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Congress Report WCLC 2023

A GLOBAL CONGRESS DIGEST ON LUNG CANCER

Report from the International Association for the Study of Lung Cancer (IASLC) 2023 World Conference on Lung Cancer, September 9th-12th , hybrid congress

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Preface

Dear Colleagues,

The International Association for the Study of Lung Cancer (IASLC) 2023 World Conference on Lung Cancer (WCLC) was held in Singapore and virtually from 9th to 12th September. This prestigious event served as a global gathering point uniting over 6,000 renowned international scientists, researchers, and devoted patient advocates. Throughout the conference, attendees had the chance to discuss the most exciting updates in the field of lung cancer and thoracic oncology, with key updates summarized in more than 100 educational and interactive sessions, as well as 459 posters and 696 ePoster sessions.

This report spans a diverse range of topics, with each of them contributing to the ever-evolving landscape of lung cancer research and care. The summaries presented with respect to the detection and treatment of early-stage lung cancer offer a look at the importance of family history for screening, intra-operative tumor visualization, and the impact of the extent of surgical resection on the rate of second primary lung cancers. Moreover, systemic treatment regimens are being explored, such as PD-1 inhibition in addition to radiotherapy, and the outcomes of perioperative immunotherapy according to the *EGFR* mutation status are discussed.

The second chapter delves into the exciting developments in the realm of targeted therapies. It focuses on EGFR- and HER2/HER3-directed therapies, such as the addition of chemotherapy to the third-generation EGFR TKI osimertinib in advanced disease. In the *HER2*-positive setting, the DESTINY-Lung02 trial has assessed benefits of the antibody-drug conjugate trastuzumab deruxtecan and the effectiveness/toxicity profile of two different dosing schedules. Other treatments discussed relate to $KRAS^{G12C}$-mutant and *ALK*-positive disease.

The article on refinement of first-line regimens for extensive-stage small-cell lung cancer highlights the progress made in optimizing treatment approaches for this challenging disease. Analyses detailed in this report relate to anti-angiogenic treatment plus immunochemotherapy, anti-PD-(L)1 antibodies in combination with chemotherapy, and a DLL3-targeting T cell engager.

Short sections are devoted to Trop-2–directed antibody-drug conjugates that were assessed in conjunction with immunotherapy in the EVOKE-02 and TROPION-Lung04 trials, and the MARS 2 trial that challenged the role of surgery (pleurectomy/decortication) in malignant pleural mesothelioma.


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Last but not least, you will find a summary of the new features of the upcoming 9th edition of the TNM classification for lung cancer, mesothelioma and thymic cancers in this report.

Overall, the IASLC 2023 WCLC provided an outstanding educational experience, serving as a platform for sharing remarkable advancements in the field of lung cancer diagnosis and treatment. As knowledge truly saves lives, the memo inOncology team and I hope that you have a fantastic time exploring this special issue.

Happy reading!

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Detection and treatment of early-stage lung cancer: recent insights

The significance of family history for screening

Given the high incidence and mortality rates of lung cancer in Taiwan and the established association between survival and disease stage at diagnosis, the Taiwanese national early detection program for lung cancer was launched in July 2022 with the aim of increasing the proportion of tumors identified at an early stage using low-dose CT (LDCT). The TALENT study, a domestic study conducted from 2007 to 2011 with 1,102 participants, had already shown that people with a family history of lung cancer are 1.6 times likelier to develop lung cancer than the population without a pertinent family history [1]. Therefore, populations eligible for the early detection program include both heavy smokers (50 to 74 years of age, >30 pack-years, currently smoking or having quitted <15 years) and individuals with a family history of lung cancer (males

aged 50 to 74 years, females aged 45 to 74 years). Overall, 167 hospitals across the country are participating in the screening program.

At WCLC 2023, Huang et al. reported the findings obtained during the first year after the start of the program [2]. Almost 50,000 individuals were screened, and 531 lung cancers were detected, which translated into a detection rate of 1.1%. Among these, 85.1% were stages 0 or 1 **(Table 1)**. As indicated by the TALENT study, family history was the dominant risk factor. Almost 75% of lung cancer patients met this criterion, while 22.2% were heavy smokers; 3.2% met both criteria. Whereas the positive LDCT screening rate was consistent among populations with a family history, heavy smoking, or both, the lung cancer detection rate was highest in the group with a family history (1.4 vs. 0.6 and 0.9 for heavy smoking and both risk factors, respectively). Likewise, the positive predictive value was twice as high in lung cancer patients with a family history than in the other groups (15.3 vs. 7.1 and 9.8, respectively).

As the authors concluded, these results warrant inviting first-degree relatives of lung cancer patients for screening. Artificial intelligence-based nodule detection algorithms are currently under development to help reduce the reading costs and to raise diagnostic accuracy. Moreover, research is being conducted on the effect of the integration of smoking cessation services in this program, as well as stage changes in newly diagnosed lung cancer cases.

Intra-operative tumor visualization

Screening programs contribute to the increasing number of small lung cancers that require resection. This poses challenges, particularly in the setting of minimally invasive surgery, as palpation cannot be used to identify the tumor. Sub-lobar resection has become the standard procedure for small (< 2 cm) peripheral cancers; here, the margin is critical to prevent recurrence, and node assessment is required to meet the criteria.

A potential solution consists in visualization of the tumor using the fluorescent probe VGT-309, which binds cathepsin in the tumor tissue and associated macrophages. In the first-in-human clinical trial, patients with suspected or proven NSCLC received VGT-309 either on the day before or on the morning of video-assisted thoracic surgery(VATS)/robotic thoracic surgery. Outcomes included the safety of increasing doses and clinically significant events (i.e., index lesion, nodes, additional lesions, unexpected involvement of margins).

According to the results reported at WCLC 2023 by Wright et al., VGT-309 appeared to be a safe and well-tolerated drug [3]. Only one drug-related serious adverse event (AE) occurred, which was asymptomatic transaminitis that recovered spontaneously within 30 days. Increasing doses correlated with increasing mean fluorescence intensity of the tumor. Among 27 participants, 23 were found to have cancer; there was one case of a carcinoid, and three had non-malignant lesions. Tumor visualization was excellent at the maximum dose of 0.32 mg/kg. All of the 12 tumors that were within 10 millimeters of the surface were identified based on fluorescence. Moreover, the data revealed a high tumor-to-background ratio without apparent false-positives.

Clinically significant events were observed in 8 of 20 patients. These included the identification of tumors, positive lymph nodes, and unsuspected pleural metastases that had not been picked up on preoperative imaging. A notable advantage is that VGT-309 works on all commercial VATS and robotic NIR platforms, which renders adaptation unnecessary. To date, further unpublished results have been obtained in a phase II extension as well as a single-center phase II study. A large multi-center phase II trial will be starting soon.

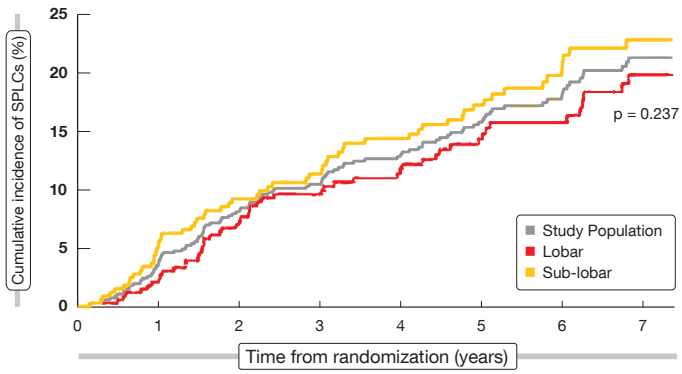
TABLE 1 **Risk factors and stages of lung cancers detected in the first year of the Taiwanese early detection program for lung cancer**

Gender	Risk factors, n (%)				Stages of lung cancer, n (%)				
	Family history	Heavy smokers	Both	Total	0	I	II	III	IV
Male	87 (42.7)	100 (49.0)	17 (8.3)	204	21 (10.3)	137 (67.2)	8 (3.9)	20 (9.8)	18 (8.8)
Female	309 (94.5)	18 (5.5)	0	327	48 (14.7)	246 (75.1)	11 (3.4)	11 (3.4)	11 (3.4)
Total	396 (74.6)	118 (22.2)	17 (3.2)	531	69 (13.0)	383 (72.1)	19 (3.6)	31 (5.9)	29 (5.5)

Second primary lung cancers in CALGB 140503

The non-inferiority of sub-lobar resection compared to lobectomy in patients with peripheral NSCLC with a tumor size of ≤ 2 cm and node-negative disease (T1aN0) has been demonstrated by the multicenter phase III CALGB 140503 trial [4]. Both disease-free survival (DFS) and overall survival (OS) were comparable across the two approaches. The analysis presented at WCLC 2023 related to the rate of second primary lung cancers (SPLCs) observed in CALGB 140503 [5]. SPLCs were defined as tumors with a different histology than the initial lung cancer, a new lung cancer which was diagnosed two years after the initial one, or a new tumor diagnosed in a different lobe or segment without intervening lymph nodes or metastases. In the sub-lobar and lobar resection arms, 340 and 357 patients were analyzed, respectively. The objective of the study was the estimation of the overall SPLC rates and the rates observed per patient per year.

After a follow-up of seven years, the analysis demonstrated a clinically significant SPLC rate, although the difference across the arms was not significant **(Figure 1)**. In the overall study population, 15.9% of patients had developed SPLCs at 5 years; after sub-lobar resection, this applied to 17.2%, and after lobar resection, to 14.7% (p = 0.237). The rates per patient per year were 3.4%, 3.8% and 3.1%, respectively. None of the risk factors for SPLCs evaluated in the univariable and multivariable analysis showed a significant effect, although there was a trend towards current tobacco use. The scientists performed an exploratory analysis that excluded SPLCs occurring during the first two years, as these tend to be more



	n	Events	HR (95 % CI)	5-year second primary rate (95 % CI)
Lobar	357	52	Reference	14.7 (10.6-18.7)
Sub-lobar	340	60	1.25 (0.86-1.82)	17.2 (12.7-21.5)
Study population	697	112		15.9 (12.9-18.9)

Figure 1: Cumulative incidence of second primary lung cancer after sub-lobar vs. lobar resection

likely due to misclassification. Again, the 5-year SPLC rates did not differ, with 14.9 % overall and 15.9 % and 14.0 % for the sub-lobar and lobar resection groups, respectively (p = 0.466). The rates per patient per year were 1.9 %, 2.1 % and 1.8 %, respectively.

In their conclusion, the authors emphasized that the optimal frequency, duration, and type of surveillance is undefined. Future studies should collect diagnostic information and treatment for SPLCs given the clinical relevant rates. In addition to the projected increase in early-stage NSCLC cases due to increased use of CT screening, improved adjuvant treatments for resected lung cancers are assumed to contribute to the rising incidence of SPLCs.

