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Congress Report ESMO 2023

A GLOBAL CONGRESS DIGEST ON LUNG CANCER

Report from the ESMO Hybrid Congress , 20th – 24th October 2023, Madrid, Spain

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Preface

Dear Colleagues,

It is a pleasure to present you the memo inOncology 2023. This time we report on the ESMO Congress held in Madrid, Spain, from 20th to 24th October 2023. It was an outstanding scientific and educational event with more than 33,000 participants from 155 countries. Of the 2,545 presented abstracts reported, fifteen abstracts were selected for presidential symposia to discuss the most exciting updates, practice-changing data, and high-quality education across different tumor types.

This issue of memo inOncology summarizes highlights in the field of lung cancer starting with insights into emerging new therapies. Chapter one draws attention to the ALK inhibitor alectinib, which has been established as a new treatment strategy in patients with resected, stage IB-IIIA NSCLC. Moreover, significant improvements in perioperative IO treatment were reported pembrolizumab and nivolumab in the KEYNOTE-671 and CheckMate 77T trials, respectively. Analyses of the CheckMate 816 and RATIONALE-315 studies further underscore the benefits of adding immunotherapy to neoadjuvant chemotherapy.

In the field of molecular alterations, new trials were reported, with agents directed against RET, Trop-2, $KRAS^{G12C}$ and HER2. Selpercatinib has shown interesting activity in patients with *RET*-positive disease, while datopotamab deruxtecan has demonstrated antitumor activity in patients with and without targetable driver aberrations.

In the setting of advanced *EGFR*-mutated NSCLC, the combination of amivantamab and lazertinib outperformed osimertinib in the MARIPOSA trial and represents a new first-line treatment standard. Moreover, amivantamab/lazertinib plus chemotherapy and amivantamab/chemotherapy demonstrated clinical benefit in *EGFR*-mutated advanced NSCLC after disease progression on osimertinib. In addition, amivantamab plus chemotherapy was shown to be effective in the treatment of advanced NSCLC with *EGFR* exon 20 insertion mutations.

Furthermore, immunotherapy combinations in advanced-stage NSCLC with failure on EGFR- or ALK-targeted treatment were reported. A combination of atezolizumab and bevacizumab with chemotherapy has demonstrated efficacy in this setting. The results of the PERLA trial indicate superiority of dostarlimab plus chemotherapy over pembrolizumab plus chemotherapy. The SAPPHIRE trial, however, did not show any advantage for the combination of sitravatinib and nivolumab compared to docetaxel. Further research

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is required to identify effective treatments after development of resistance to checkpoint inhibition in NSCLC.

Finally, in the field of the very resilient small-cell lung cancer, potential new treatment avenues were outlined, including the DLL3-targeted agents BI 764532 and tarlatamab (a bispecific antibody).

Once again, numerous ground-breaking studies were presented at this year's ESMO meeting that are primed to change the standards of cancer care. Therefore, I strongly recommend you to take the opportunity to catch up on some of the most significant data and discover how they will impact your daily practice.

Enjoy discovering this special memo inOncology issue!

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ALK-targeted adjuvant treatment and perioperative immunotherapy

Approximately 30% to 40% of patients with non–small-cell lung cancer (NSCLC) are diagnosed with resectable disease [1, 2]. Depending on the stage, the risk of disease recurrence remains high in spite of treatment [3], which calls for more effective strategies.

ALINA: alectinib in the adjuvant setting

For patients with resectable *ALK*-positive NSCLC, the guidelines recommend adjuvant platinum-based chemotherapy, while immunotherapy is not recommended [4]. The potent oral ALK tyrosine kinase inhibitor (TKI) alectinib is widely used as first-line treatment of patients with advanced *ALK*-positive NSCLC. In the open-label, global phase III ALINA trial, adjuvant alectinib was investigated after resection of stage IB (≥4 cm) to IIIA *ALK*-positive NSCLC. Patients were randomized to either alectinib 600 mg BID for two years (n = 130) or platinum-based chemotherapy Q3W for 4 cycles (n = 127). Disease-free survival (DFS) was defined as the primary endpoint. This was tested hierarchically, with DFS assessment in the stage II-IIIA group preceding testing in the intent-to-treat (ITT) population.

According to the primary results from the pre-specified interim analysis presented at ESMO 2023 by Solomon et al. after a follow-up of 28 months, DFS was significantly improved with alectinib compared to chemotherapy in the stage II-IIIA population [5]. In the experimental

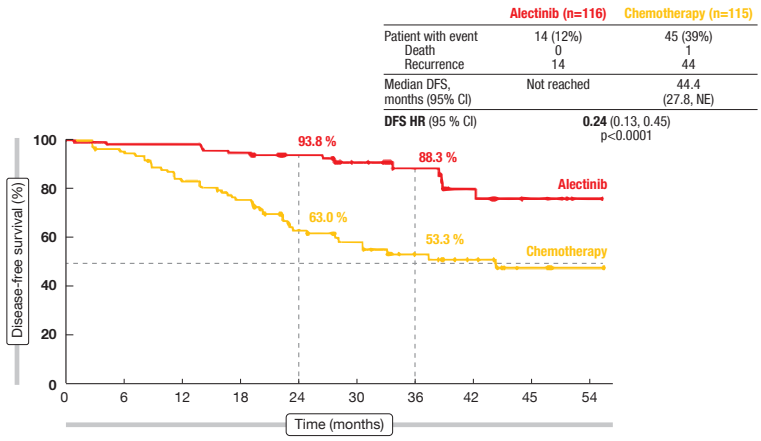

Figure 1: Improvement of disease-free survival with alectinib vs. chemotherapy in ALINA

arm, median DFS had not been reached, while this was 44.4 months in the control arm (HR, 0.24; p < 0.0001; **Figure 1**). The 3-year DFS rates were 88.3 % vs. 53.3 %. In the ITT population, the analysis revealed similar results, with median DFS not having been reached and 41.3 months for alectinib and chemotherapy, respectively (HR, 0.24; p < 0.0001). DFS benefits in favor of alectinib were seen across all of the pre-defined subgroups including disease stage and nodal status. CNS disease-free survival, which was an important exploratory endpoint, was longer in the alectinib-treated arm. CNS DFS rates of 95.5 % vs. 79.7 % at 36 months translated into a 78 % risk reduction (HR, 0.22).

In terms of patterns of failure, treatment with adjuvant alectinib resulted in lower proportions of patients with local/regional recurrences (n = 9 vs. 22) and distant recurrences (3 vs. 22). The effect on distant disease was profound, particularly in the brain (4 vs. 14), but also at other sites such as the bone (1 vs. 8). As the safety analysis showed, adjuvant alectinib was tolerable, and the events reported were in keeping with the known safety profile of this TKI. The authors noted that ALINA is the first and only positive phase III trial of an ALK inhibitor in resected, stage IB-IIIA NSCLC, with adjuvant alectinib representing an important new treatment strategy. Other key trials exploring alectinib in stage I-III NSCLC are ongoing, including NAUTIKA1 (NCT04302025), ALNEO (NCT05015010) and HORIZON-01 (NCT05170204).

Perioperative checkpoint inhibition: KEYNOTE-671…

The randomized, double-blind, phase III KEYNOTE-671 trial assessed the perioperative administration of pembrolizumab in addition to chemotherapy in the setting of stage II, IIIA, or IIIB (N2) lung cancer. Prior to surgery, the patients in the experimental arm received neoadjuvant pembrolizumab 200 mg Q3W plus cisplatin/gemcitabine or cisplatin/pemetrexed for up to 4 cycles; this was followed by adjuvant pembrolizumab 200 mg Q3W for up to 13 cycles (n = 397). In the control arm, placebo was administered instead of pembrolizumab (n = 400). According to the first interim analysis, perioperative pembrolizumab plus chemotherapy significantly improved event-free survival (EFS), major pathological response (MPR) and pathological complete response (pCR) compared to neoadjuvant chemotherapy and surgery alone [6].

The second interim analysis of KEYNOTE-671 demonstrated statistically significant, clinically important overall survival (OS) improvement with the pembrolizumab-based regimen after a median follow-up of 36.6 months [7]. Median OS had not been reached in the experimental arm and was 52.4 months in the control arm; at 48 months, 67.1 % vs. 51.5 % of patients were alive (HR, 0.72; p = 0.00517). The OS benefit was generally consistent across the majority of subgroups analyzed. As the authors pointed out, no other perioperative regimen based on immune checkpoint inhibition has previously shown OS improvement in phase III studies of resectable early-stage NSCLC.

In terms of EFS, the advantage that had been observed at the first interim analysis was maintained, with median EFS being almost 2.5 years longer in the immunotherapy-treated patients (47.2 vs. 18.3 months; HR, 0.59). EFS rates at 48 months were 48.4 % vs. 26.2 %. No new safety signals emerged over the prolonged follow-up. Among immune-mediated adverse events (AEs), hypothyroidism represented the most commonly reported event (10.9 % vs. 1.5 %), followed by pneumonitis (6.1 % vs. 1.8 %). However, the incidence of grade 3–5 immune-related events remained low. Based on the results of the KEYNOTE-671 trial, perioperative pembrolizumab has been established as a new standard of care for patients with resectable stage II, IIIA, or IIIB (N2) NSCLC.

