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ECOG-ACRIN EA5181: Phase 3 Trial of Concurrent and Consolidative Durvalumab vs Consolidation Durvalumab Alone for Unresectable Stage III NSCLC---ABSTRACT #1428

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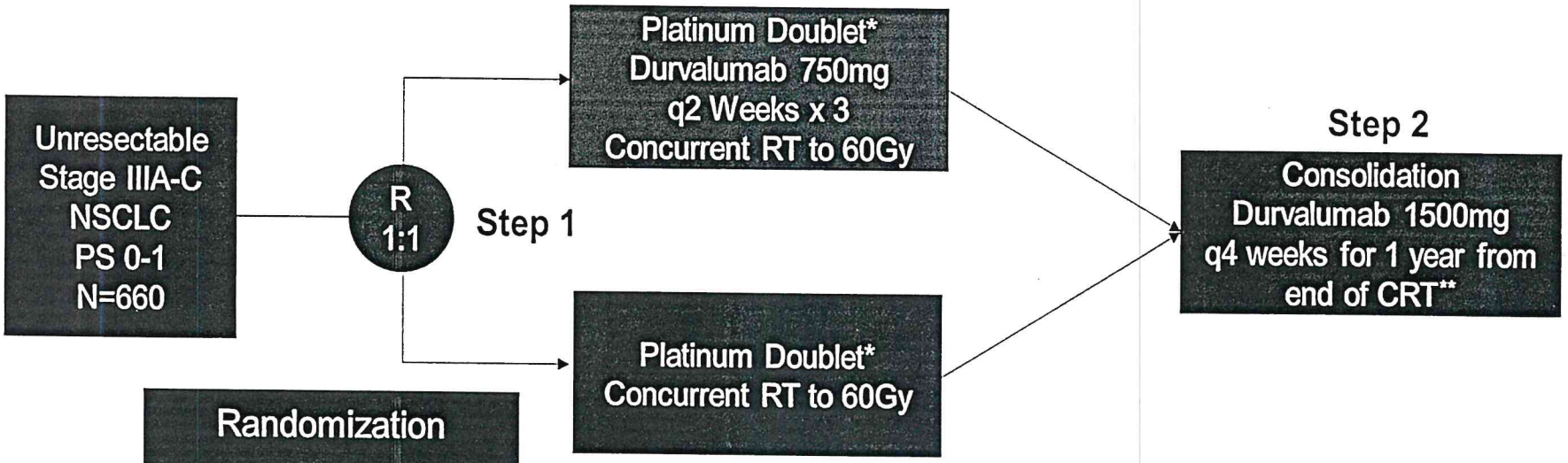
EA5181 Schema



*Investigator choice

Cisplatin 50 mg/m2 D1, 8, 29, 36; etoposide 50 mg/m2 D1-5, 29-33

Cisplatin 75 mg/m2 D1, 22; pemetrexed 500 mg/m2 D1, 22 (nonsquamous only)

Carboplatin AUC 2 D1, 8, 15, 22, 29, 36; paclitaxel 45 mg/m2 D1, 8, 15, 22, 29, 36

**Starting within 14 days of CRT unless toxicity has not resolved to ≤ grade 2, but not later than 45 days post-CRT

Primary endpoint – OS intention to treat population; 25% reduction in OS HR

Secondary endpoint –PFS, toxicity, ORRs, and Recurrence patterns

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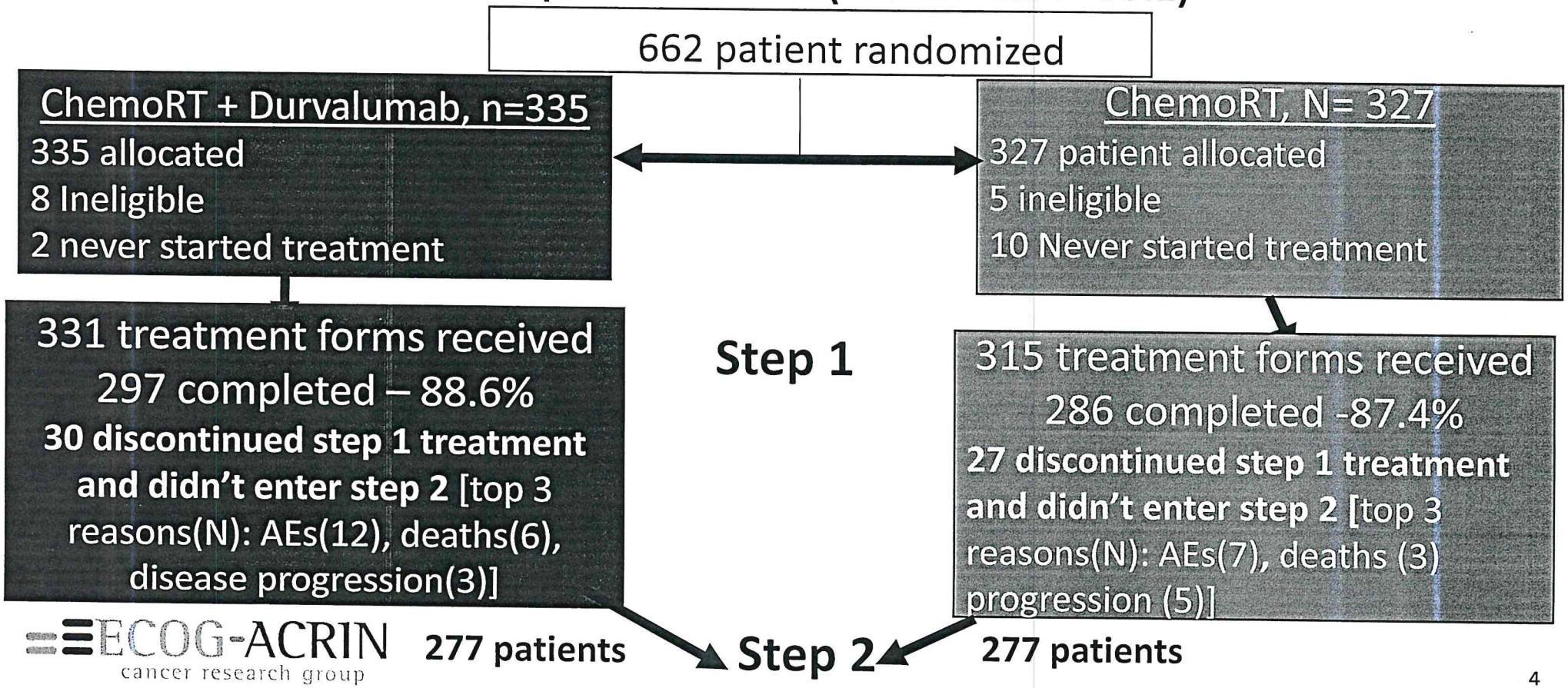
EA5181 Baseline Demographics

	ChemoRT/IO, N= 335	ChemoRT, N= 327	TOTAL
SEX- MALE	60.6%	60.6%	**60.6%**
AGE –Median(range)	67.4(37.6-86.7)	66.82(39.1-89.4)	**67.1(37.6-89.4)**
RACE			
White	85.7%	91.1%	**88.4%**
Black	10.1%	6.4%	**8.3%**
STAGE			
IIIA	166 (49.6%)	169 (51.7%)	335 (50.6%)
IIIB	141 (42.1%)	134 (41.0%)	275 (41.5%)
IIIC	26 (7.8%)	22 (6.7%)	48 (7.3%)
HISTOLOGY			
Adenocarcinoma	159 (47.3%)	164 (50.2%)	**323 (48.7%)**
Squamous Cell ca	133 (39.6%)	121 (37.0%)	254 (38.3%)
SMOKING			
Current	128 (38.2%)	136 (41.6%)	264 (39.9%)
Former	185 (55.2%)	168 (51.4%)	353 (53.3%)
Never	22 (6.6%)	23 (7.0%)	**45 (6.8%)**
CHEMOTHERAPY			
Carboplatin/paclitaxel	82.4%	82.5%	**82.5%**

EA5181-Treatment Disposition

Median follow-up: 29.9 months (95% CI: 28.4 - 33.1)



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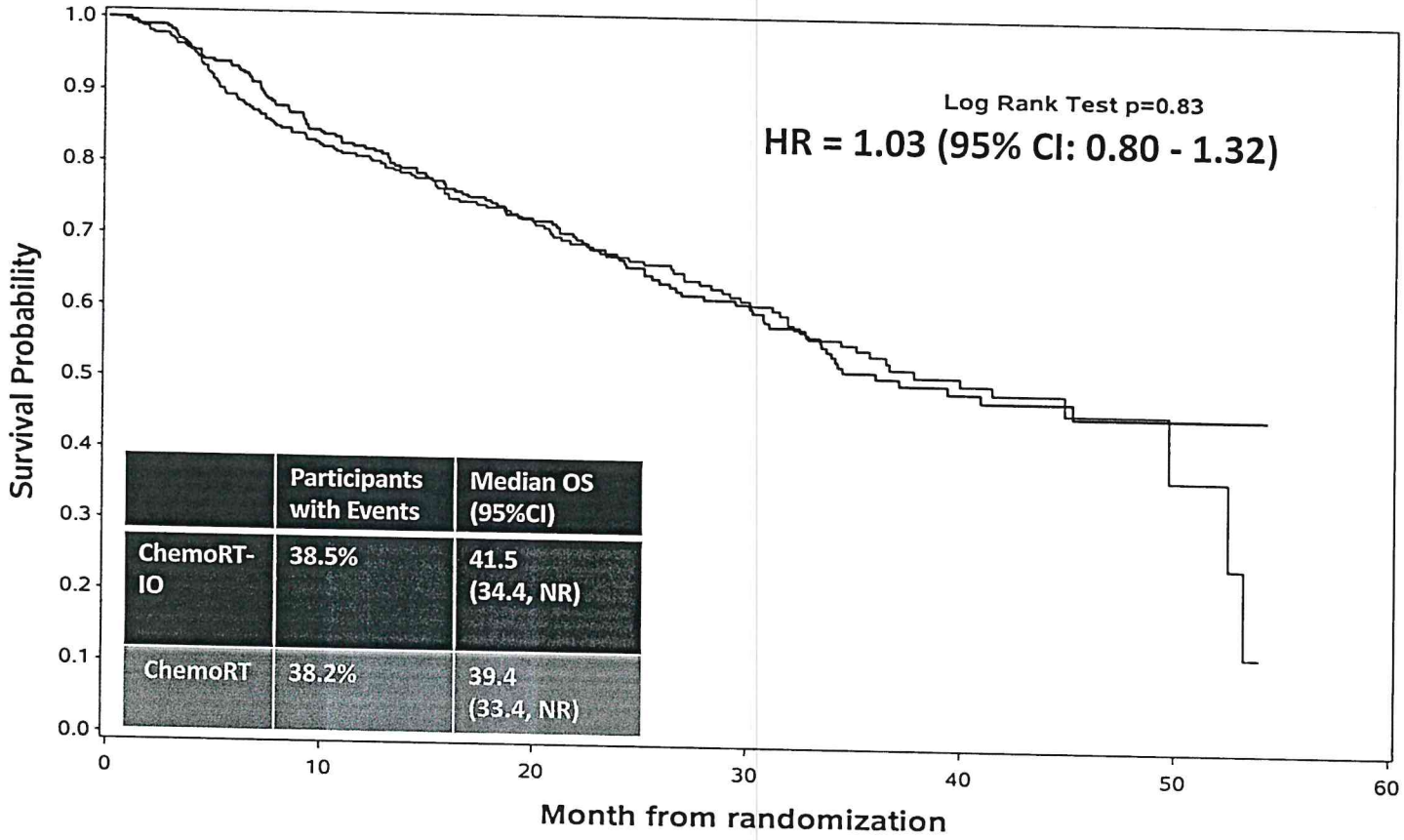
EA5181: Overall Survival



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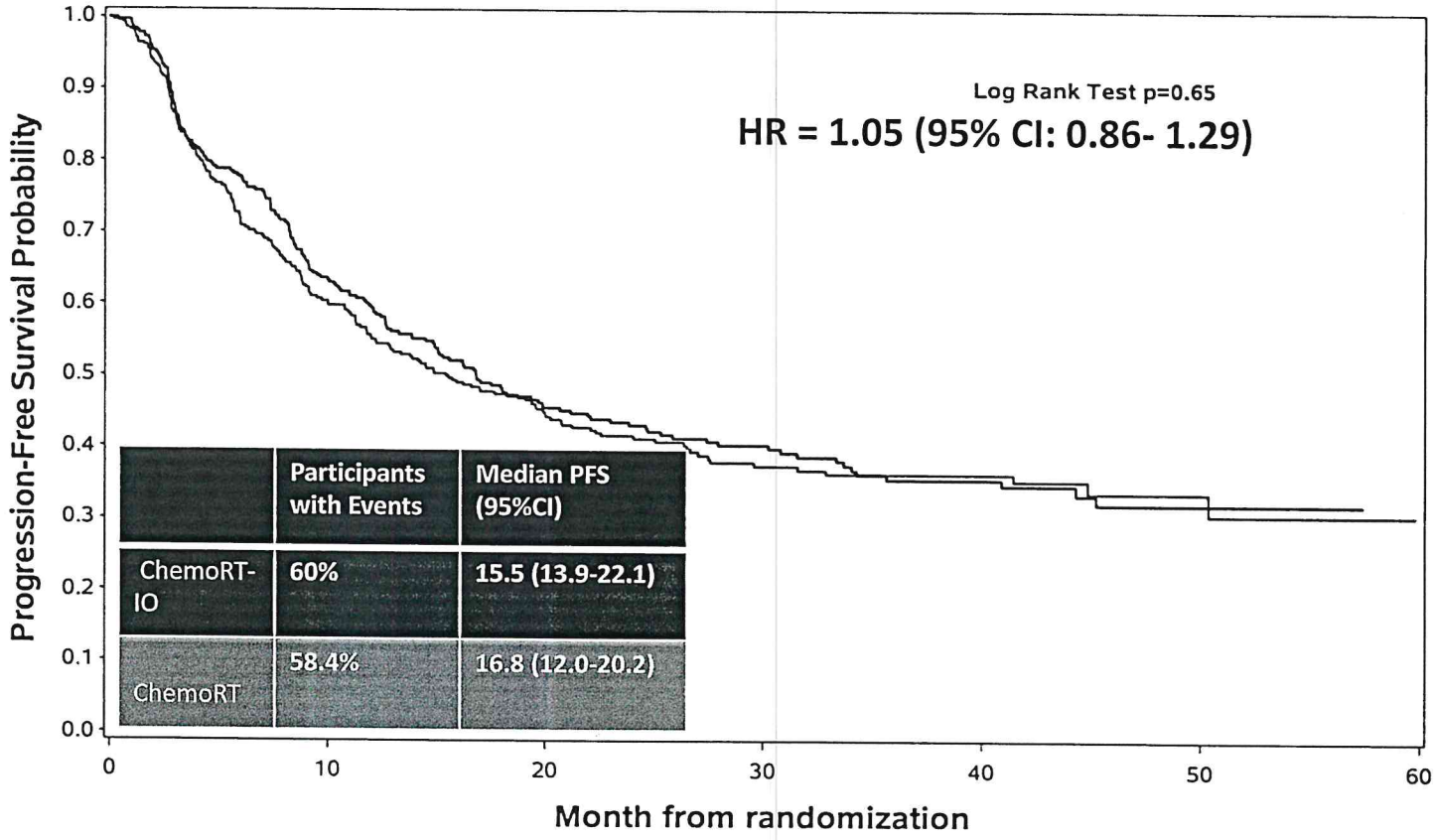
trtm_name	TOTAL	DEATH	CNSR	MEDIAN
ChemoRT	327	125	202	39.4
ChemoRT-IO	335	129	206	41.5

EA5181: Progression-free Survival



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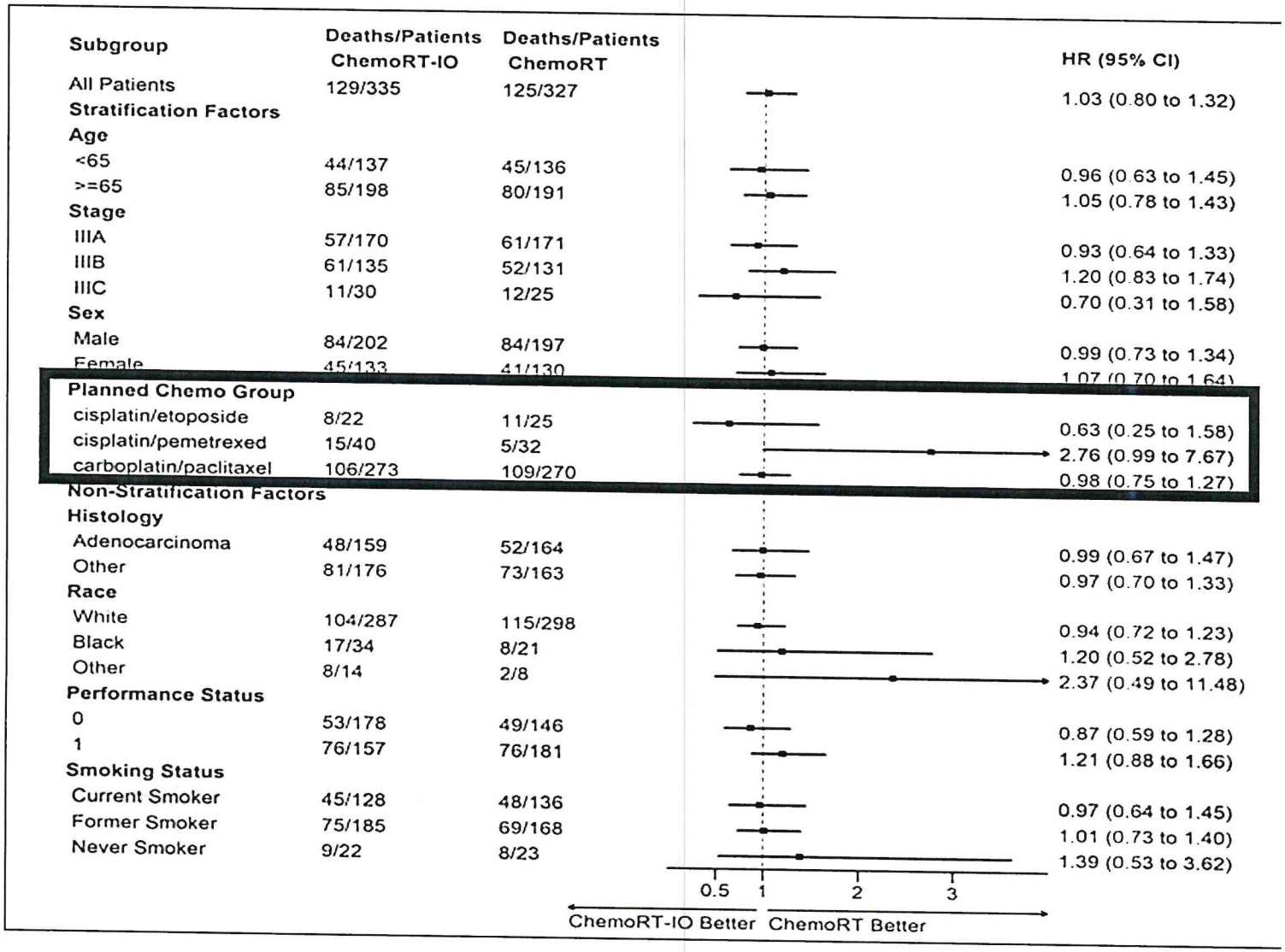
trtm_name	TOTAL	EVENT	CNSR	MEDIAN
ChemoRT	327	191	136	16.8
ChemoRT-IO	335	201	134	15.5

EA5181: OS Forest Plots



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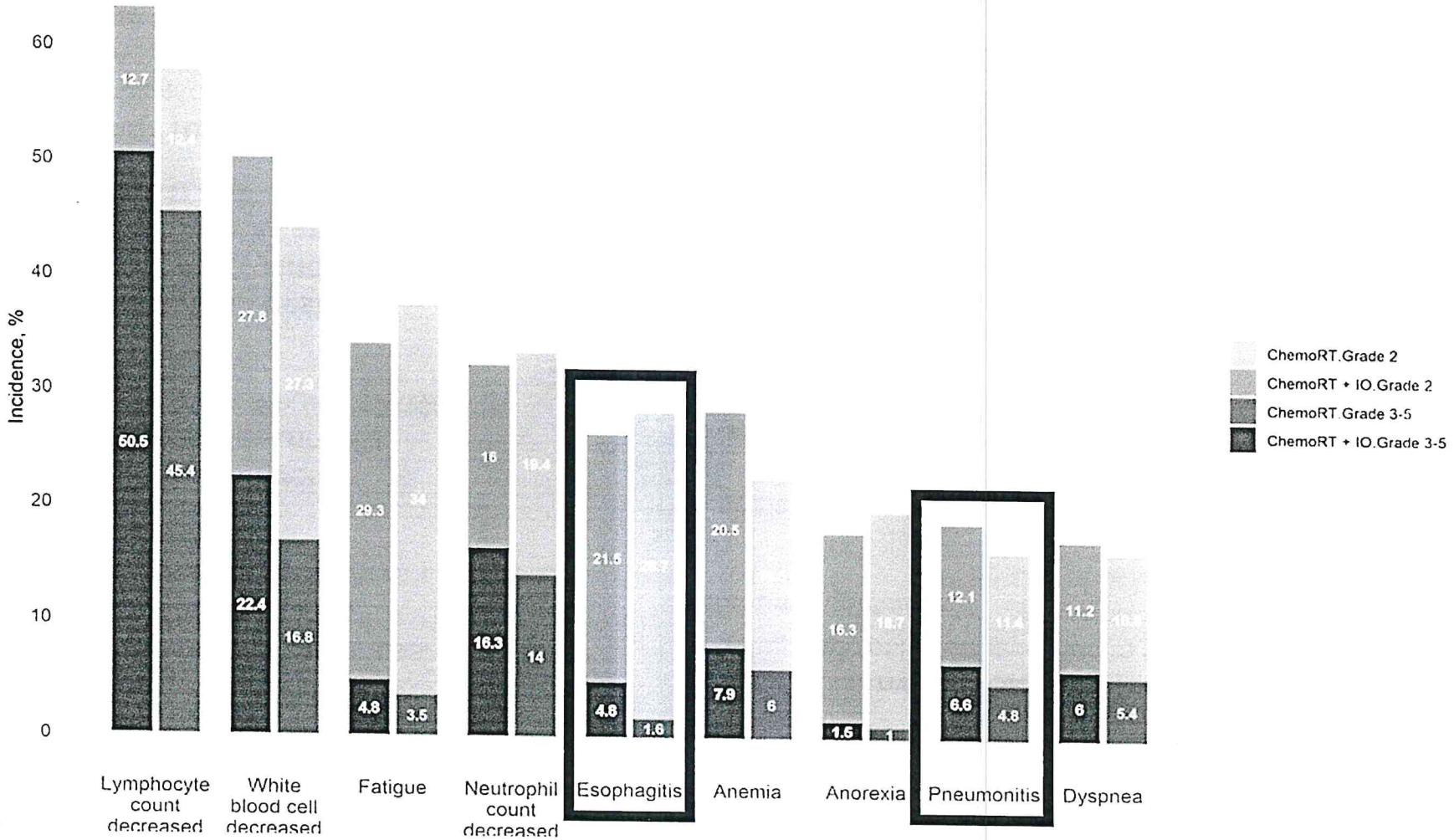
EA5181: Adverse Events