I-SABR: nivolumab plus radiotherapy

In patients with operable stage I NSCLC (tumor diameter ≤ 3 cm, N0M0), a single-arm prospective trial has demonstrated non-inferiority of stereotactic ablative radiotherapy (SABR) regarding long-term survival compared to VATS [6]. SABR has been implemented as a standard of care. However, the recurrence rates at five years were higher in the SABR arm than in the group undergoing surgery (17.6 % vs. 8 %).

To improve upon these results, an open-label, randomized, phase II trial evaluated the addition of four doses of nivolumab to SABR (50 Gy in 4 fractions or 70 Gy in 10 fractions) in patients with IA-IB (tumor size ≤ 4 cm, N0M0), stage IIA (≤ 5 cm, N0M0), or stage IIB (> 5 cm and ≤ 7 cm, N0M0) NSCLC, including multiple primary tumors. Also, patients with isolated lung parenchymal recurrent or persistent node-negative disease suitable for SABR were enrolled. The control arm received SABR only. In the experimental and control arms, 66 and 75 patients, respectively, were analyzed per protocol. Regarding baseline characteristics, there was a slight imbalance, with patients in the experimental arm harboring comparatively larger tumors (median tumor size, 2.0 vs. 1.7 cm) and a higher percentage of recurrent disease (24 % vs. 16 %). The primary endpoint was the 4-year event-free survival (EFS) rate in the per-protocol population.

Compared with SABR alone, the addition of adjuvant immunotherapy (I-SABR) significantly improved EFS, with 48-month rates of 77 % vs. 53 % (HR, 0.38; p = 0.0056) [7]. Recurrence and/or death was greatly reduced in the I-SABR arm (12.1 % vs. 36.0 %; **Table 2**). Also, the patients in the experimental arm showed a lower rate of second primary lung cancers (3.0 % vs. 8.0 %). This might suggest a preventive effect of the immunotherapy combination, although these data are only exploratory. Almost none of all patients experienced in-field failure (0 % vs. 1 %), which underscores the potency of radiotherapy.

Toxicity of the combined regimen was tolerable. Notably, fatigue occurred more commonly with I-SABR than with SABR (grade 2, 7 vs. 1 events; grade 3, 2 vs. 0 events). Grade 2 pneumonitis emerged in 2 vs. 1 patients, with no individual developing grade 3 pneumonitis. Overall, no grade 4 or 5 AEs were observed in the study. An ongoing exploratory predictive analysis using radiomic artificial intelligence modeling is attempting to identify patients in need of immunotherapy. According to the authors, I-SABR might be a treatment option in patients with early-stage, treatment-naïve NSCLC or parenchymal, node-negative recurrent lung cancer. A phase III study is required to establish this approach in routine care.

TABLE 2 **Pattern of failure with immunotherapy plus SABR vs. SABR alone**

Event	I-SABR (n = 66)	SABR (n = 75)
Local failure only	0 (0 %)	7 (9.3 %)
Regional failure only	4 (6.1 %)	2 (2.7 %)
Distant metastasis only	2 (3.0 %)	3 (4.0 %)
Local + regional failure	0 (0 %)	0 (0 %)
Local + distant failure	0 (0 %)	2 (2.7 %)
Local + regional + distant failure	0 (0 %)	1 (1.3 %)
Regional + distant failure	0 (0 %)	5 (6.7 %)
Second primary lung cancer	2 (3.0 %)	6 (8.0 %)
Any local failure	0 (0 %)	10 (13.3 %)
Any regional failure	4 (6.1 %)	8 (10.7 %)
Any distant failure	2 (3.0 %)	12 (16.0 %)
Any death	4 (6.1 %)	9 (12.0 %)
Any recurrence and/or death event	8 (12.1 %)	27 (36.0 %)
No relapse or death	58 (87.9 %)	48 (64.0 %)

Perioperative durvalumab in *EGFR*-mutant disease

AEGEAN was the first phase III study to evaluate the perioperative use of the PD-L1 inhibitor durvalumab in addition to neoadjuvant chemotherapy for patients with resectable NSCLC (stage IIA-IIIB[N2]) [8]. Durvalumab 1,500 mg plus platinum-based chemotherapy Q3W for four cycles was tested against placebo plus chemotherapy prior to lobectomy, sleeve resection, or bilobectomy. After surgery, patients in the experimental arm continued to receive durvalumab consolidation Q4W for 12 cycles, while those in the control arm were treated with placebo. The combined approach led to improvements in EFS (HR, 0.68; p = 0.003902) and the pathological complete response (pCR) rate (p = 0.000036). As enrollment started prior to the emergence of evidence indicating that patients with *EGFR/ALK* aberrations might have a limited response to immunotherapy, the protocol was amended in 2021 to exclude this population.

At WCLC, He et al. reported the outcomes for 51 patients with *EGFR* mutations who entered the AEGEAN study between 2019 and 2021 before the protocol amendment [9]. Among these, 26 and 25 were treated with durvalumab and placebo, respectively. There were some imbalances in baseline characteristics, such as higher rates of males and Asian patients in the placebo arm than in the durvalumab arm. Exon 19 deletions were present in 53.8 % vs. 36.0 % in the durvalumab and placebo groups, respectively, and L858R mutations were found in 11.5 % vs. 16.0 %. While only 3.8 % of those in the experimental arm had *EGFR* mutations categorized as "other", this was the case in 24.0 % in the control arm.

The subgroup of patients with *EGFR*-mutated NSCLC, in contrast to the modified ITT (mITT) population, did not derive a clear benefit from perioperative durvalumab in addition to neoadjuvant chemotherapy. After a median follow-up of 16.6 months, median EFS did not differ significantly (HR, 0.86), with 24-month EFS rates of 59.3 % vs. 44.9 %. The difference in pCR rates was low at 3.8 % (3.8 % vs. 0.0 %), whereas this was 13.0 % in the mITT population (17.2 % vs. 4.3 %). Similarly, major pathological responses occurred in 7.7 % vs. 4.0 % in the *EGFR*-mutant group and in 33.3 % vs. 12.3 % in the mITT population. The toxicity observed for patients with *EGFR* mutations was manageable.

These findings should be interpreted with caution due to the small numbers of patients with *EGFR*-mutant disease and wide 95 % confidence intervals. As the authors noted, EGFR testing should be considered prior to the initiation of neoadjuvant therapy in light of the robust clinical benefit demonstrated for the adjuvant administration of the EGFR TKI osimertinib in the phase III ADAURA trial after resection of *EGFR*-mutated lung cancer [10].

PACIFIC-R: outcomes by *EGFR* mutational status

Consolidation treatment with durvalumab for up to 12 months has been established as a global standard of care for patients with unresectable, stage III NSCLC after chemoradiotherapy based on the placebo-controlled, phase III PACIFIC trial, with the OS and PFS benefits being maintained over time [11]. The ongoing international, observational PACIFIC-R study has confirmed the real-world effectiveness of this regimen [12]. PACIFIC-R is being conducted as a retrospective review of medical records for patients from the PACIFIC early access program. Due to uncertainty regarding the efficacy of consolidation immunotherapy in patients with *EGFR*-mutated lung cancer, Peters et al. explored the outcomes in PACIFIC-R according to *EGFR* mutational status [13].

Within the full analysis set of 1,154 patients recruited across eight European countries plus Australia and Israel, the *EGFR* mutation status was known in 466 individuals (40.4 %). While 44 (9.4 %) had *EGFR*-mutated NSCLC, 422 (90.6 %) had *EGFR*-wildtype disease. Clinical characteristics were generally similar between the mutated and wildtype groups, although a lower proportion of *EGFR*-mutated patients was aged < 70 years, had a history of smoking, and had a performance status of 0. In approximately 75 % of cases, PD-L1 expression ≥ 1 % was present on tumor cells irrespective of *EGFR* status.

Real-world PFS in PACIFIC-R was shown to be shorter among patients with *EGFR*-mutated NSCLC than in those with *EGFR* wildtype (10.6 vs. 26.4 months; **Figure 2**). The 3-year PFS rates were 29.0 % vs. 45.0 %. At the same time, OS was comparable across the groups (46.3 months vs. not reached), with 3-year OS rates of 64.9 % vs. 67.9 %. With regard to time to death or distant metastasis, the *EGFR*-mutated group again fared worse than the *EGFR* wildtype group (24.7 vs. 38.6 months; 3-year rates, 35.3 % vs. 52.9 %). Also, time to the first subsequent treatment was shorter among patients with *EGFR*-mutant disease (16.7 vs. 43.1 months; 3-year rates, 33.3 % vs. 55.4 %). Almost half of patients with *EGFR*-mutated NSCLC experienced distant metastasis. The PFS and OS outcomes with durvalumab were broadly comparable to those obtained in the *EGFR*-mutated subgroup treated with durvalumab in the PACIFIC trial (n = 24) [14, 15]. However, the authors cautioned that small sample sizes and the retrospective nature of the PACIFIC-R study limit the interpretation of these findings.

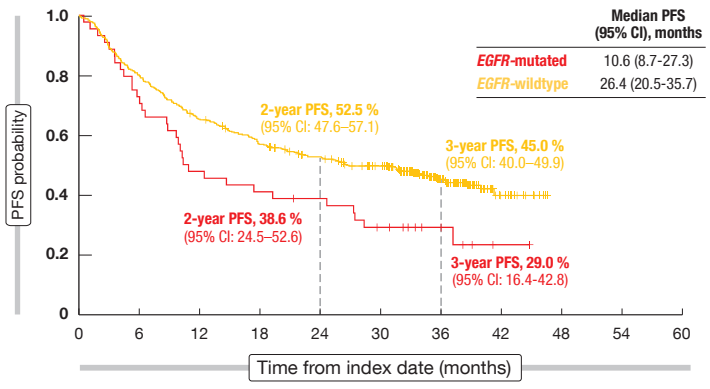


Figure 2: Investigator-assessed progression-free survival by *EGFR* status in PACIFIC-R

Osimertinib vs. durvalumab consolidation

A retrospective, multicenter analysis reported at WCLC 2023 has revealed superiority of consolidation EGFR TKI treatment with osimertinib compared to durvalumab and observation following chemoradiation for stage III, locally advanced, unresectable, *EGFR*-mutant NSCLC [16]. These patients had received ≥ 2 cycles of platinum-based concurrent chemoradiation and had shown no disease progression at the time of initiation of consolidation therapy. Within the total group of 136 individuals treated at 24 institutions around the globe, 33 and 56 received osimertinib and durvalumab consolidation, respectively, while 47 were observed. DFS and OS constituted the coprimary endpoints.

Osimertinib consolidation induced a significant DFS benefit compared to both durvalumab consolidation and observation ($p < 0.0001$). At 24 months, the DFS rate was 86 % for osimertinib, while the respective rates for durvalumab and observation were markedly lower at 31 % and 29 %, respectively. Regarding the endpoint of central nervous system DFS, however, osimertinib showed a lower 24-month rate (6.7 %) than durvalumab and observation (17 % and 11 %, respectively). No difference across the three groups was noted in terms of OS ($p = 0.31$). This might be due to the subsequent EGFR TKI therapy that was administered to substantial proportions of patients in the durvalumab and observation groups. Another factor possibly explaining the lack of difference in OS is the limited follow-up time.