… and CheckMate 77T

Another study highlighting the merits of perioperative immunotherapy is the global, double-blind phase III CheckMate 77T trial. Patients with resectable, stage IIA (> 4 cm) to IIIB (N2) NSCLC were randomized to either nivolumab 360 mg Q3W plus chemotherapy Q3W for 4 cycles (n = 229) or placebo plus chemotherapy (n = 232). Surgery was performed within six weeks of neoadjuvant treatment. The experimental arm went on to receive nivolumab 480 mg Q4W for one year, while matching placebo was administered in the control arm. A little over half of patients in each arm showed PD-L1 expression ≥ 1 %. EFS by BICR constituted the primary endpoint.

According to the results of the prespecified EFS interim analysis reported by Cascone et al. at ESMO 2023, 78 % and 77 % of the patients in the experimental and control arms, respectively, underwent definitive surgery [8]. In most cases, lobectomy was performed. R0 resection resulted in 90 % in each group. Sixty-two percent vs. 66 % of patients received adjuvant treatment. With respect to the primary endpoint, neoadjuvant nivolumab plus chemotherapy followed by surgery and adjuvant nivolumab improved EFS in a statistically significant and clinically meaningful manner compared to neoadjuvant chemotherapy and surgery alone. Median EFS had not been reached with the nivolumab-based approach and was 18.4 months with chemotherapy and surgery, which translated into a 42 % risk reduction (HR, 0.58; p = 0.00025; **Figure 2**). The experimental regimen performed better across most key subgroups. Patients with stage III disease derived a particularly pronounced EFS benefit (30.2 vs. 13.4 months; HR, 0.51),

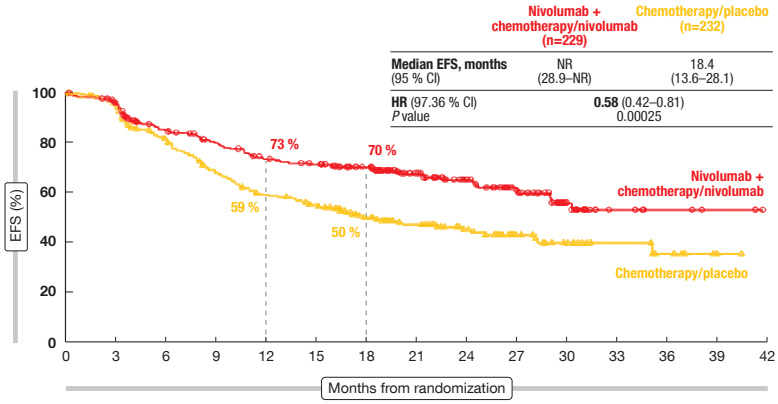

Figure 2: Primary endpoint of CheckMate 77T: event-free survival benefit with perioperative nivolumab

as did the group with PD-L1 ≥1 % (not reached vs. 15.8 months; HR, 0.52).

Furthermore, the addition of immunotherapy gave rise to improvements in the pCR rate (25.3 % vs. 4.7 %; OR, 6.64) and the MPR rate (35.4 % vs. 12.1 %; OR, 4.01). An exploratory analysis indicated EFS improvement with the nivolumab-based regimen compared to chemotherapy alone regardless of pCR status among patients eligible for adjuvant therapy; the HRs for patients with and without pCR were 0.22 and 0.63, respectively. In those unable to receive adjuvant treatment, neoadjuvant nivolumab plus chemotherapy continued to provide EFS benefit over chemotherapy only, with median EFS of 8.8 and 5.2 months, respectively (HR, 0.55). The safety analysis yielded no new signals for perioperative treatment with nivolumab. Feasibility of surgery was similar between the study arms. Taken together, CheckMate 77T supports the perioperative use of nivolumab as a potential new treatment option for patients with resectable NSCLC.

CheckMate 816: 3-year results by PD-L1 expression

In the phase III CheckMate 816 study, the addition of nivolumab to neoadjuvant chemotherapy has shown statistically significant and clinically meaningful improvements in EFS and pCR compared to chemotherapy alone [9]. Provencio Pulla et al. presented prespecified exploratory subgroup analyses that explored the outcomes in patients with PD-L1 ≥1 % or <1 % in CheckMate 816 [10].

The findings demonstrated that the combination provides clinical benefit compared to chemotherapy alone irrespective of tumor PD-L1 expression, although the magnitude of benefit was comparatively greater in the PD-L1–positive group. Patients with PD-L1 ≥1 % showed pCR rates of 32.6 % vs. 2.2 % for nivolumab plus chemotherapy vs. chemotherapy alone, whereas the pCR rates were 16.7 % vs. 2.6 % for those with PD-L1 <1 %. Median EFS had not been reached and was 26.7 months in the PD-L1–positive group (HR, 0.46); in the absence of PD-L1 positivity, this was 26.4 vs. 20.8 months (HR, 0.87). At 36 months, 85 % vs. 66 % of patients with PD-L1 ≥1 % were alive (HR, 0.37), while these proportions were 71 % vs. 60 % in those with PD-L1 <1 % (HR, 0.81). In both treatment arms, patients achieving pCR experienced improved EFS and OS compared to those without pCR.

Neoadjuvant nivolumab plus chemotherapy exhibited a manageable safety profile and did not impact the feasibility of surgery compared to chemotherapy alone, irrespective of tumor PD-L1 expression. The authors concluded that these findings reinforce the role of nivolumab plus chemotherapy as a standard neoadjuvant approach for eligible patients with resectable NSCLC and tumor PD-L1 expression ≥1 % or <1 %.

Responses to neoadjuvant tislelizumab

The perioperative use of the PD-1 inhibitor tislelizumab is being assessed in the randomized, double-blind phase III RATIONALE-315 study that is conducted in patients with resectable stage II-IIIA NSCLC. Neoadjuvant tislelizumab 200 mg Q3W plus platinum-doublet chemotherapy is administered for 3–4 cycles prior to surgery (n = 226). In the adjuvant phase, the treatment consists of tislelizumab 400 mg Q6W for up to 8 cycles. The group randomized to the control arm receives neoadjuvant chemotherapy alone, and placebo is used instead of the PD-1 inhibitor before and after surgery (n = 227). Primary endpoints include the MPR rate by blinded independent pathological review and EFS by BICR. pCR constitutes the key secondary endpoint. At ESMO 2023, Yue et al. reported the MPR and pCR findings after a median follow-up of 16.8 months [11].

Neoadjuvant tislelizumab plus chemotherapy, as compared to chemotherapy only, induced statistically significant and clinically meaningful improvement of both MPR (56.2 % vs. 15.0 %; OR, 7.5; p < 0.0001) and pCR (40.7 % vs. 5.7 %; OR, 11.5; p < 0.0001). The safety profile of the combination was consistent with the known risks of each component, and the treatment was well tolerated. Median duration of treatment was similar across the arms, as was the number of cycles received. The RATIONALE-315 study is ongoing, and further data will be shared at future meetings. ■

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Innovative agents directed against RET, Trop-2, KRAS^{G12C} and HER2

Superiority of selpercatinib in *RET*-positive disease

The highly selective and potent RET kinase inhibitor selpercatinib has been implemented in the treatment of lung cancer harboring *RET* gene fusions. At the same time, the combination of platinum, pemetrexed and pembrolizumab is an established first-line standard of care for patients without *EGFR* or *ALK* alterations. The aim of the randomized, open-label, phase III LIBRETTO-431 study was to define the optimal first-line regimen for patients with *RET*-fusion–positive NSCLC. Selpercatinib 160 mg BID (n = 129) was compared with carboplatin or cisplatin plus pemetrexed with or without pembrolizumab (n = 83) in the setting of untreated stage IIIB-IIIC or IV non-squamous, *RET*-positive NSCLC. Progression-free survival (PFS) by blinded independent central review (BICR) in the ITT-pembrolizumab population receiving chemotherapy plus pembrolizumab as well as the overall ITT population constituted the gated primary endpoints. Crossover from chemotherapy to selpercatinib was possible upon BICR-confirmed disease progression. A total of 103 centers in 23 countries participated in LIBRETTO-431.

According to the results of the protocol-specified interim analysis reported at ESMO 2023 by Loong et al., selpercatinib outperformed the control regimens by a considerable margin [1]. PFS was longer in a statistically significant and clinically meaningful manner in both the ITT-pembrolizumab population (24.8 vs. 11.2 months; HR, 0.465; p < 0.001; **Figure 1**) and the ITT population (24.8 vs. 11.2 months; HR, 0.482; p < 0.001). Consistent PFS benefits were observed across all preplanned subgroups; this involved superior outcomes in the selpercatinib arm independent of PD-L1 expression status. Furthermore, selpercatinib elicited a higher overall response rate than the control regimens (83.7 % vs. 65.1 %), and responses were more durable (24.2 vs. 11.5 months). Overall survival (OS) results were immature and confounded by the crossover (n = 42).

Improved CNS disease control

Asymptomatic brain metastases were present at baseline in approximately 20 % of patients in each arm. In this population, selpercatinib demonstrated improvements in terms of intracranial responses (82.4 % vs. 58.3 %) and intracranial PFS (16.1 vs. 10.4 months). Intracranial complete remissions resulted in 35.3 % vs. 16.7 %. Time to CNS progression was delayed with selpercatinib therapy. In patients both with and without baseline CNS metastases, the cumulative incidence of CNS progression was lower at 12 months (5.5 % vs. 20.3 %; cause-specific HR, 0.28). The 12-month cumulative incidence rates in the group with CNS lesions at baseline were 25.7 % vs. 33.3 % (cause-specific HR, 0.61). For the cohort without CNS metastases, this was 1.1 % vs. 14.7 % (cause-specific HR, 0.17).