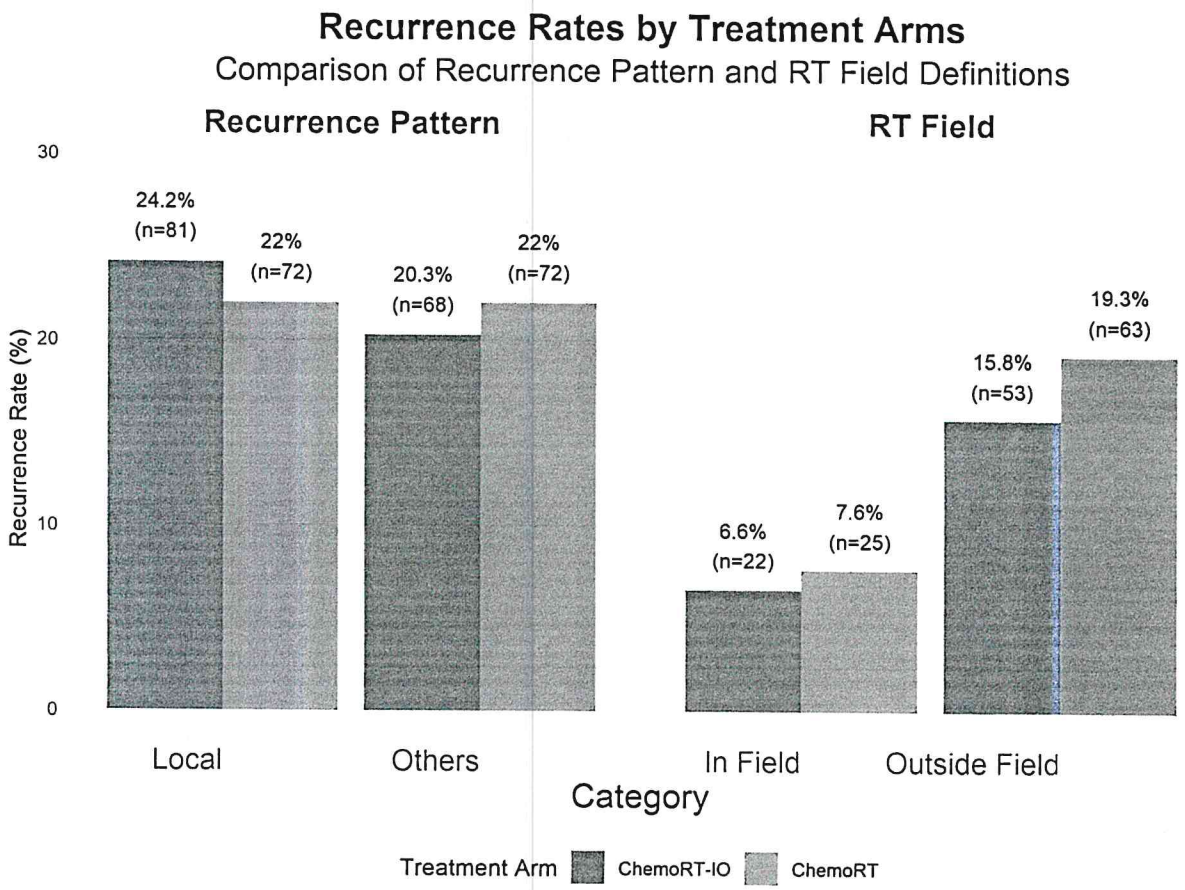
Treatment-Related Adverse Events	ChemoRT-IO (N=331)	ChemoRT (N=315)	P-VALUE
Pulmonary Events – STEP1			
Grade 2-5	188(56.8%)	166 (52.7%)	p = 0.98
Grade 3-5	30(9.1%)	19(6.0%)	p = 0.18
Cardiac Events –STEP 1			
Grade 2-5	67(20.2%)	52(16.5%)	P = 0.52
Grade 3-5	31(9.4%)	26(8.3%)	P = 0.39
Adverse Events, grade 3-4 –STEPS 1 & 2	224 (67.7%)	196 (62.2%)	P=0.16
Grade 5 events- STEPS 1 & 2	12 (3.6%)	11 (3.5%)	P = 1
Treatment Discontinuation – ADVERSE EVENTS STEPS - 1 & 2	63 (19.0%)	52 (16.5%)	P = 0.41

Treatment-related Toxicity Incidence >10%, Top 9 AEs



Recurrence Rates

- Local recurrences were 24.2%(Arm ChemoRT-IO) and 22%(Arm ChemoRT), p = 0.52.
- Radiation in-field recurrences were noted in 6.6% (Arm ChemoRT-IO) and 7.6% (Arm ChemoRT), p=0.65.
- Step 1, the overall best response rates (CR and PR) were 51.3% (Arm A) and 47.1% (Arm B), p = 0.28.
- Step 2, the overall best response rates (CR and PR) were 71.5% (Arm A) and 67.1% (Arm B), p = 0.31.
- Median and mean number of cycles of consolidative durvalumab was 10 and 8 in both Arms



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CONCLUSIONS

In patients with unresectable, Stage III, the addition of concomitant durvalumab during the course of chemo/radiation…

- Did not demonstrate a superior OS
  - **HR = 1.03 (95% CI: 0.80 - 1.32), p =0.83**
- Did not demonstrate a superior PFS
  - **HR = 1.05 (95% CI: 0.86- 1.29) , p = 0.65**
- Did not alter recurrence patterns/rates, ORR, Toxicity
- Future projects for EA 5181 will include
  - Cardiovascular and Pulmonary toxicity analyses
    - Clonal Hematopoiesis(CHIP)
    - Radiographic Studies
  - Prognosis- ctDNA(MRD), PD-L1, TBM and CHIP analyses
  - Local and distant recurrence factors

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- **Patients, families and caregivers.**
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- **Top accruing institutions**
  - 1. Michigan Cancer Research Consortium, NCORP- 67 patients
  - 2. Heartland Cancer Research, NCORP- 59 patients
  - 3. Case Western Reserve University – 30 patients

Ivonescimab plus chemotherapy versus tislelizumab plus chemotherapy as first-line treatment for advanced squamous non-small-cell lung cancer (HARMONi-6): a randomised, double-blind, phase 3 trial

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See Comment page 2034

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Summary

Background Squamous non-small-cell lung cancer (NSCLC) is associated with worse clinical outcomes than non-squamous NSCLC, but treatment options are scarce. We aimed to evaluate the efficacy and safety of ivonescimab plus chemotherapy versus tislelizumab plus chemotherapy as a first-line therapy for patients with advanced squamous NSCLC.

Methods We conducted a randomised, double-blind, phase 3 trial at 50 sites across China (HARMONi-6). Patients aged 18–75 years with previously untreated, pathologically confirmed, unresectable stage IIIB, IIIC, or stage IV squamous NSCLC and an Eastern Cooperative Oncology Group performance status score of 0 or 1 were eligible for inclusion. Patients were randomly assigned (1:1) to receive intravenous ivonescimab (20 mg/kg) or tislelizumab (200 mg), plus intravenous paclitaxel (175 mg/m²) and carboplatin (area under the curve 5 mg/mL per min) once every 3 weeks for four cycles, followed by ivonescimab (20 mg/kg) or tislelizumab (200 mg) monotherapy as maintenance treatment for up to 24 months. Randomisation was stratified by disease stage (IIIB or IIIC *vs* IV) and PD-L1 tumour proportion score (≥1% *vs* <1%). The primary endpoint was progression-free survival assessed by the independent radiographic review committee as per Response Evaluation Criteria in Solid Tumours guidelines (version 1.1) in all randomly assigned patients. Safety, defined as adverse events and serious adverse events related to treatment, as well as adverse events related to immunity or VEGF blockade, were analysed in all randomly assigned patients who received at least one dose of the assigned study treatment. This study is registered at ClinicalTrial.gov (NCT05840016), has completed enrolment, and is ongoing for treatment and follow-up.

Findings From Aug 17, 2023, to Jan 21, 2025, 761 patients were screened for eligibility, among whom 532 (70%) patients were enrolled and randomly assigned to receive ivonescimab plus chemotherapy (266 [50%] patients) or tislelizumab plus chemotherapy (266 [50%] patients). As of Feb 28, 2025, median follow-up time was 10·3 months (95% CI 9·5–11·0). Median progression-free survival was 11·1 months (95% CI 9·9–not evaluable) in the ivonescimab group and 6·9 months (5·8–8·6) in the tislelizumab group (hazard ratio 0·60 [95% CI 0·46–0·78]; one-sided p<0·0001). The progression-free survival benefit with ivonescimab plus chemotherapy was consistent regardless of PD-L1 status. 170 (64%) patients in the ivonescimab group and 144 (54%) patients in the tislelizumab group had grade 3 or higher treatment-related adverse events, with grade 3 or higher immune-related adverse events occurring in 24 (9%) patients in the ivonescimab group and in 27 (10%) patients in the tislelizumab group. Grade 3 or higher treatment-related haemorrhage occurred in five (2%) patients in the ivonescimab group and in two (1%) patients in the tislelizumab group.

Interpretation In patients with untreated advanced squamous NSCLC, ivonescimab plus chemotherapy showed significantly improved progression-free survival compared with tislelizumab plus chemotherapy, regardless of PD-L1 status, as well as a manageable safety profile. This regimen could be used as a novel first-line treatment in this patient group.

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Research in context

Evidence before this study

To understand the current status of first-line treatment for squamous non-small-cell lung cancer (NSCLC), we searched PubMed, without language restrictions, for clinical trials published between Jan 1, 2010, and June 20, 2025, using the terms: "PD-1 OR PD-L1 OR CTLA-4 OR VEGF AND metastatic AND first line OR previously untreated AND squamous AND non-small cell lung cancer OR NSCLC". This search yielded 47 results, from which we identified several randomised phase 3 trials. Many studies have compared the efficacy of anti-PD-1 or anti-PD-L1 agents plus chemotherapy with chemotherapy alone as a first-line therapy in patients with advanced squamous NSCLC, and shown the added value of these agents plus chemotherapy. Based on the KEYNOTE-407, Checkmate 9LA, EMPOWER-Lung 3, and POSEIDON trials, the US Food and Drug Administration has approved pembrolizumab plus chemotherapy, ipilimumab–nivolumab plus two cycles of chemotherapy, cemiplimab plus chemotherapy, and durvalumab–tremelimumab plus chemotherapy as first-line treatments for patients with advanced squamous NSCLC. In China, tislelizumab, camrelizumab, sugemalimab, penpulimab, sintilimab, and serplulimab plus chemotherapy have also been approved as first-line therapies for advanced squamous NSCLC. The combination of anti-PD-1 monotherapy and chemotherapy has emerged as the standard of care for patients with advanced NSCLC. However, no further progress has been made over the past 5 years.

Added value of this study

To our knowledge, the HARMONi-6 trial is the first study to compare an anti-PD-1–VEGF bispecific antibody plus chemotherapy versus an anti-PD-1 mono-antibody plus chemotherapy as a first-line treatment in patients with advanced squamous NSCLC. With the primary endpoint of progression-free survival, this study showed that ivonescimab plus chemotherapy significantly improved median progression-free survival by 4·2 months (11·1 *vs* 6·9 months; hazard ratio 0·60 [95% CI 0·46–0·78]) compared with tislelizumab plus chemotherapy. This efficacy was independent of PD-L1 expression. With a manageable safety profile, this study underscores the therapeutic role of the VEGF blockade in squamous NSCLC. The prevalence of grade 3 or higher haemorrhage related to treatment was 2% in the ivonescimab group. Immune-related adverse events of grade 3 or higher were similar between both treatment groups.

Implications of all the available evidence

Ivonescimab plus chemotherapy showed significantly improved progression-free survival compared with tislelizumab plus chemotherapy in patients with advanced squamous NSCLC, regardless of PD-L1 expression, and had a manageable safety profile. This regimen could provide a novel treatment option for this patient group.

Introduction

Lung cancer remains the leading cause of cancer-related mortality globally. Non-small-cell lung cancer (NSCLC), including both squamous and non-squamous subtypes, accounts for approximately 85% of all cases of lung cancer.[1] Squamous NSCLC constitutes roughly 20–30% of NSCLC cases and is associated with worse clinical outcomes than non-squamous NSCLC.[2] The advent of immune checkpoint inhibitors (ICIs) targeting the PD-1 or PD-L1 axis has transformed first-line treatment options for patients with advanced squamous NSCLC without driver mutations.

In addition to anti-PD-1 monotherapy, various confirmatory phase 3 trials have shown that ICI-based combination therapy confers substantial clinical benefits for patients with advanced squamous NSCLC compared with chemotherapy alone.[3–12] To date, the US Food and Drug Administration has approved pembrolizumab plus chemotherapy, ipilimumab–nivolumab plus two cycles of chemotherapy, cemiplimab plus chemotherapy, and durvalumab–tremelimumab plus chemotherapy as first-line therapy for advanced NSCLC (including the squamous subtype). In China, additional ICIs have been approved by the National Medical Products Administration to combine with chemotherapy as first-line therapy for advanced squamous NSCLC, including pembrolizumab, tislelizumab, camrelizumab, sugemalimab, penpulimab, sintilimab, and serplulimab. In studies investigating ICIs plus chemotherapy in patients with advanced squamous NSCLC, median progression-free survival has ranged from 5·1 months to 8·5 months.[3–12] Based on the RATIONALE-307 study, tislelizumab plus chemotherapy significantly prolonged median progression-free survival compared with chemotherapy alone (7·6 months *vs* 5·5 months; hazard ratio [HR] 0·52 [95% CI 0·37–0·74]).[7] This treatment regimen has been approved by the Chinese National Medical Products Administration and the European Medicines Agency for patients with previously untreated, advanced squamous NSCLC, and is also recommended in major guidelines (eg, Chinese Society of Clinical Oncology and European Society for Medical Oncology) as a standard-of-care option.

Despite these advances, a proportion of patients still derive little benefit from current regimens, underscoring the medical need for novel therapeutic strategies. Preclinical studies suggest that VEGF blockade normalises tumour vasculature, enhances T-cell infiltration, and synergises with PD-1 inhibition to overcome immune evasion.[13] This rationale has spurred the investigation of anti-PD-1 or anti-PD-L1 therapy combined with anti-VEGF therapy in patients with

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NSCLC. In the IMpower 150 study,[14] atezolizumab–bevacizumab plus chemotherapy significantly improved progression-free survival and overall survival among patients with metastatic non-squamous NSCLC, regardless of PD-L1 expression and driver mutations. However, due to the high risk of life-threatening and fatal bleeding complications in patients with squamous NSCLC, bevacizumab use is restricted to individuals with non-squamous NSCLC.

Ivonescimab is a bispecific antibody targeting PD-1 and VEGF. In-vitro studies have shown that ivonescimab possesses enhanced binding affinity to PD-1 and VEGF through cooperative binding.[15] Based on the results of the HARMONi-A study,[16] ivonescimab combined with chemotherapy has been approved in China in patients with non-squamous NSCLC who have experienced disease progression on EGFR tyrosine kinase inhibitor therapy. Ivonescimab monotherapy has also been approved as a first-line treatment in China in patients with PD-L1-positive, advanced NSCLC, based on the findings of the HARMONi-2 study.[17] In the HARMONi-2 study of 398 patients, ivonescimab showed promising efficacy and a favourable safety profile in patients with both squamous (181 [46%]) and non-squamous NSCLC (217 [55%]). In light of the few treatment options and unmet medical needs of patients with squamous NSCLC, we aimed to compare the efficacy and safety of ivonescimab plus chemotherapy versus tislelizumab plus chemotherapy as first-line therapy in this patient group. Herein, we report the preplanned interim analysis.

Methods

Study design

We conducted a randomised, double-blind, phase 3 trial (HARMONi-6) at 50 hospitals across China (appendix p 2). This trial was conducted in accordance with the study protocol (appendix pp 15–157) and Good Clinical Practice standards. The study was monitored by an independent data and safety monitoring committee. The research protocol was approved by the appropriate ethics committee at each participating centre (appendix p 2). Any protocol deviations were recorded and reported to a local institutional review board for review (appendix p 9). Information on participant sex was collected on a self-reported basis. This trial is registered with ClinicalTrials.gov (NCT05840016), has completed enrolment, and is ongoing for treatment and follow-up.

Participants

Patients aged 18–75 years with pathologically confirmed, unresectable stage IIIB, IIIC, or stage IV squamous NSCLC (classified according to the eighth edition of the cancer staging manual of the American Joint Committee on Cancer),[18] no previous systemic therapy, an Eastern Cooperative Oncology Group performance status score of 0 or 1, at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumours guidelines (RECIST; version 1.1),[19] and a survival expectation of more than 3 months were eligible for inclusion. Patients were excluded if they had pathologically confirmed, non-squamous NSCLC or small-cell lung cancer, EGFR mutation or ALK translocation, other malignant tumours within 5 years before enrolment, active autoimmune disease, or non-infectious pneumonitis or interstitial lung disease that required treatment with systemic steroids. Patients with active CNS metastatic lesions or CNS metastatic lesions at least 1·5 cm in size were also excluded. Additionally, patients were excluded if imaging at screening showed obvious tumour necrosis or cavitation and investigators determined that enrolment would pose a high risk of bleeding, or if tumours invaded major blood vessels. The full inclusion and exclusion criteria are listed in the study protocol (appendix pp 45–52). All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) to receive either ivonescimab plus chemotherapy (ivonescimab group) or tislelizumab plus chemotherapy (tislelizumab group). Randomisation was done by study investigators using an interactive web response system (Shanghai Shanhu Health Technology). Stratified block randomisation was used to generate the randomisation schedule. Stratification factors were disease stage (IIIB or IIIC *vs* IV) and PD-L1 tumour proportion score (TPS; ≥1% *vs* <1%).

Participants, investigators, clinical staff, the study sponsor, and data analysts were masked to treatment assignment. Unmasking of treatment allocation was only allowed for expedited safety reporting to regulatory authorities or emergency medical reasons. Further details on masking procedures can be found in the appendix (pp 54–56).

Procedures

Ivonescimab (20 mg/kg) or tislelizumab (200 mg), plus paclitaxel (175 mg/m²) and carboplatin (area under the curve [AUC] 5 mg/mL per min) were administered for up to four cycles, followed by ivonescimab (20 mg/kg) or tislelizumab (200 mg) for maintenance treatment. All treatments were administered intravenously once every 3 weeks. The assigned treatment was continued until no more clinical benefit was observed, as judged by investigators, unacceptable toxicity, initiation of new antitumour treatment, completion of 24 months of treatment in total, or until other criteria for treatment discontinuation were met according to the protocol, whichever occurred first. Details regarding treatment decisions and the management of adverse events are available in the protocol (appendix pp 62–72).

Tumour assessments were conducted in accordance with RECIST guidelines (version 1.1)[19] during screening,

every 6 weeks during the first 60 weeks after randomisation, and every 12 weeks thereafter. These assessments were continued until the masked independent radiology review committee (IRRC) evaluated disease progression on imaging or the study treatment was terminated (whichever occurred later), or the participant was lost to follow-up, withdrew consent, or died, or the study ended, whichever occurred first.

Adverse events and laboratory abnormalities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). Adverse events were monitored until 30 days after the last treatment or the initiation of a new antitumour treatment, whichever occurred first. Serious adverse events, defined as per the protocol (appendix p 90), were monitored until 90 days after the last treatment or the initiation of new antitumour therapy, whichever occurred first. Immune-related adverse events, definded as per the protocol (appendix p 91), were monitored for 90 days after the last treatment of ivonescimab or tislelizumab. Treatment-related adverse events were defined as treatment-emergent adverse events with a causality assessment of related, probably related, or possibly related to any study treatment (ivonescimab, tislelizumab, paclitaxel, or carboplatin), as well as events with a missing causality assessment. Adverse events possibly related to anti-VEGF therapy were adverse events which were consistent with VEGF-mediated mechanism of action (appendix p 90).

Analyses of laboratory testing, vital signs, and electrocardiography were done during screening and performed regularly throughout the study treatment. Health-related quality of life was assessed with the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30; version 3).[20] These assessments were performed every two cycles for the first seven cycles, then every four cycles after the seventh cycle, and at the end of treatment visit and safety visit at day 30 (range 23–37 days) after the last dose.

PD-L1 expression was evaluated with immunohistochemistry by use of the Dako PD-L1 IHC 22C3 pharmDx (Agilent Technologies; Santa Clara, CA, USA) in either central or local laboratories. Expression was determined by the TPS, which was defined as the percentage of viable tumour cells with membranous positivity of PD-L1 staining at any intensity.

Outcomes

The primary endpoint was progression-free survival assessed by the IRRC according to RECIST guidelines, which was defined as the time from randomisation to disease progression or death from any cause, whichever occurred first. The key secondary endpoint was overall survival, defined as the time from randomisation to death from any cause. Other secondary endpoints included the objective response rate, disease control rate, duration of response, and time to response assessed by the IRRC as per RECIST guidelines; progression-free survival, objective response rate, disease control rate, duration of response, and time to response assessed by the investigators at each site; safety; pharmacokinetic profiles; and immunogenicity characteristics. The correlation between PD-L1 status and treatment efficacy was also analysed as a secondary endpoint. An additional exploratory endpoint was the health-related quality-of-life assessment. The secondary outcomes of pharmacokinetic profiles and immunogenicity characteristics will be reported in a separate publication.

Statistical analysis

Approximately 528 participants were required to provide 86% power to detect a HR of 0·70 for progression-free survival (based on 297 progression-free survival events) and 80% power to detect a HR of 0·73 for overall survival, favouring ivonescimab plus chemotherapy over tislelizumab plus chemotherapy, with a one-sided α level of 0·025.

An interim analysis of progression-free survival was planned when approximately 208 (70%) progression-free survival events as assessed by the IRRC were observed. To strictly control the overall type 1 error at a one-sided alpha level of 0·025, we used a hierarchical testing procedure for the primary endpoint (progression-free survival) and the key secondary endpoint (overall survival). Overall survival would only be tested if progression-free survival was found to be significant. The Lan-DeMets spending function with O'Brien-Fleming boundary was used to control the type 1 error for both endpoints at the interim and final analyses. In April, 2024, the protocol was amended to adjust the sample size from 396 to 528 participants, taking into account the consideration of overall survival in the sample size estimation. Correspondingly, the number of events needed for the interim analysis on the primary endpoint increased from 186 to 208.