The analysis revealed no unanticipated safety signals. As expected, pneumonitis was more common with durvalumab (any grade, 25 %; grade ≥ 3, 13 %) than with osimertinib (any grade, 15 %; grade ≥ 3, 3 %). Among 37 patients who received EGFR TKIs after durvalumab, 38 % experienced treatment-related AEs on TKI therapy. Five of these developed pneumonitis, including two grade ≥ 3 cases, and five had diarrhea/colitis including one grade ≥ 3 event. As the authors emphasized in their summary, prospective data are required to confirm these findings. The ongoing phase III LAURA study is assessing the efficacy and safety of maintenance osimertinib in patients with unresectable, stage III, *EGFR*-mutated NSCLC who have not progressed after chemoradiotherapy (NCT03521154). ■

REFERENCES

1 Yang P, National Lung cancer screening program in Tawain: The TALENT study. J Thorac Oncol 2021; 16(3, Supplement): S58

2 Huang KP et al., The early detection program for lung cancer in Taiwan. WCLC 2023, abstract PL03.04

3 Wright GM et al., Results from a phase II trial of VGT-309, a tumor-activated fluorescent molecule for the intra-operative identification of lung cancer. WCLC 2023, abstract MA11.06

4 Altorki N et al., Lobar or sublobar resection for peripheral stage IA non-small-cell lung cancer. N Engl J Med 2023; 388(6): 489-498

5 Stinchcombe TE et al., Second primary lung cancer from Cancer and Leukemia Group B (CALGB) 140503 (Alliance) trial of lobar versus sub-lobar resection for T1aN0 non-small cell lung cancer. WCLC 2023, abstract OA12.03

6 Chang JY et al., Stereotactic ablative radiotherapy for operable stage I non-small-cell lung cancer (revised STARS): long-term results of a single-arm, prospective trial with prespecified comparison to surgery. Lancet Oncol 2021; 22(10): 1448-1457

7 Chang JY et al., Stereotactic ablative radiotherapy with or without immunotherapy for early-stage or isolated lung parenchymal recurrent node-negative NSCLC: an open-label, randomized, phase 2 trial. WCLC 2023, abstract OA12.04

8 Heymach JV et al., AEGEAN: a phase 3 trial of neoadjuvant durvalumab + chemotherapy followed by adjuvant durvalumab in patients with resectable NSCLC. Cancer Res 2023; 83 (8_Supplement): CT005

9 He J et al., Neoadjuvant durvalumab + chemotherapy followed by adjuvant durvalumab in resectable EGFR-mutated NSCLC (AEGEAN). WCLC 2023, abstract OA12.06

10 Tsuboi M et al., Overall survival with osimertinib in resected EGFR-mutated NSCLC. N Engl J Med 2023; 389(2): 137-147

11 Spigel DR et al., Five-year survival outcomes from the PACIFIC trial: Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. J Clin Oncol 2022; 40(12): 1301-1311

12 Girard N et al., Treatment characteristics and real-world progression-free survival in patients with unresectable stage III NSCLC who received durvalumab after chemoradiotherapy: Findings from the PACIFIC-R study. J Thorac Oncol 2023; 18(2): 181-193

13 Peters S et al., Real-world outcomes with durvalumab after chemoradiotherapy in unresectable stage III EGFR-mutated NSCLC (PACIFIC-R). WCLC 2023, abstract OA17.03

14 Naidoo J et al., Brief report: Durvalumab after chemoradiotherapy in unresectable stage III EGFR-mutant NSCLC: A post hoc subgroup analysis from PACIFIC. J Thorac Oncol 2023; 18(5): 657-663

15 Naidoo J et al., Durvalumab after chemoradiotherapy in unresectable, stage III, EGFR mutation-positive NSCLC: A post hoc subgroup analysis from PACIFIC. J Clin Oncol 40, 2022 (suppl 16; abstr 8541)

16 Nassar AH et al., Consolidation EGFR-tyrosine kinase inhibitor vs. durvalumab vs. observation in unresectable EGFR-mutant stage III NSCLC. WCLC 2023, abstract MA16.11

Improved anti-EGFR strategies and other targeted innovations

FLAURA2: first-line osimertinib plus chemotherapy

In the first-line setting of *EGFR*-mutant advanced NSCLC, EGFR tyrosine kinase inhibitors (TKIs) such as the third-generation agent osimertinib have been established as the standard of care, although treatment is followed by disease progression in most patients. Data on the combined administration of *EGFR* TKIs with chemotherapy suggest enhanced efficacy [1-4]. These findings have prompted the implementation of the ongoing global, open-label, randomized FLAURA2 study to investigate osimertinib 80 mg OD plus pemetrexed and carboplatin or cisplatin (n = 279) compared to osimertinib monotherapy (n = 278) as first-line treatment of patients with advanced or metastatic NSCLC with activating *EGFR* mutations (i.e., either exon 19 deletion or L858R mutation). In the experimental arm, platinum-based treatments are being administered Q3W for four cycles and are followed by maintenance osimertinib plus pemetrexed Q3W. Stable central nervous system (CNS) metastases, which included untreated lesions, were allowed and were present in approximately 40 % of patients. Jänne et al. reported the results of the primary analysis of FLAURA2 at WCLC 2023 [5].

Progression-free survival (PFS) by investigator assessment, which was defined as the primary endpoint, significantly favored the osimertinib plus platinum/pemetrexed regimen. Median PFS was improved by 8.8 months (25.5 vs. 16.7 months), which translated into a 38 % reduction in the risk of progression and mortality (HR, 0.62; p < 0.0001; **Figure 1**). At 24 months, 57 % vs. 41 % of patients were progression-free. The analysis by blinded independent central review (BICR) confirmed this observation; here, the PFS difference reached 9.5 months (29.4 vs. 19.9 months; HR, 0.62; p = 0.0002).

Clinical benefits in subgroups

The PFS benefits were consistent across all pre-defined subgroups. Patients with CNS metastases at baseline derived greater PFS benefit with the combination relative to osimertinib monotherapy (24.9 vs. 13.8 months; HR, 0.47) than those without (27.6 vs. 21.0 months; HR, 0.75). Risk reductions of approximately 40 % resulted for patients with exon 19 deletion and L858R mutation alike. Second PFS (PFS2) and overall survival (OS) findings were immature at the time of the analysis. However, patients in the experimental arm showed longer PFS2 than those in the control arm (30.6 vs. 27.8 months; HR, 0.70; p = 0.0132). The objective response rates (ORRs) were 83 % vs. 76 %. All patients achieved median best percentage changes in target lesion size of approximately - 50 %, although the median duration of response was longer with the combination (24.0 vs. 15.3 months).

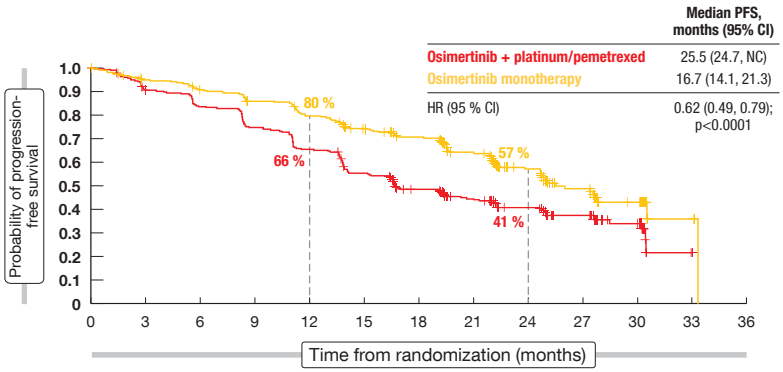


Figure 1: Primary endpoint of FLAURA2: progression-free survival per investigator

The safety profiles were as expected for each treatment and were manageable with standard medical procedures. While diarrhea was observed as the most common adverse event (AE) in the osimertinib monotherapy arm, the combined treatment most frequently gave rise to cytopenia, diarrhea and nausea. All grade 4 AEs in the osimertinib plus chemotherapy group were hematological toxicities. No common grade 4 AEs occurred in the monotherapy arm. Interstitial lung disease (ILD) was reported in 3 % vs. 4 % (all grades). Considering the statistically significant and clinically meaningful PFS improvement, osimertinib plus platinum/pemetrexed offers a new first-line treatment option for patients with advanced *EGFR*-mutated NSCLC. Ongoing analyses of the FLAURA2 trial will elucidate CNS response, patient-reported outcomes, post-progression endpoints, and ctDNA analyses.

Tepotinib plus osimertinib: INSIGHT 2

Mechanisms of resistance to first-line treatment with osimertinib are diverse, with almost half of them hitherto unidentified; for lack of other options, platinum-based chemotherapy is often administered after progression [6, 7]. A potential chemotherapy-sparing oral targeted approach is the combination of the MET inhibitor tepotinib with osimertinib, as *MET* amplification represents a common driver of secondary resistance to first-line osimertinib [8, 9]. Tepotinib 500 mg OD plus osimertinib 80 mg OD was tested in the open-label, phase II INSIGHT 2 study in patients who had advanced or metastatic *EGFR*-mutant NSCLC with acquired resistance to first-line osimertinib and *MET* amplification demonstrated by tissue-based FISH and/or next generation sequencing (NGS) based on liquid biopsy. The primary endpoint of INSIGHT 2 was the objective response by independent review in patients whose *MET* amplifications had been detected by tissue-based FISH.

Overall, 128 individuals received tepotinib plus osimertinib. The cohort meeting the definition of the primary endpoint comprised 98 patients. In this group, the primary analysis reported by Kim et al. at WCLC 2023 after a minimum follow-up of 9 months showed an ORR of 50 % [10]. Responses were rapid and long-lasting, with a median duration of response of 8.5 months. The ORR was generally consistent across predefined subgroups. Median PFS and OS were 5.6 and 17.8 months, respectively. Similar outcomes resulted in the cohort that had *MET* amplification according to NGS (ORR, 54.8 %; median duration of response, 5.7 months; median PFS, 5.5 months; median OS, 13.7 months) and in the subgroup of Asian patients **(Table 1)**.

In patients with brain lesions evaluable by RANO-BM who showed *MET* amplification determined by FISH (n = 24), the intracranial ORR was 29.2 %, with a complete response rate of 25.0 %. Intracranial disease control was achieved in 79.2 %, and intracranial PFS was 7.8 months. Systemic outcomes for patients with brain metastases were similar to those observed in the overall population. Baseline biomarker profiles were available for 69 patients. Here, the analysis demonstrated better outcomes in the absence of co-occurring mechanisms of osimertinib resistance.