The treatment-emergent adverse events (TEAEs) observed in the experimental arm were generally consistent with those previously reported and were mostly managed with dose modification. Transaminase elevations occurred as the most frequent AEs, followed by hypertension, diarrhea, edema, and dry mouth. Median time on selpercatinib treatment was approximately 70 % longer than time on control treatment (16.7 vs. 9.8 months). Assessments of pulmonary symptoms and physical function using the NSCLC Symptom Assessment Questionnaire and the EORTC QLQ-C30 showed that selpercatinib, as compared to chemo(immuno)therapy, delayed the time to deterioration of pulmonary symptoms (HR, 0.34) and overall physical function (HR, 0.60). In their summary, the authors noted that selpercatinib should be considered a first-line standard of care in *RET*-fusion–positive advanced NSCLC. Also, these results reinforce the importance of genomic testing to identify *RET* fusions at the time of diagnosis to inform initial therapy.

Dato-DXd in patients with genomic alterations

Standard-of-care second-line chemotherapy for metastatic NSCLC shows only modest clinical benefit and substantial toxicity. Therefore, innovative approaches such as the Trop-2-directed antibody drug conjugate (ADC) datopotamab deruxtecan (Dato-DXd) are being explored in pretreated patients with and without oncogenic drivers. Dato-DXd 6 mg/kg Q3W was tested in the single-arm, phase II TROPION-Lung05 study in 137 patients with stage

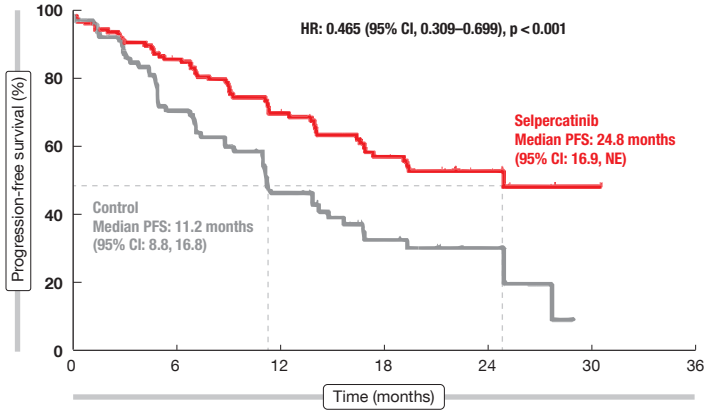

Figure 1: Progression-free survival with selpercatinib vs. platinum plus pemetrexed ± pembrolizumab

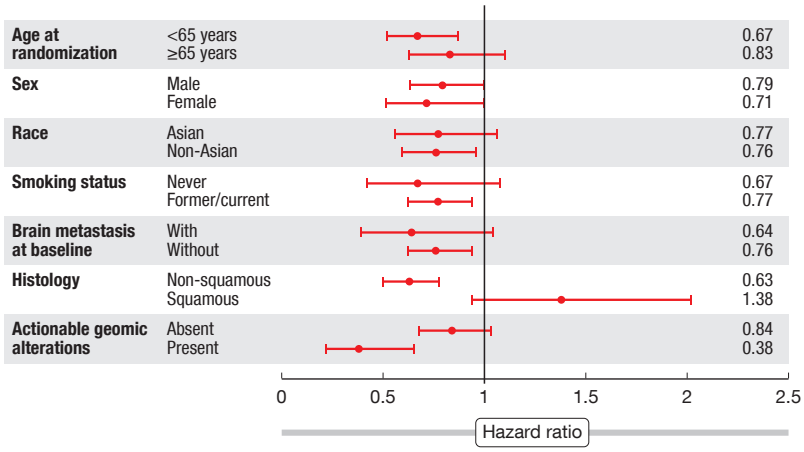

Figure 2: TROPION-Lung01 trial: progression-free survival in key subgroups

IIIB, IIIC, or IV NSCLC and at least one actionable genomic alteration (i.e., *EGFR, ALK, ROS1, NTRK, BRAF, MET* exon 14 skipping, RET). They had received ≥ 1 line of targeted treatment and 1 or 2 prior cytotoxic agent-containing therapies including platinum-based regimens in the metastatic setting; the median number of prior lines in advanced disease was 3. Radiographic disease progression had occurred after targeted therapy. *EGFR* mutations were present in 57 %, followed by *ALK* rearrangement (25 %). Half of the total population showed a history of brain metastasis. The objective response rate (ORR) by BICR constituted the primary endpoint.

Dato-DXd demonstrated encouraging antitumor activity in this heavily pretreated NSCLC population [2]. The confirmed ORR was 35.8 % in all treated patients; in the groups with *EGFR* mutations and *ALK* rearrangement, this was 43.6 % and 23.5 %, respectively. Median duration of response was 7.0 months across the groups. In the total population, complete and partial remissions resulted in 3 % and 33 %, respectively, and disease control was obtained in 78.8 %. Median PFS was 5.4 months overall; for the groups with *EGFR* mutations and *ALK* rearrangement, this was 5.8 and 4.3 months, respectively. A subset analysis of 68 patients with sensitizing mutations or T790M mutations showed that individuals previously treated with osimertinib achieved an ORR of 49.1 %.

Nausea, stomatitis and alopecia were reported as the most common TEAEs. The safety profile was characterized by low incidences of hematologic AEs and drug-related grade ≥ 3 toxicities. TEAEs necessitated dose reductions and dose withdrawal in 22 % and 10 %, respectively. In 2 %, TEAEs associated with death were reported. AEs of special interest included oral mucositis/stomatitis (all grades, 66 %), ocular surface toxicity (26 %), infusion-related reactions (16 %), and interstitial lung disease (ILD; 4 %). All of these were mostly grade 1 and 2.

TROPION-Lung01: Dato-DXd vs. chemotherapy

The randomized, phase III, open-label, global TROPION-Lung01 study is currently comparing Dato-DXd 6 mg/kg Q3W (n = 299) with docetaxel 75 mg/m² Q3W (n = 305) in stage IIIB, IIIC or IV NSCLC with or without actionable genomic alterations. Pretreatment consisted of 1 or 2 lines including platinum chemotherapy and immunotherapy in the group without driver aberrations, and 1 or 2 approved targeted agents plus chemotherapy and ≤ 1 anti-PD-(L)1 antibody in the group harboring driver aberrations. Actionable genomic alterations were found in 17 % in both arms, with *EGFR* mutation rates of 13 % and 15 % in the Dato-DXd and docetaxel groups, respectively. Squamous histology was present in 22 % and 23 %, respectively. Progression-free survival (PFS) by BICR and OS were defined as the dual primary endpoints.

According to the results presented at ESMO 2023, Dato-DXd, as compared to docetaxel, induced a 25 % reduction in the risk of progression or death, with median PFS of 4.4 vs. 3.7 months (HR, 0.75; p = 0.004) [3]. ORRs were 26.4 % vs. 12.8 %, and responses lasted for a median of 7.1 vs. 5.6 months. The PFS benefit was mainly driven by the group with non-squamous histology that derived a 37 % risk reduction (5.6 vs. 3.7 months; HR, 0.63; **Figure 2**). Likewise, the patients with non-squamous histology showed a 23 % reduction in mortality risk (HR, 0.77), while no difference was noted for OS in the overall group (12.4 vs. 11.0 months; HR, 0.90).

No new safety signals emerged in the TROPION-Lung01 study. Stomatitis and nausea were the most frequent treatment-related AEs (TRAEs) in the experimental arm and were predominantly grade 1 or 2. Fewer grade ≥ 3 TRAEs occurred with Dato-DXd than with chemotherapy (25 % vs. 41 %). Among AEs of special interest, the analysis yielded adjudicated drug-related ILD rates of 8 % vs. 4 %, with 3 % vs. 1 % classified as grade ≥ 3. Grade 5 ILD events were reported in 2 % (n = 7) vs. 0.3 % (n = 1). This highlights the need for careful monitoring and adherence to ILD management guidelines, as the authors stressed. Infusion-related reactions were noted in 8 % of patients in each arm; with the exception of one grade 3 event in the experimental arm, all of these were grade ≤ 2. Overall, Dato-DXd is the first ADC to demonstrate a statistically significant improvement in PFS over docetaxel in patients with pretreated, locally advanced or metastatic NSCLC. Dato-DXd constitutes a potential new therapy in the setting of previously treated non-squamous disease.

Adagrasib in addition to pembrolizumab

The $KRAS^{G12C}$ inhibitor adagrasib has been designed to show favorable properties including long half-life and dose-dependent pharmacokinetics, CNS penetration, and non-covalent binding affinity as well as minimized cysteine reactivity [4, 5]. These features are assumed to limit off-target effects in the liver and other organs. Indeed, in contrast to sotorasib, adagrasib can be administered concurrently or sequentially with pembrolizumab without severe hepatotoxicity impeding its use [6, 7].