Efficacy was assessed in the full analysis set, which included all randomly assigned patients. For participants who did not experience disease progression or death, progression-free survival was censored on the date of the last evaluable tumour assessment. A Kaplan–Meier analysis was used to estimate progression-free survival, duration of response, and other time-to-event variables. A stratified log-rank test was used to compare progression-free survival between both treatment groups. HRs and associated 95% CIs were calculated based on a stratified Cox proportional hazards model, with tied events handled by the exact method. Progression-free survival as assessed by investigators was analysed with the same methods as progression-free survival assessed by the IRRC. The Clopper–Pearson method was used to calculate the 95% CIs for the objective response rate and disease control rate for each treatment group. Differences in objective response rate

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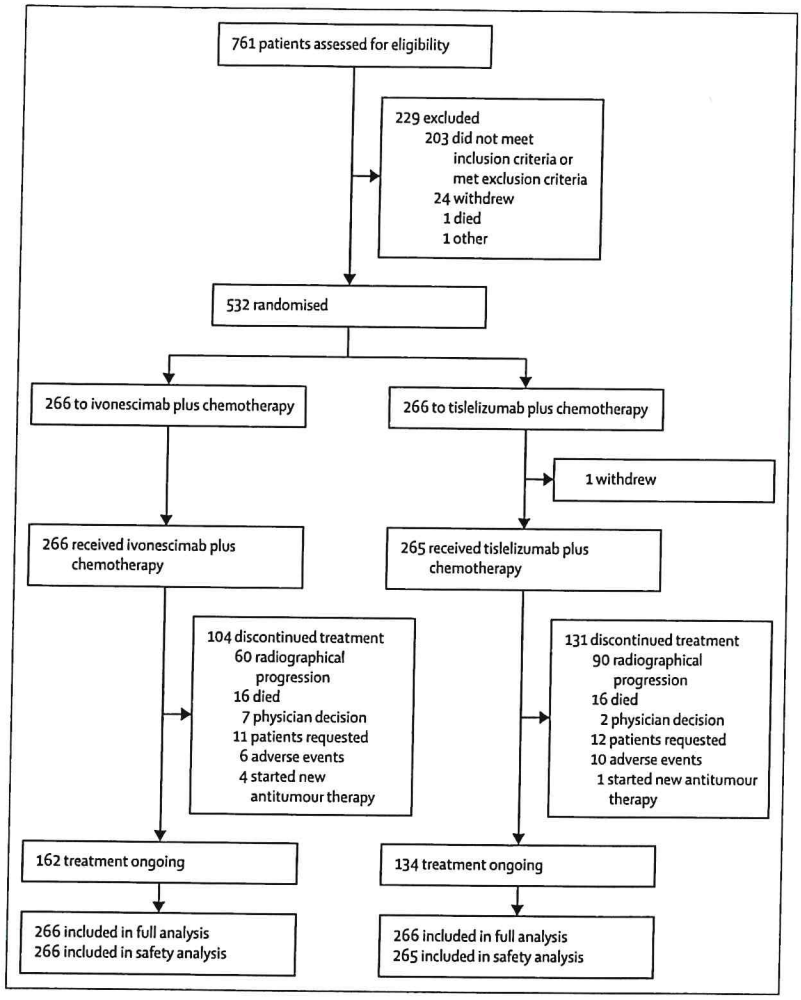

Figure 1: **Trial profile**

and disease control rate were calculated with the stratified Miettinen–Nurminen method. The prespecified subgroup analyses of progression-free survival were conducted with HRs and corresponding 95% CIs estimated from an unstratified Cox model to evaluate the consistency of treatment effect across key baseline characteristics. Safety was assessed in the safety analysis set, which included all randomly assigned patients who received at least one dose of any study treatment (ie, ivonescimab or tislelizumab, plus paclitaxel and carboplatin).

Deterioration status (ie, global health status and quality-of-life domain) was analysed in all patients who had been randomly assigned and completed a EORTC QLQ-C30 assessment at baseline and at least one EORTC QLQ-C30 questionnaire after baseline. The raw score for each scale was calculated as the mean of the scores of its constituent items. To ensure comparability across scales, raw scores were further linearly transformed into standardised scores ranging from 0 to 100. Deterioration was defined as a decrease in standard score by at least ten points from baseline score. Time to deterioration was defined as the time from the date of randomisation to the date of first deterioration. Corresponding HRs and 95% CIs were estimated from stratified and unstratified Cox regression models. The distribution of time to deterioration event was estimated with the Kaplan–Meier method for each treatment group; the rate of non-deterioration at different timepoints (every 3 months) was estimated.

The interim analysis for progression-free survival was triggered after 221 progression-free survival events assessed by the IRRC were observed, based on data with a cutoff date of Feb 28, 2025. The updated O'Brien-Fleming one-sided significance boundary at this interim analysis was 0·0094. An independent data monitoring committee reviewed efficacy and safety data. All statistical analyses were performed with SAS (version 9.4).

Role of the funding source

This study was designed by the principal investigator (SL) and the funder. The funder provided the study drug, contributed to data collection and interpretation, funded the data analysis, participated in the preparation and review of the manuscript in collaboration with all coauthors, and made the decision to submit the manuscript for publication.

Results

From Aug 17, 2023, to Jan 21, 2025, 761 patients were screened for eligibility, among whom 532 (70%) participants were enrolled. Among 229 patients excluded during screening, the most common reasons were EGFR-sensitising mutations or ALK rearrangements (36 [5%] exclusions) and brain metastases (active or ≥1·5 cm; 32 [4%]). Among the 532 eligible patients, 266 (50%) were randomly assigned to receive ivonescimab plus chemotherapy and 266 (50%) to receive tislelizumab plus chemotherapy. At data cutoff (Feb 28, 2025), 162 (61%) patients in the ivonescimab group and 134 (50%) patients in the tislelizumab group were still receiving the assigned treatment. 104 (39%) patients in the ivonescimab group and 132 (50%) in the tislelizumab group had discontinued treatment, mainly due to disease progression in 60 (23%) patients in the ivonescimab group and 90 (34%) in the tislelizumab group (figure 1).

Baseline characteristics were well balanced between the two treatment groups (table 1). Most participants were men with current or former smoking status and stage IV disease. 105 (39%) patients in the ivonescimab group and 105 (39%) in the tislelizumab group had a PD-L1 TPS of less than 1%; 178 (67%) in the ivonescimab group and 158 (59%) in the tislelizumab group had central type tumours; and 49 (18%) in the ivonescimab group and 44 (17%) in the tislelizumab group had major blood vessel encasement.

All 266 (100%) participants in the ivonescimab group and 265 (99%) patients in the tislelizumab group received at least one dose of treatment and were included in the safety analysis. Patients received a median of nine doses (IQR 4–15) of ivonescimab in the ivonescimab group and eight doses (5–13) of tislelizumab in the tislelizumab group. In both groups, patients received a median of four doses (4–4) of carboplatin and paclitaxel (appendix p 10). 53 (20%) patients in the ivonescimab group and 72 (27%) in the tislelizumab group received subsequent systemic antitumour therapy, including immunotherapy in 20 (8%) patients in the ivonescimab group and 35 (13%) in the tislelizumab group (appendix p 11).

At data cutoff, the median duration of follow-up was 10·4 months (95% CI 9·3–11·1) in the ivonescimab group and 10·1 months (9·1–11·4) in the tislelizumab group. A total of 94 (35%) patients in the ivonescimab group and 127 (48%) in the tislelizumab group experienced disease progression or death. Median progression-free survival was 11·1 months (95% CI 9·9–not evaluable [NE]) in the ivonescimab group versus 6·9 months (5·8–8·6) in the tislelizumab group (stratified HR 0·60 [95% CI 0·46–0·78]; one-sided p<0·0001), reaching the prespecified significance threshold (figure 2A).

The estimated PFS rate at 9 months was 62% (95% CI 54·2–68·4) in the ivonescimab group and 43% (95% CI 35·7–49·8) in the tislelizumab group. The PFS rate at 12 months was 48% (95% CI 40·0–56·3) in the ivonescimab group and 35% (95% CI 27·8–42·3) in the tislelizumab group. The results were similar when progression-free survival was assessed by investigators (appendix p 5).

Across most subgroups in the prespecified analysis, improved progression-free survival was found with ivonescimab plus chemotherapy compared with tislelizumab plus chemotherapy (figure 3). Median progression-free survival was 9·9 months (95% CI 8·2–12·5) in the ivonescimab group versus 5·7 months (5·5–6·9) in the tislelizumab group among patients with a PD-L1 TPS of less than 1% (unstratified HR 0·55 [95% CI 0·37–0·82]; figure 2B); 12·6 months (9·9–NE) versus 8·6 months (6·3–15·4) among those with a PD-L1 TPS of at least 1% (0·66 [0·46–0·95]; figure 2C); 12·6 months (9·8–NE) versus 6·9 months (5·5–NE) among those with a PD-L1 TPS of 1–49% (0·63 [0·41–0·98]; figure 2D); and 12·6 months (9·5–NE) versus 9·7 months (6·7–NE) among those with a PD-L1 TPS of at least 50% (0·71 [0·37–1·33]; figure 2E). In patients with liver metastases, median progression-free survival was 9·9 months (95% CI 5·2–NE) in the ivonescimab group versus 5·7 months (4·2–9·5) in the tislelizumab group (HR 0·53 [95% CI 0·26–1·08]); in patients without liver metastases, the median progression-free survival was 11·3 months (9·8–NE) versus 6·9 months (5·9–9·5; HR 0·64 [95% CI 0·48–0·85]). Corresponding Kaplan–Meier curves in

	Ivonescimab group (n=266)	Tislelizumab group (n=266)
Ethnicity		
Han	261 (98%)	259 (97%)
Other	5 (2%)	7 (3%)
Age, years	64 (59-69)	64 (59-69)
Age, years		
<65	135 (51%)	139 (52%)
≥65	131 (49%)	127 (48%)
Sex		
Male	256 (96%)	238 (89%)
Female	10 (4%)	28 (11%)
ECOG performance status score*		
0	42 (16%)	42 (16%)
1	224 (84%)	222 (83%)
Tobacco smoking status		
Never	21 (8%)	37 (14%)
Current or former	245 (92%)	229 (86%)
Disease stage		
IIIB or IIIC	21 (8%)	20 (8%)
IV	245 (92%)	246 (92%)
At least three metastatic sites		
Yes	42 (16%)	39 (15%)
No	224 (84%)	227 (85%)
Liver metastases		
Yes	28 (11%)	45 (17%)
No	238 (89%)	221 (83%)
Brain metastases		
Yes	9 (3%)	17 (6%)
No	257 (97%)	249 (94%)
PD-L1 tumour proportion score, %		
<1	105 (39%)	105 (39%)
≥1	161 (61%)	161 (61%)
1-49	112 (42%)	99 (37%)
≥50	49 (18%)	62 (23%)
History of haemoptysis		
Yes	86 (32%)	79 (30%)
No	180 (68%)	187 (70%)
Anatomical tumour type		
Central	178 (67%)	158 (59%)
Peripheral	88 (33%)	108 (41%)
Major blood vessel encasement		
Yes	49 (18%)	44 (17%)
No	217 (82%)	222 (83%)
Presence of cavity in tumour		
Yes	24 (9%)	23 (9%)
No	242 (91%)	243 (91%)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group. *ECOG scores range from 0 to 5, with higher scores indicating greater disability. Two (<1%) patients in the tislelizumab group had no ECOG performance status score.

Table 1: **Baseline participant characteristics**

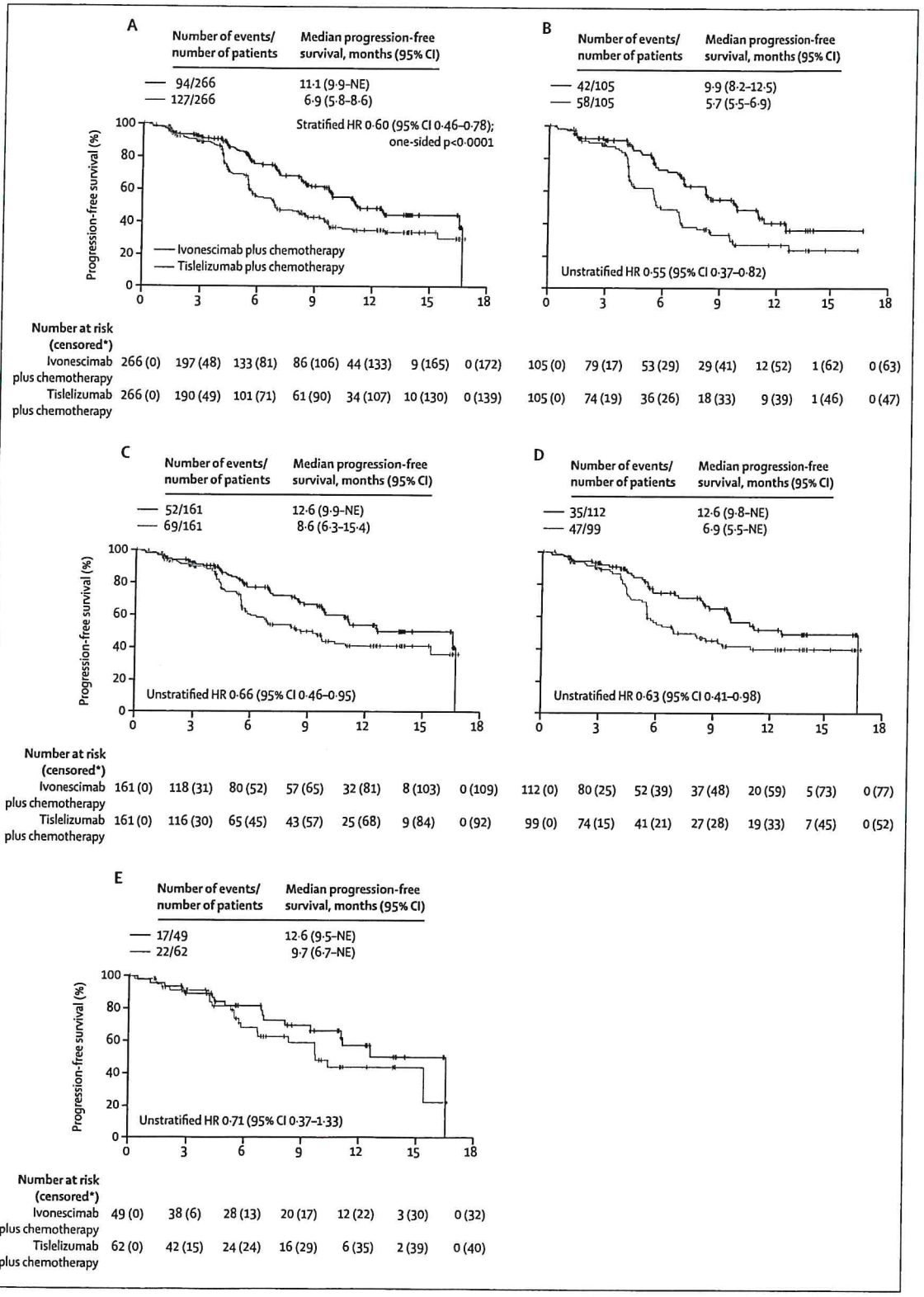

Figure 2: **Progression-free survival assessed by the independent radiology review committee**
Kaplan–Meier estimates of progression-free survival in all randomly assigned patients (A); in patients with a PD-L1 TPS of less than 1% (B); in patients with a PD-L1 TPS of at least 1% (C); in patients with a PD-L1 TPS of 1–49% (D); and in patients with a PD-L1 TPS of at least 50% (E). HR=hazard ratio. NE=not evaluable. TPS=tumour proportion score. *The number of censored cases includes administrative censoring due to data cutoff.

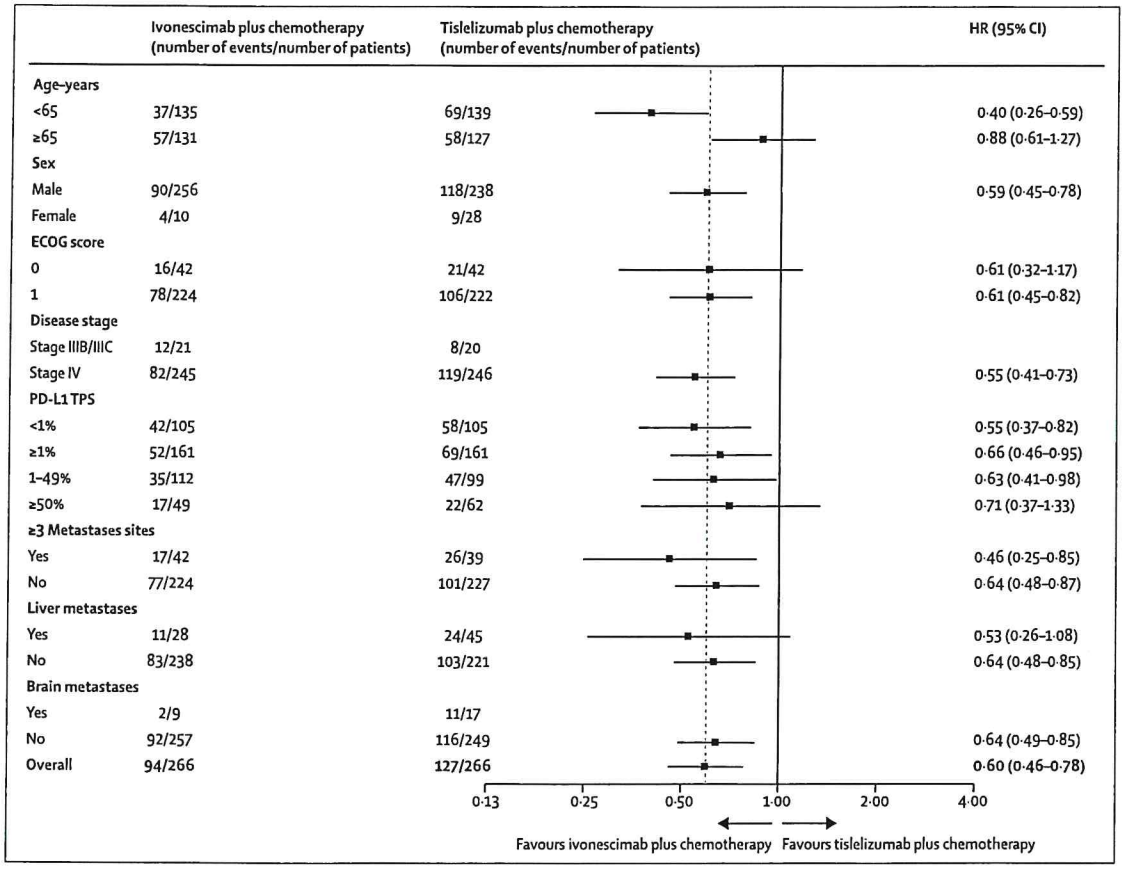

Figure 3: **Subgroup analysis of progression-free survival according to baseline characteristics**
A prespecified subgroup analysis of progression-free survival in all randomly assigned patients. If the number of events at a subgroup level is less than ten, the median progression-free survival and corresponding HR (95% CI) are not provided. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. TPS=tumour proportion score.

patients with and without liver metastasis are shown in the appendix (p 6).

As assessed by the IRRC, an objective response was observed in 202 (76%) patients (95% CI 70–81) in the ivonescimab group and 177 (67%) patients (61–72) in the tislelizumab group (table 2). These results were similar when the response was assessed by investigators (191 [72%] *vs* 175 [66%]; appendix p 12). Median duration of response was 11·2 months (95% CI 8·5–NE) in the ivonescimab group and 8·4 months (95% CI 5·7–NE) in the tislelizumab group. The duration of response rate at 9 months was 60% (95% CI 49·9–68·1) in the ivonescimab group and 50% (40·3–58·5) in the tislelizumab group. Corresponding Kaplan–Meier curves for duration of response are shown in the appendix (p 7). Time to response was 1·4 months (IQR 1·4–2·7) in both treatment groups (table 2). At data cutoff, overall survival data were not mature; only 108 patients died. The results for the other investigator-assessed outcomes are provided in the appendix (p 12).

Adverse events related to any treatment drug were reported in 264 (99%) of 266 patients in the ivonescimab

	Ivonescimab group (n=266)	Tislelizumab group (n=266)
Objective response rate*	76% (70–81)	67% (61–72)
Complete response	1 (<1%)	0
Partial response	201 (76%)	177 (67%)
Stable disease	39 (15%)	60 (23%)
Progressive disease	6 (2%)	15 (6%)
Disease control rate	91% (86–94)	89% (85–93)
Time to response, months†	1·4 (1·4–2·7)	1·4 (1·4–2·7)
Duration of response, months‡	11·2 (8·5–NE)	8·4 (5·7–NE)
Duration of response rate		
At 6 months	75% (67–82)	59% (50–67)
At 9 months	60% (50–68)	50% (40–59)
At 15 months	50% (39–60)	40% (27–54)

Data are rate (95% CI), n (%), median (IQR) for time to response, or median (95% CI) for duration of response. NE=not evaluable. *Evaluated by an independent radiology review committee according to the Response Evaluation Criteria in Solid Tumours (version 1.1). †Assessed in patients with an objective response. ‡Evaluated with the Kaplan–Meier method in patients with an objective response.

