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A SPECIAL MEETING REVIEW EDITION

Highlights in Non–Small Cell Lung Cancer From the IASLC 2023 World Conference on Lung Cancer

A Review of Selected Presentations From the IASLC 2023 WCLC • September 9-12, 2023 • Singapore

Special Reporting on:

- Sacituzumab Govitecan + Pembrolizumab in 1L Metastatic Non–Small Cell Lung Cancer: Preliminary Results of the EVOKE-02 Study
- Osimertinib With/Without Platinum-Based Chemotherapy as First-Line Treatment in Patients With *EGFR*m Advanced NSCLC (FLAURA2)
- MARS 2: A Multicentre Randomised Trial Comparing (Extended) Pleurectomy Decortication Versus No (Extended) Pleurectomy Decortication for Patients With Malignant Pleural Mesothelioma
- Benmelstobart With Anlotinib Plus Chemotherapy as First-Line Therapy for ES-SCLC: A Randomized, Double-Blind, Phase 3 Trial
- A Phase 3 Study of Serplulimab Plus Chemotherapy as First-Line Treatment for Squamous Non–Small Cell Lung Cancer (ASTRUM-004)
- ILLUMINATE: Efficacy and Safety of Durvalumab/Tremelimumab and Chemotherapy in *EGFR*-Mutant NSCLC Following Progression on EGFR Inhibitors
- Neoadjuvant Durvalumab + Chemotherapy Followed by Adjuvant Durvalumab in Resectable *EGFR*-Mutated NSCLC (AEGEAN)
- IMpower151: Phase 3 Study of Atezolizumab + Bevacizumab + Chemotherapy in 1L Metastatic Nonsquamous NSCLC
- First-Line Chemotherapy With or Without Tislelizumab for Extensive-Stage Small Cell Lung Cancer: RATIONALE-312 Phase 3 Study

PLUS Meeting Abstract Summaries

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Sacituzumab Govitecan + Pembrolizumab in 1L Metastatic Non–Small Cell Lung Cancer: Preliminary Results of the EVOKE-02 Study

In both men and women, lung cancer causes the greatest number of cancer-related deaths in the United States and across the globe.[1] Regimens that include a programmed death ligand 1 (PD-L1) inhibitor are the preferred first-line therapy for patients with metastatic non–small cell lung cancer (NSCLC), particularly for those whose tumors lack a known driver mutation.[2,3] To improve patient outcomes, novel combination therapies are being explored. Sacituzumab govitecan is an antibody-drug conjugate (ADC) that binds to Trop-2 and releases the SN-38 topoisomerase I inhibitor, leading to DNA damage and cell death. The ADC is approved in the United States for the second-line treatment of patients with metastatic triple-negative breast cancer and previously treated patients with hormone receptor–positive/HER2-negative metastatic breast cancer; the drug also received accelerated approval as a second-line treatment for patients with metastatic urothelial cancer.[4] A single-arm, multicenter trial evaluated sacituzumab govitecan monotherapy in patients with previously treated metastatic NSCLC.[5] Among 47 evaluable patients, the objective response rate (ORR) was 19%, the median duration of response (DOR) was 6.0 months (95% CI, 4.8-8.3), and the clinical benefit rate was 17% (9/54). Adverse events (AEs) of at least grade 3 included neutropenia (28%), diarrhea (7%), nausea (7%), fatigue (6%), and febrile neutropenia (4%).

The open-label, multicohort, phase 2 EVOKE-01 trial evaluated sacituzumab govitecan plus pembrolizumab, with or without platinum therapy, in patients with treatment-naive metastatic NSCLC.[6] Enrolled patients had measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, with no known actionable genomic alterations.[7] Patients in cohort A had a PD-L1 tumor proportion score (TPS) of 50% or greater and patients in cohort B had a PD-L1 TPS of less than 50%. Patients in these 2 cohorts received sacituzumab govitecan (10 mg/kg, days 1 and 8) plus pembrolizumab (200 mg, day 1) in 21-day cycles. The primary endpoint was the ORR. In a preliminary analysis, the median follow-up was 5.0 months for cohort A (n=30) and 5.8 months for cohort B (n=33). Approximately 60% to 61% of patients had nonsquamous histology, and 80% to 85% had stage IV disease at diagnosis. Half of the

Table. The Efficacy of Sacituzumab Govitecan for Patients With NSCLC in the EVOKE-02 Study

Efficacy by INV[a]	Cohort A (PD-L1 TPS ≥ 50%) SG + Pembro n = 29	Cohort B (PD-L1 TPS < 50%) SG + Pembro n = 32	Total SG + Pembro n = 61
ORR[b] (95% CI), %	**69 (49-85)**	**44 (26-62)**	**56 (42-69)**
Confirmed and unconfirmed PR, n (%) Confirmed PR, n (%)	20 (69) 18 (62)	14 (44) 12 (38)	34 (56) 30 (49)
SD, n (%)	5 (17)	11 (34)	16 (26)
PD, n (%)	3 (10)	2 (6)	5 (8)
DCR[c] (95% CI), %	86 (68-96)	78 (60-91)	82 (70-91)
Median DOR[d,e] (95% CI), mo DOR rate at 6 mo (95% CI), %	NR (5.6-NR) 88 (39-98)	NR (3.5-NR) 88 (39-98)	NR (7.9-NR) 87 (58-97)

[a]Patients without tumor assessment (cohort A, n = 1; cohort B, n = 5).
[b]PORR was defined as BOR of CR + PR.
[c]DCR was defined as BOR of CR + PR + SD for ≥6 weeks.
[d]Evaluated in patients with a confirmed CR or PR.
[e]Based on Kaplan-Meier estimates.
BOR, best overall response; CR, complete response; DR, disease control rate; DOR, duration of response; INV, Investigator assessment; NR, not reached; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death ligand 1; Pembro, pembrolizumab; PR, partial response; SD, stable disease; SG, sacituzumab govitecan; TPS, tumor proportion score.
Adapted from Cho et al. Abstract OA05.04. Presented at: IASLC 2023 WCLC; September 9-12, 2023; Singapore.[6]

patients in cohort B had a PD-L1 TPS of less than 1%. The median duration of treatment with the ADC was 4.1 months in both cohorts; the median duration of treatment with pembrolizumab was 3.6 months in cohort A and 3.8 months in cohort B. Patients in both cohorts received a median of 6 cycles of sacituzumab govitecan and a median of 6 cycles of pembrolizumab. At the time of the preliminary analysis, 37% of patients in cohort A and 58% of those in cohort B had discontinued all study treatment. In both cohorts, the most common reason for discontinuation of sacituzumab govitecan was disease progression. By investigator assessment, 69% of patients in cohort A and 44% of those in cohort B achieved a partial response (PR) (Table). The median DOR was not reached in either cohort. In each cohort, 88% of patients exhibited an ongoing response at 6 months. Significant tumor shrinkage was observed in both cohorts. Target lesions showed rapid responses that were often deep and durable. The safety profile of the ADC plus pembrolizumab was manageable and consistent with the known safety profile of each agent. The combination of sacituzumab govitecan plus pembrolizumab vs pembrolizumab monotherapy is being investigated in the phase 3 EVOKE-3 trial in patients with treatment-naive metastatic NSCLC and a PD-L1 TPS of 50% or greater.

