central nervous system AEs proved reversible. The

TABLE Responses observed with BI 764532 in neuroendocrine cancers

Response, n (%)	SCLC (n = 39)	epNEC (n = 27)	LCNEC (n = 5)
Partial response	10 (26)	5 (19)	3 (60)
Stable disease	10 (26)	7 (26)	2 (40)
Progressive disease	12 (31)	13 (48)	0
Disease control rate	20 (51)	12 (44)	5 (100)
Not estimable	7 (18)	2 (7)	0

SCLC, small-cell lung cancer; epNEC, extrapulmonary neuroendocrine carcinoma; LCNEC, large-cell neuroendocrine carcinoma of the lung

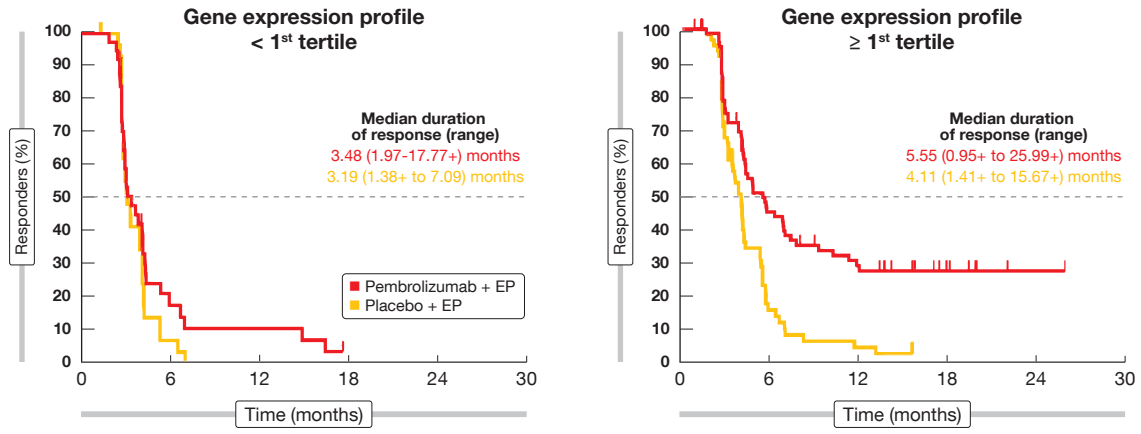

Figure: Association between duration of response with pembrolizumab plus chemotherapy and T cell-inflamed gene expression profile in KEYNOTE-604

maximum tolerated dose had not been reached at the time of the analysis. Further dose optimization is ongoing.

Biomarker analysis of KEYNOTE-604

The phase III KEYNOTE-604 study has shown PFS improvement with first-line pembrolizumab plus etoposide and platinum (EP) chemotherapy vs. EP alone in patients with ES-SCLC [5]. Notably, PFS and OS improvements were observed regardless of the PD-L1 CPS, which indicated that this marker was not predictive of the treatment outcomes. Rudin et al. reported an exploratory biomarker analysis of KEYNOTE-604 at ASCO 2023 that determined the association between efficacy outcomes and tumor mutational burden (TMB), T cell-inflamed gene expression profile ($Tcell_{inf}GEP$), and monocytic myeloid-derived suppressor cells (mMDSC) as well as granulocytic myeloid-derived suppressor cells (gMDSC) as part of the non-gene expression profile signature [6]. Assessments were based on whole exome sequencing of tumor tissue and matched normal DNA and RNA sequencing. The biomarker-evaluable population in the experimental arm included 167 and 159 patients for the TMB and $Tcell_{inf}GEP$ analysis, respectively; in the control arm, these were 151 and 157 individuals, respectively.

According to the data obtained, TMB was not positively associated with OS or PFS in the pembrolizumab plus EP group. At the same time, there was a statistically significant association between TMB and OS in the control arm, which appears to be a false-positive result based on underperformance of the chemotherapy-only regimen in the group with low TMB. The $Tcell_{inf}GEP$ assessment yielded significant associations with OS and PFS not only in the experimental arm but to a similar extent in both treatment groups. Interestingly, patients who experienced longer duration of response tended to have high $Tcell_{inf}GEP$ at baseline, with long-term responders being virtually restricted to the pembrolizumab-treated groups **(Figure)**. Low expression of mMDSC and gMDSC was potentially associated with longer PFS and OS in the pembrolizumab-treated patients.

Overall, the authors concluded that the benefit of pembrolizumab plus EP was observed across most of the biomarker subgroups analyzed. The data will need to be interpreted in the context of similar analyses of other trials to understand their role in SCLC. ■

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Targeted approaches in advanced disease

Anti-EGFR agents plus inserted chemotherapy

Acquired resistance to EGFR tyrosine kinase inhibitors (TKIs), even including the third-generation agent osimertinib, limits duration of response and survival in treated patients with *EGFR*-mutant lung tumors. A potential strategy to improve outcomes is the concomitant use of EGFR-targeted agents and platinum doublet chemotherapy [1, 2], although EGFR TKI treatment might attenuate the effect of cytotoxic agents [3-6]. According to the Norton-Simon hypothesis, however, sensitivity to chemotherapy might be increased dependent on timing [7-9]. Therefore, it was hypothesized that chemotherapy inserted after the initial response to EGFR TKI treatment, rather than at the time of progression, might lead to the elimination of emerging resistant clones. Most tumor cells would thus be EGFR-TKI–sensitive when EGFR-targeted treatment is resumed, and survival might be prolonged.