Table 2: **Tumour responses in patients treated for squamous non-small-cell lung cancer**

	Ivonescimab group (n=266)		Tislelizumab group (n=265)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Treatment-related adverse events in ≥10% of patients*				
Alopecia	174 (65%)	0	162 (61%)	0
Anaemia	141 (53%)	17 (6%)	153 (58%)	10 (4%)
Decreased neutrophil count	120 (45%)	85 (32%)	113 (43%)	68 (26%)
Decreased white blood cell count	96 (36%)	29 (11%)	90 (34%)	25 (9%)
Decreased platelet count	76 (29%)	7 (3%)	66 (25%)	8 (3%)
Hypoaesthesia	71 (27%)	0	65 (25%)	0
Decreased appetite	58 (22%)	4 (2%)	64 (24%)	1 (<1%)
Increased alanine aminotransferase	52 (20%)	2 (1%)	53 (20%)	1 (<1%)
Pain in extremity	50 (19%)	3 (1%)	33 (12%)	1 (<1%)
Proteinuria	48 (18%)	4 (2%)	19 (7%)	0
Hypertriglyceridaemia	46 (17%)	3 (1%)	33 (12%)	6 (2%)
Hypoalbuminaemia	42 (16%)	0	27 (10%)	0
Increased aspartate aminotransferase	42 (16%)	0	42 (16%)	4 (2%)
Leukopenia	38 (14%)	15 (6%)	45 (17%)	11 (4%)
Nausea	38 (14%)	2 (1%)	51 (19%)	0
Decreased weight	37 (14%)	2 (1%)	27 (10%)	0
Peripheral neuropathy	34 (13%)	0	32 (12%)	2 (<1%)
Constipation	33 (12%)	0	30 (11%)	0
Hyperuricaemia	33 (12%)	1 (<1%)	18 (7%)	0
Hypercholesterolaemia	32 (12%)	0	32 (12%)	1 (<1%)
Haemoptysis	32 (12%)	4 (2%)	10 (4%)	1 (<1%)
Increased blood urea	32 (12%)	0	19 (7%)	0
Diarrhoea	31 (12%)	3 (1%)	12 (5%)	0
Arthralgia	30 (11%)	2 (1%)	20 (8%)	0
Rash	30 (11%)	2 (1%)	29 (11%)	2 (<1%)
Increased gamma-glutamyltransferase	29 (11%)	3 (1%)	33 (12%)	5 (2%)
Hyperlipidaemia	29 (11%)	2 (1%)	12 (5%)	1 (<1%)
Hypothyroidism	28 (11%)	0	29 (11%)	0
Albuminuria	20 (8%)	2 (1%)	6 (2%)	0
Immune-related adverse event in ≥2% of patients				
Any	73 (27%)	24 (9%)	67 (25%)	27 (10%)
Hypothyroidism	21 (8%)	0	22 (8%)	0
Hyperthyroidism	13 (5%)	0	11 (4%)	0
Rash	8 (3%)	2 (1%)	12 (5%)	2 (<1%)
Immune-mediated lung disease	6 (2%)	5 (2%)	8 (3%)	2 (<1%)
Adverse events possibly related to anti-VEGF therapy				
Any	123 (46%)	20 (8%)	60 (23%)	6 (2%)
Proteinuria†	72 (27%)	6 (2%)	29 (11%)	0
Haemorrhage‡	57 (21%)	5 (2%)	25 (9%)	2 (<1%)
Hypertension§	27 (10%)	8 (3%)	12 (5%)	3 (1%)
Arterial thromboembolism¶	3 (1%)	3 (1%)	0	0
Venous thromboembolism‖	2 (1%)	0	3 (1%)	1 (<1%)
Fistula	1 (<1%)	0	0	0

Data are n (%). *Defined as treatment-emergent adverse events with a causality assessment of related, probably related, or possibly related to any treatment drug (ivonescimab, tislelizumab, paclitaxel, or carboplatin), as well as those with a missing causality assessment. †Included proteinuria and albuminuria. ‡Included haemoptysis, epistaxis, urinary occult blood positive, haematuria, gingival bleeding, respiratory tract haemorrhage, upper gastrointestinal haemorrhage, gastric haemorrhage, haematochezia, haemoglobinuria, occult blood positive, pulmonary haemorrhage, and red blood cells urine positive. §Included hypertension and increased blood pressure. ¶Included acute myocardial infarction and cerebellar infarction. ‖Included deep vein thrombosis, jugular vein thrombosis, pulmonary embolism, and venous thrombosis limb.

Table 3: **Adverse events related to treatment, immunity, and possibly anti-VEGF therapy in patients treated for squamous non-small-cell lung cancer**

group and in 261 (98%) of 265 patients in the tislelizumab group. Grade 3 or higher treatment-related adverse events were reported in 170 (64%) patients in the ivonescimab group and 144 (54%) patients in the tislelizumab group. The most frequent grade 3 or higher treatment-related adverse events were decreased neutrophil count (85 [32%] of 266 in the ivonescimab group *vs* 68 [26%] of 265 in the tislelizumab group), decreased white blood cell count (29 [11%] *vs* 25 [9%]), and anaemia (17 [6%] *vs* ten [4%]; table 3). Treatment-related adverse events leading to discontinuation of ivonescimab or tislelizumab occurred in nine (3%) patients in the ivonescimab group and 11 (4%) patients in the tislelizumab group. Serious treatment-related adverse events occurred in 86 (32%) patients receiving ivonescimab plus chemotherapy and in 80 (30%) patients receiving tislelizumab plus chemotherapy (appendix p 13). Treatment-related adverse events leading to death occurred in eight (3%) patients in the ivonescimab group and ten (4%) patients in the tislelizumab group.

73 (27%) patients in the ivonescimab group and 67 (25%) patients in the tislelizumab group had immune-related adverse events, of whom 24 (9%) in the ivonescimab group and 27 (10%) patients in the tislelizumab group had grade 3 or higher events. The most frequent immune-related adverse events were hypothyroidism, hyperthyroidism, rash, and immune-mediated lung disease (table 3). Adverse events considered to be possibly related to anti-VEGF therapy occurred more frequently in the ivonescimab group, most of which were grade 1–2. The most common grade 3 or higher adverse events possibly related to anti-VEGF therapy were hypertension, proteinuria, and haemorrhage (table 3).

A total of 233 (88%) patients in the ivonescimab group and 231 (87%) patients in the tislelizumab group were included in the quality-of-life analysis. Patient-reported data on quality of life showed that the median time to deterioration as per global health status or quality-of-life domain in the EORTC QLQ-C30 questionnaire was not reached (95% CI 7·1–NE) in the ivonescimab group and was 12·4 months (4·2–NE) in the tislelizumab group (HR 0·94 [95% CI 0·71–1·25]). Corresponding Kaplan–Meier curves for time to deterioration are shown in the appendix (p 8). The deterioration-free rate at 12 months was higher in the ivonescimab group at 53% (95% CI 45·5–60·6) versus 50% (42·2–57·7) in the tislelizumab group, but this difference was not significant.

Discussion

This study is the first phase 3 trial to compare a PD-1–VEGF-bispecific antibody (ivonescimab) plus chemotherapy versus a PD-1 mono-antibody (tislelizumab) plus chemotherapy as a first-line treatment in patients with advanced squamous NSCLC. The results show that, compared with tislelizumab plus chemotherapy, ivonescimab plus chemotherapy significantly prolonged

median progression-free survival by 4·2 months (HR 0·60; p<0·0001), and this benefit was observed among patients regardless of PD-L1 status. We also observed a higher response rate and longer duration of response with ivonescimab plus chemotherapy than with tislelizumab plus chemotherapy. These findings highlight the role of anti-VEGF therapy in the treatment of squamous NSCLC. Preclinical studies have shown synergistic effects between anti-VEGF inhibitors and ICIs.[21–23] In the final overall survival analysis of the IMpower 150 study, the combination of atezolizumab and bevacizumab plus chemotherapy persistently improved overall survival in patients with metastatic non-squamous NSCLC compared with bevacizumab plus chemotherapy alone.[24] Additionally, atezolizumab plus chemotherapy alone showed a numerical but not significant improvement in overall survival over bevacizumab plus chemotherapy, underscoring the synergistic effects of atezolizumab and bevacizumab.[24] However, bevacizumab is only recommended in patients with non-squamous NSCLC due to the high risk of life-threatening and fatal bleeding in squamous NSCLC. In the LEAP-007 study, median progression-free survival was improved with the combination of pembrolizumab and lenvatinib in patients with squamous and non-squamous NSCLC; however, the subgroup analysis showed no benefit in progression-free survival in patients with squamous NSCLC (HR 1·02).[25] HARMONi-6 is the first study to show the superior efficacy of an anti-PD-1–VEGF bispecific antibody in patients with squamous NSCLC. The efficacy of ivonescimab plus chemotherapy in this study might be attributed to the synergistic effects of anti-PD-1 and anti-VEGF mechanisms, as well as the favourable safety profile of ivonescimab. Ivonescimab is a symmetrical antibody targeting PD-1 and VEGF, which means it can target the two proteins in close proximity. Both VEGF and PD-1 are highly expressed in tumour tissue. The cooperative binding of VEGF and PD-1 in close proximity could potentially localise ivonescimab to tumour, thereby reducing toxicity associated with extra-tumoural VEGF blockade.[15,26]

The subgroup analysis showed that progression-free survival favoured ivonescimab plus chemotherapy over tislelizumab plus chemotherapy, regardless of PD-L1 expression. Specifically, ivonescimab plus chemotherapy showed a greater benefit to progression-free survival than did tislelizumab plus chemotherapy in patients with a PD-L1 TPS of less than 1% (HR 0·55 [95% CI 0·37–0·82]), 1–49% (0·63 [0·41–0·98]), or at least 50% (0·71 [0·37–1·33]). The greatest benefit to progression-free survival was observed in the subgroup of patients with a PD-L1 TPS of less than 1%, a population traditionally considered to be insensitive to immunotherapy. However, the current study was not powered to investigate subgroups and, thus, these results should be interpreted with caution.

The adverse events observed in this trial were consistent with the known profile of adverse events associated with ivonescimab, as reported in the HARMONi-A and HARMONi-2 studies.[16,17] No new types of toxicities were identified. The safety profile was similar between both treatment groups, with a similar frequency of treatment-related adverse events, treatment-related adverse events leading to discontinuation of ivonescimab or tislelizumab, serious treatment-related adverse events, and grade 3 or higher immune-related adverse events. The frequency of grade 3 or higher treatment-related adverse events was slightly higher in the ivonescimab group than in the tislelizumab group, primarily due to the increased occurrence of adverse events related to anti-VEGF therapy in the ivonescimab group. Despite an increased frequency of adverse events related to anti-VEGF therapy in the ivonescimab group, most of them were grade 1–2. Grade 3 or higher haemorrhage occurred in five (2%) of 266 patients in the ivonescimab group versus two (<1%) of 265 patients in the tislelizumab group, consistent with data reported in the HARMONi-2 study.[17] In the present study, patients at risk of bleeding were also enrolled. At baseline, 336 (63%) patients had a central tumour, 165 (31%) had a history of haemoptysis, 47 (9%) had tumour cavitation, and 93 (18%) had major blood vessel encasement. Against this background, the 2% prevalence of grade 3 or higher haemorrhage with ivonescimab is encouraging. Overall, the safety data in the current study clearly distinguish ivonescimab from bevacizumab with regard to the feasibility of safe administration in patients with squamous NSCLC.

A number of study limitations should be noted. This study was conducted in a single region, and all enrolled patients were Chinese. Additionally, data on overall survival were not mature at data cutoff and are not currently available to be reported. An extended follow-up is needed to substantiate the benefit to overall survival with this combination regimen. An ongoing international phase 3 trial (HARMONi-3) is investigating ivonescimab plus chemotherapy versus pembrolizumab plus chemotherapy in patients with untreated, advanced NSCLC, with primary endpoints of progression-free survival and overall survival (NCT05899608).

In conclusion, in patients with previously untreated, advanced squamous NSCLC, ivonescimab plus chemotherapy showed significantly prolonged progression-free survival compared with tislelizumab plus chemotherapy, regardless of the PD-L1 status, along with a manageable safety profile. This regimen could provide a new treatment option for this patient population.

Contributors

SL was the principal investigator for the study. ZC, FY, ZJ, LS, LW, ZH, YF, YZ, XL, HX, XiM, YL, ZZ, HL, XuelM, XuezM, QS, ZhoZ, RY, PW, PP, XA, JL[1], XP, ZW, JF, MH, YH, SG, JuL, HW, JZ, QC, XuL, SY, HW, HS, YJ, MZ, CC, KT, ZL, DLi, ZhiZ, JL[2], JZ, HoY, YD, HY, JS, and HC recruited patients and collected data. DLu and MH analysed the data. SL, ZC, FY, ZJ, LS, LW, WL, ZMW, BL, and MX participated in the design of the trial, interpreted the results, and reviewed the original draft of the manuscript. SL, BL, and MX accessed and verified the data in the study. All authors had access to all the data and reviewed and approved the submission of the article for publication.

Declaration of interests

SL reports receipt of research support from AstraZeneca, Hutchison, BMS, Heng Rui, Beigene, and Hansoh; and speaker fees from AstraZeneca, Roche, Hansoh, and Hengrui Therapeutics. SL is also an advisor and consultant of AstraZeneca, Pfizer, Hutchison MediPharma, ZaiLab, Yuhan Corporation, Menarini, InventisBio, Shanghai Fosun Pharmaceutical (Group), and Simcere Zaiming Pharmaceutical; and an independent director and board member of Innovent Biologics. WL, DLu, MH, ZMW, BL, and MX are employees of Akeso Biopharma. All other authors declare no competing interests.

Data sharing

The individual participant data will be ready for sharing after the indication of this product has been approved by major health authorities, including the Centre for Drug Evaluation (China), US Food and Drug Administration, and European Medicines Agency. For academic purposes, the de-identified participant data that support the findings of this study are available from the corresponding author upon reasonable request after completion of the trial and finalisation of the clinical reports. Requests with a methodologically sound proposal will be considered on a case-by-case basis.

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ORIGINAL ARTICLE

Sacituzumab Tirumotecan in EGFR-TKI–Resistant, *EGFR*-Mutated Advanced NSCLC

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ABSTRACT

BACKGROUND

Sacituzumab tirumotecan (sac-TMT) is an antibody–drug conjugate targeting trophoblast cell-surface antigen 2 that has shown significant survival benefits in patients with *EGFR*-mutated non–small-cell lung cancer (NSCLC) that has progressed after epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy and platinum-based chemotherapy.

METHODS

In this phase 3 trial, we enrolled patients with *EGFR*-mutated locally advanced or metastatic nonsquamous NSCLC that had progressed after EGFR-TKI therapy. The patients were randomly assigned, in a 1:1 ratio, to receive sac-TMT monotherapy or pemetrexed plus platinum-based chemotherapy. The primary end point was progression-free survival as assessed by blinded independent review. Overall survival was a hierarchically tested key secondary end point. In the interim analysis of progression-free survival as assessed by blinded independent review, sac-TMT monotherapy met the prespecified criterion for significance (two-sided P<0.0001); we report here the prespecified final analysis of progression-free survival and the preplanned interim analysis of overall survival.

RESULTS

Overall, 376 patients underwent randomization, with 188 assigned to each group. After a median follow-up of 18.9 months, the median progression-free survival was 8.3 months in the sac-TMT group and 4.3 months in the chemotherapy group (hazard ratio for disease progression or death, 0.49; 95% confidence interval [CI], 0.39 to 0.62). Overall survival was significantly longer with sac-TMT than with chemotherapy (hazard ratio for death, 0.60; 95% CI, 0.44 to 0.82; two-sided P=0.001); 18-month overall survival was 65.8% and 48.0%, respectively. Treatment-related adverse events of grade 3 or higher occurred in 58.0% of patients receiving sac-TMT and in 53.8% of those receiving chemotherapy, with the most common being a decreased neutrophil count (39.9% vs. 33.0%); treatment-related serious adverse events occurred in 9.0% and 17.6%, respectively.

CONCLUSIONS

In patients with *EGFR*-mutated advanced or metastatic NSCLC that had progressed after previous EGFR-TKI therapy, progression-free survival and overall survival outcomes were significantly better with sac-TMT than with platinum-based chemotherapy. (Funded by Sichuan Kelun-Biotech Biopharmaceutical; OptiTROP-Lung04 ClinicalTrials.gov number, NCT05870319.)

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A list of the OptiTROP-Lung04 trial Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Epidermal growth factor receptor (*EGFR*) mutations are present in a substantial proportion of patients with non–small-cell lung cancer (NSCLC).[1] For patients with *EGFR*-mutated advanced NSCLC who are not candidates for curative treatment or for those with metastatic disease, third-generation EGFR tyrosine kinase inhibitors (TKIs) are the standard first-line therapy.[2] However, acquired resistance to EGFR-TKIs inevitably develops, and subsequent treatment options are limited.[3,4] Platinum-based doublet chemotherapy remains a standard of care in this context, but its efficacy is modest.[5-7] Recent trials have explored chemotherapy-based combination strategies incorporating ivonescimab (an anti–programmed cell death protein 1 [PD-1] and vascular endothelial growth factor bispecific antibody),[8] sintilimab (a PD-1 inhibitor) with a bevacizumab biosimilar drug,[6] amivantamab (an EGFR and c-Met bispecific antibody) with or without lazertinib (an EGFR inhibitor for patients with *EGFR* exon 19 deletion),[9] and human epidermal growth factor receptor (HER) 3–directed antibody–drug conjugate.[10] These regimens have shown improvements in progression-free survival outcomes; however, overall survival benefits remain uncertain. Thus, there remains a need for new therapies for patients with EGFR-TKI–resistant, *EGFR*-mutated NSCLC.

Sacituzumab tirumotecan (sac-TMT) is an antibody–drug conjugate targeting trophoblast cell-surface antigen 2 (Trop-2) that was developed by conjugating the antibody to a belotecan-derived topoisomerase I inhibitor. Trop-2 is highly expressed in *EGFR*-mutated NSCLC and is associated with resistance to EGFR-TKIs.[11] Among various antigens that can be targeted with antibody–drug conjugates, Trop-2 is the most strongly and selectively expressed target in EGFR-TKI–resistant NSCLC cells.[12] Of note, the presence of *EGFR* mutations has been shown to lead to a significant increase in the internalization and lysosomal uptake of sac-TMT in NSCLC cells.[13] In the phase 1–2 KL264-01 study, sac-TMT showed encouraging antitumor activity in patients with EGFR-TKI–refractory advanced NSCLC who had not received chemotherapy.[13] These findings were further supported by the phase 2, randomized OptiTROP-Lung03 trial, in which sac-TMT showed a significant overall survival benefit over docetaxel in patients with *EGFR*-mutated NSCLC and progression after EGFR-TKI therapy and platinum-based chemotherapy.[14] This phase 3, confirmatory, randomized trial (OptiTROP-Lung04) was conducted to evaluate the efficacy and safety of sac-TMT in patients with *EGFR*-mutated and locally advanced or metastatic NSCLC that had progressed after EGFR-TKI therapy.

METHODS

TRIAL DESIGN AND PATIENTS

We conducted a phase 3, multicenter, open-label, randomized trial at 66 sites in China. Patients 18 to 75 years of age with histologically or cytologically confirmed locally advanced (stage IIIB or IIIC) or metastatic (stage IV) nonsquamous NSCLC who were not candidates for curative surgery or definitive chemoradiotherapy were eligible to enroll in the trial. All the patients had tumors harboring sensitizing *EGFR* mutations, including exon 19 deletions or exon 21 codon p.Leu858Arg (L858R) substitutions. Eligibility criteria required either progression after first- or second-generation EGFR-TKIs with documented T790M-negative status or progression after third-generation EGFR-TKIs regardless of T790M status. A score of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) performance-status scale (range, 0 to 5, with higher scores indicating greater disability) was also required. Patients with brain metastases were eligible if the lesions had been treated and were stable. Full eligibility criteria are specified in the protocol, available with the full text of this article at NEJM.org.

PROCEDURES

The patients were randomly assigned with the use of a centralized stratified block randomization system in a 1:1 ratio to receive either sac-TMT or pemetrexed plus platinum-based chemotherapy. Stratification factors included previous treatment with third-generation EGFR-TKIs (first-line use, second-line use, or no previous use) and brain metastases (presence or absence). Sac-TMT was administered intravenously at a dose of 5 mg per kilogram of body weight on day 1 and day 15 of each 28-day cycle. The chemotherapy regimen consisted of pemetrexed (500 mg per square meter of body-surface area) plus the investigator's choice of carboplatin (area under the curve of 5 mg per milliliter per minute) or cisplatin (75 mg per square meter),

all administered on day 1 of each 21-day cycle for up to four cycles, followed by pemetrexed maintenance therapy. Treatment was continued until the occurrence of disease progression, unacceptable toxic effects, patient withdrawal, or the fulfillment of any other protocol-specified discontinuation criteria. Crossover between trial groups was not allowed; however, patients who were assigned to receive chemotherapy could receive sac-TMT after disease progression, since sac-TMT has been approved and is commercially available. Interventions and dose reductions to alleviate symptoms were permitted (details are provided in Supplementary Methods in the Supplementary Appendix, available at NEJM.org).

ASSESSMENTS

Tumor response and progression were evaluated by blinded independent review according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Adverse events were monitored throughout the trial, coded according to the *Medical Dictionary for Regulatory Activities*, version 26.0, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Adverse events that emerged during treatment were defined as all adverse medical events that occurred or worsened from the time the patient first received the trial treatment until 30 days after the last dose or before the patient started new antitumor therapy (whichever occurred first). Patient-reported outcomes were evaluated with the validated European Organization for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire along with its lung cancer module.[15-17]

END POINTS

The primary end point was progression-free survival as assessed by blinded independent review according to RECIST, version 1.1. Secondary end points included overall survival; progression-free survival as assessed by investigators; objective response (complete or partial response), disease control, and response duration (each assessed by both blinded independent review and investigators); safety; and patient-reported outcomes.

TRIAL OVERSIGHT

This trial was designed by the sponsor, Sichuan Kelun-Biotech Biopharmaceutical, in collaboration with the authors. The protocol and all the amendments were approved by the institutional review board of each participating site. Written informed consent was obtained from all the participants before enrollment. The trial was conducted in accordance with the principles of the Declaration of Helsinki and all applicable local regulations. An independent data monitoring committee oversaw trial conduct, safety, and outcomes. The authors and the sponsor vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The first draft of the manuscript was prepared by authors who are not employees of the sponsor in collaboration with the sponsor, with medical writing support funded by the sponsor. Both the sponsor and the authors were involved in the collection, analysis, and interpretation of the data, and they reviewed and approved the manuscript that was submitted for publication.

STATISTICAL ANALYSIS

We calculated, on the basis of historical data, that approximately 356 participants would have to be enrolled for a total of 249 events (disease progression or death) to occur to give the trial 88% power to detect a hazard ratio of 0.67 for progression-free survival at a one-sided alpha level of 0.025.[6,18] This sample size would also provide the trial with 80% power to detect the difference between the groups in overall survival with the assumption of a hazard ratio of 0.70. Details on the sample size calculation can be found in the protocol.

An interim analysis of progression-free survival was planned to be performed after at least 174 events had been observed. A Lan–DeMets alpha-spending function was used to estimate the O'Brien–Fleming boundary to control the overall type I error. Overall survival was hierarchically tested, and an interim analysis with the use of a similar alpha-spending approach was planned to be performed after 188 deaths had occurred or 24 months after the first participant underwent randomization.

The interim analysis of progression-free survival was conducted with the data-cutoff date of July 11, 2024; the actual alpha level at the interim analysis was 0.0337 (two-sided). The results of the interim analysis were reviewed by the independent data monitoring committee, which reported that the significance boundary for progression-free survival had been met (two-sided

P<0.0001) (Fig. S1). As of the data-cutoff date of July 6, 2025, the preplanned interim analysis of overall survival (actual boundary, two-sided 0.0124, on the basis of 168 deaths observed) and the final analysis of progression-free survival were conducted, the results of which are shown here.