Adagrasib 400 mg BID plus concurrent pembrolizumab 200 mg Q3W was investigated as first-line treatment in the phase II cohorts 1a and 2 of the sin-

gle-arm KRYSTAL-7 study that enrolled patients with advanced, unresectable or metastatic NSCLC harboring *KRAS*^{G12C} mutation. Stable brain metastases were allowed. ORR was defined as the primary endpoint. At ESMO 2023, Garassino et al. reported safety in all treated patients (n = 148) and efficacy in patients with PD-L1 TPS ≥ 50 % (n = 51) after median follow-up of 8.7 and 10.1 months for all patients and those with PD-L1 TPS ≥ 50 %, respectively [8].

The combination of adagrasib and pembrolizumab showed a manageable safety profile that was consistent with either agent as monotherapy. Most commonly, nausea (any grade, 51 %) and diarrhea (44 %) occurred, as well as ALT and AST increases (38 % and 32 %, respectively). Treatment-related grade ≥ 3 elevations of ALT and AST were observed in 24 patients (16 %). Ten of these received concomitant steroids, and most were able to resume the combination treatment. Despite transaminase elevations, treatment-related hepatic events were limited to < 10 % of patients. No patient discontinued either adagrasib or pembrolizumab due to transaminase increases or hepatic TRAEs. Two grade 5 TRAEs that included pneumonia and pneumonitis were reported. Immune-related TRAEs of any grade emerged in 18 %, with grade ≥ 3 events noted in 5 %. Adagrasib dose reductions and temporary dose interruption due to TRAEs were performed in 46 % and 59 % of patients, respectively. Permanent discontinuation of adagrasib or pembrolizumab resulted in 6 % and 11 %, respectively, and in 4 %, both drugs were discontinued due to TRAEs.

Encouraging preliminary efficacy was seen in the group with PD-L1 TPS ≥ 50 % that showed an ORR of 63 % and disease control in 84 %. This was higher than expected with pembrolizumab monotherapy (39-45 %) [9, 10]. In patients who experienced any-grade hepatotoxicity, the ORR was 70 %. Moreover, the data suggested promising early signs of durability. Median duration of response had not been reached at the time of the analysis, which was also true for median PFS. The authors noted that these findings support the initiation of a phase III trial evaluating concurrent adagrasib plus pembrolizumab compared to pembrolizumab in treatment-naïve *KRAS*^{G12C}-mutated NSCLC with PD-L1 TPS ≥ 50 %.

Outcomes with T-DXd by presence of brain lesions

In the setting of advanced or metastatic *HER2*-mutant NSCLC, the ADC trastuzumab deruxtecan (T-DXd) has been evaluated in the DESTINY-Lung02 trial and in Cohort 2 of the DESTINY-Lung01 study. Li et al. presented results for patients with and without brain metastases (BM) who received T-DXd 5.4 mg/kg Q3W in DESTINY-Lung02 (32 and 70 with and without BM, respectively) or T-DXd 6.4 mg/kg Q3W in Cohort 2 of DESTINY-Lung01 and in DESTINY-Lung02 (54 and 87 with and without BM, respectively) [11]. Regarding systemic responses, the analyses yielded similar results independent of the presence of BM **(Table)**. Confirmed ORRs ranged from 46.9 % to 58.6 % across dose levels and cohorts with and without BM, and disease control rates exceeded 90 % in all groups. Median PFS was shorter in the BM cohorts compared to the non-BM groups; this also applied to median OS.

In the population with BM at baseline, T-DXd demonstrated intracranial efficacy. Reductions in BM size from baseline as best overall response were observed in 86 % and 78 % for T-DXd 5.4 mg/kg and 6.4 mg/kg, respectively. Intracranial ORRs were 50 % and 30 %, respectively, and included complete responses in three patients treated with the lower dose (21.4 %). In 92.9 % and 73.3 %, respectively, intracranial disease control was achieved. Median duration of intracranial response was 9.5 and 4.4 months, respectively. Notably, patients with treated and untreated BMs experienced comparable intracranial responses.

The safety outcomes were similar regardless of the presence of BM, although patients with BM had higher rates of grade ≥ 3 and serious TEAEs than those without. The authors noted that limitations of this post-hoc analysis include the small number of patients and the lack of a comparator arm.

Encouraging results in Beamion LUNG-1

Zongertinib, an oral tyrosine kinase inhibitor that covalently and selectively binds to the tyrosine kinase domain of HER2 while sparing wild-type EGFR, is being tested in the multicohort phase Ia/Ib Beamion LUNG-1 study in the setting of NSCLC and other cancers harboring *HER2* aberrations. Phase Ia includes patients with advanced solid tumors who have exhausted existing standard options or are not suitable for them. *HER2* aberrations comprise overexpression, amplification, somatic mutation, and gene rearrangement involving *HER2* or *NRG1*. In phase Ib, patients

TABLE **Efficacy and safety of T-DXd 5.4 mg/kg and 6.4 mg/kg in patients with and without brain metastases (BM)**

	T-DXd 5.4 mg/kg DESTINY-Lung02		Pooled T-DXd 6.4 mg/kg Cohort 2 DESTINY-Lung01 + DESTINY-Lung02	
Efficacy/safety outcome	**BM n = 32**	**Non-BM n = 70**	**BM n = 54**	**Non-BM n = 87**
Systemic cORR, n (%)	15 (46.9)	35 (50.0)	27 (50.0)	51 (58.6)
Disease control rate, n (%)	29 (90.6)	66 (94.3)	50 (92.6)	80 (92.0)
Duration of response, months	4.6	16.8	7.2	14.1
Sites of progression, n (%)				
Intracranial only	3 (9.4)	0	8 (14.8)	0
Extracranial only	6 (18.8)	14 (20.0)	9 (16.7)	23 (26.4)
Both	3 (9.4)	0	0	2 (2.3)
Missing	1 (3.1)	1 (1.4)	5 (9.3)	10 (11.5)
Median PFS, months	7.1	18.0	7.1	11.9
Median OS, months	13.6	19.5	13.8	27.9
Grade ≥ 3 TEAE, n (%)	20 (64.5)	33 (47.1)	41 (75.9)	55 (63.2)
Drug-related	12 (38.7)	27 (38.6)	32 (59.3)	39 (44.8)

cORR, confirmed objective response rate; PFS, progression-free survival; OS, overall survival; TEAE, treatment-emergent adverse event

with *HER2*-mutated NSCLC are enrolled into five cohorts.

According to the latest data presented at ESMO 2023, the planned futility analysis was passed and the Beamion LUNG-1 study is continuing, with recruitment into all cohorts ongoing [12]. The maximum tolerated dose of zongertinib was not reached in phase Ia. The doses taken into dose optimization were 240 mg and 120 mg OD. Initial efficacy results were encouraging; in phase Ia, the ORR and the disease control rate in NSCLC patients were 50.0 % and 97.1 %, respectively, and in phase Ib, this was 73.9 % and 91.3 %, respectively. Zongertinib was well tolerated, with low rates of EGFR-mediated AEs and no cases of drug discontinuation due to AEs in phase Ib. All responders were ongoing at the time of the analysis. ■

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EGFR-mutated NSCLC: practice-changing results and other notable findings

MARIPOSA: first-line amivantamab plus lazertinib

In the setting of *EGFR*-mutated NSCLC, the third-generation EGFR TKI osimertinib is the current first-line standard of care, although eventual progression is virtually inevitable. Secondary *EGFR* and *MET* alterations have been found to account for 25 % to 50 % of cases of resistance [1-3]. The global, randomized, three-arm phase III MARIPOSA trial was based on the assumption that the combination of the EGFR-MET bispecific antibody amivantamab and the third-generation EGFR TKI lazertinib, when used as a first-line strategy in locally advanced or metastatic NSCLC with *EGFR* mutations (i.e., exon 19 deletion or L858R mutation), might proactively address resistance and improve clinical outcomes without the addition of chemotherapy. MARIPOSA compared amivantamab plus lazertinib (n = 429; open-label) with osimertinib (n = 429; blinded) and also contained a lazertinib monotherapy arm (n = 216; blinded) that was introduced to assess the contribution of the components. Progression-free survival (PFS) with amivantamab/lazertinib vs. osimertinib by blinded independent review (BICR) constituted the primary endpoint.

Indeed, amivantamab/lazertinib, as compared to osimertinib, improved median PFS by 7.1 months, thus reducing the risk of progression or death by 30 % (23.7 vs. 16.6 months; HR, 0.70; p < 0.001) [4]. Forty-eight percent of patients in the experimental arm were progression-free at 24 months, while this was 34 % in the control arm. All of the subgroups favored the amivantamab-based approach over osimertinib. The study design of the MARIPOSA trial allowed for the estimation of extracranial PFS as serial brain MRIs were conducted on all patients. Median PFS estimates increased in both arms after censoring of CNS-only first progressions. However, a consistent benefit of the combination remained that translated into a 32 % risk reduction and PFS prolongation by 9 months (27.5 vs. 18.5 months; HR, 0.68; p < 0.001). Identical reductions in the risk of progression or death by 31 % resulted in patients with and without a history of brain metastases. At the same time, lazertinib monotherapy that was assessed in the third

study arm demonstrated meaningful clinical activity. Median PFS in the lazertinib-treated group was 18.5 months, with superimposable Kaplan-Meier curves for lazertinib and osimertinib.