A phase II study has tested first-line treatment with gefitinib 250 mg OD on days 1-56 followed by chemotherapy for 3 courses on days 71, 92 and 113 before gefitinib was resumed from day 134 until disease progression [10]. This strategy appeared to prevent the development of acquired resistance to EGFR TKI treatment, with favorable progression-free survival (PFS) of 19.5 months and overall survival (OS) of 48.0 months.

The open-label, randomized, phase III JCOG1404/WJOG8214L study was conducted to confirm this observation. Patients with non-squamous, stage IIIB/IV or recurrent NSCLC that harbored *EGFR* exon 19 deletions or L858R mutations were enrolled. In the experimental arm, gefitinib was administered according to the same schedule as in the phase II trial; additionally, three courses of chemotherapy with cisplatin and pemetrexed were inserted on days 71, 92 and 113. Patients in the control arm received gefitinib 250 mg OD from day 1 until progression. The EGFR TKI used in the trial was changed to osimertinib 80 mg OD in October 2018 based on the results of the FLAURA study [11]. Overall, the experimental and control arms included 251 and 250 patients, respectively. Among these, 96 and 97, respectively, received osimertinib, while 155 and 153, respectively, had been treated with gefitinib. Stable CNS metastases were present in 28.3 % of the total population. OS constituted the primary endpoint. Kanda et al. reported the findings at ASCO 2023 [12].

PFS benefit, but no OS advantage

After a median follow-up of 36 months, gefitinib/osimertinib plus inserted chemotherapy significantly improved PFS compared with EGFR TKI monotherapy in the intent-to-treat population (18.0 vs. 12.0 months; HR, 0.762; p = 0.0058; **Figure 1**). Almost all subgroups favored the experimental approach. The results obtained with gefitinib were compared to those achieved with osimertinib, which showed that both study arms fared considerably better with osimertinib (median PFS, 25.2 vs. 20.4 months; HR, 0.812; p = 0.2475) than with gefitinib (14.4 vs. 9.6 months; HR, 0.687; p = 0.0015).

With respect to the primary endpoint of OS, however, no difference resulted across the two study arms (48.0 months each; HR, 0.985; p = 0.4496). None of the subgroups analyzed appeared to derive significant benefit from the experimental approach. As with PFS, patients treated with osimertinib achieved better OS outcomes in both arms (median OS, not reached in either arm; HR, 0.835; p = 0.5154) than those who received gefitinib (45.6 vs. 43.2 months; HR, 1.016; p = 0.9124). Moreover, no difference regarding the overall response rate (ORR) was observed between the study arms (71.6 % vs. 78.0 %).

Among adverse events (AEs), decreases in neutrophils and platelet counts, nausea and anorexia were of course more frequent with the experimental regimen due to the chemotherapy component. In the experimental arm, AEs leading to treatment discontinuation occurred with gefitinib and osimertinib in 8.4 % and 14.6 %, respectively; in the control arm, this was the case in 14.4 % and 11.3 %, respectively. One patient who received osimertinib monotherapy died due to treatment-related causes. The scientists are currently investigating the mechanisms of acquired resistance using tumor tissue and liquid biopsy samples.

Sunvozertinib: pivotal findings

Approximately 2 % of patients with NSCLC harbor *EGFR* exon 20 insertion mutations [13]. The EGFR inhibitor sunvozertinib has been developed as an

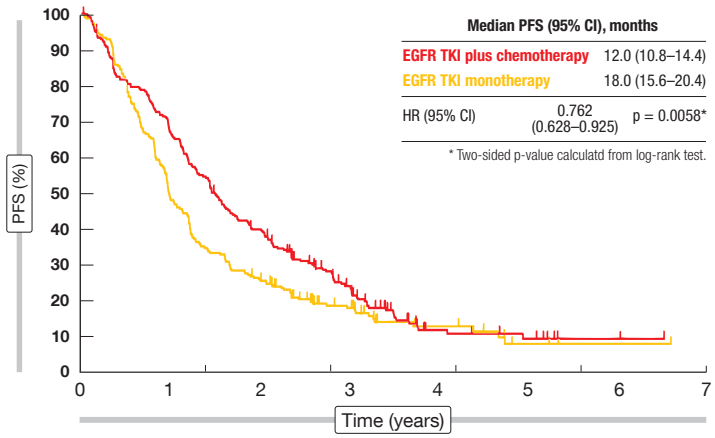

Figure 1: Progression-free survival with EGFR TKI therapy plus inserted chemotherapy vs. EGFR TKI treatment alone

oral, potent, irreversible and selective EGFR inhibitor targeting *EGFR* exon 20 insertions as well as other *EGFR* mutations [14]. In the pivotal, single-arm, phase II WU-KONG6 study, patients with locally advanced or metastatic NSCLC and confirmed *EGFR* exon 20 insertions received sunvozertinib 300 mg OD after 1–3 prior lines of systemic treatment. Their disease had progressed on or after platinum-based chemotherapy. ORR by independent review was defined as the primary endpoint.