Tepotinib plus osimertinib demonstrated a manageable safety profile. The most common any-grade AEs were diarrhea (49.2 %) and peripheral edema (40.6 %). Dose reductions due to treatment-related AEs (TRAEs) occurred in 20.3 %, and 10.2 % discontinued treatment due to TRAEs, which was most commonly pneumonitis (4.7 %). Four patients (3.1 %) had TRAEs leading to death that were considered potentially related to either trial drug (i.e., pneumonitis, respiratory failure after COVID-19 infection, and decreased platelet count). Health-related quality of life was maintained, with cough and pain improving on treatment. The safety profile observed among Asian patients was similar to the overall safety profile.

TABLE 1 Efficacy of tepotinib plus osimertinib in Asian patients

	FISH based on tissue (n = 52)	NGS based on liquid biopsy (n = 14)
Objective response rate, % (95 % CI)	59.6 (45.1, 73.0)	71.4 (41.9, 91.6)
Median duration of response, months (95 % CI)	7.3 (4.7, NE)	5.6 (2.9, NE)
Median progression-free survival, months (95 % CI)	6.9 (5.4, 8.4)	5.5 (4.2, 8.4)
Median overall survival, months (95 % CI)	19.8 (13.6, NE)	12.0 (5.9, NE)

NE, not estimable

Update of CHRYSALIS-2

The single-arm CHRYSALIS-2 trial was conducted based on the assumption that the combination of EGFR/MET inhibition with platinum-based chemotherapy might address the diverse and polyclonal resistance after progression on osimertinib. Patients enrolled in this study had *EGFR*-mutant, advanced NSCLC after TKI treatment for a maximum of three prior lines. They received the EGFR-MET bispecific antibody amivantamab together with the third-generation EGFR TKI lazertinib and carboplatin/pemetrexed. While carboplatin was discontinued after four cycles, the other components of treatment were administered until progression.

The findings of the CHRYSALIS-2 trial presented at WCLC 2023 for 20 patients after a median follow-up of 13.1 months showed that the safety profile was consistent with that of the individual components [11]. Most AEs were grade 1 or 2. Ninety percent of patients developed neutropenia that was classified as grade ≥ 3 in 70 %, while thrombocytopenia emerged in 40 % (grade ≥ 3, 25 %). The highest rates for both types of cytopenia were seen in cycle 1, and grade ≥ 3 events decreased markedly after completion of carboplatin therapy. No cases of neutropenic fever occurred.

Fifty-five percent of patients remained on treatment at the time of the analysis. The ORR was 50 %, with eight of ten responders showing ongoing responses. The clinical benefit rate was estimated at 80 %. Among seven patients with disease stabilization, three had a stable disease duration of ≥ 6 months, and two remained on treatment. Median PFS in the total group was 14.0 months, while median OS had not been reached yet. At 12 months, 80 % of patients were alive, and 59 % were progression-free. As the authors noted, this suggests immune-driven durability of the treatment effect.

Overall, the combination of amivantamab, lazertinib and chemotherapy appeared promising and likely to address resistance after progression on osimertinib. Data from the randomized, phase III MARIPOSA-2 trial (NCT04988295) that is evaluating the safety and efficacy of this regimen in the post-osimertinib setting will be reported at the ESMO Congress 2023.

HERTHENA-Lung01

In the phase I setting, the HER3-directed antibody-drug conjugate patritumab deruxtecan (HER3-DXd) has shown efficacy in patients with *EGFR*-mutated NSCLC harboring diverse mechanisms of resistance to EGFR TKIs [12]. The phase II HERTHENA-Lung01 trial was initiated to evaluate HER3-DXd in patients with advanced *EGFR*-mutated NSCLC who have progressed on prior EGFR TKI therapy and platinum-based chemotherapy. This patient group faces a substantial unmet medical need given limited benefits of salvage treatment options after chemotherapy. Moreover, CNS metastases are common in this population, and novel therapies effectuating CNS control are called for.

Patients treated in HERTHENA-Lung01 were initially randomized to either fixed-dose HER3-DXd 5.6 mg/kg or to the uptitration arm in which treatment was escalated from 3.2 mg/kg to 6.4 mg/kg. After a benefit-risk assessment supported closure of the uptitration arm, enrollment was discontinued in this group, while it continued in the fixed-dose arm. Data for 225 patients treated with HER3-DXd 5.6 mg/kg were reported by Yu et al. at WCLC 2023 [13]. The design of HERTHENA-Lung01 allowed for inactive or pretreated asymptomatic brain metastases. Fifty-one percent of patients had a history of CNS metastases, and 32 % had brain metastases at baseline. Liver metastasis was present in 33 %. The median number of previous treatment

lines was 3, and 93 % had previously received third-generation EGFR TKI therapy. The primary endpoint of the HERTHENA-Lung01 trial was confirmed ORR (cORR) by BICR.

Efficacy independent of resistance mechanisms

Indeed, HER3-DXd provided clinically meaningful and durable efficacy. The cORR was 29.8 % and 29.2 % in the total group and in the subset of patients after third-generation EGFR TKI treatment, respectively **(Table 2)**. In 73.8 % and 72.7 %, respectively, disease control was obtained. Responses lasted for a median of 6.4 months in both the overall population and the subgroup pretreated with third-generation EGFR TKI therapy. Similarly, PFS was 5.5 months and OS was 11.9 months for both populations. Thirty patients had brain metastasis at baseline without prior radiotherapy. In this group, HER3-DXd gave rise to a cORR of 33.3 %, with complete remission observed in 30.0 % and a disease control rate of 76.7 %. Responses lasted for a median of 8.4 months.

Tumor reductions occurred across diverse mechanisms of EGFR TKI resistance. cORRs were 32.4 % and 27.2 % for patients with EGFR-dependent and EGFR-independent resistance mechanisms, respectively. In the group that had both of these mechanisms, the cORR was 37.5 %. When no mechanisms of EGFR TKI resistance were identified, 27.3 % of patients responded. Moreover, the treatment showed efficacy across a broad range of pretreatment tumor HER3 membrane expression levels.

The safety profile of HER3-DXd in this heavily pretreated cohort was manageable and tolerable. Nausea, thrombocytopenia, decreased appetite, neutropenia, constipation, anemia and fatigue were noted as the most common AEs, with the majority graded as 1 or 2. Hematological toxicities typically occurred early on, were transient, and were not associated with clinical sequelae. Treatment-emergent AEs (TEAEs) prompted treatment discontinuation in 7.1 % and dose reductions in 21.3 %. Adjudicated ILD occurred in 12 patients (5.3 %). Most of these (n = 8) had grade 2 ILD, although one patient died due to this complication (0.4 %). In their conclusions, the authors noted that HER3-DXd has emerged as a promising option for patients with *EGFR*-mutated NSCLC after failure of EGFR TKI treatment and platinum-based chemotherapy.

Trastuzumab deruxtecan in *HER2*-mutant disease

In the setting of metastatic *HER2*-mutated lung cancer, the randomized, international, non-comparative, phase II DESTINY-Lung02 trial is assessing the antibody-drug conjugate trastuzumab deruxtecan (T-DXd) at doses of 5.4 mg/kg Q3W (n = 102) and 6.4 mg/kg Q3W (n = 50). The patients enrolled in this study have already received ≥ 1 prior anticancer treatment including platinum-based chemotherapy, with a median of two lines in both arms. In the T-DXd 5.4 and 6.4 mg/kg arms, 34.3 % and 44.0 %, respectively, showed baseline CNS lesions. cORR by BICR is defined as the primary endpoint. Both patients and investigators are blinded to the dose levels.

The primary analysis of DESTINY-Lung02 reported at WCLC 2023 demonstrated deep and durable responses for both T-DXd doses [14]. cORRs were 49.0 % and 56.0 %, respectively, and disease control was observed in 93.1 % and 92.0 %, respectively. Median duration of response was 16.8 months in the 5.4 mg/kg dose group and had not been reached in the 6.4 mg/kg cohort. Responses occurred irrespective of *HER2* mutation type, *HER2* amplification status, and number or type of prior anticancer therapies. Median PFS was 9.9 and 15.4 months for the 5.4 mg/kg and 6.4 mg/kg doses, respectively, with 12-month PFS rates of 53 % and 45 %. Median OS was 19.5 months and had not been reached, respectively. The 12-month OS rates were 73 % and 67 %, respectively.

Both doses showed an acceptable and generally manageable safety profile, although the results favored the 5.4 mg/kg dose, which conferred a lower incidence of drug-related grade ≥ 3 TEAEs (38.6 % and 58.0 %), serious TEAEs (13.9 % and 24.0 %) as well as TEAEs associated with discontinuation (13.9 % and 20.0 %), dose reduction (16.8 % and 32.0 %), and dose interruption (26.7 % and 48.0 %). The most common grade ≥ 3 TEAEs included neutropenia (18.8 % and 36.0 %) and anemia (10.9 % and 16.0 %). Any-grade ILD was lower with the 5.4 mg/kg dose (12.9 % vs. 28.0 %). Taken together, the results of the primary analysis of DESTINY-Lung02 support the use of T-DXd 5.4 mg/kg for patients with previously treated *HER2*-mutated NSCLC and reinforce T-DXd as the standard of care in this population.

TABLE 2 **Responses and survival in the total population of HERTHENA-Lung01 and in the subset after third-generation TKI treatment**

Confirmed responses and survival	Prior EGFR TKI (any) and platinum-based chemotherapy (n = 225)	Prior third-generation EGFR TKI and platinum-based chemotherapy (n = 209)
Objective response rate, %	29.8	29.2
Complete response	1 (0.4)	1 (0.5)
Partial response	66 (29.3)	60 (28.7)
Stable disease	99 (44.0)	91 (43.5)
Progressive disease	43 (19.1)	41 (19.6)
Not evaluable	16 (7.1)	16 (7.7)
Disease control rate, %	73.8	72.7
Duration of response, months	6.4	6.4
Progression-free survival, months	5.5	5.5
Overall survival, months	11.9	11.9

Phase I data for HER2 TKI therapy

The novel TKI zongertinib (BI 1810631) covalently and selectively binds to the tyrosine kinase domain (TKD) of *HER2*. This agent is under investigation as an oral treatment for NSCLC harboring *HER2* TKD mutations, including exon

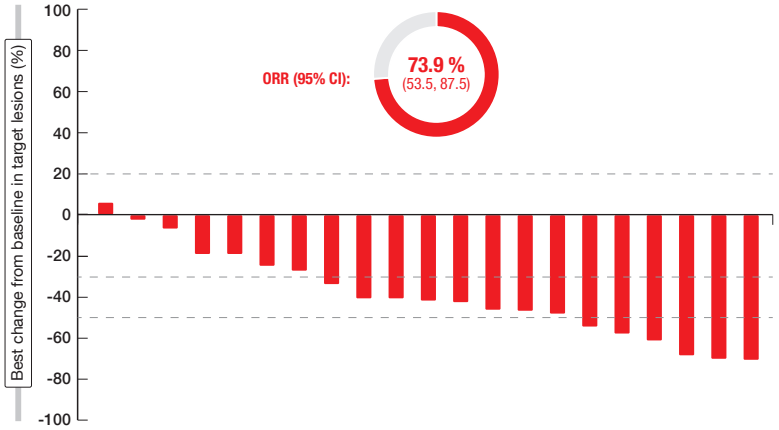


Figure 2: Reductions in tumor volume and ORR with zongertinib in the phase Ib setting

20 insertion mutations. Yamamoto et al. reported results for the ongoing phase Ia/Ia BEAMION LUNG-1 trial conducted in patients with various advanced solid tumors harboring *HER2* aberrations (phase Ia) as well as patients with *HER2*-positive NSCLC (phase Ib, Cohort 1) [15].