Efficacy analyses were conducted in the intention-to-treat population, which included all the patients who underwent randomization. The safety analysis included all the patients who received at least one dose of trial treatment and had safety assessment data. The Kaplan–Meier method was used to estimate median survival. Stratified Cox proportional-hazards models were used to calculate hazard ratios and corresponding 95% confidence intervals. Between-group comparisons of survival were performed with stratified log-rank tests. Stratified analyses were based on the factors used at randomization. For time-to-event end points, missing data were handled under the assumption of noninformative censoring (see Table S1 in the Supplementary Appendix for detailed censoring rules).

The percentage of patients with an objective response was calculated with exact (Clopper–Pearson) confidence intervals, and between-group differences were assessed with the Cochran–Mantel–Haenszel test with adjustment for stratification factors. In the case of missing data for tumor response in patients who did not receive treatment, who had no postbaseline assessments, or who had imaging that could not be evaluated, the patients were conservatively assumed not to have had a response. Missing data for other end points were assumed to be missing at random. Confidence intervals for end points that were not part of the hypothesis testing were not adjusted for multiplicity and should be interpreted as descriptive only. Prespecified subgroup analyses and a supplementary analysis are detailed in the statistical analysis plan (Supplementary Appendix). All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS AND TREATMENT

Between July 6, 2023, and April 24, 2024, a total of 596 patients were screened, of whom 376 were enrolled and randomly assigned to receive sac-TMT (188 patients) or chemotherapy (188 patients) (Fig. S2). The median age of the patients was 60 years (range, 31 to 75), and 39.6% were men. The majority of the patients (74.5%) had never smoked. Most of the patients (97.6%) had stage IV disease at enrollment. All the patients had an ECOG performance-status score of 0 or 1 (20.7% and 79.3%, respectively). Most of the patients (94.7%) had received previous third-generation EGFR-TKIs, particularly as first-line therapy (in 62.5%). The baseline characteristics of the patients were generally balanced between the two groups (Table 1). This trial was conducted in China and enrolled only Asian persons. The characteristics of the patients were largely representative of the broad population of Chinese patients with *EGFR*-mutated NSCLC (Table S2).

As of the data-cutoff date of July 6, 2025, a total of 40 patients (21.3%) in the sac-TMT group and 3 patients (1.6%) in the chemotherapy group were still receiving trial treatments (Fig. S2). All the patients were included in the intention-to-treat population, whereas the safety population included 188 patients in the sac-TMT group and 182 patients in the chemotherapy group (6 patients were excluded because they underwent randomization but did not receive trial treatment).

PROGRESSION-FREE SURVIVAL

After a median follow-up of 18.9 months, disease progression (as assessed by blinded independent review) or death had occurred in 144 patients (76.6%) in the sac-TMT group and in 159 patients (84.6%) in the chemotherapy group. The median progression-free survival as assessed by blinded independent review was longer among the patients in the sac-TMT group (8.3 months; 95% confidence interval [CI], 6.7 to 9.9) than among those in the chemotherapy group (4.3 months; 95% CI, 4.2 to 5.5), with a hazard ratio for disease progression or death of 0.49 (95% CI, 0.39 to 0.62). Progression-free survival at 12 months was 32.3% (95% CI, 25.5 to 39.2) in the sac-TMT group and 7.9% (95% CI, 4.4 to 12.8) in the chemotherapy group (Fig. 1A). The most common sites of progression were lung and central nervous system (Table S3). Results according to investigator assessment were consistent with those by blinded independent review, with a median progression-free survival of 8.4 months (95% CI, 7.1 to 9.7) among the patients in the sac-TMT group and 4.8 months (95% CI, 4.2 to 5.5) among those in the chemotherapy group, and with a hazard ratio of 0.51 (95% CI, 0.41 to 0.65).

Table 1. **Baseline Characteristics of the Patients (intention-to-Treat Population).***

Characteristic	Sacituzumab Tirumotecan (N=188)	Chemotherapy (N=188)
Age		
Median (range) — yr	60 (31–75)	59 (33–75)
≥65 yr — no. (%)	58 (30.9)	51 (27.1)
Male sex — no. (%)	66 (35.1)	83 (44.1)
Asian race — no. (%)	188 (100.0)	188 (100.0)
Smoking history — no. (%)		
Current or former smoker	43 (22.9)	53 (28.2)
Never smoked	145 (77.1)	135 (71.8)
ECOG performance-status score — no. (%)†		
0	35 (18.6)	43 (22.9)
1	153 (81.4)	145 (77.1)
Adenocarcinoma — no. (%)	188 (100.0)	188 (100.0)
Disease stage — no. (%)‡		
IIIB or IIIC	6 (3.2)	3 (1.6)
IV	182 (96.8)	185 (98.4)
Brain metastases — no. (%)	33 (17.6)	36 (19.1)
Liver metastases — no. (%)	25 (13.3)	33 (17.6)
≥3 Metastatic sites — no. (%)	128 (68.1)	126 (67.0)
EGFR mutation subtype — no. (%)§		
Exon 21 L858R substitution	84 (44.7)	71 (37.8)
Exon 19 deletion	106 (56.4)	118 (62.8)
Other	8 (4.3)	7 (3.7)
T790M mutation status — no. (%)¶		
Negative	48 (25.5)	40 (21.3)
Positive	29 (15.4)	36 (19.1)
Unknown	111 (59.0)	112 (59.6)
Previous third-generation EGFR-TKI — no.(%)‖	178 (94.7)	178 (94.7)
First-line therapy	118 (62.8)	117 (62.2)
Second-line therapy	60 (31.9)	60 (31.9)

* The intention-to-treat population included all the patients who underwent randomization. TKI denotes tyrosine kinase inhibitor.

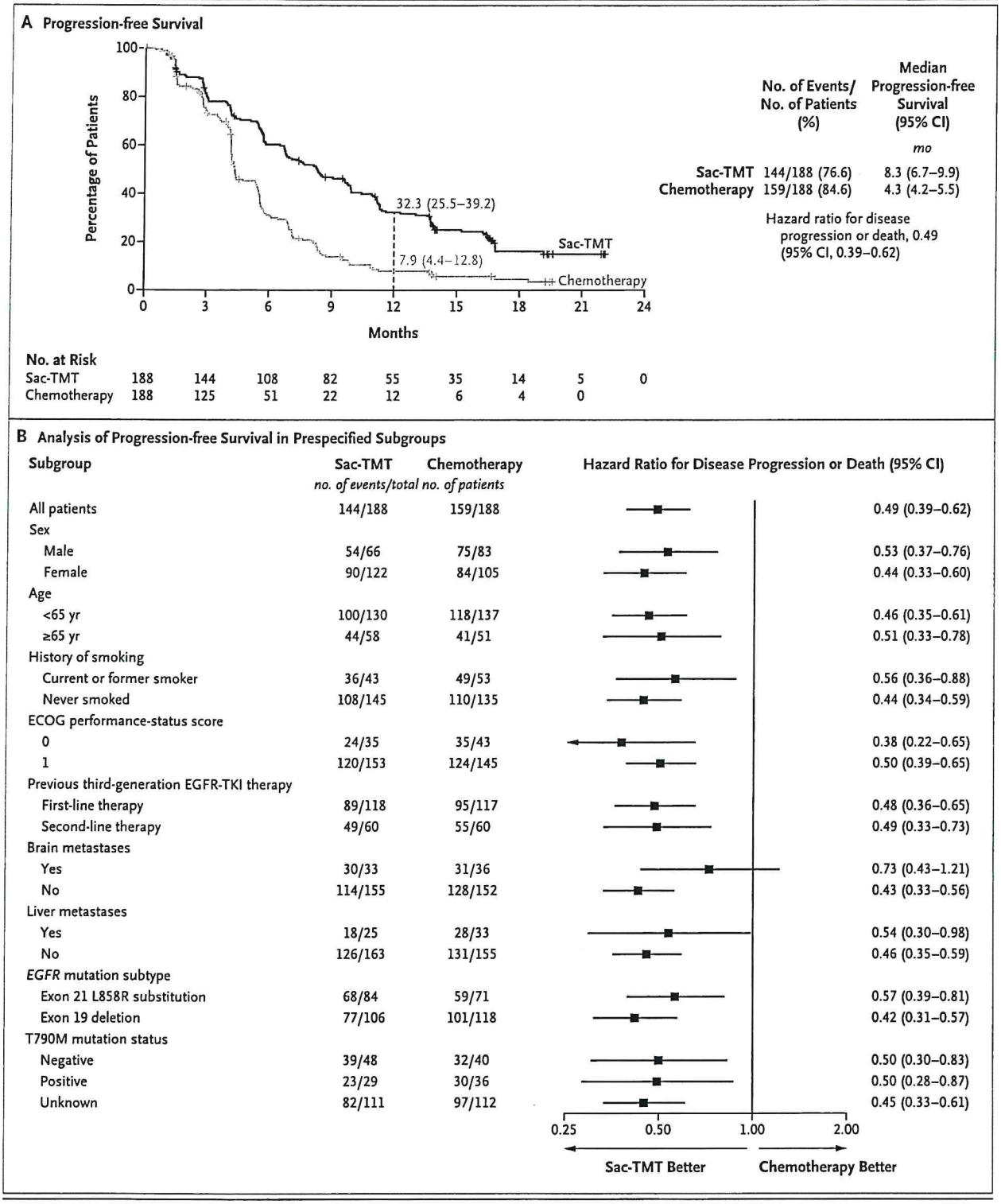
† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.

‡ Disease stage was determined according to the American Joint Committee on Cancer, 8th edition, tumor–node–metastasis staging system.

§ The sum of percentages exceeds 100 because of overlapping mutations in some patients. The subcategory "Other" includes other *EGFR* mutations co-occurring with exon 21 L858R substitution or exon 19 deletion.

¶ The high percentage of patients with unknown T790M status reflects the eligibility criterion allowing patients to be enrolled if their disease had progressed after they had received treatment with third-generation EGFR-TKIs regardless of T790M mutation status. Many such patients lacked T790M testing results.

‖ The total number of patients who received previous treatment with third-generation EGFR-TKIs (356) does not equal the sum of patients who received first-line or second-line third-generation EGFR-TKIs (355) because one patient in the chemotherapy group had previously received osimertinib but discontinued it owing to toxic effects. This patient's disease later progressed after treatment with a second-generation EGFR-TKI, and the patient was enrolled in the trial (T790M mutation negative). Consequently, this patient is categorized as having previous third-generation EGFR-TKI use but is not included in the count for first-line or second-line third-generation EGFR-TKI therapy.



Progression-free survival at 12 months according to investigator assessment was 34.7% (95% CI, 27.7 to 41.7) and 10.7% (95% CI, 6.5 to 16.0), respectively (Fig. S3A). The progression-free survival benefit with sac-TMT appeared to be consistent across most of the prespecified subgroups; however, the confidence intervals crossing 1.00 should be interpreted with caution because of

Figure 1 (facing page). **Final Analysis of Progression-free Survival.**

Shown are the results in the intention-to-treat population (all 376 patients who underwent randomization) as of the data-cutoff date of July 6, 2025. Panel A shows Kaplan–Meier estimates for the final analysis of progression-free survival as assessed by blinded independent review. Panel B shows a forest plot of progression-free survival as assessed by blinded independent review in prespecified subgroups.
Progression-free survival was defined as the time from randomization to the first documented disease progression or death from any cause. Tumor assessments were conducted by blinded independent review according to Response Evaluation Criteria in Solid Tumors, version 1.1. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. Confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. Sac-TMT denotes sacituzumab tirumotecan.

the limited size of the subgroups (Fig. 1B and Fig. S3B).

OVERALL SURVIVAL

At the preplanned interim analysis of overall survival, 67 deaths (35.6% maturity) had occurred in the sac-TMT group and 101 deaths (53.7% maturity) had occurred in the chemotherapy group after a median follow-up of 18.9 months. Overall survival was significantly longer with sac-TMT than with chemotherapy (median, could not be estimated vs. 17.4 months), with a hazard ratio for death of 0.60 (95% CI, 0.44 to 0.82) and a two-sided P value of 0.001, which crossed the prespecified significance boundary (two-sided alpha of 0.0124). Overall survival at 18 months was 65.8% (95% CI, 58.3 to 72.3) with sac-TMT and 48.0% (95% CI, 40.2 to 55.4) with chemotherapy (Fig. 2A).

Of the patients who discontinued the trial treatment (148 patients in the sac-TMT group and 179 in the chemotherapy group), 72.3% and 85.5%, respectively, received subsequent anticancer treatment. Among the patients who discontinued the trial treatment, 41.9% of those in the sac-TMT group and 53.6% of those in the chemotherapy group received subsequent chemotherapy; 37.2% and 12.8%, respectively, received pemetrexed-based chemotherapy. Subsequent antibody–drug conjugates were used in 1.4% of the patients in the sac-TMT group and in 19.6% of those in the chemotherapy group (Table S4). In the supplementary analysis, in which data were censored at the start date of subsequent antibody–drug conjugate treatment, the hazard ratio for death was 0.56 (95% CI, 0.41 to 0.77), and overall survival at 18 months was 66.1% (95% CI, 58.6 to 72.6) in the sac-TMT group and 44.6% (95% CI, 35.9 to 52.9) in the chemotherapy group (Fig. S4).

Analyses in the prespecified subgroups are shown in Figure 2B. Among the patients with brain metastases, the hazard ratio for death was 0.65 (95% CI, 0.32 to 1.30); among those with liver metastases, the hazard ratio was 0.53 (95% CI, 0.26 to 1.10). The wide confidence intervals for both of these subgroups (brain and liver metastases) were a reflection, in part, of the small numbers of patients.

RESPONSE

The percentage of patients with an objective response as assessed by blinded independent review was 60.6% (95% CI, 53.3 to 67.7) in the sac-TMT group and 43.1% (95% CI, 35.9 to 50.5) in the chemotherapy group, which yielded an estimated between-group difference of 17.0 percentage points (95% CI, 7.0 to 27.1) (Table 2). The median duration of response was 8.3 months (95% CI, 6.2 to 10.0) with sac-TMT and 4.2 months (95% CI, 3.0 to 4.4) with chemotherapy, and the estimated percentage of patients with a response duration of at least 12 months was 36.3% (95% CI, 27.3 to 45.3) and 8.1% (95% CI, 3.3 to 15.8), respectively (Fig. S5). These findings were consistent with those according to investigator assessment (Table S5).

SAFETY

In the safety population, as of the data-cutoff date of July 6, 2025, the median duration of treatment was 9.6 months (range, 0.5 to 23.5) in the sac-TMT group and 4.9 months (range, 0.7 to 22.6) in the chemotherapy group (Table S6). Adverse events that emerged during treatment are shown in Table S7. Most of the patients had treatment-related adverse events (100% in the sac-TMT group and 98.4% in the chemotherapy group). Treatment-related adverse events of grade 3 or higher were reported in 58.0% of the patients in the sac-TMT group and in 53.8% of those in the chemotherapy group (Table 3). Treatment-related serious adverse events occurred less frequently in the sac-TMT group than in the chemotherapy group (9.0% vs. 17.6%); details of the

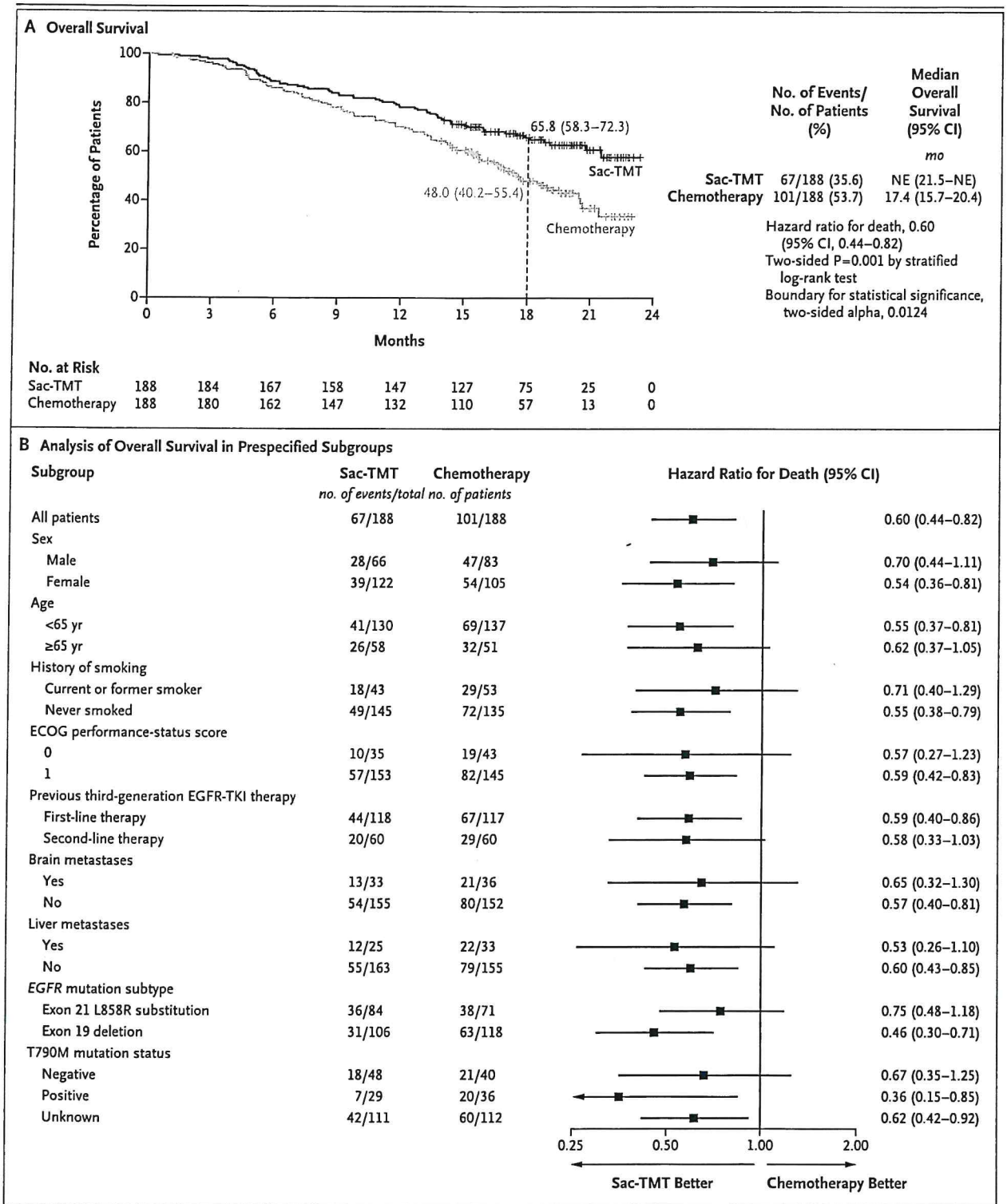


Figure 2. **Interim Analysis of Overall Survival.**

Shown are the results from the intention-to-treat population (all 376 patients who underwent randomization) as of the data-cutoff date of July 6, 2025. Panel A shows Kaplan–Meier estimates of overall survival. Panel B shows a forest plot of overall survival in prespecified subgroups. Overall survival was defined as the time from randomization to death from any cause. For Panel B, the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. NE denotes could not be estimated.

Table 2. Efficacy End Points as Assessed by Blinded Independent Review (Intention-to-Treat Population).*

End Point	Sacituzumab Tirumotecan (N=188)	Chemotherapy (N=188)	Difference (95% CI)
Best overall response — no. (%)			
Complete response	1 (0.5)	0	
Partial response	113 (60.1)	81 (43.1)	
Stable disease	50 (26.6)	70 (37.2)	
Progressive disease	20 (10.6)	26 (13.8)	
Imaging could not be evaluated	1 (0.5)	0	
No assessment†	3 (1.6)	11 (5.9)	
Objective response — no. (% [95% CI])‡	114 (60.6 [53.3–67.7])	81 (43.1 [35.9–50.5])	17.0 (7.0 to 27.1)
Disease control — no. (% [95% CI])§	164 (87.2 [81.6–91.6])	151 (80.3 [73.9–85.7])	6.7 (–0.7 to 14.0)
Median response duration (95% CI) — mo¶	8.3 (6.2–10.0)	4.2 (3.0–4.4)	
Response duration ≥12 mo (95% CI) — %‖	36.3 (27.3–45.3)	8.1 (3.3–15.8)	

* Tumor response was evaluated by blinded independent review according to the Response Evaluation Criteria in Solid Tumors, version 1.1. The data-cutoff date was July 6, 2025. The intention-to-treat population included all the patients who underwent randomization. Confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. The between-group difference was estimated with the Cochran–Mantel–Haenszel test.

† Three patients in the sac-TMT group and 11 in the chemotherapy group had no postbaseline tumor imaging assessments. Among them, 6 patients in the chemotherapy group did not receive treatment and therefore had no post-treatment tumor evaluations.

‡ Objective response was defined as a complete or partial response.

§ Disease control was defined as a complete response, partial response, or stable disease.

¶ Response duration was defined as the time from the first documentation of response to disease progression or death, whichever occurred first. The median response duration was estimated with the Kaplan–Meier method, with its 95% confidence interval calculated by the Brookmeyer–Crowley method.

‖ The percentages of patients with a response duration of at least 12 months were estimated with the Kaplan–Meier method, and the corresponding 95% confidence intervals were estimated with the exponential Greenwood formula.

events are shown in Table S8. The treatment-related adverse event of grade 3 or higher that occurred most frequently in both groups was a decreased neutrophil count (39.9% with sac-TMT vs. 33.0% with chemotherapy). The use of granulocyte colony-stimulating factor was recorded in 59.0% of the patients in the sac-TMT group and in 57.7% of those in the chemotherapy group. Febrile neutropenia occurred in one patient (0.5%) in the sac-TMT group and in five patients (2.7%) in the chemotherapy group. Sac-TMT was associated with a lower incidence of anemia of grade 3 or higher than chemotherapy (11.2% vs. 14.3%), as well as a lower incidence of thrombocytopenia of grade 3 or higher (2.1% vs. 16.5%). None of the treatment-related adverse events led to treatment discontinuation in the sac-TMT group (Table 3).

Regarding drug-related adverse events of special interest (Table S9), the sac-TMT group had a higher incidence of stomatitis than the chemotherapy group (64.4% vs. 4.9%). In the sac-TMT group, grade 1 stomatitis occurred in 42 patients (22.3%), grade 2 in 70 patients (37.2%), and grade 3 in 9 patients (4.8%); no cases of grade 4 or 5 were reported. A total of 19 patients (10.1%) in the sac-TMT group had dose reductions because of stomatitis, but no discontinuations occurred because of stomatitis. With appropriate interventions and dose reductions to alleviate symptoms, all nine cases of grade 3 stomatitis improved to grade 2 or lower without treatment discontinuation within a median of 10 days after diagnosis. Ocular-surface toxic effects (e.g., dry eye syndrome, increased lacrimation, and keratitis) occurred in 9.6% of the patients in the sac-TMT group and in 0.5% of those in the chemotherapy group, with no cases of grade 3 or higher (Table S9). Only one infusion-related reaction (grade 2) was reported, which was in the sac-TMT group.