The analysis of the WU-KONG6 data presented at ASCO 2023 included 97 patients with 30 different subtypes of *EGFR* exon 20 insertions after a median of two prior anti-cancer therapies [15]. Sunvozertinib gave rise to an ORR of 60.8 %, which met its predefined target with statistical significance ($p < 0.0001$). Disease control was achieved in 87.6 %. More than 90 % of patients obtained tumor shrinkage. Responses occurred irrespective of age, sex, smoking status, presence of baseline brain metastases, lines of prior therapy, previous PD-(L)1 treatment, mutation subtypes, and insertion locations. Median duration of response had not been reached yet; 64.4 % of responders were still responding.

Sunvozertinib showed a well-tolerated safety profile that was similar to the safety profiles of other EGFR TKIs. Diarrhea, increased plasma levels of creatine phosphokinase and rash constituted the most common all-grade treatment-emergent AEs. Most of the side effects were grade 1 or 2. Among grade ≥ 3 treatment-emergent AEs, increases in creatine phosphokinase levels ranged first (17.3 %) followed by diarrhea (7.7 %) and anemia (5.8 %). Overall, these data suggest that sunvozertinib is a potential treatment option for patients with NSCLC and *EGFR* exon 20 insertions. The randomized, multinational phase III WU-KONG28 study is currently evaluating first-line sunvozertinib versus platinum-based chemotherapy in patients with NSCLC and *EGFR* exon 20 insertions (NCT05668988).

Beamion Lung 1: *HER2*-positive disease

HER2 mutations are found in lung cancer in 2–4 % of cases, with approximately 50 % classified as *HER2* exon 20 insertion mutations that show poor response to TKIs [16-19]. TKIs that target both EGFR and HER are typically limited by toxicities associated with the inhibition of wild-type *EGFR* [18, 20]. The novel oral TKI BI 1810631 has been designed to target wild-type and mutant *HER2* including exon 20 insertions and to avoid toxicity due to the inhibition of wild-type *EGFR*. It is being tested in tumors with *HER2* alterations in the phase I Beamion Lung 1 study. Phase Ia of Beamion Lung 1 is the dose escalation phase and includes patients with solid tumors harboring *HER2* aberrations. Heymach et al. presented data for 43 patients including 24 lung cancer patients at ASCO 2023 [21].

Two BI 1810631 doses of 240 mg and 120 mg OD Q3W have been taken into dose optimization. To date, the maximum tolerated dose has not been reached with either the BID or OD schedule. Diarrhea was the most commonly reported AE. The majority of events was graded as 1 or 2, as only four patients developed grade ≥ 3 treatment-related AEs (9.3 %). AEs led to dose reduction and treatment discontinuation in 4.7 % each. Encouraging preliminary activity was observed: NSCLC patients showed objective responses in 46 %, and disease control was achieved in 96 %. In phase Ib of the Beamion Lung 1 study, BI 1810631 will be globally assessed in patients with NSCLC harboring *HER2* mutations including exon 20 insertion mutations. Cohort 1 that contains pretreated individuals is ongoing, and four additional NSCLC cohorts are planned.

Predictive biomarkers for amivantamab/lazertinib

The combination of the EGFR-MET bispecific antibody amivantamab and the third-generation EGFR TKI lazertinib has shown activity in cohort A of the CHRYSALIS-2 study that contained patients with *EGFR*-mutated NSCLC who had progressed after osimertinib and chemotherapy [22]. According to exploratory data, EGFR/MET immunohistochemistry (IHC) staining may predict for responses to this combination. At ASCO 2023, Besse et al. reported results for cohort D of the CHRYSALIS-2 study whose objective was the prospective validation of potential biomarkers based on IHC or ctDNA next-generation sequencing (NGS) [23]. The treatment consisted of amivantamab 1,050 mg (1,400 mg in patients with ≥ 80 kg body weight) i. v. plus lazertinib 240 mg p. o. Prior to study enrollment, the patients had received osimertinib in the first (70 %) or second (30 %) line and were chemotherapy-naïve. Plasma and tissue were collected at baseline. Among 101 response-evaluable patients, 77 had sufficient tissue for MET IHC staining. A predefined Bayesian process allowed for biomarker retraining/validation.

Consistent with previous reports, amivantamab plus lazertinib demonstrated activity with durable responses. In the entire cohort, the ORR was 30 %, and responses lasted for a median of 10.8 months **(Table 1)**. According to the biomarker analysis, a retrained signature of MET 3+ staining on ≥ 25 % of tumor cells (MET+) by IHC was identified as predictive of response to amivantamab and lazertinib regardless of the type of molecular resistance mechanism. In patients with MET+ (n = 28; 36 %), as compared to those with MET- (n = 49; 64 %), the analysis showed advantages regarding ORR, duration of response, clinical benefit rate, and PFS **(Table 1)**. In 17 of the 28 MET+ patients, responses were ongoing at the time of the analysis. Baseline NGS of ctDNA, on the other hand, did not predict responses to amivantamab plus lazertinib.

No new safety signals occurred in the study, and the individual AEs were mostly grade 1 or 2. Treatment-related dose interruptions, reductions, and discontinua-

TABLE 1 **Clinical outcomes in the entire cohort D of the CHRYSALIS-2 study and according to a new predictive signature**

Endpoint	Response-evaluable group (n = 101)	MET+ (n = 28)	MET- (n = 49)
Objective response rate, %	30	61	14
Median duration or response, months	10.8	10.8	6.8
Clinical benefit rate, %	69	86	61
Median progression-free survival, months	5.7	12.2	4.2

tions of both drugs were reported in 22 %, 6 %, and 5 %, respectively. In summary, MET+ by IHC might be a predictive biomarker for response to amivantamab plus lazertinib in chemotherapy-naïve patients after osimertinib pretreatment. This marker will be prospectively validated in the CHRYSALIS-2 study.