Data indicating long-term benefits

The confirmed objective response rates (ORRs) by BICR did not differ between amivantamab/lazertinib and osimertinib (80 % vs. 76 %), although median duration of response was improved by 9 months in the experimental arm (25.8 vs. 16.8 months). PFS2, which was PFS after the first subsequent therapy, was significantly longer in the amivantamab-treated patients, with 24-month rates of 72 % vs. 64 % (HR, 0.75; p = 0.03). While overall survival (OS) data were not mature yet, early results indicated a trend favoring amivantamab/lazertinib (HR, 0.80; p = 0.11).

In terms of safety, the combination was shown to induce higher adverse event (AE) rates related to EGFR and MET inhibition except for diarrhea, which occurred more commonly on osimertinib treatment. Most AEs were classified as grade 1 or 2. The rates of interstitial lung disease (ILD)/pneumonitis remained low, at approximately 3 % for both arms. Treatment-related AEs leading to discontinuations of all agents were observed in 10 % vs. 3 %.

Venous thromboembolism (VTE) as an AE of special interest was noted more frequently with amivantamab/lazertinib than with osimertinib (37 % vs. 9 %; **Table**), although the majority of events were grade 1 or 2. Discontinuation rates due to AEs were low and comparable across arms. In most cases, the first VTE event occurring in the experimental arm was reported during the first four months of treatment, while most patients did not receive anticoagulation therapy. The authors pointed out that prophylactic anticoagulation is now recommended for the first four months of treatment in ongoing trials of amivantamab/lazertinib. In light of the findings from the MARIPOSA trial, amivantamab/lazertinib represents a new first-line standard of care in patients with *EGFR*-mutated advanced NSCLC.

MARIPOSA-2: amivantamab plus chemotherapy ± lazertinib

Patients who had progressed on or after osimertinib monotherapy as the most recent line in the setting of advanced *EGFR*-mutated NSCLC were eligible for the global, randomized phase III MARIPOSA-2 trial. This three-arm study investigated the use of amivantamab plus chemotherapy with or without lazertinib to address osimertinib-related resistance. The patients were randomized to either amivantamab/lazertinib plus chemotherapy (n = 263), amivantamab/chemotherapy (n = 131), or chemotherapy alone (n = 263). Treated and untreated stable brain metastases were allowed. Almost half of patients showed a history of brain lesions, with 41 % to 51 % not having received brain irradiation. Serial brain MRIs were required for the total population.

MARIPOSA-2 had a dual primary endpoint of PFS by BICR: both amivantamab/lazertinib plus chemotherapy and amivantamab/chemotherapy were compared with chemotherapy only. During the study, the amivantamab/lazertinib plus chemotherapy regimen was modified to start lazertinib after carboplatin completion due to increased hematologic toxicities, and an extension cohort was established that enrolled new patients. Future analyses will explore the impact of this modification. Per protocol, the primary endpoint evaluated all randomized patients in the amivantamab/lazertinib plus chemotherapy arm irrespective of the dosing regimen administered.

The results reported at ESMO 2023 by Passaro et al. showed that compared to chemotherapy only, both amivantamab-based regimens improved PFS [5]. At a median follow-up of 8.7 months, amivantamab/lazertinib plus chemotherapy and amivantamab/chemotherapy gave rise to reductions in the risk of progression or death by 56 % (median PFS, 8.3 vs. 4.2 months; HR, 0.44; p < 0.001) and 52 % (6.3 vs. 4.2 months; HR, 0.48; p < 0.001), respectively **(Figure 1)**. All of the subgroups favored both regimens *versus* chemotherapy alone. Moreover, the ORRs were significantly higher with amivantamab/lazertinib plus chemotherapy and amivantamab/chemotherapy (63 % and 64 %, respectively) than with chemotherapy only (36 %; p < 0.001 each). Median duration of response in the experimental arms was numerically longer than in the control arm (9.4 months and 6.9 months, respectively, vs. 5.6 months).

Improvement of intracranial outcomes

Likewise, both amivantamab-containing regimens diminished the risk of intracranial progression or death, with reductions of 42 % (HR, 0.58; p < 0.001) and 45 % (HR, 0.55; p = 0.001), respectively. Among patients with a history of brain metastases who had not undergone prior

TABLE **Occurrence and timing of venous thromboembolism (VTE) as an adverse event of special interest in the MARIPOSA trial**

	Amivantamab + lazertinib (n = 421)	Osimertinib (n = 428)
Any VTE, n (%)	157 (37)	39 (9)
Grade 1	5 (1)	0
Grade 2	105 (25)	24 (6)
Grade 3	43 (10)	12 (3)
Grade 4	2 (0.5)	1 (0.2)
Grade 5	2 (0.5)	2 (0.5)
Any VTE leading to death, n (%)	2 (0.5)	2 (0.5)
Any VTE leading to any discontinuation, n (%)	12 (3)	2 (0.5)
Anticoagulant use at time of first VTE, n (%)		
On anticoagulants	5 (1)	0
Not on anticoagulants	152 (36)	39 (9)
Median onset to first VTE	84 days	194 days
Within first 4 months, n (%)	97 of 157 (62)	13 of 39 (33)

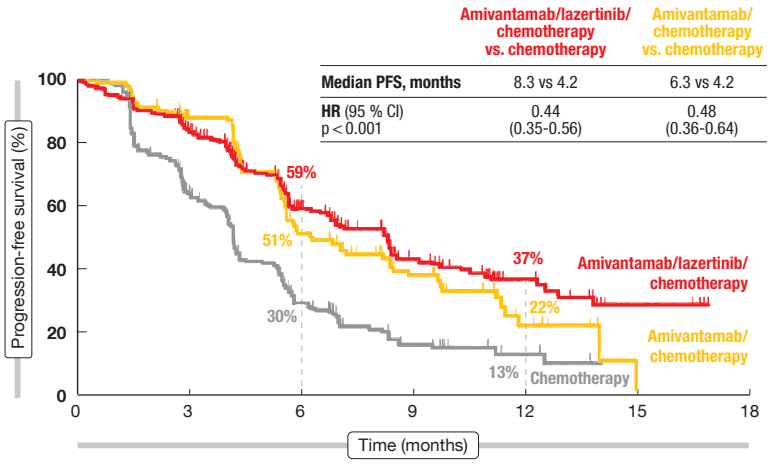

Figure 1: MARIPOSA-2: progression-free survival with amivantamab/lazertinib plus chemotherapy and amivantamab/chemotherapy vs. chemotherapy alone

radiotherapy, intracranial PFS was improved by 56 % (HR, 0.44; p = 0.005) and 64 % (HR, 0.36; p = 0.013), respectively. Early data on OS indicated a trend favoring amivantamab/chemotherapy over chemotherapy alone (HR, 0.77).

Median duration of treatment was longer for the amivantamab-containing arms than for chemotherapy. However, grade ≥ 3 AEs and dose modifications were more common in these arms, particularly in the lazertinib-treated group. Treatment-related AEs necessitated discontinuations of all agents in 10 %, 8 % and 2 %, respectively. Neutropenia and thrombocytopenia mostly occurred during cycle 1, and rates of febrile neutropenia were low. VTE was most frequent with amivantamab/lazertinib plus chemotherapy (22 % vs. 10 % and 5 %), while rates of discontinuation due to VTE were low and no grade 5 events occurred. Less than 3 % of patients across all arms developed ILD.

The authors stressed that amivantamab/lazertinib plus chemotherapy and amivantamab/chemotherapy are the first regimens to demonstrate improved PFS compared to chemotherapy in *EGFR*-mutated advanced NSCLC after disease progression on osimertinib. Next steps include the evaluation of subcutaneous amivantamab that is expected to improve convenience and quality of life.

Osimertinib plus ramucirumab: PFS advantage in RAMOSE…

Dual inhibition of EGFR and VEGF has been identified as an intensification strategy in the setting of *EGFR*-mutant NSCLC. As demonstrated in the RELAY, NEJ026 and ARTemis studies, this has the potential to delay resistance and prolong PFS [6-8]. At ESMO 2023, Le et al. presented the results of the randomized phase II RAMOSE trial that explored the addition of the anti-VEGFR2 antibody ramucirumab 10 mg/kg Q3W to osimertinib 80 mg OD in 93 US-based patients with advanced *EGFR*-mutated (i.e., deletion 19, L858R mutation) NSCLC [9]. This combination was compared to single-agent osimertinib 80 mg OD (n = 46). The patients were treatment-naïve regarding both EGFR TKI therapy and anti-VEGF approaches. CNS metastases were present in 43.0 % and 52.0 % in the groups receiving ramucirumab plus osimertinib and osimertinib alone, respectively.

After a median follow-up of 16.6 months, the combined regimen significantly improved PFS, which was the primary endpoint, compared to osimertinib monotherapy (24.8 vs. 15.6 months; HR, 0.55; p = 0.026; **Figure 2**). The PFS benefit was consistent across the pre-defined subgroups that included patients with and without brain metastases. No differences were noted across the arms in terms of ORR (76.3 % vs. 80.4 %) or the disease control rate (96.8 % vs. 95.7 %). The combination regimen was well tolerated, with discontinuation rates being similarly low for both regimens (9.7 % vs. 8.7). No grade 5 events occurred, and only one grade 4 event was reported, which was hyponatremia in the combination arm. As the authors summarized, the RAMOSE trial demonstrated that the addition of ramucirumab to osimertinib can be safe and efficacious with regard to PFS in the frontline setting.