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Osimertinib With/Without Platinum-Based Chemotherapy as First-Line Treatment in Patients With *EGFR*m Advanced NSCLC (FLAURA2)

Epidermal growth factor receptor gene (*EGFR)* mutations are frequently observed in NSCLC adenocarcinomas, the most common aberrations being exon 19 deletion and L858R mutation in exon 21.[1-3] For patients with advanced or metastatic *EGFR*-mutated NSCLC, the first-line recommended treatment is a tyrosine kinase inhibitor (TKI) directed against the EGFR kinase domain. The phase 3 FLAURA2 trial evaluated osimertinib plus pemetrexed and a platinum-containing agent in patients with untreated, locally advanced or metastatic, *EGFR*-mutated NSCLC.[4] Enrolled patients had pathologically confirmed nonsquamous NSCLC with an *EGFR* exon 19 deletion or L858R mutation. Stable central nervous system (CNS) metastases were allowed. Before randomization, patients were stratified according to race, *EGFR* mutation testing (local or central) results, and World Health Organization performance status (PS). Patients in arm 1 received osimertinib (80 mg, daily) plus pemetrexed (500 mg/m^2) and either carboplatin (area under the curve [AUC], 5) or cisplatin (75 mg/m^2) every 3 weeks for 4 cycles. Patients in arm 2 received osimertinib (80 mg, daily). The primary endpoint was progression-free survival (PFS) by investigator assessment based on RECIST version 1.1.[5]

The FLAURA2 study randomized 276 patients to an osimertinib combination arm and 275 to an osimertinib monotherapy arm. An initial safety run-in was performed on 30 patients to provide a preliminary evaluation of the combination of osimertinib plus chemotherapy.[6] Patient characteristics were balanced in the 2 arms. Patients had a median age of 61 to 62 years (range, 26-85), and approximately two-thirds of patients had never smoked. *EGFR* mutations included exon 19 deletion (61%-62%) and L858R mutation (38%). Extrathoracic metastases were observed in 53% to 54% of patients and CNS metastases in 40% to 42%. At the time of data analysis, 44% of patients in the combination arm and 55% in the monotherapy arm had discontinued osimertinib. Disease progression and AEs were the most common reasons for discontinuation of any study therapy. The study met its primary endpoint, demonstrating a median PFS per investigator assessment of 25.5 months with osimertinib plus pemetrexed and platinum vs 16.7 months with osimertinib monotherapy (hazard ratio [HR], 0.62; 95% CI, 0.49-0.79; *P*<.0001) (Figure 1). Assessment of median PFS by blinded, independent central review yielded a median PFS of 29.4 months with the osimertinib combination vs 19.9 months with

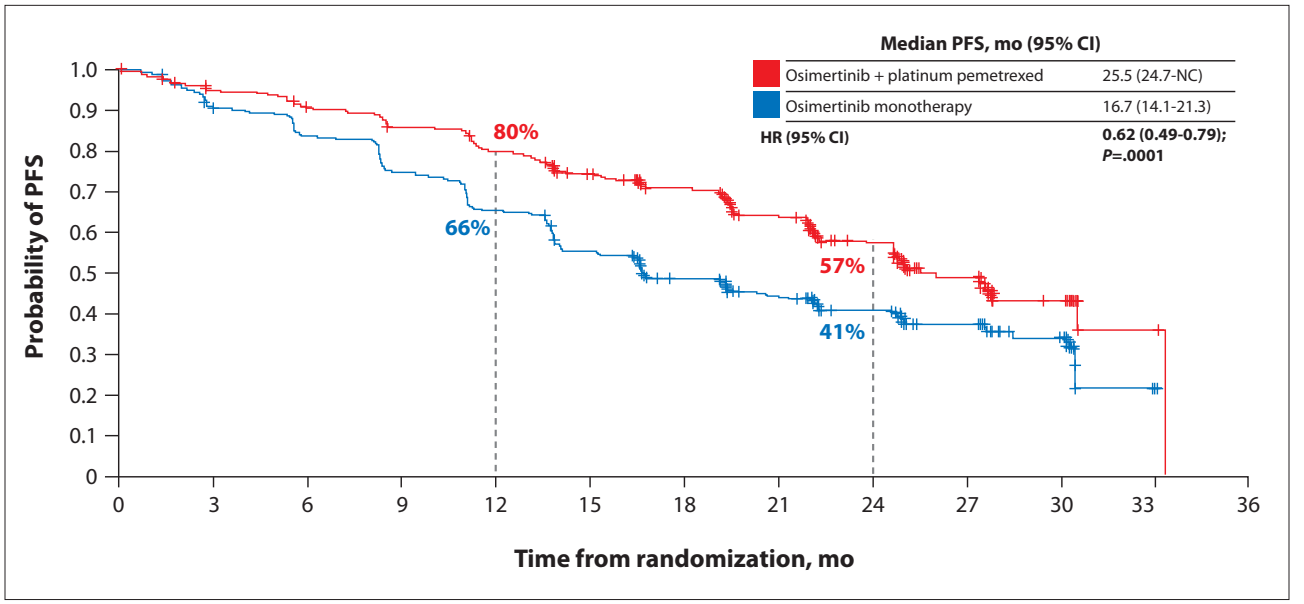

Figure 1. The PFS per investigator in patients with EGFRm advanced NSCLC from the FLAURA2 trial. CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival. Adapted from Janne et al. Abstract PL03.13. Presented at: IASLC 2023 WCLC; September 9-12, 2023; Singapore.[4]

osimertinib monotherapy (HR, 0.62; 95% CI, 0.48-0.80; *P*=.0002). The combination of osimertinib plus chemotherapy yielded a benefit in comparison with osimertinib monotherapy across all predefined subgroups.

AEs of grade 3 or higher that were possibly related to treatment were more common with the osimertinib combination than with monotherapy (53% vs 11%). AEs leading to death occurred in 5 patients (2%) in the combination arm vs 1 patient (<1%) in the osimertinib monotherapy arm. Serious AEs were observed in 19% of patients in arm 1 vs 5% in arm 2. Most AEs in both arms were manageable with standard intervention.

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MARS 2: A Multicentre Randomised Trial Comparing (Extended) Pleurectomy Decortication Versus No (Extended) Pleurectomy Decortication for Patients With Malignant Pleural Mesothelioma

Mesothelioma is a rare, lethal cancer. The combination of a platinum-based agent plus pemetrexed is the cornerstone of treatment, but it provides only modest improvement in survival.[1] As a result, surgical cytoreduction is recommended, with pleurectomy decortication emerging as the preferred surgical approach.[1-3] The multicenter phase 3 MARS2 trial was designed to evaluate whether either pleurectomy/decortication or extended pleurectomy/decortication plus chemotherapy would be superior to chemotherapy alone in patients with pleural mesothelioma; the primary endpoint was overall survival (OS).[4,5] Enrolled patients had tissue-confirmed mesothelioma in 1 hemithorax that was deemed surgically resectable. Patients initially received

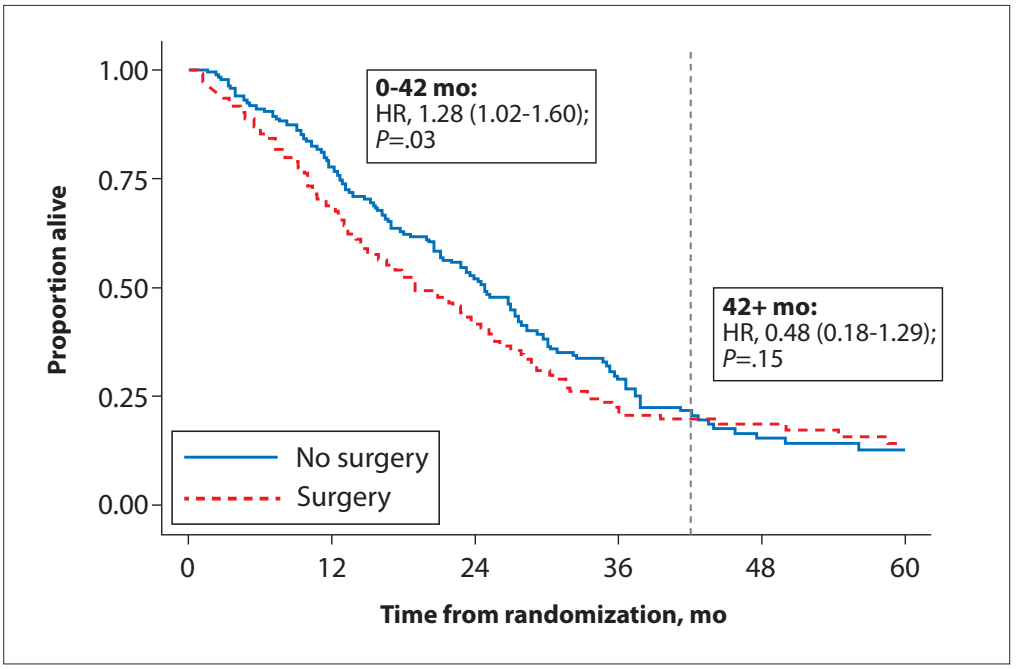

Figure 2. The primary outcome of OS in patients with pleural mesothelioma from the MARS 2 trial. HR, hazard ratio; mo, months. Adapted from Lim et al. Abstract PL03.10. Presented at: IASLC 2023 WCLC; September 9-12, 2023; Singapore.[4]

2 cycles of pemetrexed plus a platinum-containing agent, after which computed tomography was performed to determine whether resection was feasible. Patients with resectable disease were randomized to surgical resection plus 4 additional cycles of pemetrexed and a platinum-containing agent or to 4 additional cycles of chemotherapy without surgical resection.