Primary endpoint of SCARLET: sotorasib plus chemotherapy

The combination of the KRAS^{G12C} inhibitor sotorasib with carboplatin/pemetrexed in patients with *KRAS*^{G12C}-mutated NSCLC is being explored in the single-arm, phase II SCARLET study. Thirty patients with advanced, non-squamous NSCLC harboring *KRAS*^{G12C} mutations who are naïve for both KRAS inhibition and cytotoxic chemotherapy are receiving sotorasib 960 mg plus carboplatin AUC 5/pemetrexed 500 mg/m² Q3W for 4 cycles. The induction phase is followed by sotorasib plus pemetrexed Q3W as maintenance until disease progression.

Sakata et al. reported the primary endpoint of SCARLET, which is ORR by blinded independent central review (BICR), at ASCO 2023 [24]. Indeed, the analysis showed favorable outcomes with an ORR of 88.9 % and ongoing responses in most patients. Changes in target lesions were observed across all PD-L1 expression levels. Median PFS by BICR was 5.7 months; at 6 months, almost 50 % of patients were alive and progression-free. Median OS had not been reached yet, and the 6-month OS rate was 87.3 %. Among treatment-related AEs, anemia as well as decreases in platelet and neutrophil counts were most common, followed by gastrointestinal toxicity. Cytopenias made up the majority of grade ≥ 3 events. One patient died due to grade 5 pneumonia. Dose reductions and interruptions of sotorasib were necessary in 31.0 % and 37.9 %, respectively.

According to a translational analysis based on plasma samples, *KRAS*^{G12C} was still detectable in 50 % of patients at 3 weeks. In this group, responses appeared to be less frequent than in patients who had *KRAS*^{G12C} negativity already at baseline and in those whose *KRAS*^{G12C} allele frequency had decreased during treatment. On the other hand, ORR did not differ according to the presence of *TP53*, which was the second most common mutation.

Co-alterations in CodeBreaK 200

Sotorasib has demonstrated superior PFS and ORR compared to docetaxel in patients with advanced *KRAS*^{G12C}-mutated NSCLC after ≥ 1 prior treatment line in CodeBreaK 200, which was the first randomized phase III trial of a KRAS^{G12C} inhibitor [25]. Given the unmet need to inform treatment decisions using molecular markers, Skoulidis et al. conducted prespecified subgroup analyses of tissue and/or plasma samples from CodeBreaK 200 to identify key genomic alterations [26]. The biomarker-evaluable population comprised 318 patients with tumor and/or plasma NGS data. According to central NGS, co-alterations mainly included *TP53* (57 %), *STK11* (38 %) and *KEAP1* mutations (26 %); these were well balanced across the two treatment arms, which also applied to combinations of *STK11* and *KEAP1* (17 %). Further aberrations of interest included *EGFR* mutations (21 %), *NTRK* fusions (19 %), *MET* alterations (12 %), *ALK* translocations (11 %), *RET* fusions (7 %), *ROS1* rearrangements (5 %) and *BRAF* mutations (5 %).

Sotorasib showed consistent clinical benefit compared to docetaxel regarding both PFS and ORR across the key co-alteration subgroups. PD-L1 expression did not affect the outcomes observed with sotorasib, as the treatment improved PFS over docetaxel in all three PD-L1 categories (i.e., < 1 %, ≥ 1 % and < 50 %, ≥ 50 %). High baseline plasma tumor burden turned out to be a negative prognostic marker irrespective of the type of treatment used in CodeBreaK 200.

Hypothesis-generating findings included the potential association of non-G12C *KRAS* co-alterations with primary resistance to either treatment. In this group, neither sotorasib nor docetaxel elicited remissions, and median PFS was 1.8 and 2.5 months with sotorasib and docetaxel, respectively. These results align with preclinical data suggesting that some non-G12C *KRAS* aberrations mediate sotorasib resistance [27]. Moreover, sotorasib-treated patients with mutated *NOTCH1* tended to experience early progression, whereas this was not the case with docetaxel treatment **(Figure 2)**. This signal warrants further exploration. Additional studies will explore and validate the roles of non-G12C *KRAS* and *NOTCH1* co-alterations as potential biomarkers for sotorasib treatment.

Encorafenib/binimetinib in *BRAF*^{V600E}-mutated tumors

The BRAF inhibitor encorafenib in combination with the MEK inhibitor binimetinib has shown clinical efficacy in patients with metastatic *BRAF*$^{V600E/K}$-mutant melanoma [28]. In the setting of lung cancer, the ongoing single-arm, open-label, multicenter phase II PHAROS trial is evaluating this regimen in patients with metastatic *BRAF*^{V600E}-mutant NSCLC after ≤ 1 prior line of treatment. Encorafenib 450 mg OD plus binimetinib 45 mg BID is administered until progression. The study population includes 59 treatment-naïve and 39 previously treated patients. ORR by independent radiologic review represents the primary endpoint.