… but not in OSIRAM-1

Another phase II study evaluating osimertinib plus ramucirumab in advanced untreated non-squamous NSCLC with activating *EGFR* mutations is the OSIRAM-1 trial. This study was conducted in Japanese patients and had the same design as RAMOSE, although with biweekly rather than triweekly administration of ramucirumab 10 mg/kg in addition to osimertinib 80 mg OD. Fifty-nine and 61 patients received the combination and osimertinib monotherapy, respectively. Individuals with asymptomatic brain metastases were eligible for enrolment.

However, OSIRAM-1 was a negative trial, with PFS by BICR showing no difference across the arms both of which performed well (20.0 vs. 24.0 months; HR, 1.054; p = 0.4621) [10]. The subgroup analysis suggested that some

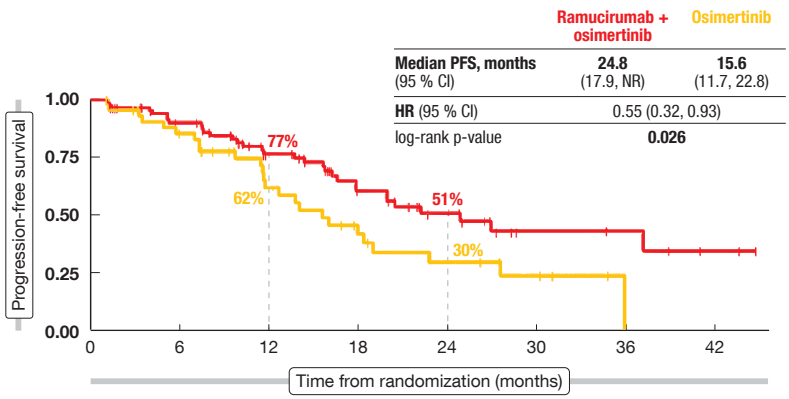

Figure 2: Primary endpoint of RAMOSE: improved progression-free survival with the addition of ramucirumab to osimertinib

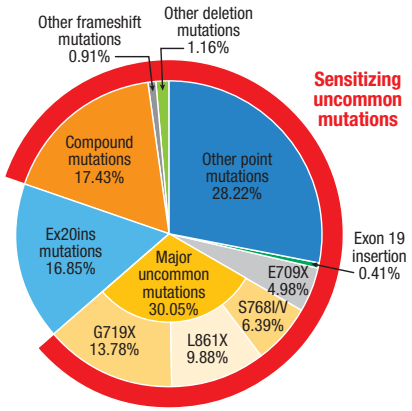

Figure 3: Sensitizing uncommon *EGFR* mutations: uncommon/compound mutations without exon 20 insertion and de-novo T790M mutation

groups such as older patients (≥ 75 years), those with L858R mutation and those with brain metastases derived greater PFS benefit from the combination. In the cohort that had brain metastases at baseline, a 34 % risk reduction was noted in the experimental arm *versus* the control arm (HR, 0.655).

According to the safety analysis, the combination treatment was associated with higher rates of diminished platelet counts (all grades, 55.9 % vs. 27.4 %; grade ≥ 3, 0 % vs. 1.6 %) and neutrophil counts (all grades, 30.5 % vs. 25.8 %; grade ≥ 3, 10.2 % vs. 3.2 %), which led to early discontinuation of ramucirumab. The authors pointed out that OSIRAM-1 was conducted during the critical phase of the COVID-19 pandemic, which could have had a negative impact on the optimal administration of ramucirumab that required biweekly hospital visits. A cross-trial comparison showed that exposure to ramucirumab had been considerably longer in RAMOSE than in OSIRAM-1 (14.4 vs. 4.7 months) [11].

Ex20ins-positive NSCLC: amivantamab/chemotherapy

In the setting of advanced NSCLC with *EGFR* exon 20 insertion mutations (Ex20ins), the outcomes are historically poor [12-14]. Ex20ins are largely insensitive to EGFR TKIs, and checkpoint inhibitors have failed to show benefit in this setting. Platinum-based chemotherapy is usually administered, but has limited efficacy. Amivantamab has been established as a treatment option after progression on platinum-based chemotherapy. The randomized phase III PAPILLON study presented at ESMO 2023 attempted to increase the efficacy of amivantamab by combining it with carboplatin and pemetrexed in the first-line treatment of patients with locally advanced or metastatic, Ex20ins-positive NSCLC (n = 153). Chemotherapy alone was administered in the control arm (n = 155). Patients who progressed in this group were allowed to cross over to second-line amivantamab monotherapy.

PFS by BICR, which was defined as the primary endpoint, was significantly improved by the addition of amivantamab to chemotherapy, with a 60 % reduction in the risk of progression or death (11.4 vs. 6.7 months; HR, 0.395; p < 0.0001) [15]. At 18 months, 31 % vs. 3 % of patients were progression-free. All of the predefined subgroups favored the combined approach with regard to PFS.

Similarly, the ORR was significantly higher in the experimental arm (73 % vs. 47 %; OR, 3.0; p < 0.0001), and the duration of response was longer (9.7 vs. 4.4 months). Amivantamab/chemotherapy gave rise to significantly improved PFS2, i.e., PFS after the first subsequent therapy (not reached vs. 17.2 months; HR, 0.493; p = 0.001), with 24-month PFS2 rates of 57 % vs. 35 %. This finding supports the first-line use of the combination. Sixty-six percent of patients in the control arm whose disease progressed crossed over to amivantamab. Regarding interim OS, amivantamab/chemotherapy showed a trend with a 32 % reduction in mortality (not reached vs. 24.4 months; HR, 0.675; p = 0.106).

The safety profile of amivantamab plus chemotherapy was consistent with the profiles of the individual agents. Across the arms, the rates of discontinuation of all study agents due to AEs were similar. For amivantamab, the analysis showed a low discontinuation rate of 7 % due to treatment-related events. Pneumonitis developed in 4 (3 %) patients in the combination arm. EGFR- and MET-related AEs were increased in the experimental arm, although these were mainly grade 1 or 2. Chemotherapy-associated gastrointestinal and hematologic AEs were comparable except for neutropenia that occurred more frequently with the combination (all grades, 59 % vs. 45 %; grade ≥ 3, 33 % vs. 23 %), although it was transient and led to low rates of discontinuation. The authors concluded that amivantamab plus chemotherapy represents the new standard of care for the first-line treatment of patients with advanced NSCLC harboring *EGFR* exon 20 insertion mutations.

Afatinib in uncommon *EGFR* mutations

To date, there has been a lack of randomized phase III trial in patients harboring sensitizing uncommon mutations defined as uncommon/compound *EGFR* mutations without Ex20ins and de-novo T790M mutation **(Figure 3)**. Therefore, the randomized phase III ACHILLES/TORG1834 trial was initiated to compare the second-generation EGFR TKI afatinib 40 mg or 30 mg OD (n = 73) with platinum plus pemetrexed (n = 36) as first-line treatment of locally advanced or metastatic non-squamous NSCLC harboring sensitizing uncommon mutations. At ESMO 2023, Miura et al. reported the first results of the ACHILLES/TORG1834 study [16].

Afatinib significantly improved PFS compared to platinum doublet chemotherapy. After a median follow-up of 12.5 months, treatment with the EGFR TKI led to a 58 % risk reduction (median PFS, 10.6 vs. 5.7 months; HR, 0.422; p = 0.0007). Thus, the study met its primary endpoint. The 12-month PFS rates were 42.1 % vs. 19.3 %. All of the subgroups derived PFS benefit from afatinib treatment compared to chemotherapy. The ORRs did not differ significantly across the treatment arms (61.4 % vs. 47.1 %; p = 0.2069).

No new safety signals were reported for afatinib compared to previous reports; diarrhea, paronychia, rash and mucositis occurred as the most common AEs. In their summary, the authors concluded that ACHILLES/TORG1834 confirmed afatinib as the standard of care for patients with treatment-naïve non-squamous NSCLC harboring sensitizing uncommon *EGFR* mutations. ■

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Immunotherapy combinations in advanced-stage disease

As is known, immune checkpoint inhibition plays only a limited role after failure of EGFR- or ALK-targeted treatment in patients with advanced NSCLC; this applies to both monotherapy and combinations with chemotherapy as demonstrated by the CheckMate 722 and KEYNOTE-789 trials [1, 2]. It was hypothesized that inhibition of VEGF might enhance the activity of chemoimmunotherapy by increasing lymphocyte trafficking to the tumor microenvironment and reversing VEGF-mediated immunosuppression [3, 4]. Indeed, a subgroup analysis of the phase III IMpower150 study has shown improved efficacy of the PD-L1 inhibitor atezolizumab in combination with anti-angiogenic therapy, particularly in *EGFR*-mutated NSCLC [5].