Table 3. **Treatment-Related Adverse Events (Safety Population).***

Event	Sacituzumab Tirumotecan (N=188)		Chemotherapy (N=182)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
	number of patients (percent)			
Any treatment-related adverse event	188 (100.0)	109 (58.0)	179 (98.4)	98 (53.8)
Leading to dose reduction	57 (30.3)	—	41 (22.5)	—
Leading to dose interruption	69 (36.7)	—	60 (33.0)	—
Leading to treatment discontinuation	0	—	1 (0.5)	—
Leading to death†	0	—	1 (0.5)	—
Any treatment-related serious adverse event	17 (9.0)	—	32 (17.6)	—
Treatment-related adverse event with an incidence of ≥10% in either group				
Anemia	159 (84.6)	21 (11.2)	139 (76.4)	26 (14.3)
White-cell decreased	157 (83.5)	52 (27.7)	127 (69.8)	40 (22.0)
Alopecia	157 (83.5)	0	17 (9.3)	0
Neutrophil count decreased	142 (75.5)	75 (39.9)	126 (69.2)	60 (33.0)
Stomatitis‡	121 (64.4)	9 (4.8)	9 (4.9)	0
Nausea	89 (47.3)	1 (0.5)	86 (47.3)	2 (1.1)
Anorexia	78 (41.5)	0	58 (31.9)	0
Fatigue	72 (38.3)	7 (3.7)	73 (40.1)	4 (2.2)
Weight loss	52 (27.7)	0	28 (15.4)	1 (0.5)
Thrombocytopenia	51 (27.1)	4 (2.1)	85 (46.7)	30 (16.5)
Vomiting	50 (26.6)	0	39 (21.4)	1 (0.5)
Alanine aminotransferase increased	46 (24.5)	1 (0.5)	63 (34.6)	2 (1.1)
Constipation	39 (20.7)	0	31 (17.0)	0
Aspartate aminotransferase increased	35 (18.6)	1 (0.5)	63 (34.6)	2 (1.1)
Rash	35 (18.6)	0	14 (7.7)	0
Lymphocyte count decreased	30 (16.0)	6 (3.2)	23 (12.6)	7 (3.8)
Hypoalbuminemia	23 (12.2)	0	27 (14.8)	0
γ-Glutamyltransferase increased	20 (10.6)	2 (1.1)	27 (14.8)	3 (1.6)
Hyperuricemia	20 (10.6)	0	17 (9.3)	0
Diarrhea	19 (10.1)	1 (0.5)	6 (3.3)	0
Hypokalemia	14 (7.4)	4 (2.1)	23 (12.6)	7 (3.8)

* The data-cutoff date for the safety analysis was July 6, 2025. The safety population included all the patients who received at least one dose of the assigned trial treatment and underwent a safety assessment. Adverse events were coded according to the *Medical Dictionary for Regulatory Activities*, version 26.0, and graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Adverse events that emerged during treatment were defined as all adverse medical events that occurred or worsened from the time the patient first received the trial treatment until 30 days after the last dose or before the patient started new antitumor therapy (whichever occurred first).

† One patient (0.5%) in the chemotherapy group died from a treatment-related adverse event (cardiorespiratory arrest).

‡ Stomatitis was reported as a group term that included stomatitis, oral ulcer, and aphthous ulcer. In the sac-TMT group, grade 1 stomatitis occurred in 42 patients (22.3%), grade 2 in 70 (37.2%), and grade 3 in 9 (4.8%); no cases of grade 4 or 5 were reported. In the chemotherapy group, 7 patients (3.8%) had grade 1 stomatitis and 2 (1.1%) had grade 2 stomatitis.

No drug-related interstitial lung disease or pneumonitis was reported in the sac-TMT group.

PATIENT-REPORTED OUTCOMES

Among the patients who underwent randomization, 97.3% of the patients in the sac-TMT group and 89.9% of those in the chemotherapy group were able to be evaluated for quality of life. The time to a deterioration of quality of life related to global health status and to a deterioration of clinical status defined by the presence of key lung cancer–related symptoms including dyspnea, cough, and chest pain over the duration of trial treatment appeared to be longer with sac-TMT than with chemotherapy (Table S10 and Fig. S6). The curves for these patient-reported outcomes showed a slight overlap during the initial 3-month period and consistent separation thereafter.

DISCUSSION

In this phase 3, randomized trial, sac-TMT led to significantly better progression-free survival and overall survival outcomes than platinum-based chemotherapy in patients with EGFR-TKI–resistant, *EGFR*-mutated advanced NSCLC. These benefits appeared to be generally consistent across the subgroups. Sac-TMT was associated with a lower incidence of treatment-related serious adverse events and hematologic toxic effects, such as anemia and thrombocytopenia, than chemotherapy. No new safety signals were identified.

Recent therapeutic advances have primarily involved multiagent regimens combining chemotherapy with an immune checkpoint inhibitor, antiangiogenic agent, or bispecific EGFR and c-Met antibody or a HER3-directed antibody–drug conjugate, as investigated in the HARMONi-A, ORIENT-31, MARIPOSA-2, and HERTHENA-Lung02 trials, respectively, but the overall survival benefit did not reach significance.[6,8-10] Of note, sac-TMT monotherapy in our trial showed a significant benefit at the preplanned interim analysis of overall survival after a median follow-up of 18.9 months.

Recent in vitro experiments showed that the presence of *EGFR* mutations in NSCLC cells markedly increased sac-TMT internalization and lysosomal uptake as compared with wild-type cells.[13] *EGFR*-mutated NSCLC cells with EGFR-TKI resistance showed even greater sac-TMT uptake than cells that had not received a TKI. This enhanced internalization further translated into higher antitumor activity in *EGFR*-mutated than in wild-type patient-derived lung cancer organoids.[13] These findings contribute to an understanding of the significant survival benefit observed with sac-TMT as compared with docetaxel in the OptiTROP-Lung03 trial, which specifically enrolled patients with NSCLC harboring sensitizing *EGFR* mutations,[14] whereas other Trop-2-antibody–drug conjugates have not shown a significant survival benefit in unselected NSCLC populations with or without actionable genomic alterations.[19,20] The overall survival benefit shown in the present trial further supports the potent antitumor efficacy of sac-TMT in *EGFR*-mutated NSCLC in the context of EGFR-TKI resistance.

Analyses in prespecified subgroups showed patterns favoring sac-TMT for both progression-free and overall survival, including among patients with brain metastases, a population with particularly limited treatment options and an unfavorable prognosis.[21] Since first- and second-generation EGFR-TKIs remain a recommendation for first-line therapy according to the Chinese guidelines, a small proportion of patients in our trial with negative T790M mutation status had received first- or second-generation EGFR-TKIs. Treatment efficacy with sac-TMT was seen in patients whose tumors had progressed after previous treatment with third-generation EGFR-TKIs — the current standard for *EGFR*-mutated advanced NSCLC — either as first-line or second-line therapy.[22-24] These collective findings reinforce sac-TMT as an effective therapeutic option for the broad population of patients with *EGFR*-mutated advanced NSCLC with progression after EGFR-TKIs.

The safety results are consistent with those in previous reports of sac-TMT and suggest that no new safety signals were observed.[13,14,25,26] Sac-TMT was associated with a higher incidence of stomatitis than chemotherapy, with most cases being mild and with grade 3 or higher cases reported in very few patients (4.8%; all were grade 3). Furthermore, the time to deterioration of global quality of life was longer with sac-TMT than with chemotherapy, which indicated that the adverse

events did not compromise global quality of life. With sufficient premedication, only one infusion-related reaction (grade 2) was reported in the sac-TMT group. Other drug-related adverse events of special interest were rare, with a low incidence of ocular-surface toxic effects, and no interstitial lung disease or pneumonitis was observed.

A strength of our trial is that the results for overall survival reached statistical significance. A limitation is that although this trial used a multicenter design, it was conducted in one region and enrolled only Asian persons, which raises a question regarding the ability to extrapolate these outcomes to other patient groups. An exploration of biomarkers in *EGFR*-mutated NSCLC may be valuable for determining patient selection,[27] and future studies may focus on this question.

Currently, other active agents, such as amivantamab or ivonescimab, are typically administered in combination with chemotherapy and have shown limited or uncertain overall survival benefits. On the other hand, sac-TMT was administered as monotherapy in this trial and has shown significant progression-free survival and overall survival benefits over pemetrexed plus platinum-based chemotherapy. Therefore, sac-TMT could be considered to be a favorable treatment option before pemetrexed plus platinum-based chemotherapy for EGFR-TKI–resistant NSCLC is considered.

Among patients with advanced *EGFR*-mutated NSCLC that had progressed after EGFR-TKI therapy, progression-free survival and overall survival outcomes were significantly better with sac-TMT than with standard pemetrexed plus platinum-based chemotherapy.

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ORIGINAL ARTICLE

Survival with Osimertinib plus Chemotherapy in *EGFR*-Mutated Advanced NSCLC

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ABSTRACT

BACKGROUND

The primary analysis of this trial showed that first-line treatment with osimertinib plus chemotherapy with a platinum-based agent and pemetrexed led to significantly longer progression-free survival than osimertinib monotherapy among patients with epidermal growth factor receptor (*EGFR*)–mutated advanced non–small-cell lung cancer (NSCLC). Results from the planned final analysis of overall survival are needed.

METHODS

In this phase 3, international, open-label trial, we randomly assigned in a 1:1 ratio patients with *EGFR*-mutated (exon 19 deletion or L858R mutation) advanced NSCLC who had not previously received treatment for advanced disease to receive either osimertinib (80 mg once daily) plus chemotherapy with pemetrexed (500 mg per square meter of body-surface area) and a platinum-based agent (cisplatin [75 mg per square meter] or carboplatin [pharmacologically guided dose]) or osimertinib monotherapy (80 mg once daily). The key secondary end point was overall survival.

RESULTS

A total of 557 patients were randomly assigned to the osimertinib plus platinum–pemetrexed group (279 patients) or the osimertinib monotherapy group (278 patients). The median overall survival was 47.5 months in the osimertinib plus platinum–pemetrexed group and 37.6 months in the osimertinib monotherapy group (hazard ratio for death, 0.77; 95% confidence interval, 0.61 to 0.96; P=0.02). Grade 3 or higher adverse events of any cause were reported in 70% of the patients in the osimertinib plus platinum–pemetrexed group and in 34% of the patients in the osimertinib monotherapy group; adverse events leading to the discontinuation of osimertinib were reported in 12% and 7%, respectively.

CONCLUSIONS

Among patients with *EGFR*-mutated advanced NSCLC, first-line treatment with osimertinib plus platinum–pemetrexed led to significantly longer overall survival than osimertinib monotherapy and was associated with an increased risk of reversible adverse events of grade 3 or higher. (Funded by AstraZeneca; FLAURA2 ClinicalTrials.gov number, NCT04035486.)

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*A complete list of the FLAURA2 investigators is provided in the Supplementary Appendix, available at NEJM.org.

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OSIMERTINIB IS A THIRD-GENERATION, irreversible, central nervous system (CNS)–active epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR-TKI) that potently and selectively inhibits both EGFR-TKI–sensitizing and *EGFR* p.Thr790Met (T790M) resistance mutations.[1-6] On the basis of findings from the phase 3, international FLAURA trial,[3,7] osimertinib monotherapy is a preferred first-line treatment for patients with *EGFR*-mutated advanced non–small-cell lung cancer (NSCLC).[8-10]

Findings from previous randomized trials showed prolonged progression-free survival and overall survival with the combination of gefitinib (a first-generation EGFR-TKI) and chemotherapy with a platinum-based agent and pemetrexed, as compared with gefitinib alone.[11-14] The phase 3, international, open-label, randomized FLAURA2 trial evaluated the combination of osimertinib and chemotherapy with a platinum-based agent and pemetrexed as first-line treatment for patients with *EGFR*-mutated advanced NSCLC.[15] In the primary analysis (data cutoff, April 3, 2023), this combination therapy led to significantly longer investigator-assessed progression-free survival than osimertinib monotherapy (hazard ratio for disease progression or death, 0.62; 95% confidence interval [CI], 0.49 to 0.79; P<0.001), and the progression-free survival benefit with osimertinib plus platinum–pemetrexed was consistent across prespecified subgroups.[15] Furthermore, the safety profile of osimertinib plus platinum–pemetrexed was consistent with the established profiles of the individual agents.[15-17]

On the basis of the prolonged progression-free survival and the favorable benefit–risk profile observed in the primary analysis of the FLAURA2 trial, clinical-practice guidelines recommend osimertinib plus platinum–pemetrexed as a first-line treatment option for patients with *EGFR*-mutated advanced NSCLC.[8-10,18-20] Here, we report the results of the planned final analysis of overall survival, the key secondary end point of the trial.

METHODS

PATIENTS

Eligibility criteria have been reported previously[15] and are described in the trial protocol (available with the full text of this article at NEJM.org). In brief, patients were eligible for inclusion in the trial if they were 18 years of age or older (or ≥20 years of age in Japan) and had locally advanced or metastatic nonsquamous NSCLC with local or central confirmation of an *EGFR* mutation (exon 19 deletion or L858R mutation). Patients had not previously received systemic treatment for advanced disease and had a World Health Organization (WHO) performance-status score of 0 or 1 (scores range from 0 to 5, with higher scores indicating greater disability). Patients with asymptomatic or stable CNS metastases were eligible.

TRIAL DESIGN AND TREATMENT

Patients were randomly assigned in a 1:1 ratio to receive either osimertinib plus platinum–pemetrexed or osimertinib monotherapy. Combination therapy consisted of osimertinib (80 mg) administered orally once daily plus chemotherapy with pemetrexed (500 mg per square meter of body-surface area) and a platinum-based agent (the investigator's choice of either cisplatin [75 mg per square meter] or carboplatin [a pharmacologically guided dose defined as an area under the concentration–time curve of 5 mg per milliliter per minute]) administered intravenously once every 3 weeks for four cycles. This induction therapy was followed by maintenance therapy with osimertinib (80 mg once daily) plus pemetrexed (500 mg per square meter once every 3 weeks). Monotherapy consisted of osimertinib (80 mg once daily).

Randomization was stratified according to patient-reported race (Asian Chinese vs. Asian non-Chinese vs. non-Asian), WHO performance-status score (0 vs. 1), and method used for tissue testing for the *EGFR* mutation (central vs. local). The randomized trial treatment was continued until the occurrence of disease progression, which was assessed by the investigator with Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; until the occurrence of unacceptable toxic effects; or until another discontinuation criterion was met. Continuation of trial treatment beyond disease progression was permitted if the investigator determined that the patient had a continued clinical benefit; such treatment was considered to be a continuation of first-line treatment. After the discontinuation of trial treatment, subsequent treatments were chosen by the investigator.

The trial was designed by the sponsor (AstraZeneca) in consultation with the investigators. The sponsor was responsible for data collection

and analysis and had a role in data interpretation. The first draft of the manuscript was written by the authors, with medical writing assistance funded by the sponsor in accordance with Good Publication Practice guidelines.[21] The authors had access to the data and contributed to the development of the manuscript, which included approval of the final version before submission. The authors vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol. Details of trial oversight are provided in the Supplementary Appendix (available at NEJM.org).

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival on the basis of investigator assessment with RECIST, version 1.1; the results of the primary analysis have been reported previously.[15] The key secondary end point was overall survival, which was defined as the time from randomization until death from any cause. Survival status was assessed every 12 weeks until the occurrence of death, withdrawal of consent, or the data cutoff for the final analysis of overall survival. Other secondary end points (assessed in time-to-event analyses) included receipt of a first subsequent treatment or death, second progression-free survival, and receipt of a second subsequent treatment or death; definitions are provided in the Supplementary Appendix. Adverse events with an onset date occurring on or after the date of the first dose, up to and including 28 days after the discontinuation of treatment, and before the start of a subsequent anticancer therapy are reported. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

STATISTICAL ANALYSIS

The full analysis set included all the patients who had undergone randomization and was used for the summary of baseline characteristics and for efficacy assessments. The safety analysis set included all the patients who had undergone randomization and received at least one dose of trial treatment, according to the actual treatment received.

Time-to-event end points, including overall survival, were analyzed with a log-rank test that was stratified according to patient-reported race, WHO performance-status score, and method used for tissue testing for the *EGFR* mutation. The Efron method was used for handling ties. For overall survival, proportional hazards were tested by first examining plots of complementary log–log (event times) as compared with log (time) and then fitting a time-dependent covariate (adding a treatment-by-time or treatment-by-natural log [time] interaction term). Median values with 95% confidence intervals were calculated with the Kaplan–Meier method. An exploratory subgroup analysis of overall survival, which included the same subgroups that were prespecified for the subgroup analysis of progression-free survival, was performed with a Cox proportional-hazards model. In the subgroup analysis, the widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects.

Progression-free survival and overall survival were tested in a hierarchical procedure. Analyses of overall survival were to be performed at the time of the primary analysis of progression-free survival (reported previously) and again at approximately 60% data maturity, when approximately 334 deaths had been observed across the two treatment groups. In the analyses of overall survival, the type I error was controlled at 5% (two-sided) with an O'Brien–Fleming spending rule. In the final analysis of overall survival, statistical significance was defined by a two-sided P value of less than 0.04953. Additional details regarding the testing procedure for overall survival are provided in the Supplementary Appendix. The data cutoff for the final analysis of overall survival was June 12, 2025.

RESULTS

PATIENTS AND TREATMENT

Between June 1, 2020, and December 22, 2021, a total of 557 patients were randomly assigned to the osimertinib plus platinum–pemetrexed group (279 patients) or the osimertinib monotherapy group (278 patients).[15] The characteristics of the patients at baseline were balanced between the two groups (Table S1).[15] The demographic characteristics of the trial population were generally similar to those of an international population of patients with *EGFR*-mutated NSCLC, although Black patients were underrepresented (Table S2).

Overall, 276 patients received osimertinib plus platinum–pemetrexed and 275 received osimer-

tinib monotherapy; 6 patients received no trial treatment. At the data cutoff, the median duration of total exposure to osimertinib (including treatment beyond disease progression) was 30.5 months (range, 0.1 to 59.0) in the osimertinib plus platinum–pemetrexed group and 21.2 months (range, 0.1 to 59.2) in the osimertinib monotherapy group. In the osimertinib plus platinum–pemetrexed group, the median duration of total exposure to pemetrexed was 8.3 months (range, 0.7 to 58.9), with patients receiving a median of 11 cycles (range, 1 to 67), and the median duration of total exposure to carboplatin or cisplatin was 2.8 months (range, 0.7 to 4.1), with patients receiving a median of 4 cycles (range, 1 to 6). The 2 patients who received more than 4 cycles of carboplatin or cisplatin were recorded as having important protocol deviations.

At the data cutoff, osimertinib treatment was ongoing in 76 of the 276 patients (28%) who received the trial treatment in the osimertinib plus platinum–pemetrexed group and in 49 of the 275 patients (18%) who received the trial treatment in the osimertinib monotherapy group (Fig. S1); pemetrexed treatment was ongoing in 12 patients (4%) in the osimertinib plus platinum–pemetrexed group. The most common reasons for the discontinuation of osimertinib were disease progression (occurring in 127 patients [46%] in the osimertinib plus platinum–pemetrexed group and in 185 patients [67%] in the osimertinib monotherapy group) and adverse events (occurring in 34 [12%] and 20 [7%], respectively). The most common reason for the discontinuation of pemetrexed was adverse events (occurring in 139 patients [50%] in the osimertinib plus platinum–pemetrexed group). In the osimertinib plus platinum–pemetrexed group, 77% of the patients completed the 4 planned cycles of carboplatin or cisplatin, and no patients were receiving ongoing carboplatin or cisplatin treatment at the data cutoff.

Overall, osimertinib treatment was continued beyond disease progression (defined according to RECIST or the investigator) in 125 patients (45%) in the osimertinib plus platinum–pemetrexed group and in 171 patients (62%) in the osimertinib monotherapy group. The duration of exposure to osimertinib as treatment beyond disease progression was similar in the two treatment groups (Table S3).

EFFICACY

At the data cutoff, 144 patients (52%) in the osimertinib plus platinum–pemetrexed group and 171 patients (62%) in the osimertinib monotherapy group had died (57% overall data maturity). The median duration of follow-up for overall survival among all the patients was 42.6 months (range, 0.1 to 60.4) in the osimertinib plus platinum–pemetrexed group and 35.7 months (range, 0.1 to 60.1) in the osimertinib monotherapy group. The median overall survival was 47.5 months (95% CI, 41.0 to not calculable) in the osimertinib plus platinum–pemetrexed group and 37.6 months (95% CI, 33.2 to 43.2) in the osimertinib monotherapy group (hazard ratio for death, 0.77; 95% CI, 0.61 to 0.96; P=0.02) (Fig. 1). An early intersection of the Kaplan–Meier curves was observed; separation of the curves in favor of osimertinib plus platinum–pemetrexed started at approximately 16 months and was maintained until the data cutoff. Formal testing of the proportional-hazards assumption did not show significant evidence of a violation (P=0.10 by the Wald chi-square test of the time-dependent interaction coefficient). Overall survival at 36 months was 63% (95% CI, 57 to 69) in the osimertinib plus platinum–pemetrexed group and 51% (95% CI, 45 to 57) in the osimertinib monotherapy group.

Overall survival in prespecified subgroups is shown in Figure 2. Kaplan–Meier plots of overall survival in subgroups defined according to CNS metastases status at baseline and *EGFR* mutation are shown in the Supplementary Appendix. Among patients with CNS metastases at baseline, 36-month overall survival was 57% (95% CI, 48 to 66) in the osimertinib plus platinum–pemetrexed group and 40% (95% CI, 31 to 49) in the osimertinib monotherapy group (Fig. S2); among patients without CNS metastases at baseline, 36-month overall survival was 67% (95% CI, 59 to 74) and 58% (95% CI, 50 to 65), respectively. Among patients with *EGFR* L858R mutations, 36-month overall survival was 54% (95% CI, 44 to 63) in the osimertinib plus platinum–pemetrexed group and 42% (95% CI, 32 to 51) in the osimertinib monotherapy group (Fig. S3); among patients with *EGFR* exon 19 deletions, 36-month overall survival was 69% (95% CI, 61 to 75) and 57% (95% CI, 49 to 64), respectively. Results for other secondary end points are shown in Table S4.