The intention-to-treat analysis included 169 patients randomized to surgery plus chemotherapy and 166 to chemotherapy alone. Baseline characteristics were well balanced in the 2 arms. In the combined population of 335 patients, the median age was 69 years, 87% of patients were male, and 86% of patients had epithelioid mesothelioma. Clinical TNM stage analysis indicated that the tumor characteristics at baseline were also well balanced in the 2 arms. Of the patients who were randomized to surgery, 88.5% underwent extended pleurectomy/decortication, 8.3% underwent pleurectomy/decortication, and 1.9% underwent partial pleurectomy. The most common resection and reconstruction procedures included diaphragm resection (82.8%), diaphragm reconstruction (81.5%), and pericardium resection (66.9%). Macroscopic complete resection was achieved in 84% of patients. Microscopic residual tumor was observed in 81% of patients. The in-hospital mortality rate was 3.8%, the 30-day mortality rate was also 3.8%, and the 90-day mortality rate was 8.9%. Patients who were randomized to surgery were more likely to complete 6 cycles of chemotherapy (56.0% vs 39.1%) and were more likely to receive additional treatment consisting of immunotherapy (38.6% vs 21.9%) or additional chemotherapy (39.2% vs 20.7%).

After a median follow-up of 22.4 months (range, 11.3-30.8), the median OS was 19.3 months for the patients randomized to surgery plus chemotherapy vs 24.8 months for those randomized to chemotherapy alone. The trial failed to meet its primary endpoint, and during the first 42 months of the trial, the risk for death was 28% greater in the patients randomized to surgery plus chemotherapy than in those randomized to chemotherapy alone (HR, 1.28; 95% CI, 1.02-1.60; *P*=.03) (Figure 2). Median PFS did not differ between the 2 arms (HR, 0.90; 95% CI, 0.72-1.11; *P*=.33). At 42 months, only 15 patients remained in each arm; therefore, analysis beyond 42 months was not considered meaningful. The number of serious AEs was 3.6-fold higher among the patients who were randomized to surgery plus chemotherapy, reflecting higher rates of cardiac disorders, thoracic disorders, infections, and repeat interventions.

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Benmelstobart With Anlotinib Plus Chemotherapy as First-Line Therapy for ES-SCLC: A Randomized, Double-Blind, Phase 3 Trial

Small cell lung cancer (SCLC) is an aggressive tumor that is associated with a poor prognosis and short survival.[1,2] Benmelstobart is a novel immune-checkpoint inhibitor consisting of a humanized antibody that binds to PD-L1. Anlotinib is a TKI that inhibits angiogenesis by binding to the vascular endothelial growth factor receptor and other receptors. ETER701, a multicenter, placebo-controlled phase 3 trial, randomized 738 patients with previously untreated, advanced SCLC evenly into 3 arms to receive anlotinib with or without benmelstobart in combination with etoposide plus carboplatin or to receive etoposide plus carboplatin alone.[3] Maintenance therapy consisted of benmelstobart plus anlotinib (arm 1), placebo plus anlotinib (arm 2), or 2 placebos (arm 3). Key eligibility criteria included a confirmed age of 18 to 75 years, a pathologically confirmed diagnosis of extensive-stage SCLC (ES-SCLC), no prior systemic therapy, and measurable disease per RECIST version 1.1.[4] Brain metastases were permitted if they were asymptomatic or treated and stable. The primary endpoints were PFS and OS, determined by independent review.

As indicated by data from arm 1 and arm 3, the baseline characteristics were well balanced in these 2 study subpopulations. The median age was 62 to 63 years (range, 30-75), 22% to 24% of patients were never-smokers, and 89% to 91% had stage IV disease. Approximately 10% had brain metastasis and 32% had liver metastasis. The trial demonstrated a median PFS of 6.9 months with the 4-drug combination (arm 1) vs 4.2 months in the placebo control arm (HR, 0.32; 95% CI, 0.26-0.41; *P*<.0001). The 12-month PFS rate was 27.9% with the benmelstobart combination vs 2.3% with etoposide plus carboplatin. The trial met its second primary endpoint, demonstrating an OS of 19.3 months with the benmelstobart combination vs 11.9 months with the control therapy (HR, 0.61; 95% CI, 0.46-0.79; *P*=.0002) (Figure 3). The 24-month OS rate was 41.8% with the 4-drug combination vs 24.2% with etoposide plus carboplatin. The DOR also was better in arm 1 than in arm 3 (5.8 vs 3.1 months; HR, 0.31; 95% CI, 0.24-0.41; *P*<.0001). The 4-drug combination yielded a significantly superior median OS and PFS in nearly every subgroup examined, except for PFS in a small

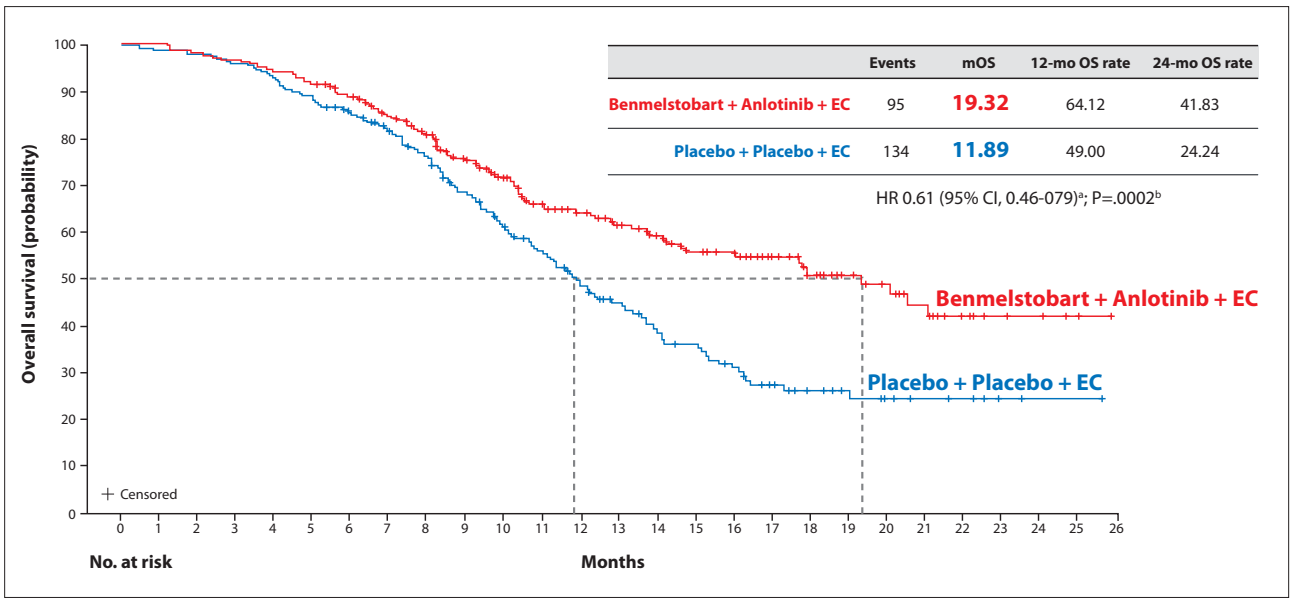

Figure 3. OS of the ITT ES-SCLC patient population from the ETER701 trial.
[a]HR in sensitivity analysis was estimated using unadjusted Cox proportional hazards model.
[b]P-value in sensitivity analysis was done using unstratified log-rank test.
EC, Etoposide plus carboplatin; ES-SCLC, extensive-stage small cell lung cancer; HR, hazard ratio; ITT, intention-to-treat; mOS, median overall survival; No., number; OS, overall survival. Adapted from Cheng et al. Abstract OA01.03. Presented at: IASLC 2023 WCLC; September 9-12, 2023; Singapore.[3]

number of patients with limited-stage disease. The rates of serious AEs were 37.4% with the 4-drug combination and 25.6% with the control regimen. AEs in the benmelstobart-treated arm were generally manageable.