According to the results reported by Riely et al. at ASCO 2023, the combination demonstrated meaningful clinical benefits with an acceptable safety profile [29]. ORRs were 75 % and 46 % for the treatment-naïve and pretreated cohorts, respectively. Complete remissions resulted in 15 % and 10 %, respectively. In the treatment-naïve group, median du-

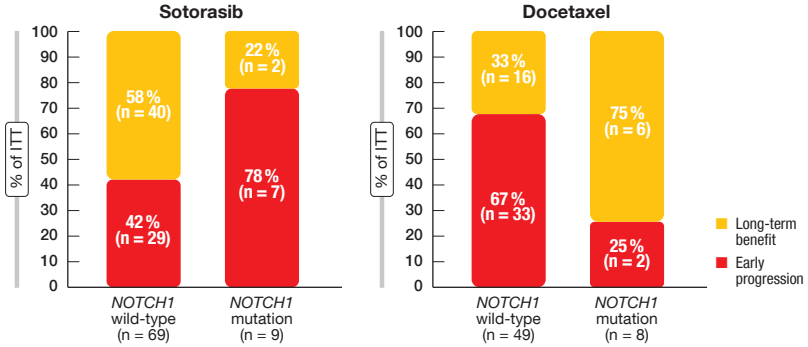

Figure 2: Early progression with sotorasib, but not docetaxel, in the presence of *NOTCH1* mutations

ration of response as well as median PFS had not been reached, while in the previously treated group, median duration of response and median PFS were 16.7 months and 9.3 months, respectively. At 24 weeks, 64 % vs. 41 % of patients had obtained disease control.

The safety profile was consistent with that observed in the setting of melanoma. Nausea, diarrhea and fatigue occurred as the most common events. Permanent discontinuation of both encorafenib and binimetinib due to treatment-related AEs resulted in 15 %. The majority of AEs was restricted to grades 1 and 2. Overall, these findings indicate that encorafenib plus binimetinib represents a potential new treatment option for patients with *BRAF*^{V600E}-mutated metastatic NSCLC.

TRIDENT-1: repotrectinib

ROS1 TKI therapy is the standard of care in patients with NSCLC harboring *ROS1* fusions, although achieving durable benefit remains a challenge with the established agents crizotinib and entrectinib [30-32]. The next-generation TKI repotrectinib, which is selectively active against ROS 1, TRK and ALK, has been developed to improve durability of benefit by decreasing the potential for emergence of resistance mutations and circumventing known resistance mutations [33]. Also, repotrectinib has favorable properties for human brain penetration. This agent is currently under evaluation in the global pivotal phase I/II TRIDENT-1 study that includes four phase II dose expansion cohorts with *ROS1*-positive advanced NSCLC. Lin et al. reported the first data on repotrectinib in patients with *ROS1*-positive NSCLC with or without baseline CNS metastases [34]. The efficacy-evaluable population per BICR comprised 71 ROS1-TKI–naïve patients (18 and 53 with and without brain lesions, respectively) and 56 patients who had received one prior ROS1 TKI but no chemotherapy before trial entry (24 and 32 with and without brain lesions, respectively).

TABLE 2 **Systemic efficacy of repotrectinib in patients with *ROS1*-positive NSCLC with or without baseline CNS metastases**

Endpoint	ROS1-TKI-naïve (n = 71)	1 prior ROS1 TKI and no prior chemotherapy (n = 56)
Patients with CNS metastases, n (%)	*18 (25)*	*24 (43)*
Confirmed ORR, %	89	33
Complete remission, %	6	0
Partial remission, %	83	33
Stable disease, %	6	46
Duration of response ≥ 6 months, %	100	62
Duration of response ≥ 12 months, %*	93	-
Progression-free survival ≥ 6 months, %	94	57
Progression-free survival ≥ 12 months, %*	87	-
Patients without CNS metastases, n (%)	*53 (75)*	*32 (57)*
Confirmed ORR, %	75	41
Complete remission, %	6	9
Partial remission, %	70	31
Stable disease, %	19	44
Duration of response ≥ 6 months, %	87	92
Duration of response ≥ 12 months, %*	84	-
Progression-free survival ≥ 6 months, %	90	75
Progression-free survival ≥ 12 months, %*	77	-

* Not reported for the TKI-pretreated cohort due to small number of patients at risk

Repotrectinib demonstrated durable clinical activity irrespective of ROS1 TKI-pretreatment and CNS status. Confirmed ORRs ranged from 33 % to 89 %, and substantial proportions of patients showed long duration of response as well as freedom from progression **(Table 2)**. In the group with measurable baseline CNS metastases, the treatment induced deep reductions in intracranial tumor burden across the groups. Intracranial responses occurred in 88 % and 42 % in the TKI-naïve and -pretreated cohorts, respectively. Moreover, the CNS activity of repotrectinib proved durable. Intracranial PFS ranged from 0.0+ to 16.4+ months and from 1.6+ to 12.8+ months in the TKI-naïve and -pretreated cohorts, respectively.