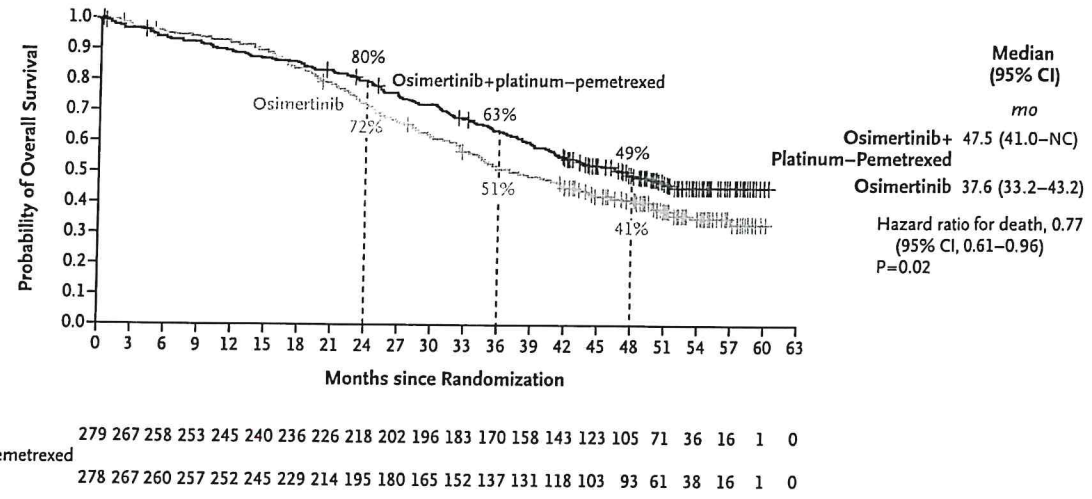

Figure 1. **Overall Survival.**

Kaplan–Meier estimates of overall survival in the full analysis set are shown. Tick marks indicate censored data; patients who had not died at the time of the analysis had their data censored at the last recorded known survival date. Dashed lines indicate the 24-month, 36-month, and 48-month landmark estimates. The median duration of follow-up among patients with censored data was 51.2 months (range, 0.2 to 60.4) in the osimertinib plus platinum–pemetrexed group and 51.3 months (range, 0.1 to 60.1) in the osimertinib monotherapy group; the median duration of follow-up among all the patients, regardless of censoring, was 42.6 months (range, 0.1 to 60.4) and 35.7 months (range, 0.1 to 60.1), respectively. NC denotes not calculable.

FIRST SUBSEQUENT ANTICANCER TREATMENT

Among patients who had discontinued first-line treatment with osimertinib owing to disease progression, 88 of 127 patients (69%) in the osimertinib plus platinum–pemetrexed group and 143 of 185 patients (77%) in the osimertinib monotherapy group received a first subsequent treatment (Fig. 3). In the osimertinib plus platinum–pemetrexed group, the most common first subsequent treatments were platinum-based chemotherapy (received by 39 of 88 patients [44%]) and non–platinum-based chemotherapy (received by 26 of 88 patients [30%]). In the osimertinib monotherapy group, the most common first subsequent treatment was platinum-based chemotherapy (received by 103 of 143 patients [72%]).

SAFETY

Overall, 551 patients received at least one dose of trial treatment (276 in the osimertinib plus platinum–pemetrexed group and 275 in the osimertinib monotherapy group). With more than 2 years of additional follow-up, safety findings were consistent with those reported at the time of the primary analysis (Table 1).[15] The most common adverse events are summarized in Table 2. Grade 3 or higher adverse events of any cause were reported in 193 patients (70%) in the osimertinib plus platinum–pemetrexed group and in 94 patients (34%) in the osimertinib monotherapy group; most of the grade 3 or higher adverse events that were reported in the osimertinib plus platinum–pemetrexed group were related to myelosuppressive effects (Table S5).

Serious adverse events of any cause were reported in 126 patients (46%) in the osimertinib plus platinum–pemetrexed group and in 75 patients (27%) in the osimertinib monotherapy group (Table S6), and adverse events leading to death were reported in 22 (8%) and 10 (4%), respectively (Table S7). Overall, 5 patients (2%) in the osimertinib plus platinum–pemetrexed group and 2 patients (1%) in the osimertinib monotherapy group had adverse events leading to death that were considered by the investigator to be possibly causally related to trial treatment; all these patients had died by the data cutoff for the primary analysis, except for 1 patient in the osimertinib monotherapy group.[15] The adverse events leading to death that were considered by the investigator to be possibly causally related to osimertinib plus platinum–pemetrexed were pneumonia, sepsis, pulmonary embolism, respiratory failure, and cardiac failure (occurring in 1 patient each).

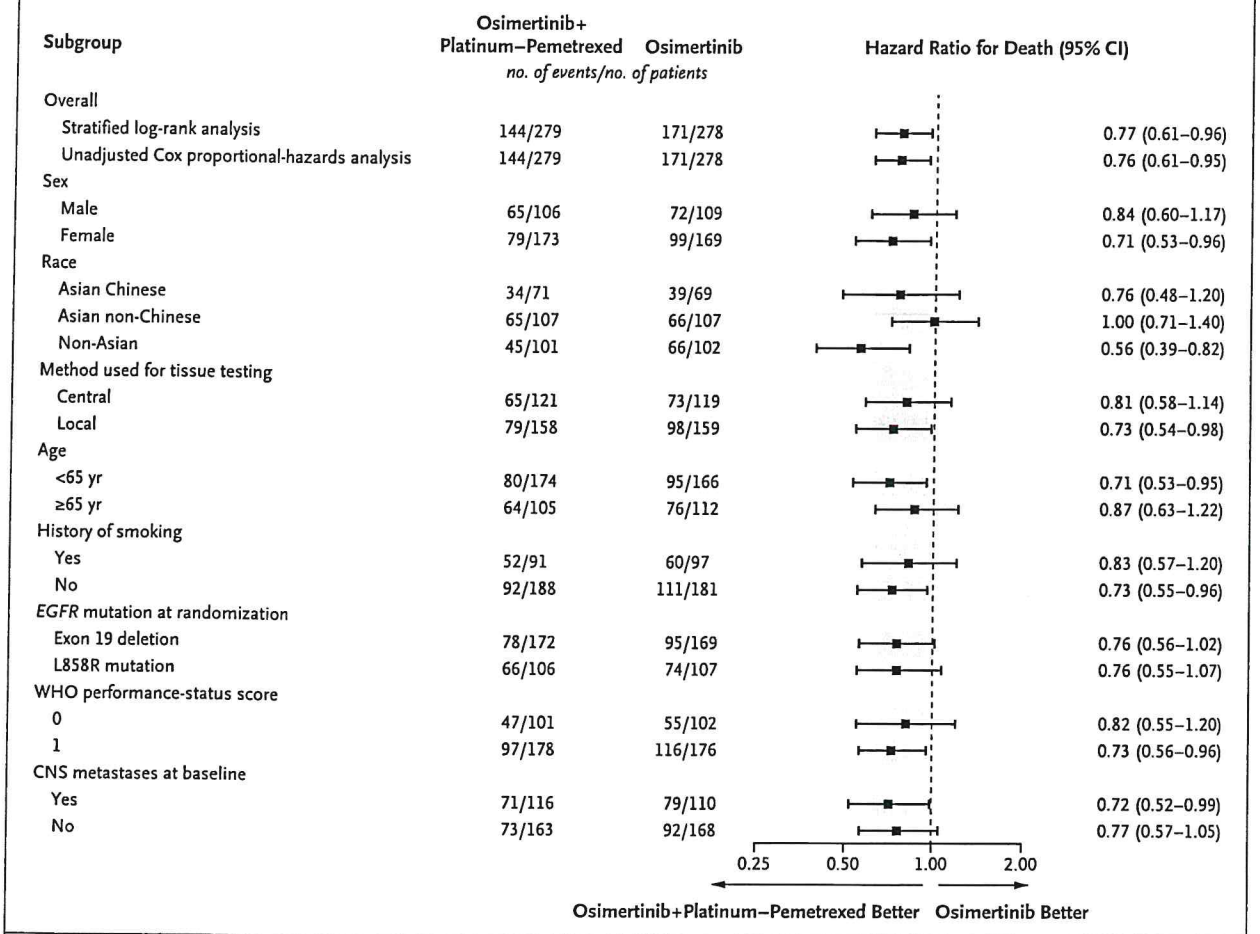

Figure 2. **Subgroup Analysis of Overall Survival.**

A forest plot of overall survival in prespecified subgroups is shown. A hazard ratio of less than 1 indicates a lower risk of death with osimertinib plus platinum–pemetrexed than with osimertinib monotherapy. The Cox proportional-hazards model included the randomized trial treatment, the subgroup covariate of interest, and the treatment according to subgroup interaction. Race was reported by the patient; options were given on a drop-down list at randomization. *EGFR* is the gene that encodes the epidermal growth factor receptor. Patients with co-occurrence of an exon 19 deletion and a L858R mutation were included in the subgroup for exon 19 deletion. World Health Organization (WHO) performance-status scores range from 0 to 5, with higher scores indicating greater disability. A score of 0 indicates that the patient is fully active and able to carry out all predisease activities without restrictions, and a score of 1 indicates that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature, such as light housework or office work. Central nervous system (CNS) metastases status at baseline was based on investigator assessment of data in the electronic case-report form regarding the CNS lesion site at baseline, medical history, surgical history, or history of radiotherapy for CNS metastases. The shaded area indicates the 95% confidence interval for the overall hazard ratio for death among all the patients. In the subgroup analysis, the widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects.

Adverse events leading to the discontinuation of osimertinib were reported in 34 patients (12%) in the osimertinib plus platinum–pemetrexed group and in 20 patients (7%) in the osimertinib monotherapy group. Interstitial lung disease was the most common of these events, occurring in 5 patients (2%) in the osimertinib plus platinum–pemetrexed group and in 6 patients (2%) in the osimertinib monotherapy group (Table S8). (Information on dose modification for osimertinib is provided in the Supplementary Appendix.) Adverse events leading to the discontinuation of pemetrexed were reported in 137 patients (50%) in the osimertinib plus platinum–pemetrexed

group; anemia and neutropenia were the most common of these events, occurring in 16 patients (6%) and 14 patients (5%), respectively (Table S9). Adverse events leading to the discontinuation of carboplatin or cisplatin were reported in 46 patients (17%) in the osimertinib plus platinum–pemetrexed group; thrombocytopenia and decreased neutrophil count were the most common, occurring in 6 (2%) and 5 (2%), respectively (Table S10).

DISCUSSION

Results from the FLAURA2 trial showed significantly longer overall survival with osimertinib plus platinum–pemetrexed than with osimertinib monotherapy as first-line treatment among patients with *EGFR*-mutated advanced NSCLC. With more than 2 years of additional follow-up since the primary analysis, no new toxic effects emerged. The incidence of grade 3 or higher adverse events was greater with osimertinib plus platinum–pemetrexed than with osimertinib monotherapy, a difference driven mainly by myelosuppressive effects, which are expected with a chemotherapy-containing regimen. Overall, the percentages of patients with grade 3 or higher adverse events (70% in the osimertinib plus platinum–pemetrexed group and 34% in the osimertinib monotherapy group) were similar to those reported at the time of the primary analysis (64% and 27%, respectively).[15] Grade 4 adverse events were uncommon.

Data from the time of the primary analysis (data cutoff, April 3, 2023) showed that the onset of most adverse events in the osimertinib plus platinum–pemetrexed group was highest during the induction period, and the frequency decreased over time during the maintenance period.[17] This finding suggests that the burden of toxic effects associated with osimertinib plus platinum–pemetrexed diminishes over time as patients progress from receiving the initial induction therapy to receiving maintenance therapy with osimertinib plus pemetrexed and eventually receiving maintenance therapy with osimertinib alone. Health-related quality-of-life data from the primary analysis suggest that patient quality of life was maintained with the combination therapy[22]; however, quality-of-life data were not collected beyond the data cutoff for the primary analysis. The effect of the duration of exposure to pemetrexed on clinical outcomes requires further investigation.[23]

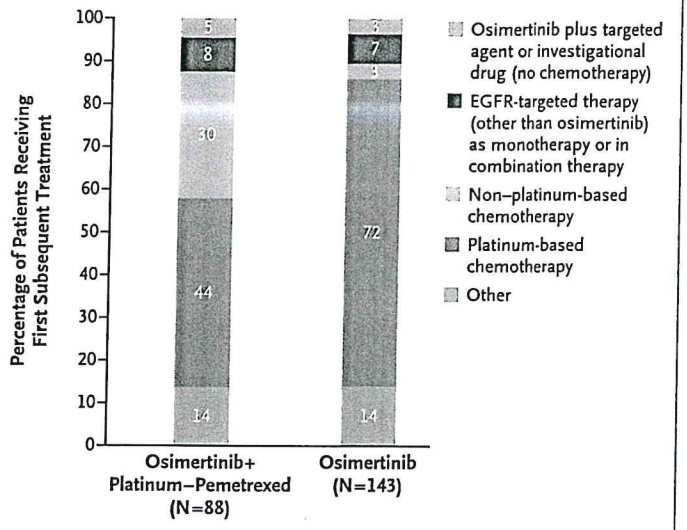

Figure 3. Summary of First Subsequent Treatments Received.

Bar plots of the first subsequent treatments received among patients who had discontinued first-line treatment with osimertinib owing to disease progression are shown. Subsequent treatments were chosen by the investigator. Trial treatment that was continued beyond disease progression was considered to be first-line treatment and is not included here. The "other" category included antibody–drug conjugates, immunotherapies (programmed death 1 and programmed death ligand 1 inhibitors), other investigational anticancer therapies, antiangiogenic therapies (vascular endothelial growth factor [VEGF] and VEGF receptor inhibitors), catequentinib hydrochloride, savolitinib, and unspecified herbal and traditional anticancer medicines. One patient in the osimertinib plus platinum–pemetrexed group and eight patients in the osimertinib monotherapy group received osimertinib in combination with platinum-based doublet chemotherapy as the first subsequent treatment. EGFR denotes epidermal growth factor receptor.

The median overall survival with osimertinib plus platinum–pemetrexed was 47.5 months (95% CI, 41.0 to not calculable). The previous benchmark for overall survival among patients with *EGFR*-mutated advanced NSCLC was set in the FLAURA trial, which established osimertinib monotherapy as standard care by showing significantly longer progression-free survival and overall survival than those seen with first-generation EGFR-TKIs.[8-10,18-20] The median overall survival with osimertinib monotherapy in the FLAURA trial was 38.6 months (95% CI, 34.5 to 41.8),[7] which is consistent with the median overall survival of 37.6 months (95% CI, 33.2 to 43.2) seen in the osimertinib monotherapy group in the FLAURA2 trial. Both results represent an improve-

Table 1. **Summary of Adverse Events.***

Event	Primary Analysis (data cutoff, April 3, 2023)		Final Analysis of Overall Survival (data cutoff, June 12, 2025)	
	Osimertinib + Platinum–Pemetrexed (N=276)	Osimertinib (N=275)	Osimertinib + Platinum–Pemetrexed (N=276)	Osimertinib (N=275)
	number of patients (percent)			
Adverse event of any cause	276 (100)	268 (97)	276 (100)	269 (98)
Grade ≥3 adverse event	176 (64)	75 (27)	193 (70)	94 (34)
Adverse event leading to death	18 (7)	8 (3)	22 (8)	10 (4)
Serious adverse event	104 (38)	53 (19)	126 (46)	75 (27)
Adverse event leading to discontinuation of treatment				
Discontinuation of any trial treatment	132 (48)	17 (6)	150 (54)	20 (7)
Discontinuation of osimertinib	30 (11)	17 (6)	34 (12)	20 (7)
Discontinuation of carboplatin or cisplatin†	46 (17)	—	46 (17)	—
Discontinuation of pemetrexed	119 (43)	—	137 (50)	—
Adverse event considered by the investigator to be possibly causally related to any trial treatment	269 (97)	241 (88)	269 (97)	242 (88)
Grade ≥3 adverse event	146 (53)	29 (11)	152 (55)	35 (13)
Adverse event leading to death	5 (2)	1 (<1)	5 (2)	2 (1)
Serious adverse event	52 (19)	15 (5)	56 (20)	18 (7)

* The safety analysis set included all the patients who had undergone randomization and received at least one dose of trial treatment, according to the actual treatment received. Adverse events with an onset date occurring on or after the date of the first dose, up to and including 28 days after the discontinuation of treatment, and before the start of a subsequent anticancer therapy are reported. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

† Carboplatin or cisplatin treatment was capped at four cycles; 77% of the patients in the osimertinib plus platinum–pemetrexed group completed four cycles.

ment over the median overall survival of 31.8 months (95% CI, 26.6 to 36.0) reported with comparator first-generation EGFR-TKIs in the FLAURA trial.[7]

This prespecified final analysis of overall survival from the FLAURA2 trial confirms that the prolonged antitumor effect that was seen with osimertinib plus platinum–pemetrexed in the primary analysis translates into a significant overall survival benefit, reinforcing the long-term efficacy of the combination therapy. Although most patients in the osimertinib monotherapy group who had discontinued first-line treatment with osimertinib owing to disease progression received platinum-based doublet chemotherapy as the first subsequent treatment, results for overall survival in this group were inferior to those seen with the combination therapy. This observation supports the notion that the initiation of combination therapy from the onset may be a preferred treatment approach, although the trial was not designed to compare sequential treatment (first-line osimertinib monotherapy followed by second-line chemotherapy) with combination treatment (first-line osimertinib plus platinum–pemetrexed chemotherapy), and comparisons between clinical trials are difficult. The overall survival benefit observed with osimertinib plus platinum–pemetrexed as compared with osimertinib monotherapy in the FLAURA2 trial underscores the importance of initiating effective combination therapies as first-line treatment.

The combination therapy used in this trial was associated with a higher incidence of grade 3 or higher adverse events and of adverse events leading to the discontinuation of treatment than osimertinib monotherapy. Most high-grade toxic effects associated with the combination therapy were related to myelosuppressive effects, which are generally dose-related and reversible, with supportive interventions available to ameliorate such effects.[24-31] Data from the phase 3 MARIPOSA

Table 2. **Most Common Adverse Events.***

Event	Osimertinib + Platinum–Pemetrexed (N=276)				Osimertinib (N=275)			
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
	number of patients (percent)									
Anemia	132 (48)	28 (10)	48 (17)	56 (20)	0	31 (11)	19 (7)	8 (3)	4 (1)	0
Diarrhea	129 (47)	84 (30)	36 (13)	9 (3)	0	116 (42)	93 (34)	22 (8)	1 (<1)	0
Nausea	120 (43)	80 (29)	36 (13)	4 (1)	0	32 (12)	26 (9)	6 (2)	0	0
Decreased appetite	90 (33)	51 (18)	30 (11)	9 (3)	0	31 (11)	21 (8)	7 (3)	3 (1)	0
Constipation	89 (32)	65 (24)	23 (8)	1 (<1)	0	31 (11)	25 (9)	6 (2)	0	0
Rash	81 (29)	56 (20)	23 (8)	2 (1)	0	61 (22)	48 (17)	13 (5)	0	0
Fatigue	81 (29)	44 (16)	29 (11)	8 (3)	0	30 (11)	27 (10)	2 (1)	1 (<1)	0
Vomiting	79 (29)	55 (20)	21 (8)	3 (1)	0	20 (7)	15 (5)	4 (1)	1 (<1)	0
Covid-19†	73 (26)	27 (10)	42 (15)	3 (1)	0	47 (17)	22 (8)	25 (9)	0	0
Stomatitis	71 (26)	42 (15)	28 (10)	1 (<1)	0	51 (19)	31 (11)	19 (7)	1 (<1)	0
Paronychia	70 (25)	29 (11)	39 (14)	2 (1)	0	75 (27)	36 (13)	38 (14)	1 (<1)	0
Neutropenia	68 (25)	4 (1)	27 (10)	30 (11)	7 (3)	11 (4)	4 (1)	5 (2)	2 (1)	0
Neutrophil count decreased	65 (24)	6 (2)	27 (10)	25 (9)	7 (3)	18 (7)	7 (3)	9 (3)	2 (1)	0
ALT level increased	58 (21)	36 (13)	17 (6)	5 (2)	0	23 (8)	17 (6)	4 (1)	2 (1)	0
Dry skin	54 (20)	46 (17)	8 (3)	0	0	68 (25)	64 (23)	4 (1)	0	0
Platelet count decreased	53 (19)	20 (7)	12 (4)	18 (7)	3 (1)	22 (8)	19 (7)	3 (1)	0	0
Thrombocytopenia	51 (18)	19 (7)	13 (5)	16 (6)	3 (1)	13 (5)	7 (3)	3 (1)	3 (1)	0
Blood creatinine level increased	50 (18)	35 (13)	15 (5)	0	0	16 (6)	11 (4)	5 (2)	0	0
AST level increased	50 (18)	43 (16)	6 (2)	1 (<1)	0	15 (5)	12 (4)	0	3 (1)	0
White-cell count decreased	46 (17)	9 (3)	28 (10)	8 (3)	1 (<1)	20 (7)	9 (3)	10 (4)	1 (<1)	0
Peripheral edema	44 (16)	34 (12)	10 (4)	0	0	16 (6)	13 (5)	3 (1)	0	0
Cough	43 (16)	32 (12)	11 (4)	0	0	38 (14)	24 (9)	14 (5)	0	0

* Adverse events of any cause that were reported in at least 15% of the patients in either group are listed according to the preferred term from the *Medical Dictionary for Regulatory Activities*, version 27.1. The safety analysis set included all the patients who had undergone randomization and received at least one dose of trial treatment, according to the actual treatment received. Adverse events with an onset date occurring on or after the date of the first dose, up to and including 28 days after the discontinuation of treatment, and before the start of a subsequent anticancer therapy are reported. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. For each patient, only the maximum reported grade for each preferred term is listed. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

† One patient in the osimertinib plus platinum–pemetrexed group died from coronavirus disease 2019 (Covid-19).

trial showed that combination therapy with amivantamab and lazertinib had better efficacy than osimertinib monotherapy among patients with *EGFR*-mutated advanced NSCLC and was also associated with an increased incidence of toxic effects.[32,33] The increased risk of toxic effects associated with these combination therapies underscores the need for clinical vigilance to promptly identify and manage adverse events in routine practice. This consideration may be particularly relevant for chemotherapy-eligible patients who are deemed frail, especially given that such patients are typically underrepresented in clinical trials[34] — including the FLAURA2 trial, in which most participants had a WHO performance-status score of 0 or 1. These factors emphasize the need for shared decision making with patients, in which the greatest survival benefit is balanced against the increased risk of toxic effects from the addition of chemotherapy to osimertinib when used as first-line treatment.