ATTLAS: ABCP vs. PC

Therefore, the multicenter, open-label, randomized phase III ATTLAS study was initiated to evaluate atezolizumab plus the anti-VEGF antibody bevacizumab in addition to chemotherapy with carboplatin and paclitaxel (ABCP) in the setting of stage IV, non-squamous NSCLC harboring activating *EGFR* or *ALK* alterations after progression on ≥ 1 EGFR or ALK tyrosine kinase inhibitors (TKIs). In the absence of *EGFR* T790M mutations, EGFR TKIs of the first or second generation had been used, while third-generation TKI pretreatment was required in patients with T790M mutations. Induction treatment in the experimental arm entailed the administration of ABCP Q3W for 4 to 6 cycles (n = 154). This was followed by the maintenance phase consisting of atezolizumab plus bevacizumab Q3W until disease progression or loss of clinical benefit. Patients in the control arm (n = 74) received chemotherapy alone, i.e., pemetrexed plus carboplatin or cisplatin (PC) Q3W for 4 to 6 cycles followed by pemetrexed maintenance Q3W until disease progression or loss of clinical benefit. Progression-free survival (PFS)

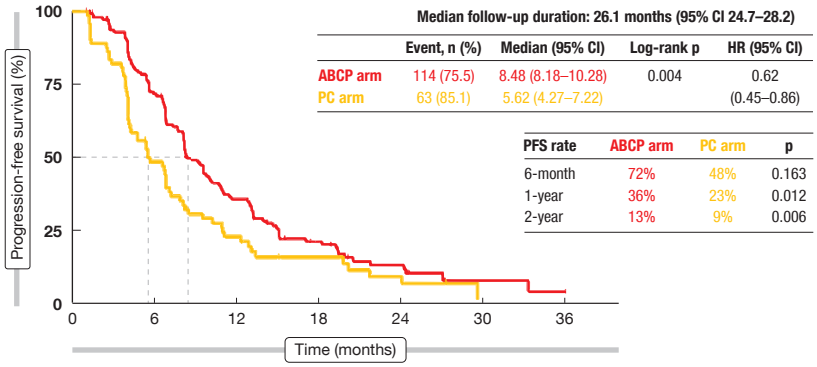

Figure 1: ATTLAS study: improvement of progression-free survival with atezolizumab, bevacizumab and paclitaxel/carboplatin (ABCP) compared to pemetrexed plus platinum (PC)

was the primary endpoint. Brain metastases were present in more than 40 % of patients in each study arm.

Results from the first analysis of ATTLAS were reported at ESMO 2023 by Ahn et al. [6]. The ABCP regimen, as compared to PC, gave rise to a statistically significant and clinically meaningful PFS improvement (8.48 vs. 5.62 months; HR, 0.62; p = 0.004; **Figure 1**). At 12 months, 36 % vs. 23 % of patients were progression-free (p = 0.012). Particularly large risk reductions resulted in the subgroups with brain metastases (HR, 0.32), L858R mutation (HR, 0.52) and those without acquired T790M mutations (HR, 0.44). According to an exploratory analysis, the PFS benefit of ABCP was greatest in the patients showing the highest PD-L1 expression (TPS ≥ 50 %) as well as in those with inflamed scores ≥ 20 % vs. < 20 %.

No difference was observed regarding overall survival (OS; 20.63 vs. 20.27 months; HR, 1.01; p = 0.975). Objective responses resulted in 69.5 % vs. 41.9 % and disease control in 96.7 % vs. 87.8 %. The median best reductions in target lesion size were -43.8 % vs. -26.0 % with ABCP vs. PC. Treatment-related adverse events (AEs) occurred more commonly with ABCP than PC, as did dose interruptions or modifications and permanent discontinuation. However, AEs proved manageable, and no new safety signals emerged during the study. Taken together, the data obtained in the ATTLAS trial showed that the addition of atezolizumab and bevacizumab to chemotherapy should be considered a feasible option in patients with NSCLC harboring activating *EGFR* or *ALK* alterations after progression on targeted treatment.

OS findings with dostarlimab plus chemotherapy

The anti-PD-1 antibody dostarlimab that binds to PD-1 at distinct bindings sites with different binding orientations from other PD-1 inhibitors has been shown to significantly improve outcomes in rectal and endometrial cancer [7-9]. PERLA was the first global, randomized, double-blind head-to-head study comparing dostarlimab with pembrolizumab in the setting of NSCLC. In this phase II trial, patients with untreated metastatic non-squamous NSCLC devoid of known targetable oncogenic driver aberrations received either dostarlimab 500 mg Q3W plus chemotherapy (n = 121) or pembrolizumab 200 mg Q3W plus chemotherapy (n = 122). The overall response rate (ORR) by blinded independent review was defined as the primary endpoint based on the scientists' hypothesis that the ORRs might be similar across the two regimens. According to the primary analysis, PERLA met its primary endpoint, demonstrating favorable numerical trends in ORR and PFS for the dostarlimab-based regimen [10]. Peters et al. presented the pre-planned updated OS results at ESMO 2023 [11].

Dostarlimab plus chemotherapy continued to exhibit strong clinical efficacy. Consistent with the primary analysis, the ORR remained numerically higher in the experimental arm (45 % vs. 39 % **Figure 2**). Median duration of exposure was longer in the dostarlimab-treated group (9 vs. 6 months), with a median of 13 vs. 7.5 cycles administered. After a median follow-up of 21 months, a trend favored the dostarlimab-based strategy in terms of OS (19.4 vs. 15.9 months; HR, 0.75). This numerical superiority held true in all patients with positive PD-L1 assessment (PD-L1 TPS ≥ 1 %). Also, median PFS was longer for dostarlimab plus chemotherapy than pembrolizumab plus chemotherapy in the group without PD-L1 expression (TPS < 1 %), although the Kaplan Meier curves crossed twice.

Similar proportions of patients across the two arms experienced AEs and grade ≥ 3 AEs. In the experimental arm, fewer patients developed AEs leading to treatment discontinuation, serious AEs and immune-related AEs. In their summary, the authors pointed out that these updated results are consistent with the study hypothesis that dostarlimab and pembrolizumab have similar efficacy. These findings support further investigation of dostarlimab as a backbone in combination with standard-of-care regimens.

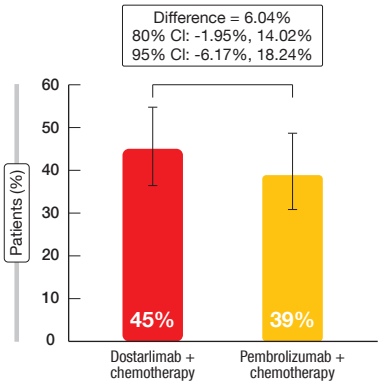

Figure 2: Confirmed overall response rates with dostarlimab/chemotherapy *vs.* pembrolizumab/chemotherapy

Negative results for sitravatinib/nivolumab

No advantage was found for the combination of the multi-kinase inhibitor sitravatinib with nivolumab that was tested against docetaxel in the phase III SAPPHIRE study [12]. Patients with unresectable, locally advanced or metastatic non-squamous NSCLC that had no actionable genomic alterations participated in the trial after one or two prior regimens. The most recent regimen included immune checkpoint inhibition with or after platinum-based chemotherapy. Based on the observation that checkpoint inhibitor resistance is driven by an immunosuppressive tumor microenvironment (TME), it was hypothesized that sitravatinib might shift the TME towards a less immunosuppressive state and thus improve outcomes when administered in combination with nivolumab after failure of checkpoint inhibition.

OS, which was the primary objective, did not differ significantly for sitravatinib/nivolumab vs. docetaxel (12.2 vs. 10.6 months; HR, 0.86; p = 0.144), which also applied to PFS (4.4 vs. 5.4 months; HR, 1.08; p = 0.452), ORR (16 % vs. 17 %; p = 0.597) and duration of response (7.4 vs. 7.1 months; p = 0.924). None of the subgroups appeared to benefit from the combination in a notable manner; indeed, never smokers and patients who had previously received sequential checkpoint inhibition and platinum-based chemotherapy fared better with docetaxel. The safety profiles for sitravatinib/nivolumab and docetaxel were consistent with the known profiles. Immune-related AEs of any grade occurred in 46 % of combination-treated patients, the most frequent being hypothyroidism (14 %) and diarrhea (12 %). The authors concluded that further studies are needed to identify treatment options for patients with NSCLC who have developed resistance against immune checkpoint inhibition. ■

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Small-cell lung cancer: insights and new treatment options centering around DLL3

Target with prognostic and predictive value

The cell surface protein delta-like-ligand 3 (DLL3) is an emerging therapeutic target in neuroendocrine tumors and neuroendocrine carcinomas such as small-cell lung cancer (SCLC). Approximately 75 % of SCLCs express DLL3 [1]. Data reported at ESMO 2023 showed that high DLL3 expression is associated with poor overall survival, advanced pathological grade, and a distinct immune landscape across neuroendocrine neoplasms found in the lung, prostate, and bladder [2]. A Chinese study group developed a prediction model for the 12-month survival probability of patients with SCLC based on the expression of DLL3 and PD-L1 and other factors **(Table 1)** that showed excellent performance and might assist physicians in clinical decision making [3].