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A Phase 3 Study of Serplulimab Plus Chemotherapy as First-Line Treatment for Squamous Non–Small Cell Lung Cancer (ASTRUM-004)

Squamous cell NSCLC tumors commonly lack targetable genetic alterations. For patients with such tumors, the preferred first-line treatment is chemotherapy plus a programmed death 1 (PD-1)/PD-L1 inhibitor.[1] Serplulimab is a novel anti-PD-1 antibody that has been approved in China for the treatment of various solid tumors, including ES-SCLC and squamous cell NSCLC.[2] The multicenter, international, double-blind phase 3 ASTRUM-004 trial evaluated the safety and efficacy of serplulimab vs placebo in combination with carboplatin plus nab-paclitaxel in patients with treatment-naive, locally advanced or metastatic squamous cell NSCLC.[2] Enrolled patients had no known *EGFR* mutation or *ALK*/*ROS1* rearrangement. Stratification factors included level of PD-L1 expression, race, and disease stage. Patients were randomized 2:1 to receive serplulimab (4.5 mg/kg, day 1) or placebo. All patients also received nab-paclitaxel (100 mg/m^2, days 1, 8, and 15) plus carboplatin (AUC, 5 or 6; day 1). Treatment was administered in 21-day cycles, with up to 6 cycles for chemotherapy and up to 2 years for serplulimab or placebo. The primary endpoint was PFS by independent review based on RECIST version 1.1.[3]

The trial included 358 patients in the serplulimab-plus-chemotherapy arm and 179 in the placebo-plus-chemotherapy arm. Baseline characteristics were well balanced in the 2 arms. Patients had a median age of 63 years (range, 35-86). Two-thirds were Asian and one-third were White. Most patients (71%-73%) had stage IV disease. PD-L1 expression, determined by TPS, was lower than 1% in 38% of patients, higher than 1% but lower than 50% in 32% to 33% of patients, and 50% or greater in 29% to 30% of patients. In the serplulimab vs the placebo arm, liver metastasis was observed in 11% vs 10% of patients and brain metastasis in 6% vs 10% of patients. With a median 31.1 months of follow-up, the trial met its primary

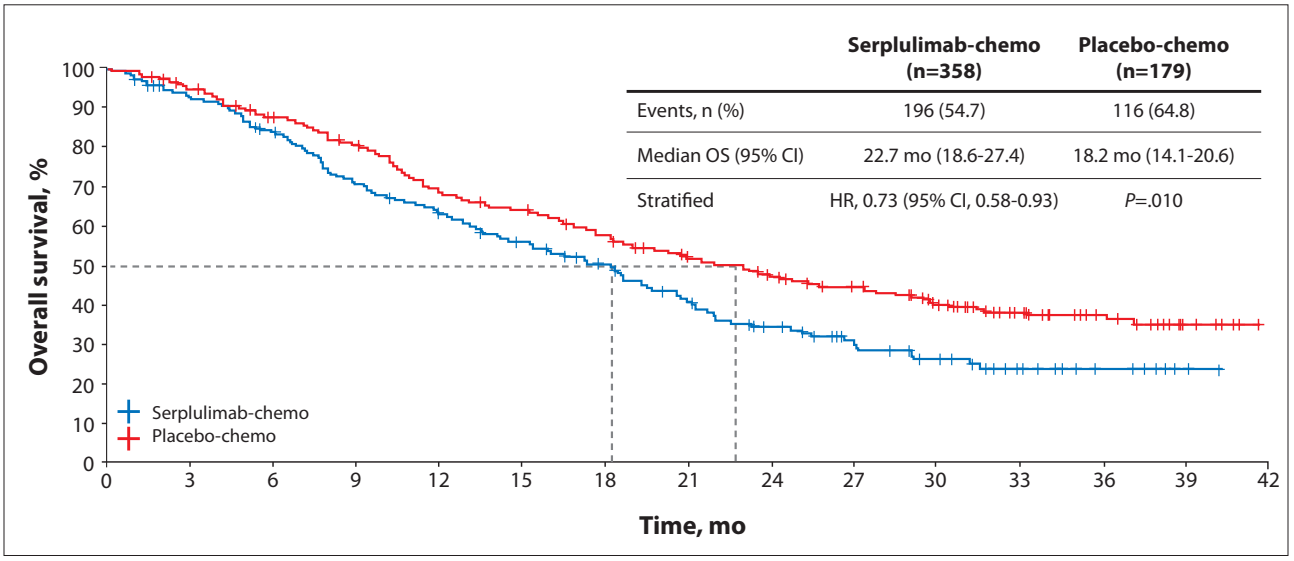

Figure 4. The OS of serplulimab plus chemotherapy for patients with squamous NSCLC from the ASTRUM-004 trial.
Chemo, chemotherapy; HR, hazard ratio; mo, months; NSCLC, non–small cell lung cancer; OS, overall survival. Adapted from Zhou et al. Abstract OA09.05. Presented at: IASLC 2023 WCLC; September 9-12, 2023; Singapore.[3]

endpoint, demonstrating a median PFS of 8.3 months with serplulimab plus chemotherapy vs 5.7 months with placebo plus chemotherapy (HR, 0.55; 95% CI, 0.43-0.69; *P*<.001). A consistent benefit was observed with serplulimab vs placebo in most subgroups in prespecified subgroup analysis. In addition, the trial showed a significant improvement in median OS with serplulimab plus chemotherapy vs the placebo control regimen (22.7 vs 18.2 months; HR, 0.73; 95% CI, 0.58-0.93; *P*=.010) (Figure 4). The median DOR was also better with the novel anti-PD-1 antibody than with placebo (11.1 vs 5.5 months; HR, 0.45; 95% CI, 0.32-0.65). Treatment with the serplulimab combination was generally well tolerated. In the serplulimab vs the placebo arm, rates of treatment-related serious AEs were 33% vs 27%; rates of treatment-related AEs leading to death were 1.1% vs 2.8%; and rates of treatment-related AEs of grade 3 or higher were 36% vs 32%, respectively.

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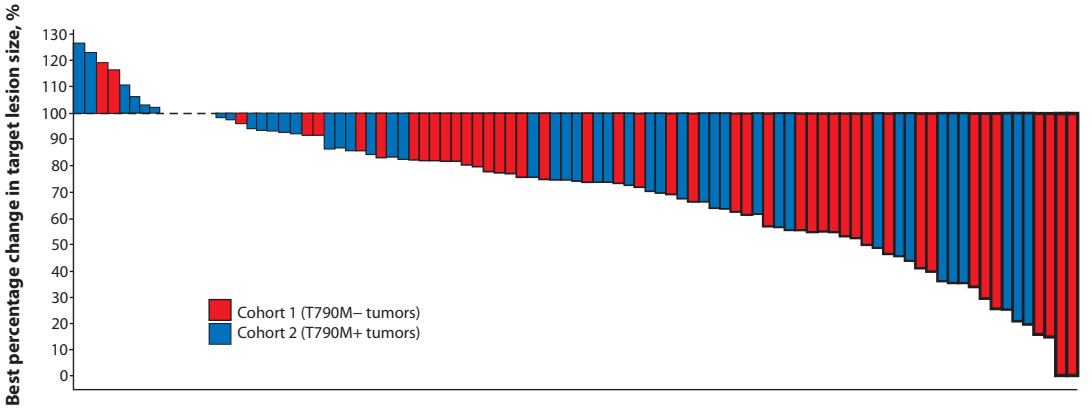
ILLUMINATE: Efficacy and Safety of Durvalumab/Tremelimumab and Chemotherapy in *EGFR*-Mutant NSCLC Following Progression on EGFR Inhibitors

Despite advances in TKI therapy for the treatment of *EGFR*-mutated NSCLC, the development of treatment resistance and disease progression are nearly universal, and the need for more effective second-line therapies is ongoing.[1] Durvalumab and tremelimumab are 2 immune-checkpoint inhibitors that bind to PD-L1 and CTLA4, respectively. A noncomparative, 2-cohort, phase 2 study evaluated the safety and efficacy of durvalumab and tremelimumab combined with pemetrexed plus carboplatin in patients with *EGFR*-mutated NSCLC whose disease had progressed on therapy with an EGFR TKI.[2] On the basis of the absence (cohort 1) or presence (cohort 2) of a T790M mutation, assessed by testing of tumor tissue and plasma, 100 patients