The safety profile of repotrectinib was similar in patients with and without CNS metastases, which also applied to nervous system AEs. Side effects leading to treatment discontinuation were reported in 3 % to 10 % across the groups. Dizziness occurred in 57 % and 63 % of patients with and without brain lesions, respectively; these events were mostly grade 1 or 2 and did not necessitate treatment discontinuation. As the authors pointed out, the data from TRIDENT-1 are the first analysis of outcomes on repotrectinib in patients with *ROS1*-positive NSCLC with or without baseline CNS metastases and suggest that repotrectinib could represent a new treatment option in this population. ■

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Stage IV lung cancer: miscellaneous treatment strategies

Portable antimitotic fields

Considering the need for new, well tolerated and effective treatments to improve survival in metastatic NSCLC after platinum-based chemotherapy, Tumor Treating Fields (TTFields) therapy represents an innovative option. TTFields are electric fields that exert physical forces on electrically charged cellular components in dividing cancer cells, thus disrupting cell function [1, 2]. The result is an anti-mitotic effect and induction of immunogenic cell death, which in itself triggers a systemic antitumor immune response [3-5]. This non-invasive locoregional treatment has already been approved in the USA for glioblastoma and malignant pleural mesothelioma [6, 7] and is delivered by a wearable medical device connected to two pairs of adhesive bandages with biocompatible insulated ceramic discs that are placed on the chest. A pilot study has demonstrated the safety and feasibility of this approach in advanced NSCLC [9]. The patients are able to perform their regular activities of daily living during TTFields therapy, while all other treatments and patient care continue to be provided.

Preclinical NSCLC models have suggested that TTFields therapy amplifies effects of immune checkpoint inhibitors (ICIs) and taxanes [4, 5, 8]. The randomized phase III LUNAR study was initiated to evaluate the safety and efficacy of TTFields therapy together with standard-of-care (SOC) treatment vs. SOC alone in patients with metastatic NSCLC progressing on or after platinum-based therapy. Overall, 137 and 139 patients were analyzed in the experimental and control arms; within either group, approximately half had received ICI as SOC treatment, and the other half had been treated with docetaxel. Leal et al. reported the findings at the ASCO 2023 Congress [10].

More favorable findings in the ICI group

Median exposure to treatment was longer in the experimental arm than in the control arm (14.6 vs. 10.3 weeks), with mean TTFields therapy duration being approximately 2-fold greater in the ICI group than in the docetaxel group. Regarding the primary endpoint of overall survival (OS), the TTFields treatment in addition to SOC induced a statistically and clinically significant 3-month improvement compared to SOC alone in the ITT population (median OS, 13.2 vs. 9.9 months; HR, 0.74; p=0.035; **Table 1**). In the subgroup of ICI-treated patients, this difference was almost as large as 8 months (18.5 vs. 10.8 months; HR, 0.63; p=0.03), thus exceeding the survival benefit observed for docetaxel-treated individuals who showed a trend favoring the combined approach **(Table 1)**. Progression-free survival (PFS) did not differ across the two arms in the ITT population (4.8 vs. 4.1 months; HR, 0.85; p=0.23), which also applied to the overall response rates (ORR; 20% vs. 17%; p=0.5). Five complete responses occurred, which included four with TTFields and one with SOC alone; all of these were observed in ICI-treated patients.

TABLE 1 Overall survival results obtained for TTFields therapy plus standard-of-care treatment

	ITT population		ICI-treated patients		Docetaxel-treated patients	
	TTFields + SOC (n = 137)	*SOC (n = 139)*	*TTFields + ICI (n = 66)*	*ICI (n = 68)*	*TTFields + DTX (n = 71)*	*DTX (n = 71)*
Median overall survival, months	13.2	9.9	18.5	10.8	11.1	8.7
	HR, 0.74 p = 0.035		HR, 0.63 p = 0.03		HR, 0.81 p = 0.28	
1-year survival, %	53	42	60	46	46	38
3-year survival, %	18	7	27	9	9	5

TTFields therapy did not add any systemic toxicity to SOC therapy. Dermatitis was the most frequent treatment-emergent adverse event (AE) in the experimental arm (all grades, 43 % vs. 2 %), followed by fatigue (28 % vs. 37 %) and musculoskeletal pain (36 % vs. 27 %). In the majority of cases, dermatitis was restricted to grade 1 or 2. No grade 4 or 5 toxicities were attributable to TTFields therapy. The authors stated in their summary that TTFields therapy should be considered part of SOC for advanced metastatic NSCLC. Additional pivotal studies evaluating TTFields therapy plus SOC as first-line treatment of metastatic NSCLC as well as early-stage disease are planned.

Dato-DXd + pembrolizumab ± chemotherapy

Datopotamab deruxtecan (Dato-DXd), an antibody-drug conjugate containing a TROP2-directed antibody linked to a highly potent cytotoxic payload, has demonstrated encouraging activity as monotherapy in patients with heavily pretreated advanced NSCLC [11]. Based on the assumption that the efficacy of Dato-DXd might be increased by the addition of combination partners, the phase Ib TROPION-Lung02 study was conducted to assess doublet therapy with Dato-DXd plus the PD-1 antibody pembrolizumab (cohorts 1 and 2) and triplet therapy with Dato-DXd plus pembrolizumab and carboplatin or cisplatin (cohorts 3-6) at different doses. TROPION-Lung 2 is the first study to evaluate these regimens in advanced NSCLC without actionable genomic alterations. Sixty-four and 72 patients with advanced/metastatic NSCLC received the doublet and triplet regimens, respectively, with 37 and 54, respectively, being treated in the first-line setting. Immunotherapy had previously been administered in the entire group in 19 % and 25 %, respectively.

In both the first line and later lines, Dato-DXd plus pembrolizumab with or without chemotherapy showed encouraging efficacy **(Table 2)** [12]. Confirmed plus pending ORR was 38 % and 49 % for the doublet and triplet groups, respectively; in the first line, ORRs of 50 % and 57 %, respectively, were achieved. Disease control rates were 84 % and 87 %, respectively, in all patients. Median duration of response had not been reached in either group, and the treatment gave rise to deep responses. Many patients obtained tumor burden reduction regardless of their PD-L1 expression status. The preliminary median PFS in all patients was 8.3 and 7.8 months, respectively.