In phase Ia, the maximum tolerated dose of zongertinib was not reached in 50 individuals, neither with the BID schedule nor the OD schedule. Rates of EGFR-mediated AEs were low. The zongertinib doses taken into dose optimization were 240 mg and 120 mg OD. Regarding antitumor activity in the group with NSCLC (n = 34), the analysis revealed encouraging preliminary efficacy of zongertinib. The ORR was 50 % and the disease control rate 97.1 %.

In the phase Ib setting, 42 patients have been treated to date in Cohort 1 that includes pretreated patients with *HER2* TKD mutations. Dose reduction became necessary in one patient due to TRAEs (i.e., grade 3 febrile neutropenia and decreased neutrophil count). No discontinuation occurred due to AEs. At 28.6 % and 21.4 %, diarrhea and rash, respectively, represented the most frequent TRAEs of zongertinib. The initial efficacy results were promising, with an ORR of 73.9 % and a disease control rate of 91.3 % **(Figure 2)**. The median best percentage change in target lesions from baseline was - 41.2 %.

CodeBreaK 101: sotorasib plus chemotherapy

Sotorasib has been introduced as the first-in-class KRAS^{G12C} inhibitor for the treatment of *KRAS*^{G12C}-mutated NSCLC. The single-arm, phase Ib CodeBreaK 101 trial is the first global study to assess the efficacy and safety of sotorasib in addition to carboplatin/pemetrexed in patients with *KRAS*^{G12C}-mutated advanced NSCLC. Sotorasib 960 mg OD orally is administered together with pemetrexed and carboplatin Q3W for four cycles during the induction phase. During the maintenance phase, the treatment consists of sotorasib plus pemetrexed Q3W. While 25 individuals are being treated in the first-line setting, 13 patients constitute the second-line cohort.

According to the results presented by Clarke et al. at WCLC 2023, sotorasib plus pemetrexed/carboplatin showed predictable toxicity and promising clinical activity [16]. Common TRAEs were consistent with sotorasib and platinum-doublet-based regimens. Neutropenia/neutrophil count decreases occurred most commonly (all grades, 53 %; grade 3-4, 32 %), followed by anemia (all grades, 39 %; grade 3-4; 21 %) and thrombocytopenia/platelet count decrease (all grades, 37 %; grade 3-4; 16 %). TRAEs led to treatment discontinuation in 12 % and 31 % in the first-line and second-line groups, respectively. No fatal AEs occurred.

With regard to efficacy, the analysis yielded ORRs of 65 % and 54 % in the first- and second-line settings, respectively. Disease control resulted in 100 % and 85 %, respectively. The ORRs were similar across PD-L1 expression levels, ranging from 50 % to 75 %. After a median follow-up of 3.0 months, the observations indicated rapid and durable responses. PFS and OS findings were not mature yet. A longer follow-up is ongoing to assess the durability of the combination. Furthermore, first-line sotorasib plus pemetrexed/carboplatin is being tested against pembrolizumab plus pemetrexed/carboplatin in patients with *KRAS*^{G12C}-mutated, PD-L1–negative NSCLC in the phase III CodeBreaK 202 trial (NCT05920356).

Local consolidation in addition to brigatinib

ALK TKIs are the standard of care for the treatment of *ALK*-rearranged metastatic NSCLC, although it has been shown that approximately 95 % of patients with initial remission exhibit incomplete responses that result in residual disease, which might elicit acquired resistance [17]. The BRIGHTSTAR study tested the hypothesis that minimizing or eliminating residual disease with local consolidation therapy (LCT) might delay the development of resistance in all-comer patients with *ALK*-positive, stage IV or recurrent NSCLC. These were either TKI-naïve or had received brigatinib for ≤ 8 weeks, and had ≥ 1 site of residual disease. Patients without disease progression according to CT/PET and brain MRI after 8 weeks of brigatinib therapy received brigatinib until progression in addition to local LCT with radiotherapy, surgery, or both. In patients with < 3 active sites of disease, LCT was administered to all sites, while in those with > 3, the physicians decided which sites to treat. The primary objective of BRIGHTSTAR was the safety and tolerability of the combined approach.

Results for 34 patients were presented at WCLC 2023 by Elamin et al. [18]. In this group, 82 % had > 3 metastases at baseline. At 8 weeks, 79 % and 21 % had achieved partial response and stable disease with brigatinib treatment, respectively. Thirty-two patients successfully completed LCT as planned. Radiation was administered in 79 %, surgery in 9 %, and both in 6 %. In the remaining cases, residual disease was not amenable to LCT after induction therapy, or consent was withdrawn. Complete LCT to all sites of residual disease was possible in 62 %. In 10 of 29 patients who underwent radiotherapy, brigatinib therapy was continued during treatment. Surgical procedures included

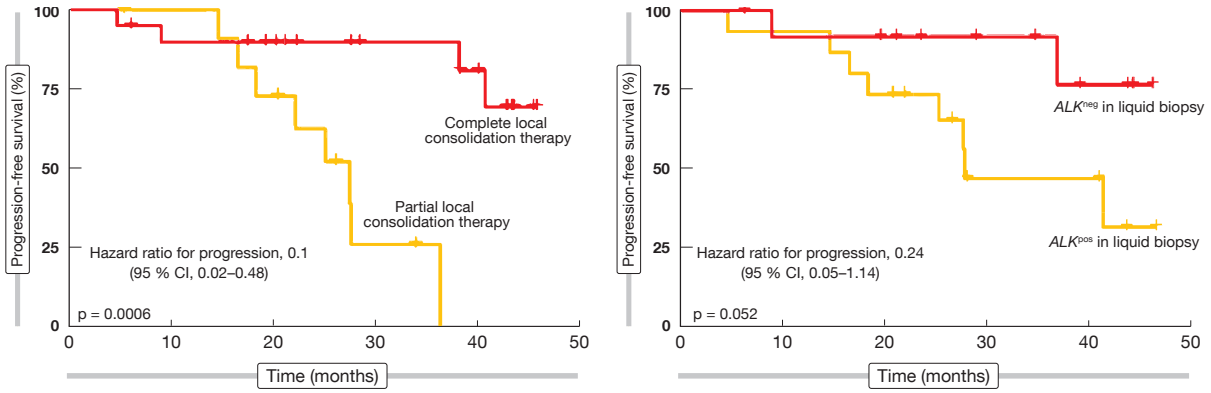


Figure 3: Predictors of progression-free survival benefit with brigatinib plus local consolidation therapy (LCT): complete LCT (left) and *ALK* negativity at baseline

lobectomy (n = 3), sub-lobar resection (n = 1) and adrenalectomy (n = 1).

Brigatinib plus LCT was demonstrated to be safe. Six grade ≥ 3 LCT-related AEs occurred, which included grade 4 bronchopulmonary hemorrhage, grade 3 anemia, grade 3 pneumonitis, grade 3 esophagitis, and grade 3 vomiting and nausea. No grade 5 events related to LCT were noted. The combined approach yielded promising results compared to historical outcomes. The PFS rates at 2 and 3 years were 80 % and 66 %, respectively. In the pivotal ALTA-1L trial that had assessed first-line, single-agent brigatinib, these rates had been 56 % and 47 %, respectively, in patients who had not progressed at 12 weeks [19].

In addition, the authors explored predictors of outcome. Improved PFS with LCT was seen for complete vs. partial LCT and for *ALK*-negative status in the plasma at baseline according to liquid biopsy **(Figure 3)**. Also, lower tumor volume at baseline as well as after induction therapy predicted increased treatment benefit. On the other hand, the number of metastases at baseline (oligometastatic vs. polymetastatic disease) did not affect the outcomes. The randomized BRIGHTSTAR-2 trial will compare LCT and chemotherapy as intensification strategies with brigatinib monotherapy in the first-line setting of *ALK*-positive NSCLC. ■

REFERENCES

1 Hosomi Y et al., Gefitinib alone versus gefitinib plus chemotherapy for non-small-cell lung cancer with mutated epidermal growth factor receptor: NEJ009 Study. J Clin Oncol 2020; 38(2): 115-123
2 Noronha V et al., Gefitinib versus gefitinib plus pemetrexed and carboplatin chemotherapy in *EGFR*-mutated lung cancer. J Clin Oncol 2019; 38(2): 124-136
3 Oizumi S et al., Updated survival outcomes of NEJ005/TCOG0902: a randomised phase II study of concurrent versus sequential alternating gefitinib and chemotherapy in previously untreated non-small cell lung cancer with sensitive *EGFR* mutations. ESMO Open 2018; 3(2): e000313
4 Saito R et al., Phase 2 study of osimertinib in combination with platinum and pemetrexed in patients with previously untreated *EGFR*-mutated advanced non-squamous non-small cell lung cancer: The OPAL Study. Eur J Cancer 2023; 185: 83-93
5 Jänne PA et al., Osimertinib with/without platinum-based chemotherapy as first-line treatment in patients with EGFRm advanced NSCLC (FLAURA2). WCLC 2023, abstract PL03.13
6 Choudhury NJ et al., Molecular biomarkers of disease outcomes and mechanisms of acquired resistance to first-line osimertinib in advanced *EGFR*-mutant lung cancers. J Thorac Oncol 2023; 18(4): 463-475
7 Han B et al., Efficacy of pemetrexed-based regimens in advanced non-small cell lung cancer patients with activating epidermal growth factor receptor mutations after tyrosine kinase inhibitor failure: a systematic review. Onco Targets Ther 2018; 11: 2121-2129
8 Rios-Hoyo A et al., Acquired mechanisms of resistance to osimertinib-the next challenge. Cancers (Basel) 2022; 14(8): 1931
9 Wang Y et al., Clinical analysis by next-generation sequencing for NSCLC patients with *MET* amplification resistant to osimertinib. Lung Cancer 2018; 118: 105-110
10 Kim TM et al., Tepotinib + osimertinib in *EGFR*-mutant NSCLC with *MET* amplification following 1L osimertinib: INSIGHT 2 primary analysis. WCLC 2023, abstract OA21.05
11 Lee SH et al., Amivantamab, lazertinib plus platinum-based chemotherapy in post-TKI EGFR-mutated advanced NSCLC: updated results from CHRYSALIS-2. WCLC 2023, abstract MA13.06
12 Jänne PA et al., Efficacy and safety of patritumab deruxtecan (HER3-DXd) in *EGFR* inhibitor-resistant, *EGFR*-mutated non-small cell lung cancer. Cancer Discov 2022; 12(1): 74-89
13 Yu HA et al., Patritumab deruxtecan (HER3-DXd) in EGFR-mutated NSCLC following EGFR TKI and platinum-based chemotherapy: HERTHENA-Lung01. WCLC 2023, abstract OA05.03
14 Jänne PA et al., Trastuzumab deruxtecan in patients with *HER2*-mutant metastatic non-small cell lung cancer: primary results of DESTINY-Lung02. WCLC 2023, abstract MA13.10
15 Yamamoto N et al., BEAMION LUNG-1, a phase IA/IB trial of the HER2 TKI zongertinib (BI 1810631) in patients with advanced solid tumors with *HER2* aberrations. WCLC 2023, abstract MA13.08
16 Clarke JM et al., CodeBreaK 101: Safety and efficacy of sotorasib with carboplatin and pemetrexed in *KRAS*^{G12C}-mutated advanced NSCLC. WCLC 2023, abstract MA06.05
17 Biovona TG, Doebele RC, A framework for understanding and targeting residual disease in oncogene-driven solid cancers. Nat Med 2016; 22(5): 472-478
18 Elamin YY et al., Local consolidative therapy with brigatinib in tyrosine kinase inhibitor-naïve ALK-rearranged metastatic NSCLC. WCLC 2023, abstract OA22.04
19 Camidge DR et al., Brigatinib versus crizotinib in ALK inhibitor-naive advanced ALK-positive NSCLC: Final results of phase 3 ALTA-1L trial. J Thorac Oncol 2021; 16(12): 2091-2108