		Cohort 1 (T790M– tumors)	Cohort 2 (T790M+ tumors)
Confirmed ORR	n/N	15/48	10/48
	%	31 (95% CI, 20-45)	21 (95% CI, 12-34)
Unconfirmed ORR	n/N	20/48	17/48
	%	42 (95% CI, 29-56)	35 (95% CI, 23-50)

Figure 5. The ORR for patients with metastatic EGFR-mutant NSCLC from the ILLUMINATE trial. EGFR, epidermal growth factor receptor gene; NSCLC, non–small cell lung cancer; ORR, objective response rate. Adapted from Lee et al. Abstract OA09.04. Presented at: IASLC 2023 WCLC; September 9-12, 2023; Singapore.[2]

were evenly enrolled in the 2 cohorts. Patients in both cohorts received durvalumab (1500 mg), tremelimumab (75 mg), cisplatin (75 mg/m^2), and pemetrexed (500 mg/m^2) every 3 weeks for 4 cycles. Maintenance therapy consisted of durvalumab plus pemetrexed until disease progression, lack of tolerability, patient withdrawal, or death. The primary endpoint was ORR.

Patients had a median age of 64 years (range, 32-77), 64% were female, 77% were Asian, and 27% were current or former smokers. Genomic abnormalities included *EGFR* exon 19 deletion (57%) and L858R mutation (42%). PD-L1 status was 49% or less in 47% and 50% or greater in 12% of patients; 50% of patients had received more than 1 prior line of therapy. Among patients without a T790M mutation (cohort 1), the confirmed ORR was 31% (95% CI, 20%-45%). Among patients with a T790M mutation, the confirmed ORR was 21% (95% CI, 12%-34%) (Figure 5). The median PFS in cohort 1 was 6.5 months, and that in cohort 2 was 4.9 months. Analysis of the patients in cohort 1 by PD-L1 status indicated a significantly better median PFS among those with a level of PD-L1 expression of 50% or greater than among those whose level of PD-L1 expression was less than 50% (13.1 vs 4.8 months; *P*=.0044). Only 2 patients in cohort 2 had a level of PD-L1 expression level of less than 50%, and the median PFS for a high level of PD-L1 expression was not significantly different from that for a low level of PD-L1 expression (*P*=.26). The novel therapeutic combination was generally well tolerated, with no treatment-emergent fatal AEs. Rates of immune-related grade 3/4 AEs were similar in the 2 cohorts. Grade 3/4 immune-related AEs included colitis (8%), hepatitis (4%), adrenal insufficiency (2%), and pneumonitis (1%).

ABSTRACT SUMMARY: TROPION-Lung08: Datopotamab Deruxtecan Plus Pembrolizumab in Untreated Advanced/Metastatic Non–Small Cell Lung Cancer (NSCLC)

Datopotamab deruxtecan is an ADC comprising a humanized anti-Trop2 antibody and a topoisomerase I inhibitor payload (Abstract P2.08-01). The global, open-label, active-controlled, randomized, phase 3 TROPION-Lung08 trial will evaluate the ADC plus pembrolizumab vs pembrolizumab alone as first-line therapy in patients with advanced or metastatic NSCLC. Study participants must have stage IIIB or IIIC NSCLC that is ineligible for curative therapy or stage IV disease and no prior therapy for metastatic disease. Key eligibility requirements include lack of actionable genomic alterations and a level of PD-L1 expression of 50% or greater as determined by central testing. The trial has a targeted enrollment of 720 patients. The primary endpoints are PFS and OS.

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Neoadjuvant Durvalumab + Chemotherapy Followed by Adjuvant Durvalumab in Resectable *EGFR*-Mutated NSCLC (AEGEAN)

The double-blind, placebo-controlled, phase 3 AEGEAN study evaluated neoadjuvant durvalumab plus chemotherapy followed by surgery and adjuvant durvalumab for patients with resectable NSCLC.[1] The study demonstrated a superior event-free survival (EFS) rate for durvalumab vs placebo among patients whose disease lacked *EGFR* or *ALK* aberration (not reached vs 25.9 months; HR, 0.68; 95% CI, 0.53-0.88; *P*=.003902). However, the study was designed and initiated before it was found that tumors with *EGFR* or *ALK* aberrations might respond minimally to immunotherapy.[2] The study protocol was therefore amended to exclude patients with *EGFR*-mutated disease. A subsequent analysis evaluated outcomes in 51 patients with *EGFR* mutation who were enrolled in the AEGEAN study before protocol amendment.[3]

The AEGEAN study enrolled patients with treatment-naive stages IIA through IIIB NSCLC that was resectable per recommendations by the American Joint Committee on Cancer.[4] The planned surgery was lobectomy, sleeve resection, or bilobectomy, and PD-L1 status was obtained before enrollment. Before 1:1 randomization, patients were stratified by disease stage and level of PD-L1 expression. Patients in the experimental arm received durvalumab (1500 mg) plus platinum-based chemotherapy every 3 weeks for 4 cycles, followed by surgery and then durvalumab (1500 mg) every 4 weeks for 12 cycles. Patients in the control arm received the same treatment but with placebo in place of durvalumab. The primary endpoints were the pathologic complete response (CR) rate, determined by central

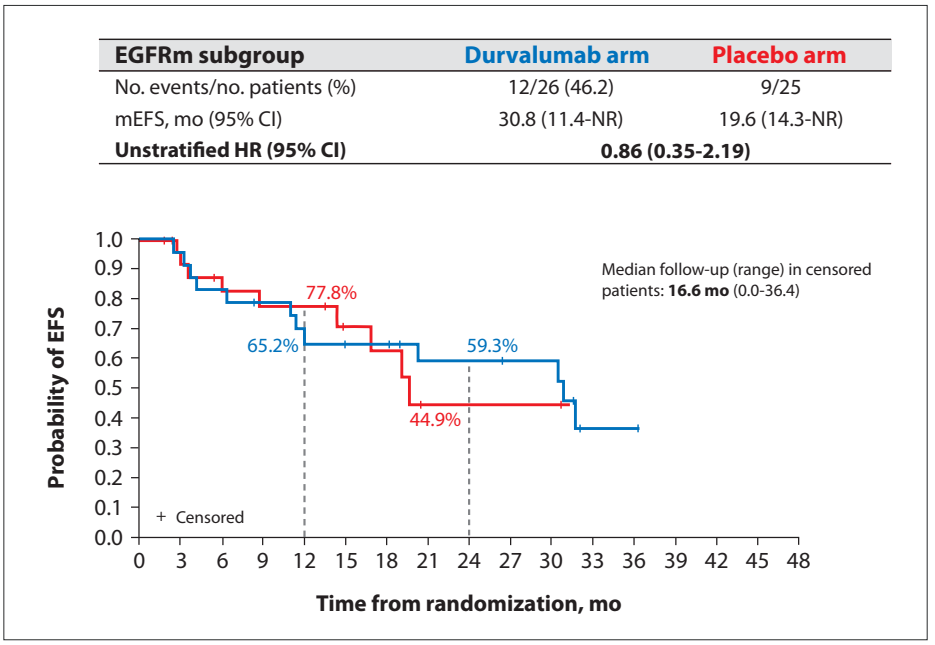

Figure 6. The EFS for patients with EGFRm NSCLC by BICR using RECIST v1.1 from the AEGEAN trial.
BICR, Blinded Independent Central Review; EGFRm, epidermal growth factor receptor gene mutation; HR, hazard ratio; mEFS, median event-free survival; mo, months; No., number; NSCLC, non–small cell lung cancer.
Adapted from He et al. Abstract OA12.06. Presented at: IASLC 2023 WCLC; September 9-12, 2023; Singapore.[3]

laboratory analysis, and the EFS rate, determined by blinded independent review.