During the dose-finding phase, two patients receiving Dato-DXd plus pembrolizumab and chemotherapy experienced dose-limiting toxicities, which were neutropenia and thrombocytopenia. Finally, Dato-DXd 6 mg/kg proved to be safe in each combination. Treatment-related AEs grade ≥ 3 emerged in 31 % and 58 % with the doublet and triplet regimens, respectively. In 23 % and 28 %, respectively, Dato-DXd was discontinued due to AEs. No treatment-related deaths occurred. The most frequent AEs of any grade comprised stomatitis, nausea, anemia, and fatigue. Hematologic AEs, particularly those of grade ≥ 3, were more frequently observed with triplet than with doublet therapy.

Among AEs of special interest, oral mucositis/stomatitis was the most common event but was predominantly grade 1 or 2. Interstitial lung disease(ILD)/pneumonitis occurred in 17 % and 22 % in the doublet and triplet groups, respectively, with 3 % each graded as ≥ 3. No grade 4 or 5 adjudicated ILD/pneumonitis events were observed. At present, Dato-DXd plus pembrolizumab with or without chemotherapy is being compared with first-line SOC regimens in the pivotal phase III TROPION-Lung07 (NCT5555732) and TROPION-Lung08 (NCT05215340) trials.

KEYNOTE-789: IO after failure of EGFR TKIs

ICI therapy has defined new standards in the setting of metastatic NSCLC without driver alterations. However, pembrolizumab and other ICIs have also shown activity in TKI-resistant, *EGFR*-mutant NSCLC [13-15]. To extend the benefit of ICIs in this population, pembrolizumab plus chemotherapy was evaluated in patients with stage IV nonsquamous NSCLC with *EGFR* deletion 19

TABLE 2 TROPION-Lung02: response rates with Dato-DXd plus pembrolizumab (doublet) and Dato-DXd plus pembrolizumab and platinum (triplet)

	All patients		Patients in first line	
Response	Doublet (n = 61)	Triplet (n = 71)	Doublet (n = 34)	Triplet (n = 53)
Confirmed + pending objective response rate, n (%)	23 (38)	35 (49)	17 (50)	30 (57)
Confirmed + pending best overall response, n (%)				
Confirmed complete response	0	1 (1)	0	1 (2)
Pending complete response	0	0	0	0
Confirmed partial response	21 (34)	34 (48)	15 (44)	29 (55)
Pending partial response	2 (3)	0	2 (6)	0
Stable disease, n (%)	30 (49)	27 (38)	16 (47)	18 (34)
Disease control rate, n (%)	51 (84)	62 (87)	31 (91)	48 (91)

or L858R mutation and disease progression after TKI therapy in the randomized phase III KEYNOTE-789 trial. The patients had progressed either after first-/second-generation EGFR TKI treatment without T790M resistance mutation or with T790M mutation and osimertinib failure, or had experienced osimertinib failure in the first-line setting regardless of T790M status. Patients in the experimental arm (n = 245) received pembrolizumab 200 mg plus pemetrexed and carboplatin or cisplatin Q3W for 4 cycles followed by pembrolizumab 200 mg Q3W for 31 cycles plus pemetrexed Q3W. In the control arm (n = 247), placebo was administered in addition to the same chemotherapy regimen. The design contained an optional crossover from the control arm to pembrolizumab 200 mg Q3W for 35 cycles in case of progression. PFS by blinded independent central review and OS were defined as the dual primary endpoint.

According to the data presented by Yang et al. at ASCO 2023, the addition of pembrolizumab to chemotherapy prolonged PFS and OS, although the results did not reach statistical significance per the prespecified statistical analysis plan [16]. PFS findings at the time of the second interim analysis showed a 20% risk reduction (median PFS, 5.6 vs. 5.5 months; HR, 0.80; p = 0.0122) with 12-month rates of 14.0% vs. 10.2% and 24-month rates of 4.7% vs. 3.5%. Median OS at the time of the final analysis was 15.9 vs. 14.7 months (HR, 0.84; p = 0.0362). No subgroup derived a particularly pronounced OS benefit from the ICI-based therapy. However, patients with PD-L1–positive tumors (TPS ≥ 1%) experienced greater mortality reduction (median OS, 18.6 vs. 14.1 months; HR, 0.77) than those without PD-L1 expression (TPS < 1%; 15.7 vs. 14.7 months; HR, 0.91).

ORRs were 29.0% vs. 27.1% for pembrolizumab plus chemotherapy vs. chemotherapy alone, and responses lasted for a median of 6.3 vs. 5.6 months. At 9 months, ongoing responses were found in 34.0% vs. 22.9%. The AEs presented themselves manageable, with no new safety signals identified. Treatment-related grade 3–5 AEs occurred in 43.7% vs. 38.6%. Discontinuation of pembrolizumab or placebo resulted in 9.8% vs. 4.5%. Taken together, the findings from the KEYNOTE-789 study are consistent with prior data showing that the benefit obtained with anti-PD-(L)1–based treatment is smaller in patients with TKI-resistant, *EGFR*-mutant metastatic NSCLC than in those with *EGFR* wild-type tumors. As the authors noted, additional biomarker research is required to determine which of these patients might benefit as there remains a great unmet need for this population.