Refining first-line regimens for extensive-stage small-cell lung cancer

Benmelstobart plus anlotinib and chemotherapy

Improving long-term survival remains an unmet need in the setting of extensive-stage small-cell lung cancer (ES-SCLC). This might be attributed at least in part to the complexity of the tumor microenvironment, which is characterized by immunosuppression, angiogenesis and vascularization [1, 2]. It was hypothesized that microenvironment reprogramming and tumor vessel normalization could promote immune cell infiltration, thus improving synergy with immunotherapy [1-3]. The novel PD-L1 inhibitor benmelstobart combined with the anti-angiogenic multi-target tyrosine kinase inhibitor anlotinib was tested by the randomized, double-blind, phase III ETER701 trial in addition to standard chemotherapy in patients with ES-SCLC who had not received any prior systemic therapy. At WCLC 2023, Cheng et al. reported findings for 246 patients treated with benmelstobart 1,200 mg on day 1 plus anlotinib 12 mg on days 1–14 and etoposide/carboplatin for four 21-day cycles [4]. The control group contained 247 patients who received double placebo instead of benmelstobart and anlotinib in addition to etoposide/carboplatin. After the induction phase, maintenance consisted of benmelstobart plus anlotinib in the experimental arm and placebo in the control arm. Overall survival (OS) and progression-free survival (PFS) constituted the primary endpoints. ETER701 has a third study arm testing placebo plus anlotinib and chemotherapy, for which no results were reported.

Indeed, median OS was significantly prolonged with the four-drug regimen as compared to chemotherapy alone (19.3 vs. 11.9 months; HR, 0.61; p = 0.0002; **Figure**). At 12 months, the OS rates were 64.1 % vs. 49.0 %, and at 24 months, 41.8 % vs. 24.2 %. For PFS, the treatment benefit was equally impressive, with median PFS of 6.9 vs. 4.2 months (HR, 0.32; p < 0.0001) and 12-month PFS rates of 27.9 % vs. 2.3 %. All of the subgroups favored benmelstobart plus anlotinib and chemotherapy with regard to both OS and PFS. Also, duration of response was significantly improved in the experimental arm (5.8 vs. 3.1 months; HR, 0.31; p < 0.0001), as was the confirmed objective response (81.3 % vs. 66.8 %; p = 0.0001). For disease control, the analysis yielded no significant difference (90.7 % vs. 87 %).

The safety profile of the four-drug combination proved tolerable and manageable. Cytopenia was the most common toxicity in both study arms. Any-grade immune-related adverse events (irAEs) were observed in 42.7 % (grade ≥ 3, 16.7 %) with benmelstobart plus anlotinib and chemotherapy vs. 19.1 % with chemotherapy only (grade ≥ 3, 6.9 %). In the experimental arm, irAEs necessitated dose reductions and discontinuation in 6.5 % and 8.1 %, respectively. Death due to irAEs occurred in five cases (2.0 %) vs. one case in the control arm (0.4 %). The authors concluded that the addition of the anti-angiogenic agent anlotinib to immunochemotherapy in the first-line treatment of ES-SCLC resulted in the historically longest PFS and OS, thus supporting this regimen as a new treatment option.

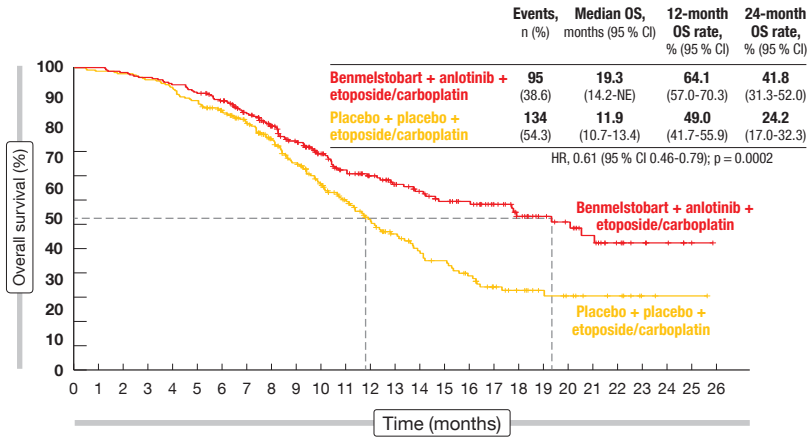


Figure: Benmelstobart plus anlotinib and chemotherapy vs. placebo plus chemotherapy: overall survival

Addition of tislelizumab: RATIONALE-312

Phase II data have shown promising activity of the anti–PD-1 antibody tislelizumab in combination with chemotherapy in patients with untreated ES-SCLC [5]. The randomized, double-blind, placebo-controlled, phase III RATIONALE-312 study was conducted to compare tislelizumab 200 mg on day 1 plus carboplatin or cisplatin and etoposide Q3W (n = 227) with placebo plus chemotherapy (n = 230) in the untreated ES-SCLC setting. After four cycles of induction treatment, the patients in the experimental and control arms received tislelizumab 200 mg Q3W and placebo, respectively, as maintenance. The majority of patients in both arms had ≥ 3 metastatic sites.

RATIONALE-312 met its primary endpoint, demonstrating a statistically significant and clinically meaningful OS improvement for the addition of tislelizumab to chemotherapy compared with chemotherapy alone (15.5 vs. 13.5 months; HR, 0.75; p = 0.0035) [6]. At 24 months, 33.2 % vs. 22.4 % of patients were alive. The risk of progression or death was reduced by 37 % in the experimental arm, with 12-month PFS rates of 20.7 % vs. 4.5 % (HR, 0.63; p < 0.0001). All of the predefined subgroups benefited from the combined approach in terms of both OS and PFS. This was accompanied by an increase in the overall response rate (ORR; 68.3 % vs. 61.7 %) and more durable responses (median duration of response, 4.3 vs. 3.7 months).

Tislelizumab plus chemotherapy showed a manageable safety profile. The combined approach did not give rise to higher rates of the most common AEs that included anemia, alopecia, neutropenia, decreased white blood cell count, thrombocytopenia, and nausea. Treatment-emergent AEs leading to discontinuation occurred in 13.2 % vs. 3.1 %. Immune-mediated AEs were observed in 38.3 % vs. 17.9 % and infusion-related reactions in 3.5 % vs. 2.2 %. The most common immune-mediated AEs on tislelizumab-based treatment included hypothyroidism (13.7 %), rash (13.2 %), and hyperthyroidism (5.7 %). As the authors concluded, RATIONALE-312 confirms that tislelizumab in combination with chemotherapy can improve OS in ES-SCLC, adding supporting evidence for the first-line use of PD-1 inhibitors in this setting.

IMbrella A: long-term survivors from IMpower133

The PD-L1 inhibitor atezolizumab plus carboplatin and etoposide has been established as a first-line treatment standard for patients with ES-SCLC by the double-blind, placebo-controlled, phase III IMpower133 trial [7]. Four 21-day cycles were followed by atezolizumab maintenance. Compared to placebo plus chemotherapy, the atezolizumab-based approach led to improvement of both OS (12.3 vs. 10.3 months; HR, 0.70; p = 0.007) and PFS (5.2 vs. 4.3 months; HR, 0.77; p = 0.02). Updated results showed continued OS benefit [8]. The patients included in the experimental arm of IMpower133 were eligible to roll over to the open-label, non-randomized, multicenter, phase IV IMbrella A study if they continued to receive atezolizumab at study closure or were in survival follow-up. Between December 2019 and July 2020, 18 patients entered the extension and long-term observational study. Compared to all 201 patients randomized to atezolizumab plus carboplatin/etoposide in IMpower133, the IMbrella A cohort was younger, had a better performance status and was less likely to have liver metastasis. Liu et al. presented a merged analysis from IMpower133 and IMbrella A with a clinical cutoff date of 16 March 2023 [9]. This is the first report of 5-year survival outcomes for ES-SCLC patients who received first-line immunotherapy plus chemotherapy.

The 5-year OS rate obtained with atezolizumab plus chemotherapy was 12 %, with the landmark analyses suggesting a plateau in the survival curve **(Table)**. These data compare favorably with historical 5-year OS rates of approximately 2 % in ES-SCLC patients treated with chemotherapy alone [10-12]. All patients who rolled over to IMbrella A achieved either complete or partial responses; no patients with stable disease rolled over. Eleven patients remained alive at 5 years, six of whom continued to receive atezolizumab.

The scientists assessed the distribution of transcriptional subtypes as defined by Gay et al. [13] in patients who were alive and on-study in IMbrella A after 5 years of follow-up. Baseline RNA-seq data were available for seven of eleven patients. According to this analysis, four patients had the SCLC-N (NEUROD1-driven) subtype, two the SCLC-I (inflamed) subtype and one the SCLC-A (ASCL1-driven) subtype. In the full RNAseq-evaluable IMpower133 cohort (n = 271), the SCLC-A subtype had been the most common one. Conclusions cannot be drawn due to the small sample size, although it appears that transcriptional subtypes alone do not predict long-term survival.