Among 802 randomized patients, 51 had an *EGFR* mutation; of these, 26 were in the durvalumab arm and 25 in the placebo arm. Some imbalances in baseline characteristics were observed. *EGFR* mutations in the durvalumab vs the placebo arm included exon 19 deletion (53.8% vs 36.0%), L858R mutation (11.5% vs 16.0%), other (3.8% vs 24.0%), and not specified (30.8% vs 28.0%). Fewer patients in the durvalumab arm had cisplatin as the planned platinum agent (23.1% vs 36.0%). In the durvalumab arm, 85% of patients completed 4 cycles of durvalumab, 85% underwent resection, and 100% of the resections were rated R0 (19/19). In the placebo arm, 88% of patients completed 4 cycles of placebo, 88% underwent surgery, and 90% of resections were rated R0 (18/20). Among the 51 patients with *EGFR* mutation, the median EFS was 30.8 months with durvalumab vs 19.6 months with placebo (unstratified HR, 0.86; 95% CI, 0.35-2.19) (Figure 6), and the pathologic CR rate was 3.8% vs 0% (difference, 3.8%; 95% CI, –10.0% to 19.1%). No new safety signals emerged.

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IMpower151: Phase 3 Study of Atezolizumab + Bevacizumab + Chemotherapy in 1L Metastatic Nonsquamous NSCLC

The phase 3 IMpower150 study demonstrated a significant improvement in survival endpoints with atezolizumab vs placebo in combination with bevacizumab, carboplatin, and paclitaxel in patients with metastatic nonsquamous NSCLC.[1,2] In 2020, the phase 3 IMpower151 study compared the same 2 drug regimens in a similar patient population to address regional differences in *EGFR* mutation rates and differences in clinical practice (eg, the use of pemetrexed).[3] Patients enrolled in the IMpower151 study had stage IV nonsquamous NSCLC and had not received chemotherapy for their metastatic disease. Patients with sensitizing alterations in *EGFR* or *ALK* were permitted, and the proportion of patients with a wild-type *EGFR* gene was limited to 50% of the total study population. Patients with a sensitizing alteration in *EGFR* or *ALK* were required to have had disease pro-

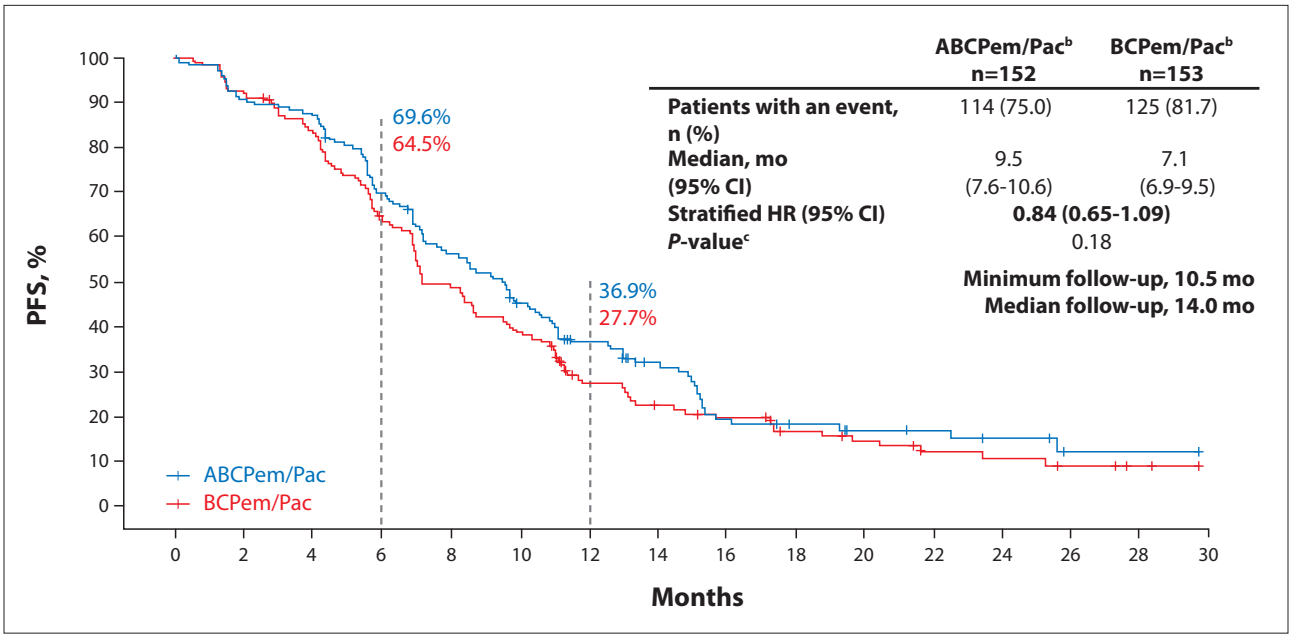

Figure 7. The INV-PFS from the ITT population of patients with metastatic nonsquamous NSCLC from the IMpower151 study.
[a]IRF-PFS (HR, 0.88) was consistent with INV-PFS.
[b]In the ABCPem/Pac arm, 98% of patients received Pem; in the BCPem/Pac arm, 97% of patients received Pem.
[c]Stratified log-rank.
INV, investigator; IRF, independent review facility; ITT, intention-to-treat; NSCLC, non–small cell lung cancer; PFS, progression-free survival. Adapted from Zhou et al. Abstract OA09.06. Presented at: IASLC 2023 WCLC; September 9-12, 2023; Singapore.[3]

gression after therapy with at least one TKI. After stratification by *EGFR/ALK* status and level of PD-L1 expression, study participants were evenly randomized into the 2 arms. Patients in arm A received induction therapy with atezolizumab (1200 mg), bevacizumab (15 mg/kg), and carboplatin (AUC, 6) plus either pemetrexed (500 mg/m^2) or paclitaxel (175 mg/m^2). Patients in arm B received placebo in place of atezolizumab. After 4 cycles of induction, patients received atezolizumab (arm A) or placebo (arm B) plus bevacizumab and pemetrexed as maintenance therapy. The primary endpoint was investigator-assessed PFS in the intention-to-treat population.

The study included 152 patients in arm A and 153 in arm B. Patients had a median age of 61 years (range, 30-76), 59% were male, and 49% to 54% were never-smokers. A level of PD-L1 expression of less than 50% was noted in 70% of patients. Rates of metastasis were similar in the 2 arms (liver, 11%; brain, 9%-13%; bone, 49%-51%), and 46% to 47% of patients in each arm had wild-type *EGFR* and *ALK*. Fifty-three percent of patients in arm A and 47% in arm B had received 2 or more prior lines of TKI therapy. The trial did not meet its primary endpoint, although numerical improvements were observed in PFS for arm A vs arm B (median PFS, 9.5 vs 7.1) (Figure 7). Among patients with a sensitizing *EGFR* mutation or *ALK* alteration, the median PFS was 8.5 months with the atezolizumab combination vs 8.3 months with placebo (HR, 0.86; 95% CI, 0.61-1.21).

ABSTRACT SUMMARY: Phase I/II Study of Rucaparib and Pembrolizumab Maintenance in Stage IV NSCLC After Carboplatin, Pemetrexed, and Pembrolizumab

A single-arm, multicenter, investigator-initiated, phase 1/2 trial evaluated maintenance therapy with a poly(ADP-ribose) polymerase (PARP) inhibitor plus pembrolizumab for patients with stage IV nonsquamous NSCLC (Abstract P2.06-08). The study enrolled 25 patients with treatment-naive disease, who received 4 cycles of induction therapy with carboplatin, pemetrexed, and pembrolizumab. The 14 patients who did not experience disease progression continued to maintenance therapy with rucaparib plus pembrolizumab. The study was terminated early for economic reasons. The median PFS from the time of enrollment was 11.4 months, and the median OS was 37.6 months. The ORR was 64%, including 1 CR and 8 PRs. The 2-drug combination showed a manageable safety profile.

Among patients with wild-type *EGFR* and *ALK*, the median PFS was 10.4 months with the atezolizumab combination vs 7.0 months with placebo (HR, 0.81; 95% CI, 0.55-1.19). The atezolizumab combination regimen was generally well tolerated.