Cohort C of VARGADO by *KRAS* and PD-L1 status

Cohort C of the ongoing, prospective, non-interventional VARGADO study is investigating anti-angiogenic treatment with nintedanib in addition to docetaxel after first-line ICI plus chemotherapy in patients with adenocarcinoma of the lung. At ASCO 2023, Grohé et al. reported an updated analysis of Cohort C (n = 219) that focused on the safety and efficacy of the nintedanib combination according to PD-L1 and *KRAS* mutational status [17].

In the overall population, median PFS and OS were 4.5 and 9.6 months, respectively. Among patients with documented *KRAS* mutation status (n = 119), 75 had *KRAS* wildtype. In this group, median PFS and OS were 3.7 and 7.7 months, respectively. For the cohort with *KRAS* mutations, median PFS and OS were 5.1 and 6.7 months, respectively. Non-G12C *KRAS* mutations were found in 33 patients; here, median PFS and OS were 5.0 and 6.7 months, respectively. Likewise, ORR did not differ greatly across all of these groups (range, 18.2% to 27.3%). The corresponding disease control rates ranged from 45.3% to 48.5%. Also, the PD-L1 expression status prior to the first-line treatment did not affect OS (10.6 and 10.5 months for PD-L1 expression < 1% and ≥ 1%, respectively) or disease control rates (51.2% and 51.3%, respectively). AEs related to nintedanib mostly included diarrhea (any grade, 34.7%), nausea (14.2%), vomiting (8.2%) and fatigue (7.8%). The authors concluded that in patients with adenocarcinoma of the lung, nintedanib plus docetaxel is an effective and safe second-line treatment option after ICI plus chemotherapy independent of PD-L1 expression and *KRAS* mutation status. ■

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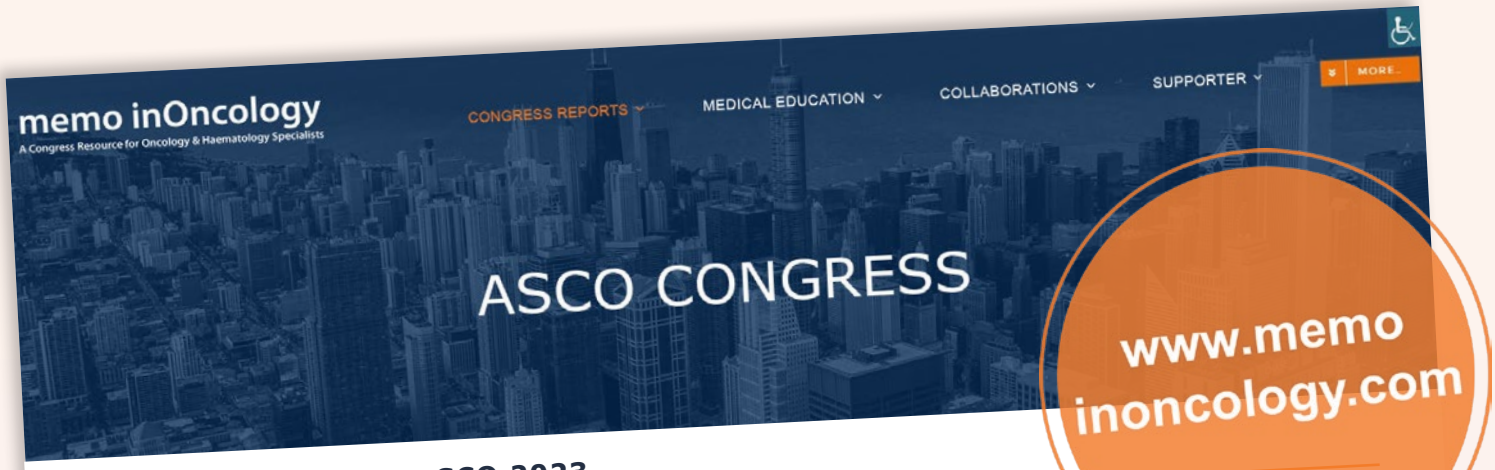

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Expert interviews at ASCO 2023

John Heymach provides an overview on the expected benefits of HER2-selective tyrosine kinase inhibitors compared to anti-HER2-antibodies while highlighting the Beamion Lung 1 data. Moreover, he talks about RET inhibitor sensitivity and resistance in lung cancer and shares which study, presented at this year's ASCO congress, is most likely to impact standard of care treatment in NSCLC.

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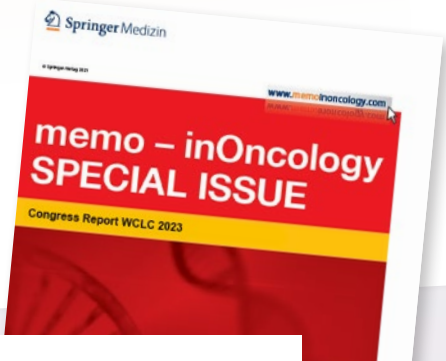

Forthcoming Special Issue

This special issue will be offering a synopsis from the WCLC 2023 that will be held in September 2023. The report promises to make for stimulating reading, as the WCLC Congress itself draws on the input from a number of partner organizations, representing a multidiscplinary approach to lung cancer treatment and care. Stay tuned for the latest news in oncology and its subspecialties.

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