TABLE **Landmark analyses for overall survival with atezolizumab plus chemotherapy vs. chemotherapy alone**

Overall survival rate (95 % CI), %	IMpower133 and IMbrella A Atezolizumab + carboplatin/etoposide (n = 201)	IMpower133 only Placebo + carboplatin/etoposide (n = 202)
1-year	52 (45-59)	39 (32-46)
2-year	22 (16-28)	16 (11-21)
3-year	16 (11-21)	Not estimable
4-year	13 (8-18)	Not estimable
5-year	12 (7-17)	Not estimable

The final safety analysis for patients from IMpower133 and IMbrella A was consistent with the primary analysis. There was a low incidence of serious AEs and AEs of special interest; only one late-onset immune-related toxicity occurred, which was hypothyroidism grade 2. Taken together, these results demonstrated the potential for a durable survival benefit with atezolizumab plus chemotherapy.

BI 764532 in DLL3-positive tumors

The novel DLL3-targeting T cell engager BI 764532 has been designed to bind to both CD3 on T cells and the antigen DLL3 that is expressed on neuroendocrine carcinomas [14]. Thus, T cells are redirected to the tumor where they induce cell death. Wermke et al. presented findings from the first-in-human phase I dose escalation trial investigating BI 764532 in patients with advanced, DLL3-positive SCLC or neuroendocrine carcinoma (NEC) [15]. These had either progressed after available standard therapies, including ≥ 1 line of platinum-based chemotherapy for SCLC patients, or were ineligible for them. In the group of 107 patients evaluated in the analysis, 53 % had SCLC, while 38 % and 8 % had extrapulmonary NEC and large-cell NEC of the lung (LCNEC), respectively. One third had been treated with ≥ 3 lines, and almost half had received prior immune checkpoint inhibition.

BI 764532 was found to show an acceptable and manageable safety profile at clinically efficacious dose levels in patients with SCLC and LCNEC. Cytokine release syndrome (CRS) occurred as the most common AE (all grades, 48 %), although these events were mostly grade 1 and 2 and usually emerged during initial drug administrations. They were managed with supportive care, corticosteroids and/or anti–IL-6R antibodies. Further AEs included asthenia (32 %), dysgeusia (27 %), constipation (27 %), transient decreases in lymphocyte counts (24 %), and nausea (23 %). Pyrexia, which emerged in 17 %, was restricted to grade 1 and 2 events. At 6 %, the treatment discontinuation rate due to treatment-related AEs was low. Dose-limiting toxicities comprised CRS grade 3–4, confusional state grade 3, infusion-re-

lated reaction grade 2, and nervous system disorder grade 3. All of these were reversible, and the maximum tolerated dose had not been reached at the time of the analysis.

With respect to efficacy, the assessments demonstrated tumor shrinkage at doses ≥ 90 µg/kg, with ORRs of 26 % and 60 % in the SCLC and LCNEC groups, respectively. Disease control was achieved in 51 % and 100 %, respectively. Responses appeared to be durable, although it was too early to assess the median duration of response. Further dose optimization is ongoing. ■

REFERENCES

1 Li T, Qiao T, Unraveling tumor microenvironment of small-cell lung cancer: Implications for immunotherapy. Semin Cancer Biol 2022; 86(Pt 2): 117-125
2 Chan JM et al., Signatures of plasticity, metastasis, and immunosuppression in an atlas of human small cell lung cancer. Cancer Cell 2021; 39(11): 1479-1496
3 Augustin HG, Koh GY, Antiangiogenesis: Vessel regression, vessel normalization, or both? Cancer Res 2022; 82(1): 15-17
4 Cheng Y et al., Benmelstobart with anlotinib plus chemotherapy as first-line therapy for ES-SCLC: a randomized, double-blind, phase III trial (ETER701). WCLC 2023, abstract OA01.03
5 Wang Z et al., A phase 2 study of tislelizumab in combination with platinum-based chemotherapy as first-line treatment for advanced lung cancer in Chinese patients. Lung Cancer 2020; 147: 259-268
6 Cheng Y et al., First-line chemotherapy with or without tislelizumab for extensive-stage small cell lung cancer: RATIONALE-312 phase 3 study. WCLC 2023, abstract OA01.06
7 Horn L et al., First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 2018; 379(23): 2220-2229
8 Liu SV et al., Updated overall survival and PD-L1 subgroup analysis of patients with extensive-stage small-cell lung cancer treated with atezolizumab, carboplatin, and etoposide (IMpower133). J Clin Oncol 2021; 39(6): 619-630
9 Liu SV et al., Five-year survival in patients with ES-SCLC treated with atezolizumab in IMpower133: IMbrella A extension study results. WCLC 2023, abstract OA01.04
10 Zhang S, Cheng Y, Immunotherapy for extensive-stage small-cell lung cancer: current landscape and future perspectives. Front Oncol 2023; 13: 1142081
11 Arriola E et al., Prognostic value of clinical staging according to TNM in patients with SCLC: A real-world surveillance epidemiology and end-results database analysis. JTO Clin Res Rep 2022; 3(1): 100266
12 Schabath MB et al., Temporal trends from 1986 to 2008 in overall survival of small cell lung cancer patients. Lung Cancer 2014; 86(1): 14-21
13 Gay CM et al., Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. Cancer Cell 2021; 39(3): 346-360.e.7
14 Hipp S et al., A bispecific DLL3/CD3 IgG-like T-cell engaging antibody induces antitumor responses in small cell lung cancer. Clin Cancer Res 2020; 26(19): 5258-5268
15 Wermke M et al., Phase I dose escalation trial of the DLL3/CD3 IgG-like T cell engager BI 764532 in patients with DLL3+ tumors: focus on SCLC and LCNEC. WCLC 2023, abstract OA01.05

Trop-2–directed ADCs in conjunction with immunotherapy: EVOKE-02 and TROPION-Lung04

Immune checkpoint inhibitor-based regimens have been established as the standard-of-care first-line treatment in the setting of metastatic NSCLC. However, novel combination approaches are called for to further improve outcomes. Clinical trials are exploring the efficacy and safety of antibody-drug conjugates directed against trophoblast cell-surface antigen 2 (Trop-2), such as sacituzumab govitecan and datopotamab deruxtecan, together with immune checkpoint inhibitors.

First-line findings for SG plus pembrolizumab

Sacituzumab govitecan (SG) in combination with pembrolizumab is being assessed in the open-label, multicohort phase II EVOKE-02 study in hitherto untreated patients who have been diagnosed with stage IV NSCLC. At WCLC 2023, Cho et al. presented preliminary results for the Cohorts A and B into which the study participants had been allocated according to their PD-L1 expression status [1]. Cohort A had PD-L1 TPS ≥ 50 % (n = 30), while PD-L1 TPS was < 50 % in Cohort B (n = 33). All patients received SG 10 mg/kg on days 1 and 8 of 21-day cycles until disease progression in addition to pembrolizumab 200 mg on day 1 for up to 35 cycles.

After a median follow-up of 5.0 and 5.8 months for Cohorts A and B, respectively, SG plus pembrolizumab showed encouraging antitumor activity across the PD-L1 subgroups. The objective response rates (ORR) were 69 % and 44 % for Cohorts A and B, respectively, with disease control achieved in 86 % and 78 %, respectively **(Table)**. Only 10 % and 6 % of patients, respectively, had progressive disease as best response, which suggests that the addition of SG might contribute to overcoming primary resistance to pembrolizumab. Responses were rapid, deep and durable. The waterfall plot indicated significant tumor shrinkage in the majority of patients regardless of PD-L1 expression. Median duration of response had not been reached yet in either cohort. At 6 months, the duration of response rate was 88 % in both groups.

The safety profile was manageable and consistent with the known safety of each agent. Treatment-emergent AEs (TEAEs) primarily included diarrhea (any grade, 54 %), anemia (48 %), asthenia (38 %), alopecia (37 %), and nausea (32 %), which were predominantly grade 1 or 2. Neutropenia occurred in 27 %, with grade ≥ 3 events noted in 18 %. Immune-mediated TEAEs were consistent with the safety profile of pembrolizumab. Pneumonitis was reported in 8 % (grade ≥ 3, 3 %), hyperthy-

TABLE **Efficacy of sacituzumab govitecan (SG) plus pembrolizumab according to investigator**

Endpoint	Cohort A SG + pembrolizumab (n = 29)	Cohort B SG + pembrolizumab (n = 32)	Total SG + pembrolizumab (n = 61)
Objective response rate, %	69	44	56
Confirmed partial response, n (%)	18 (62)	12 (38)	30 (49)
Stable disease, n (%)	5 (17)	11 (34)	16 (26)
Progressive disease, n (%)	3 (10)	2 (6)	5 (8)
Disease control rate, %	86	78	82
Median duration of response, months	Not reached	Not reached	Not reached
Duration of response rate at 6 months, %	88	88	87

roidism in 5 % (no grade ≥ 3 events), and colitis in 4 % (grade ≥ 3, 2 %). TEAEs prompting treatment discontinuation and dose reduction emerged in 18 % each. One case of fatal sepsis (2 %) was deemed related to the study treatment.

As the authors emphasized in their summary, these preliminary findings warrant further investigation of SG plus pembrolizumab for the first-line treatment of patients with metastatic NSCLC. The ongoing, open-label, randomized, phase III EVOKE-03 trial is evaluating SG plus pembrolizumab *versus* pembrolizumab monotherapy in patients with untreated metastatic NSCLC and PD-L1 TPS ≥ 50 % (NCT05609968).

Dato-DXd and durvalumab ± chemotherapy

The multicenter, open-label, dose escalation/confirmation and expansion TROPION-Lung04 study is investigating datopotamab deruxtecan (Dato-DXd) in combination with different immunotherapy agents with or without carboplatin across eleven cohorts of patients with advanced or metastatic NSCLC. Papadopoulos et al. reported an interim analysis for the Cohorts 2 and 4 of this phase Ib trial [2]. In Cohort 2, Dato-DXd 6 mg/kg is being administered together with durvalumab 1,120 mg Q3W (n = 19). Cohort 4 is testing the same regimen in addition to four cycles of carboplatin AUC 5 Q3W (n = 14). Most patients are receiving the Dato-DXd combination in the first-line setting, while smaller proportions in each arm (26.3 % and 7.1 %, respectively) are being treated in the second line and beyond. In both cohorts, 21 % have a history of brain metastases.

Throughout the dose escalation and dose expansion phases, no new safety signals were observed in either cohort. The most frequent any-grade TEAEs were stomatitis, alopecia and nausea. In general, grade ≥ 3 TEAEs were more commonly observed with the triplet than with the doublet combination (57.1 % vs. 31.6 %), which was mainly driven by higher rates of cytopenia and was largely attributed to carboplatin being part of the triplet regimen. Interstitial lung disease (ILD) adjudicated as drug-related occurred in 15.8 % and 7.1 % in Cohorts 2 and 4, respectively. In the triplet-treated group, grade 2 ILD was reported in one patient (7.1 %), while in the group receiving the doublet, one patient each (5.3 %) developed grade 1, 2, and 4 ILD. No grade 5 adjudicated ILD events were reported. Discontinuation of any drug due to TEAEs was necessary in 21 % in both cohorts.