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First-Line Chemotherapy With or Without Tislelizumab for Extensive-Stage Small Cell Lung Cancer: RATIONALE-312 Phase 3 Study

Tislelizumab is a monoclonal antibody that binds with high affinity and specificity to PD-1.[1] In a phase 2 study, the antibody in combination with chemotherapy showed promising efficacy in patients with untreated ES-SCLC.[2,3] The multicenter, phase 3 RATIONALE-312 study investigated the safety and efficacy of tislelizumab vs placebo combined with etoposide plus platinum for patients with previously untreated ES-SCLC in China.[4] After stratification by PS, platinum agent, and brain metastasis status, patients were evenly randomized into arm 1 or arm 2. Patients in arm 1 received tislelizumab (200 mg, day 1), and patients in arm 2 received matching placebo. All patients also received carboplatin (AUC, 5) or cisplatin (75 mg/m^2) on day 1 of each cycle, plus etoposide (100 mg/m^2, days 1-3). Induction therapy was administered in 21-day cycles for 4 cycles. Patients received tislelizumab (arm 1) or placebo (arm 2) for maintenance therapy until disease progression or intolerable toxicity. The primary endpoint was OS.

The RATIONALE-312 trial randomized 227 patients into arm 1 and 230 into arm 2. Patients had a median age of 62.5 years (range, 31-78), 35% to 39% were male, and 23% to 26% were never-smokers. Liver metastasis was noted in 28% of patients in arm 1 and 26% in arm 2, and the proportions of patients with 3 or more metastatic sites were 81% vs 71%, respectively. Most patients in both arms received carboplatin as the platinum-containing agent (78%-79%). The trial met its primary endpoint. The median OS was 15.5 months with the tislelizumab combination vs 13.5 months with the placebo combination (HR, 0.75; 95% CI, 0.61-0.92; *P*=.0035) (Figure 8). Tislelizumab yielded a significantly better OS in comparison with placebo in subgroups based on current or past smoking, presence or absence of liver metastasis at baseline, stage IV disease, and other factors. The median PFS was also significantly longer with the

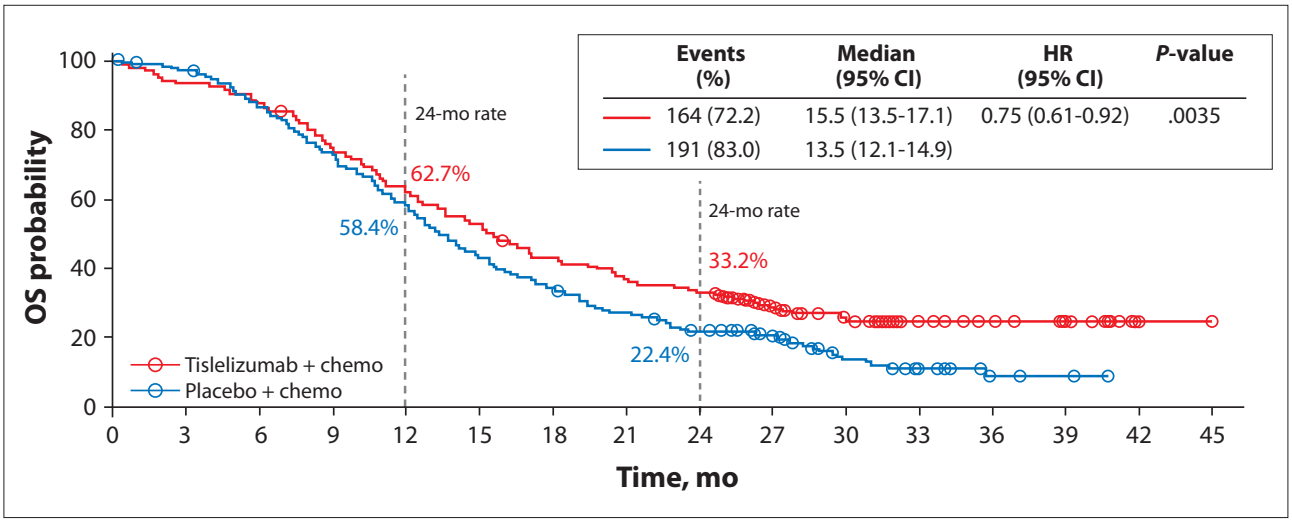

Figure 8. The OS of patients with extensive-stage SCLC from the RATIONALE-312 study.
HR, hazard ratio; mo, months; OS, overall survival; SCLC, small cell lung cancer. Adapted from Cheng et al. Abstract OA01.06. Presented at: IASLC 2023 WCLC; September 9-12, 2023; Singapore.[3]

tislelizumab combination than with placebo (4.8 vs 4.3 months; HR, 0.63; 95% CI, 0.51-0.78; *P*<.0001). AEs that were more frequent in arm 1 than arm 2 included treatment-emergent AEs leading to discontinuation (13% vs 3%), treatment-emergent AEs leading to death (6% vs 2%), and immune-mediated AEs leading to death (0.4% vs 0.0%).

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Highlights In Non–Small Cell Lung Cancer From the IASLC 2023 World Conference on Lung Cancer: Commentary

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The IASLC 2023 World Conference on Lung Cancer (WCLC), hosted by the International Association for the Study of Lung Cancer, was held in Singapore this October. The meeting highlighted the most advanced treatments, clinical trials, and studies in the field of lung cancer and thoracic oncology.

Sacituzumab Govitecan

Antibody-drug conjugates (ADCs) like sacituzumab govitecan have generated a great deal of enthusiasm.[1] With any new drug, a significant push is made—at least by the makers of the drug—to get it into the first-line treatment paradigm. Ongoing studies are comparing sacituzumab govitecan vs docetaxel in previously treated patients with metastatic non–small cell lung cancer (NSCLC). However, if this agent is to be used in front-line treatment, it will likely need to be combined with an immune-checkpoint inhibitor.

In the phase 2 EVOKE-02 study, which was one cohort of a multicohort study, the goal was to evaluate the safety and efficacy of adding sacituzumab govitecan to pembrolizumab, an immune-checkpoint inhibitor.[2] The safety profile seemed reasonable, but interpreting efficacy in a small population is challenging. We know that sacituzumab govitecan is a potentially effective drug, and that the immune-checkpoint inhibitor also has the potential for efficacy. This begs the question: is this combination something that we would want to incorporate into our treatment paradigms? Particularly in that we know it is already possible to give chemotherapy plus an immune-checkpoint inhibitor, as regimens with platinum-based chemotherapy are currently available. This study shows that it is generally feasible to combine sacituzumab govitecan with pembrolizumab. However, for approval of this approach, we will need randomized trials. For usage, we would need both regulatory approval and data to suggest that it is superior to standard chemotherapy plus pembrolizumab, in regard to either efficacy or toxicity.

Osimertinib

The phase 3 FLAURA2 trial provides one of the 2 truly clinically actionable results from the meeting.[3] Although the result may not be clinically actionable immediately, practitioners will have this option available assuming that regulatory approval is granted.

In this study, patients with untreated, locally advanced or metastatic, epidermal growth factor receptor (*EGRF)*-mutated NSCLC were randomized to receive single-agent osimertinib, which is a current common practice, or osimertinib plus chemotherapy.[4] The results showed that progression-free survival (PFS) was longer when chemotherapy was added to osimertinib.[3] The analysis for overall survival (OS) is preliminary because the number of events is not yet sufficient.

The key takeaway is that, on regulatory approval, the addition of chemotherapy to osimertinib will be an available option. Practitioners will have a choice between osimertinib alone or osimertinib plus chemo-

therapy. It is important to note that the addition of chemotherapy clearly improves PFS. To date, we do not have enough data to indicate if there will be a survival benefit, and the current data are not particularly convincing. However, practitioners will need to decide whether the potential benefits are sufficient to warrant the additional toxicity associated with chemotherapy. One significant question will be whether any specific subsets of patients will benefit the most from the addition. The most obvious group would be those with a *TP53* mutation, a group known to have less-favorable outcomes with single-agent osimertinib. To date, we have not seen data that differentiate on the basis of biomarkers. Hence, it is challenging to determine if the benefits were more pronounced in those with biomarkers indicating poorer outcomes with single-agent osimertinib.

Pleurectomy Decortication

In my opinion, MARS 2 is the pivotal abstract presented at the conference.[5] The data surrounding surgery for mesothelioma have never been of particularly high quality.[6] We have seen good outcomes in patients who have undergone surgery. However, is it possible the reason these patients have good outcomes is that they are clinically in better shape? The question has been whether the surgery itself added to the outcome.