TABLE 1 **Survival prediction in SCLC: nomogram score**

Variable		Point
Neuron-specific enolase per 50 mg/ml		6.16
Stage	Limited	0
	Extensive	20.47
Treatment	Yes	0
	No	100
DLL3	Negative	0
	Positive	24.69
PD-L1	Negative	0
	Positive	44.50

DLL3-targeted agents such as the bispecific DLL3/CD3 T-cell engager BI 764532 are currently under clinical development. BI 764532 binds to both DLL3 on cancer cells and CD3 on the surface of T-cells, which leads to T-cell activation and cancer cell apoptosis [4]. In an ongoing phase I dose escalation and expansion study, BI 764532 has induced tumor shrinkage at clinically active doses in patients with SCLC and other neuroendocrine carcinomas [5]. Based on the observation that BI 764532 upregulates the PD-L1 pathway, the combination of the T-cell engager with the PD-1 inhibitor ezabenlimab will be evaluated in a phase I dose escalation trial in the setting of DLL3-positive SCLC and other neuroendocrine neoplasms expressing DLL3 (NCT05879978) [6]. The patients participating in this trial have failed available standard therapies or are not eligible for them.

DeLLphi-301: tarlatamab at two doses

Another bispecific DLL3/CD3 T-cell engager is tarlatamab that was investigated in the open-label phase II DeLLphi-301 study in patients with extensive-stage SCLC who had previously received ≥ 2 treatment lines including platinum-doublet therapy. In the dose evaluation part of the study (part 1), 88 patients each received either tarlatamab 10 mg or 100 mg in a randomized manner. The treatment started with a 1 mg dose on day 1 that was followed by either 10 or 100 mg on days 8, 15 and Q2W thereafter. The 10 mg dose was selected for further assessment. In the dose expansion part (part 2), 12 patients received tarlatamab 10 mg according to the same dosing schedule. Part 3 of the study entailed reduced inpatient monitoring; here, 34 patients were treated with tarlatamab 10 mg. DLL3 expression was no prerequisite for study entry. Treated and stable brain metastases were permitted.

The objective response rate (ORR) constituted the primary endpoint, as well as treatment-emergent adverse events (TEAEs) and tarlatamab serum concentrations. At ESMO 2023, Paz-Ares et al. presented the primary analysis of the DeLLphi-301 trial [7]. Across parts 1 and 2, 100 patients had received tarlatamab 10 mg, while 88 had been treated with 100 mg in part 1. In these two groups, 33 % and 43 %, respectively, had received ≥ 3 prior lines of therapy, with anti-PD-(L)1 treatment having been administered in 73 % and 70 %, respectively. DLL3 expression was present in 96 % in each group.

Durable antitumor activity

In this heavily pretreated patient population, tarlatamab 10 mg demonstrated clinical efficacy with an ORR of 40 % and a disease control rate (DCR) of 70 % **(Table 2)**. Tarlatamab 100 mg gave rise to an ORR of 32 % and a DCR of 63 %. Responses occurred regardless of DLL3 expression and were also observed in patients whose tissue samples were not evaluable for DLL3 expression. Among 68 responders (n = 40 and 28 with 10 mg and 100 mg, respectively), 59 % showed duration of response of ≥ 6 months. Median duration of response had not been reached at the time of the analysis. Median progression-free survival was 4.9 and 3.9 months for tarlatamab 10 mg and 100 mg, respectively. At 6 months, 40.4 % and 34.1 % of patients, respectively, were progression-free. Data were not mature for overall survival (OS). Median OS was 14.3 months for the 10 mg dose and had not been reached for the 100 mg dose. The 6-month OS rates were 73.4 % and 71.4 %, respectively. At data cutoff, 57 % and 51 % of patients in the 10 mg and 100 mg groups, respectively, were alive.

Tarlatamab demonstrated a favorable safety profile. Cytokine release syndrome (CRS) represented the most common TEAE, with rates of 49 %, 61 % and 56 % for tarlatamab 10 mg (part 1 and 2), 100 mg, and 10 mg (part 3), respectively. CRS events were generally confined to the first or second dose, classified as grade 1 or 2, and manageable with supportive care. Other AEs included decreased appetite, pyrexia, constipation, and anemia. Immune effector cell-associated neurotoxicity syndrome (ICANS) occurred infrequently and was predominantly observed with the 100 mg dose.

Dose interruptions or reductions due to TEAEs occurred in 14 %, 29 % and 9 % with tarlatamab 10 mg (part 1 and 2), 100 mg, and 10 mg (part 3), respectively. The discontinuation rates due to treatment-related AEs were low at 4 %, 3 % and 0 %, respectively. Shorter inpatient monitoring as performed in part 3 did not alter the safety profile. In their conclusion, the authors emphasized that these results support the use of tarlatamab in patients with pretreated SCLC. The ongoing phase III DeLLphi-304 study will compare tarlatamab 10 mg Q2W with standard-of-care chemotherapy in the setting of relapsed SCLC (NCT05740566).

TABLE 2 **Responses observed with tarlatamab 10 mg and 100 mg**

Outcome	Tarlatamab 10 mg (n = 100)	Tarlatamab 100 mg (n = 88)
Objective response rate, n (%)	40 (40)	28 (32)
Complete response	1 (1)	7 (8)
Partial response	39 (39)	21 (24)
Stable disease	30 (30)	27 (31)
Progressive disease	20 (20)	13 (15)
Not evaluable/no post-baseline scan	10 (10)	20 (23)
Observed duration of response ≥ 6 months, %	58	61
Disease control rate, n (%)	70 (70)	55 (63)

Recruitment halt in TREASURE

The randomized TREASURE trial was initiated based on the hypothesis that consolidation thoracic irradiation in addition to atezolizumab maintenance after induction therapy consisting of 4 cycles of carboplatin/etoposide plus atezolizumab might improve OS in extensive-stage SCLC. Patients in arm A of the TREASURE study underwent thoracic radiotherapy with 30 Gy over 10 days plus atezolizumab maintenance, while those in arm B received atezolizumab maintenance only. OS and toxicity (pneumonitis grade ≥ 3) were defined as the primary endpoints.

However, unexpected safety signals necessitated a recruitment halt. At ESMO 2023, Bozorgmehr et al. reported that during a routine safety review by the Safety Monitoring Committee, a potential imbalance in the total number of fatal AEs was identified, with 5 vs. 1 cases in arms A vs. B [8]. An unplanned interim OS analysis was conducted and recruitment was stopped. A re-analysis performed three months later showed no change in OS but a three times higher number of severe AEs in the intervention arm (28 vs. 9), along with a further increase in fatal AEs (6 vs. 1).

The causes of death in the experimental arm were diverse and not clearly tied to either immunotherapy or irradiation. They included two cases of sepsis and one case each of multi-organ failure, lung infection, pneumonitis, and worsening of the patient's general condition. In the control arm, one patient died due to hepatic failure. An in-depth serious AE analysis on a case-to-case basis did not reveal any common thread. Nevertheless, it was decided to permanently halt recruitment due to the imbalance in number, severity and seriousness of severe AEs. Factors leading to this unexpected outcome remain to be identified. The authors expressed hope that the final analysis including radiotherapy and biomarker parameters might contribute to further insights. ■

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Expert interviews at ESMO 2023

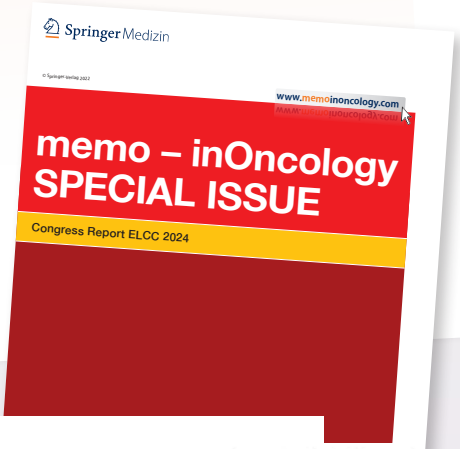
Gerrina Ruiter explains the limitations of previous HER2 agents tested in solid tumors while highlighting the encouraging preliminary results of the BEAMION Lung-1 trial of zongertinib in HER2–mutant solid tumors. Lastly, she talks about the challenges of bispecific antibodies, which have recently shown robust efficacy in solid tumors.

Sebastian Kobold discusses the growing interest in using CAR-T cell therapy as an innovative approach to treat solid tumors in the future, as well as T cell receptor T cell therapy. Although there are still some hurdles to overcome, he discusses what remarkable developments can be expected in this field in the coming years.

David C. Currow highlights the encouraging results of two Phase 3 randomized trials that investigated a ghrelin antagonist to combat cachexia in NSCLC patients. He also provides an overview of the recent advancements in integrating palliative care for cancer patients, and addresses the ongoing challenges that we still face in terms of end-of-life care in everyday practice.

James R. M. Black provides an overview of the potential of ctDNA in pre-operative disease stratification for early lung cancer by highlighting data from an ultra-sensitive and specific ctDNA approach. Considering the challenges of comprehensive tissue sampling and that subclones may evade tumor biopsy detection due to undersampling of metastatic sites at relapse, he finally discusses what insights ctDNA-based methods could provide into the process of metastasis spread.

Åslaug Helland summarizes the results from the NIPU trial combining UV1 vaccination and immunotherapy in the setting of malignant mesothelioma. Furthermore, she explains how study designs might be modified to expand treatment options in personalized medicine and explains which data could potentially be used as external comparator arms where randomized controlled trials might be unethical, or no defined standard treatment and/or too small patient groups are available.



Forthcoming Special Issue

This special issue will be offering a synopsis from the ELCC 2024 that will be held in March 2024. The report promises to make for stimulating reading, as the ELCC 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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