With respect to efficacy, the analysis suggested durable responses with promising ORRs for both strategies. In the first-line setting, ORRs were 50 % and 76.9 % in Cohorts 2 and 4, respectively. Both cohorts obtained disease control in 92 %. The overall population that includes patients treated in the first and later lines showed ORRs of 47.4 % and 71.4 % for Cohorts 2 and 4, respectively. Responses were numerically higher with the triplet than with the doublet approach and were observed across all PD-L1 expression levels. Combinations of Dato-DXd with immune checkpoint inhibitors are being evaluated as first-line treatment options in the phase III AVANZAR (NCT05687266), TROPION-Lung07 (NCT05555732), and TROPION-Lung08 (NCT05215340) trials in patients with advanced or metastatic NSCLC. ■

REFERENCES

1 Cho BC et al., Sacituzumab govitecan + pembrolizumab in 1L metastatic non-small cell lung cancer: preliminary results of the EVOKE-02 study. WCLC 2023, abstract OA05.04
2 Papadopoulos KP et al., Datopotamab deruxtecan (Dato-DXd) + durvalumab ± carboplatin in advanced/metastatic NSCLC: initial results from the phase 1b TROPION-Lung04 study. WCLC 2023, abstract OA05.06

MARS 2: no benefit of decortication in early-stage malignant mesothelioma

Surgery in the form of maximum cytoreduction is recommended to reduce all visible disease in the setting of resectable malignant pleural mesothelioma [1-4]. Extra-pleural pleurectomy/decortication has been established as the predominant approach offered worldwide. However, this approach has never been evaluated in a randomized controlled trial. Therefore, the multicenter, randomized, controlled MARS 2 trial was initiated to compare the clinical efficacy and cost-effectiveness of (extended) pleurectomy/decortication plus chemotherapy with chemotherapy alone for patients with resectable pleural mesothelioma confined to one hemi-thorax. After two cycles of platinum plus pemetrexed, patients underwent computed tomography to confirm resectability and were randomized to either (extended) pleurectomy/decortication followed by up to four further cycles of platinum plus pemetrexed (n = 169), or chemotherapy alone (n = 166).

Eighty-six percent of patients in each arm had epithelioid mesothelioma. In 88.5 % of cases, extended pleurectomy/decortication was performed, while 8.3 % and 1.9 % underwent pleurectomy/decortication and partial pleurectomy, respectively. R0 resection without residual tumor tissue was achieved in 3.2 %. The proportion of patients completing six chemotherapy cycles was lower in the surgery group than in the chemotherapy-only group (39.1 % vs. 56.0 %). Also, fewer patients who underwent decortication were able to receive subsequent immunotherapy or other agents known to improve survival (21.9 % vs. 38.6 %). Overall survival (OS) constituted the primary outcome.

More serious AEs and lower quality of life

According to the analysis presented at WCLC 2023, extended pleurectomy/decortication did not confer any survival advantage [5]. On the contrary, patients who underwent surgery had shorter OS than those receiving chemotherapy alone, with a 28 % increase in the risk of death **(Figure)**. Even if the analysis was confined to patients with epithelioid histology that showed longer OS than the non-epithelioid subgroup, the mortality risk was increased by 12 %. In the control arm, survival was excellent; due to this, the trial had to be extended by six months to obtain the required number of deaths. No difference resulted for progression-free survival across the arms (HR, 0.90; p = 0.33).

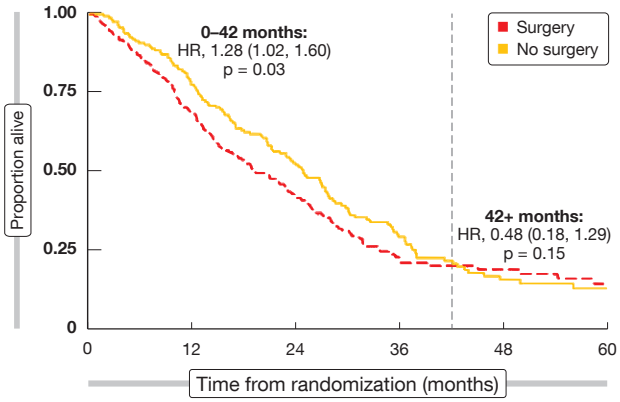


Figure: Reduction in overall survival with (extended) pleurectomy/decortication vs. chemotherapy alone

The in-hospital 90-day mortality rate after surgery was 8.9 %. With respect to grade ≥ 3 adverse events, the risk was 3.6-fold higher in the surgically treated arm than in the chemotherapy arm (p < 0.001). This difference centered around cardiac disorders, infections, repeat interventions and events classified as any respiratory, thoracic or mediastinal disorders. Sensitivity analyses consistently favored the chemotherapy-only approach even after adjustment for factors such as the number of first-line chemotherapy cycles and additional treatments.

The quality-of-life analysis according to the EORTC QLC-C30 questionnaire revealed sustained global health status/quality of life scores in the control group, while patients undergoing surgery reported deterioration for every outcome assessed. Quality of life by the EQ-5D questionnaire was markedly lower with pleurectomy/decortication than with chemotherapy alone throughout the study. Finally, in addition to the increased risk of death, more serious complications and poorer quality of life, the surgical approach was accompanied by higher costs of 20,102 $. The authors noted that relinquishing the concept of resectability in the context of mesothelioma would open access to effective systemic therapies currently licensed for disease that is defined as unresectable. ■

REFERENCES

1 Kindler HD et al., Treatment of malignant pleural mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018; 36(13): 1343-1373
2 NCCN Guidelines Pleural Mesothelioma, version 1.2023
3 Popat S et al., Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines diagnosis, treatment and follow-up. Ann Oncol 2022; 33(2): 129-142
4 Tsao AS et al., Current and future management of malignant mesothelioma: a consensus report from the National Cancer Institute Thoracic Malignancy Steering Committee, International Association for the Study of Lung Cancer, and Mesothelioma Applied Research Foundation. J Thorac Oncol 2018; 13(11): 1655-1667
5 Lim E et al., MARS 2: a multicentre randomised trial comparing (extended) pleurectomy decortication versus no (extended) pleurectomy decortication of patients with malignant pleural mesothelioma. WCLC 2023, abstract PL03.10

Proposals for the 9th edition of the TNM classification

The 8th edition of the TNM classification of lung cancers has been in effect since 2017. These recommendations have been summarized in publications issued by the Union for International Cancer Control (UICC), the American Joint Committee on Cancer (AJCC), and the International Association for the Study of Lung Cancer (IASLC) [1-3]. In January 2024, they will be replaced by the 9th edition of the TNM classification. The Staging and Prognostic Factors Committee of the IASLC and the non-profit organization Cancer Research and Biostatistics (CRAB®) have collaborated in the third staging project to revise the staging system for lung, mesothelioma and thymic cancers based on the data of 87,339 patients. Among these, 83 % and 7 % had NSCLC and SCLC, respectively. Fifty-six percent were Asians or Australians, while 25 % were from Europe and 16 % from North America. At WCLC 2023, Asamura et al. presented the final proposals for the new TNM classification [4].

Regarding T descriptors, the 9th edition will not recommend any changes compared to the current criteria. Within the N category, the N2 stage has been subdivided: while N2a denotes single N2 station involvement, N2b relates to multiple N2 station involvement. Similarly, the M1c stage will be divided into two subcategories. In patients with multiple extra-thoracic metastases, M1c1 will be used when these lesions are found in a single organ system. If they are located in multiple organ systems, the disease should be classified as M1c2. M1a and M1b, meanwhile, remain as previously defined. Naturally, the changes with respect to N and M descriptors have resulted in a revised TNM stage grouping **(Table)**. For both clinical and pathological stages according to the new definitions, the survival curves showed no significant overlap.

REFERENCES

1 Union for International Cancer Control. Briely JD, Gospodarowicz MK, Wittekind CH eds. TNM Classification of Malignant Tumors, 8th ed. Oxford UK and Hoboken, NJ: John Wiley; 2017

2 American Joint Committee on Cancer. Amin MB ed. AJCC Cancer Staging Manual, 8th ed. Springer; 2017

3 International Association for the Study of Lung Cancer. Rami-Porta R, ed. Staging Manual in Thoracic Oncology, 2nd Ed. North Fort Myers: Editorial Rx Press; 2016

4 Asamura H, Nishimura K, IASLC 9th edition TNM stage proposal. WCLC 2023, abstract PL04.03

TABLE **TNM stage grouping according to the proposed 9th edition of the TNM classification of lung cancers**

T/M	Label	N0	N1	N2		N3
				N2a	N2b	
T1	T1a ≤ 1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b > 1 to ≤ 2 cm	IA2	IIA	IIB	IIIA	IIIB
	T1c > 2 to ≤ 3 cm	IA3	IIA	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB	IIIB
	T2a > 3 to ≤ 4 cm	IB	IIB	IIIA	IIIB	IIIB
	T2b > 4 to ≤ 5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3	T3 > 5 to ≤ 7 cm	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Satellite nodules	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 > 7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral nodules	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Contralateral nodules	IVA	IVA	IVA	IVA	IVA
	M1a Pleural, pericardial effusion	IVA	IVA	IVA	IVA	IVA
	M1b Single extra-thoracic lesion	IVA	IVA	IVA	IVA	IVA
	M1c1 Multiple extra-thoracic lesions in a single organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Multiple extra-thoracic lesions in multiple organ systems	IVB	IVB	IVB	IVB	IVB

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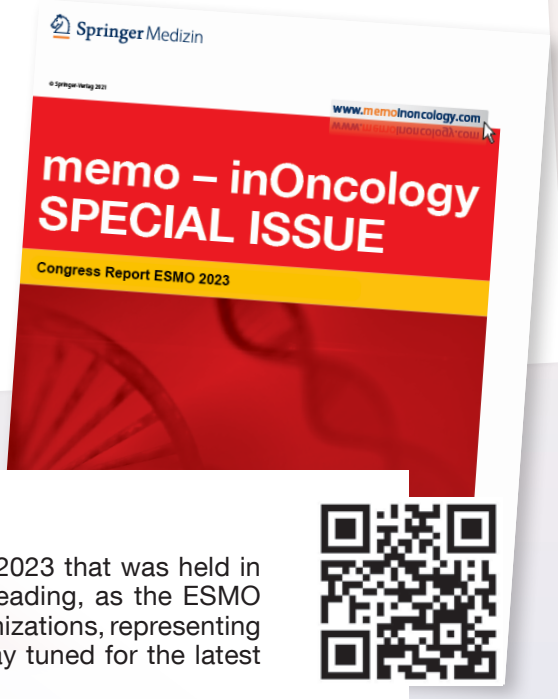

Forthcoming Special Issue

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

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