Historically, very aggressive surgical approaches, including extrapleural pneumonectomy, have been used.[7] However, in a prior study, outcomes with a more limited surgical approach were superior in comparison with a more aggressive one.[8] Building on that finding, this large, randomized trial compared medical therapy alone (simply chemotherapy) vs the same approach but with surgery included as part of the regimen.[5] The results showed that patients who underwent surgery had inferior outcomes. The *P*-value was .03 in favor of the no-surgery group. Over the course of the study, patients who underwent surgery were likely to die sooner.

From my perspective, this finding was immediately practice-changing. No high-quality data in favor of surgery have been reported, and we now possess high-quality data against surgery in this context. The key message here is that surgery for mesothelioma should be considered only in the context of clinical trials. It should not be part of standard practice, and at this point, no cases of mesothelioma should be considered "resectable" without further substantiating data.

Anlotinib

The randomized, phase 3 ETER701 trial for patients with small cell lung cancer (SCLC) is more relevant to a Chinese audience; its applicability in the United States is limited.[9] Anlotinib is a small molecule with antiangiogenic properties that has been widely studied in China and is available there.[10] This study, which evenly divided patients with previously untreated, advanced SCLC into 3 arms to receive anlotinib with or without benmelstobart, is one of several studies emerging from China that are essentially using an outdated control arm.[9]

In the United States, the current standard practice, which is chemotherapy plus a programmed death ligand 1 (PD-L1) inhibitor such as durvalumab or atezolizumab, would be an appropriate comparator. We are now seeing several studies similar to this. A major question on this study is, does it make us rethink the role of antiangiogenesis in SCLC? My personal bias is that the data from these drugs are not going to be used in the United States because support for that is not sufficient at this time. Nevertheless, it is intriguing for further studies on the roles of antiangiogenesis in a time of evolving treatment paradigms for extensive-stage SCLC.

The implications from this study suggest that there is something significant about the addition of the antiangiogenic, prompting us to question whether this avenue should be reexplored in the era of immunotherapy. That said, interpreting the data was somewhat challenging because this was a 3-arm study. One arm did not receive benmelstobart, but the results for that arm of the study were not reported, making it difficult to determine the role of anlotinib in the results. Therefore, although the findings are intriguing, the analysis of this study is essentially hindered by our inability to access data on one-third of the study population at the time of the presentation.

Serplulimab

The ASTRUM-004 study is looking at patients with squamous NSCLC.[11] This is a setting in which we already have approved chemoimmunotherapy

ABSTRACT SUMMARY: FURVENT, Phase 3 Trial Testing Furmonertinib vs Chemotherapy as First-Line Treatment for Advanced NSCLC With *EGFR* Exon 20 Insertions

Furmonertinib is a third-generation EGFR TKI that crosses the blood-brain barrier (Abstract P2.09-18). The open-label, multicenter, phase 3 FURVENT trial is currently enrolling patients with treatment-naive NSCLC to evaluate 2 dose levels of furmonertinib vs standard platinum-based chemotherapy. Approximately 375 patients will be evenly randomized into 3 arms. Therapy will consist of furmonertinib (160 mg, daily) or furmonertinib (240 mg, daily) or pemetrexed combined with cisplatin or carboplatin. Eligible patients must have an *EGFR* exon 20 insertion mutation and measurable disease. The primary endpoint is PFS.

approaches that are widely used in the United States.[12] The study demonstrated impressive results. In China, given the push for drug development by companies there, I believe this study will influence usage, at least within China.[11] In some ways, it is validating something that we have already recognized, which is that outcomes are likely to improve when patients receive an immune-checkpoint inhibitor in the front-line setting. One reason that these data are important is that they assist in the evaluation of chemoimmunotherapy approaches using a PD-(L)1 inhibitor vs approaches using a PD-(L)1 inhibitor plus a cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) inhibitor. Some have suggested that these patients do particularly well with nivolumab and ipilimumab, and less well with chemotherapy and pembrolizumab. However, the data with chemotherapy plus durvalumab and tremelimumab are less convincing. The data from ASTRUM-004 can help us assess the role of chemotherapy plus a PD-1 inhibitor in squamous cell disease.

Durvalumab

The ILLUMINATE trial contributes to a body of literature that essentially argues that we have not been successful in determining how to incorporate immune-checkpoint inhibitors effectively in the treatment of patients with *EGFR* mutations.[13] This trial explores aggressive immunotherapy approaches and, once again, has not convincingly shown a benefit in this population. The take-home message here is that intensifying immunotherapy and applying it alongside chemotherapy for patients with *EGFR* mutations is not a validated approach. It is not for lack of investigation. These approaches have been thoroughly investigated, and frankly, they have not shown much promise.

The AEGEAN study has been presented before, showing a benefit to neoadjuvant and adjuvant durvalumab.[14] The presentation by Dr Harpole and colleagues focused on a group of patients with resectable NSCLC who had targetable *EGFR* mutations.[15] They were eventually excluded from the protocol, meaning that although they were enrolled up to a point, their enrollment stopped, and they were not part of the intent-to-treat analysis. This was done to provide full disclosure regarding that population, and again it demonstrated that *EGFR* mutation–positive patients are a unique population when it comes to immune-checkpoint inhibitors and, unfortunately, one that does not derive the same benefit. These are a group of patients for whom we have recently seen a survival advantage with the incorporation of osimertinib in this setting. Although a skeptic could argue that this analysis was designed to show that from one drug maker's portfolio, rather than using one product (durvalumab), you should use another (osimertinib) in this setting, I think that would be overly negative. It does appear that the data for osimertinib are compelling, whereas the data for durvalumab in this setting are not particularly compelling.

ABSTRACT SUMMARY: Cemiplimab-Based Treatment in Advanced NSCLC With Liver Metastases: Updated Analysis From EMPOWER-Lung 1 and EMPOWER-Lung 3

An exploratory analysis evaluated longer-term outcomes in patients from the EMPOWER-Lung1 and EMPOWER-Lung3 trials (Abstract P2.06-01). Both trials evaluated cemiplimab, an anti-PD-1 antibody, with or without chemotherapy in patients with advanced NSCLC. Among 95 patients with liver metastasis in EMPOWER-Lung1, the median OS was 20.4 months with cemiplimab vs 7.6 with chemotherapy (HR, 0.526; 95% CI, 0.312-0.886). Among 70 patients with liver metastasis from part 2 of the EMPOWER-Lung3 trial, the median OS was 15.5 months with cemiplimab plus chemotherapy vs 8.9 months with placebo plus chemotherapy (HR, 0.649; 95% CI, 0.350-1.203).

EGFR Mutations

What is particularly important about the phase 3 IMpower151 study is that approximately half of the patients had *EGFR* mutations.[16] IMpower150, which had a similar design and was a global study, included a small population of patients with *EGFR* mutations. This group seemed to benefit from a 4-drug regimen of carboplatin, paclitaxel, bevacizumab, and atezolizumab.[17] In IMpower151, they are examining the same concept of chemoimmunotherapy, but with a larger number of patients who have *EGFR* mutations.[16] The benefit was harder to establish convincingly, which highlights a recurring theme at this meeting—the incorporation of immune-checkpoint inhibitors for patients with *EGFR* mutations remains a challenge. One caveat is that although paclitaxel was mandated as part of the IMpower 150 trial, most of the patients in this trial received pemetrexed rather than paclitaxel, and that difference cannot be ruled out as a contributor to the disparate results.

Tislelizumab

The RATIONALE-312 phase 3 study confirmed the role of tislelizumab, an immune-checkpoint inhibitor, plus chemotherapy in the front-line setting for extensive-stage SCLC.[18] However, it uses a somewhat outdated comparator group. One thing to note, especially with Western drugs, is that none of the programmed death 1 (PD-1) inhibitors have shown a statistically significant endpoint in OS. Part of the prior failures of PD-1 inhibitors in this setting is likely strategic, in the sense that the results—for instance, when

pembrolizumab was evaluated in this setting— were quite good, similar to what we have seen with durvalumab and atezolizumab, but because of the statistical design, they did not meet the threshold for statistical significance. Nivolumab was not directly evaluated in this setting in a randomized trial, so its role is difficult to determine. So, although some data for a PD-1 inhibitor in this context are now available, I believe any effect in the United States is unlikely.

Disclosure

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