Phase 3 trials of combination therapies with EGFR-TKIs and angiogenesis inhibitors have shown a significant improvement in progression-free survival, but with no corresponding improvement in overall survival.[35-37] Further investigation to determine the reason that an overall survival benefit is observed in some, but not all, trials of EGFR-TKI–based combination therapies is warranted. Combination therapy with an EGFR-TKI and platinum–pemetrexed chemotherapy may be a particularly effective strategy, given that *EGFR* mutations predominantly occur in adenocarcinomas,[38] which express lower levels of thymidylate synthase than other histologic types of NSCLC.[39] An association between lower levels of thymidylate synthase and improved survival outcomes has been reported with the use of pemetrexed.[40]

Most patients in the FLAURA2 trial who discontinued first-line treatment with osimertinib owing to disease progression went on to receive second-line treatment (69% of the patients in the osimertinib plus platinum–pemetrexed group and 77% of those in the osimertinib monotherapy group). Subsequent treatments were chosen by the investigator, and the choices were consistent with current treatment guidelines.[8-10,20] Nearly half the patients in the osimertinib plus platinum–pemetrexed group who discontinued first-line treatment with osimertinib owing to disease progression were rechallenged with platinum-based doublet chemotherapy, and another 30% received non–platinum-based chemotherapy. In most patients who received osimertinib plus platinum–pemetrexed, first-line treatment with osimertinib was continued long after the cessation of pemetrexed maintenance therapy (the median duration of exposure was 30.5 months with osimertinib and 8.3 months with pemetrexed). The long chemotherapy-free period before disease progression might have allowed many patients to receive platinum-based chemotherapy again, although we acknowledge that the choice of subsequent treatment is influenced by multiple factors.

Beyond chemotherapy, new options are emerging for second-line or later treatment that may yield further improvements in overall survival, including antibody–drug conjugates directed toward trophoblast cell surface antigen 2 (TROP2) and cMET-targeted therapies.[41-44] Known acquired resistance mechanisms for osimertinib plus platinum–pemetrexed are similar to those reported for osimertinib monotherapy,[45] which suggests that second-line treatment that targets resistance mechanisms will probably not be influenced by the addition of chemotherapy to osimertinib in first-line treatment. However, additional research would help to inform the best therapeutic sequence, including treatment options that are not guided by biomarkers.

Results from this trial provide evidence that first-line treatment with osimertinib plus platinum–pemetrexed led to significantly longer overall survival than osimertinib monotherapy among patients with *EGFR*-mutated advanced NSCLC.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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First-line Osimertinib + Chemotherapy Versus Osimertinib Monotherapy in EGFRm Advanced NSCLC: FLAURA2 Final Overall Survival

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FLAURA2 phase III study[1]

Patients with untreated locally advanced / metastatic EGFRm NSCLC

Key inclusion criteria:

- Aged ≥18 years
- Pathologically confirmed non-squamous NSCLC
- Ex19del / L858R (local / central test)
- WHO PS 0 / 1
- Stable CNS metastases were allowed
- Brain scans at baseline (MRI / CT; mandatory)

N=557

R 1:1

Stratified by:

- Race (Asian Chinese / Asian non-Chinese / non-Asian)
- EGFRm test (local / central)
- WHO PS (0 / 1)

Osimertinib 80 mg (QD) + pemetrexed 500 mg/m² + carboplatin AUC5 or cisplatin 75 mg/m² (Q3W for 4 cycles for platinum-based treatments)

Maintenance osimertinib 80 mg (QD) + pemetrexed 500 mg/m² (Q3W)

Treatment beyond PD allowed per investigator discretion

Osimertinib 80 mg (QD)

Follow-up:

- RECIST v1.1 assessment at 6 and 12 weeks, then Q12W until RECIST v1.1-defined radiological PD
- Survival follow-up for Q12W until data cut-off for the planned final OS analysis

- **Primary endpoint:** Investigator-assessed PFS (RECIST v1.1)[1]
- **Secondary endpoints included:** OS, TFST, DoR, DCR, PFS2, TSST, HRQoL

OS was a key secondary endpoint*

Final OS analysis performed at 57% maturity

NCT04035486

1. Planchard D, et al. N Engl J Med 2020;389:1935-1948.

*For statistical significance of OS, a two-sided p value of less than 0.04653, as determined by the O'Brien-Fleming spending rule, was required.

AUC, area under the curve; CNS, central nervous system; CT, computed tomography; DCR, disease control rate; DoR, duration of response; EGFRm, epidermal growth factor receptor mutated; Ex19del, exon 19 deletion; HRQoL, health-related quality of life; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, time from randomization to second progression on a subsequent treatment; QD, once daily; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TFST, time to first subsequent treatment or death; TSST, time to second subsequent treatment or death; WHO PS, World Health Organization performance status.

D. Planchard. First-line Osimertinib + Chemotherapy Versus Osimertinib Monotherapy in EGFRm Advanced NSCLC: FLAURA2 Final Overall Survival

Baseline characteristics[1]

Characteristic, %*	Osi + CTx (n=279)	Osi mono (n=278)
Sex: male / female	38 / 62	39 / 61
Age: median (range), years	61 (26–83)	62 (30–85)
Race: Asian Chinese / Asian non-Chinese / non-Asian / missing†	25 / 39 / 35 / <1	25 / 38 / 36 / 1
WHO PS: 0 / 1‡	37 / 62	37 / 63
Smoking status: never / current / former	67 / 1 / 31	65 / 1 / 33
Histology: adenocarcinoma / adenosquamous / other	99 / 1 / 1	99 / 0 / 1
EGFR mutation type: Ex19del / L858R§	61 / 38	60 / 38
Locally advanced / metastatic	5 / 95	3 / 97
CNS metastases present at baseline	42	40
Baseline tumour size: median (range), mm	57 (10–284)	57 (11–221)

Data cut off: 03 April 2023

*Percentages calculated and rounded to nearest whole number. †Race was reported by the patient. ‡One patient in the osi + CTx arm had a WHO PS of 2
§Central and local EGFR mutation test; three patients in the osi + CTx arm and one patient in the osi mono arm had both Ex19del and L858R mutations – one patient in the osi + CTx arm and two patients in the osi mono arm had unknown / not detected EGFR mutations
CNS, central nervous system; CTx, chemotherapy; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; mono, monotherapy; osi, osimertinib; WHO PS, World Health Organization performance status

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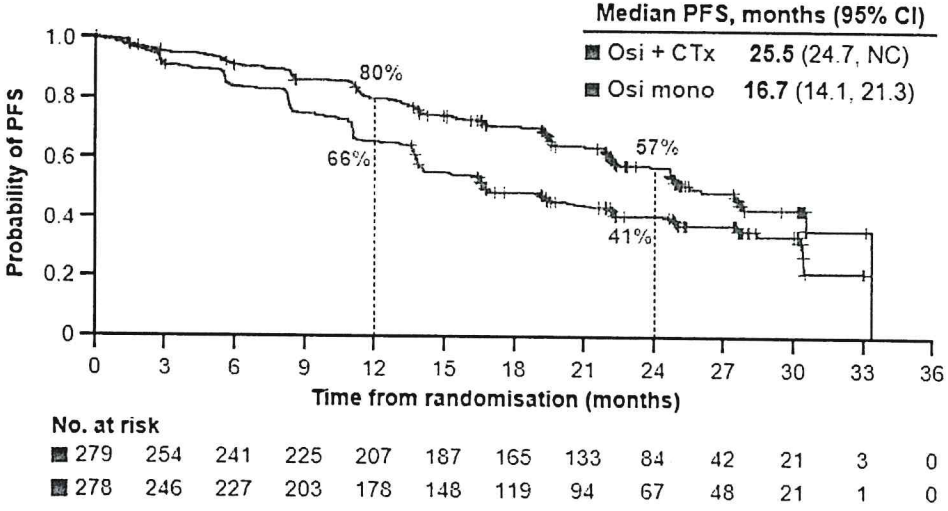
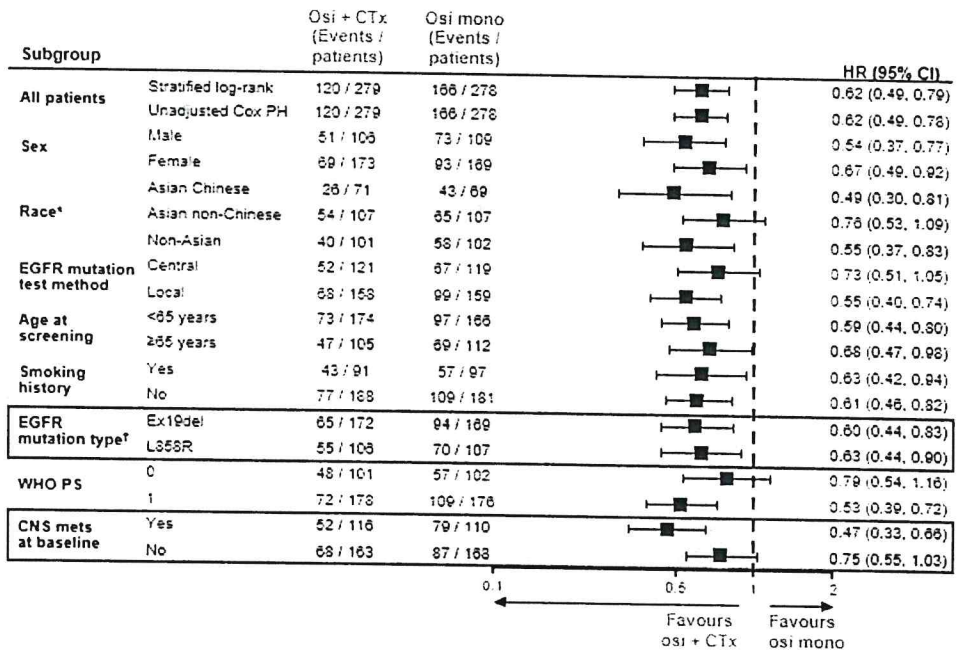
Primary analysis: Progression-free survival[1]

Investigator-assessed PFS: HR=0.62 (95% CI: 0.49, 0.79); p<0.001





Osi + CTx showed a statistically significant and clinically meaningful improvement in PFS versus osi mono; PFS benefit was consistent across predefined subgroups

Figures from N Engl J Med Planchard D, Jänne PA, Cheng Y, et al. Osimertinib with or without Chemotherapy in *EGFR* Mutated Advanced NSCLC. 389:1935-48. Copyright © (2023) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

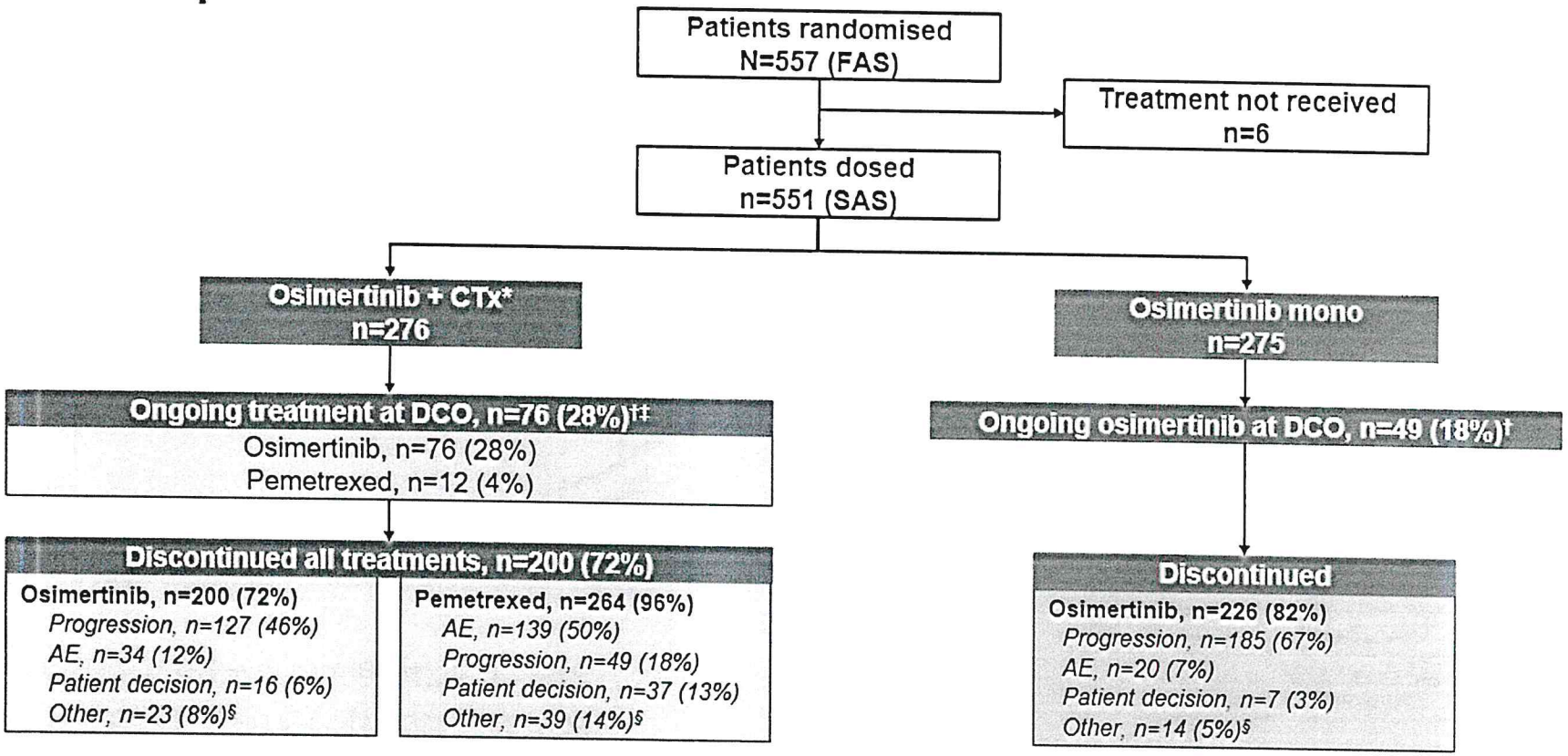
Data cut off, 03 April 2023

1. Planchard D, et al. N Engl J Med 2023;389:1935-1948

D Planchard. First-line Osimertinib + Chemotherapy Versus Osimertinib Monotherapy in EGFRm Advanced NSCLC: FLAURA2 Final Overall Survival

*Race was reported by the patient. †For EGFR mutation type, patients with both Ex19del and L858R mutations were included in the Ex19del group. CI, confidence interval; CNS, central nervous system; CTx, chemotherapy; EGFR, epidermal growth factor receptor; HR, hazard ratio; mets, metastases; mono, monotherapy; NC, not calculable; osi, osimertinib; PFS, progression free survival; PH, proportional hazard; WHO PS, World Health Organization performance status

Patient disposition



D. Planchard. First line Osimertinib + Chemotherapy Versus Osimertinib Monotherapy in EGFRm Advanced NSCLC: FLAURA2 Final Overall Survival

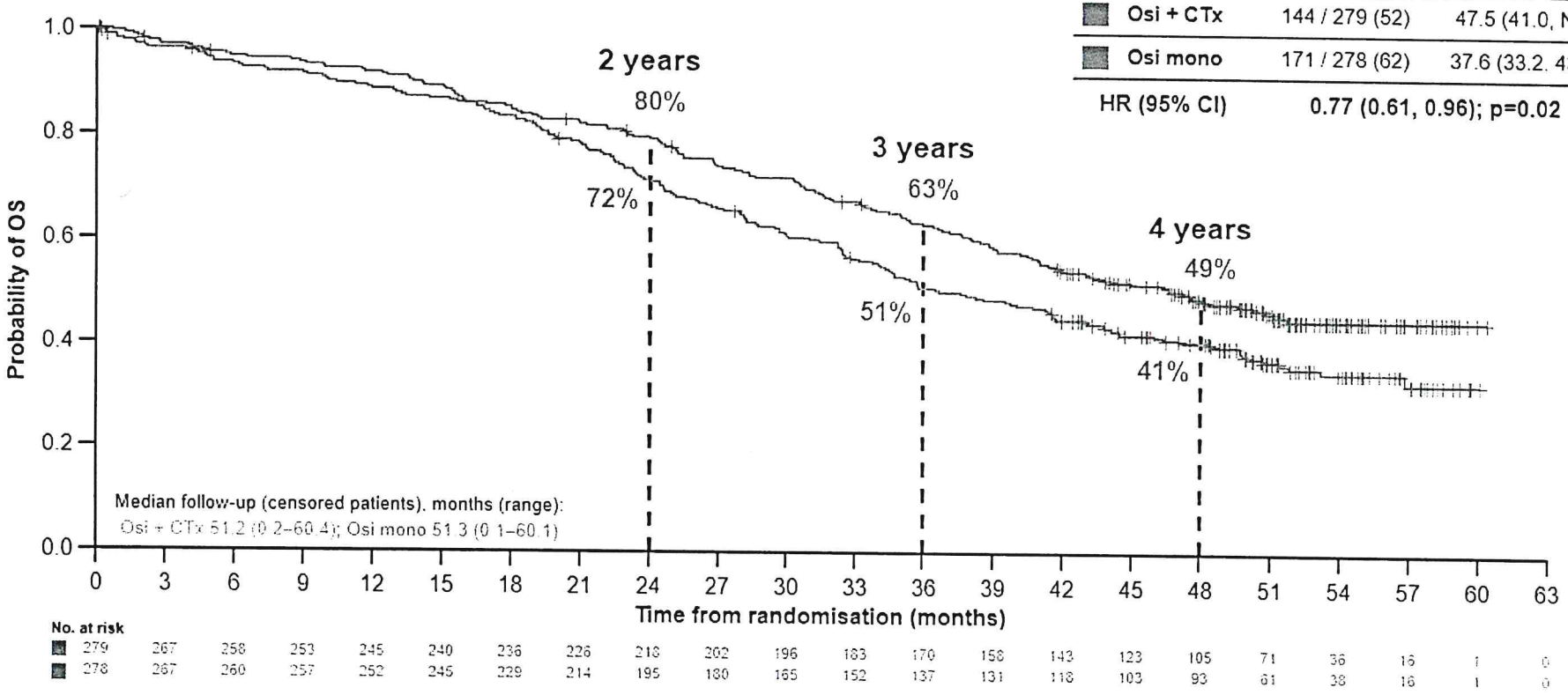
*One patient randomised to osi + CTx received only osi. †Includes treatment beyond progression. ‡Cisplatin / carboplatin capped at 4 cycles per CSP; 77% completed 4 cycles. §Includes development of study specific discontinuation criteria, severe non compliance to protocol, lack of therapeutic response, condition under investigation improved, and other reason. AE, adverse event; CSP, clinical study protocol; CTx, chemotherapy; DCO, data cut off; FAS, full analysis set; mono, monotherapy; osi, osimertinib; SAS, safety analysis set.

Data cut off, 12 June 2025

FLAURA2: Overall survival

Median OS with osi + CTx was 47.5 months

	No. Events / no. patients (%)	Median OS, months (95% CI)
Osi + CTx	144 / 279 (52)	47.5 (41.0, NC)
Osi mono	171 / 278 (62)	37.6 (33.2, 43.2)
HR (95% CI)	0.77 (0.61, 0.96); p=0.02	



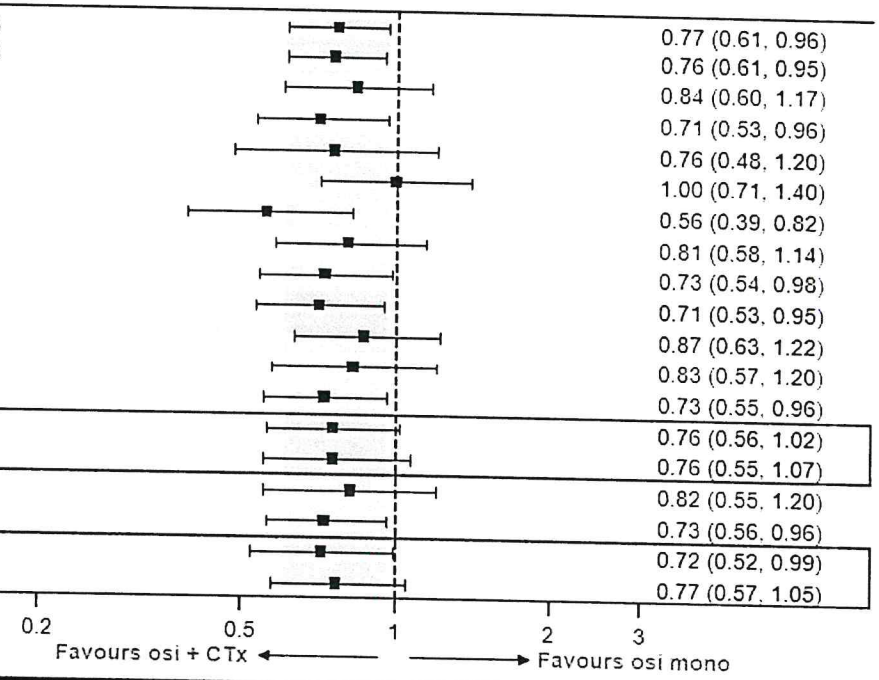
D. Planchard. First-line Osimertinib + Chemotherapy Versus Osimertinib Monotherapy in EGFRm Advanced NSCLC: FLAURA2 Final Overall Survival

Tick marks indicate censored data. A two-sided p value of <0.04953 was considered to indicate statistical significance at the final OS analysis.
CI, confidence interval; CTx, chemotherapy; HR, hazard ratio; mono, monotherapy; NC, not calculable; OS, overall survival; osi, osimertinib

Data cut off: 12 June 2025

Overall survival across subgroups

Subgroup*		Osi + CTx (Events / patients)	Osi mono (Events / patients)	HR (95% CI)
All patients	Stratified log-rank	144 / 279	171 / 278	0.77 (0.61, 0.96)
	Unadjusted Cox PH	144 / 279	171 / 278	0.76 (0.61, 0.95)
Sex	Male	65 / 106	72 / 109	0.84 (0.60, 1.17)
	Female	79 / 173	99 / 169	0.71 (0.53, 0.96)
Race†	Asian Chinese	34 / 71	39 / 69	0.76 (0.48, 1.20)
	Asian non-Chinese	65 / 107	66 / 107	1.00 (0.71, 1.40)
	Non-Asian	45 / 101	66 / 102	0.56 (0.39, 0.82)
EGFR mutation test method	Central	65 / 121	73 / 119	0.81 (0.58, 1.14)
	Local	79 / 158	98 / 159	0.73 (0.54, 0.98)
Age at screening	<65 years	80 / 174	95 / 166	0.71 (0.53, 0.95)
	≥65 years	64 / 105	76 / 112	0.87 (0.63, 1.22)
Smoking history	Yes	52 / 91	60 / 97	0.83 (0.57, 1.20)
	No	92 / 188	111 / 181	0.73 (0.55, 0.96)
EGFR mutation type‡	Ex19del	78 / 172	95 / 169	0.76 (0.56, 1.02)
	L858R	66 / 106	74 / 107	0.76 (0.55, 1.07)
WHO PS	0	47 / 101	55 / 102	0.82 (0.55, 1.20)
	1	97 / 178	116 / 176	0.73 (0.56, 0.96)
CNS mets at baseline	Yes	71 / 116	79 / 110	0.72 (0.52, 0.99)
	No	73 / 163	92 / 168	0.77 (0.57, 1.05)



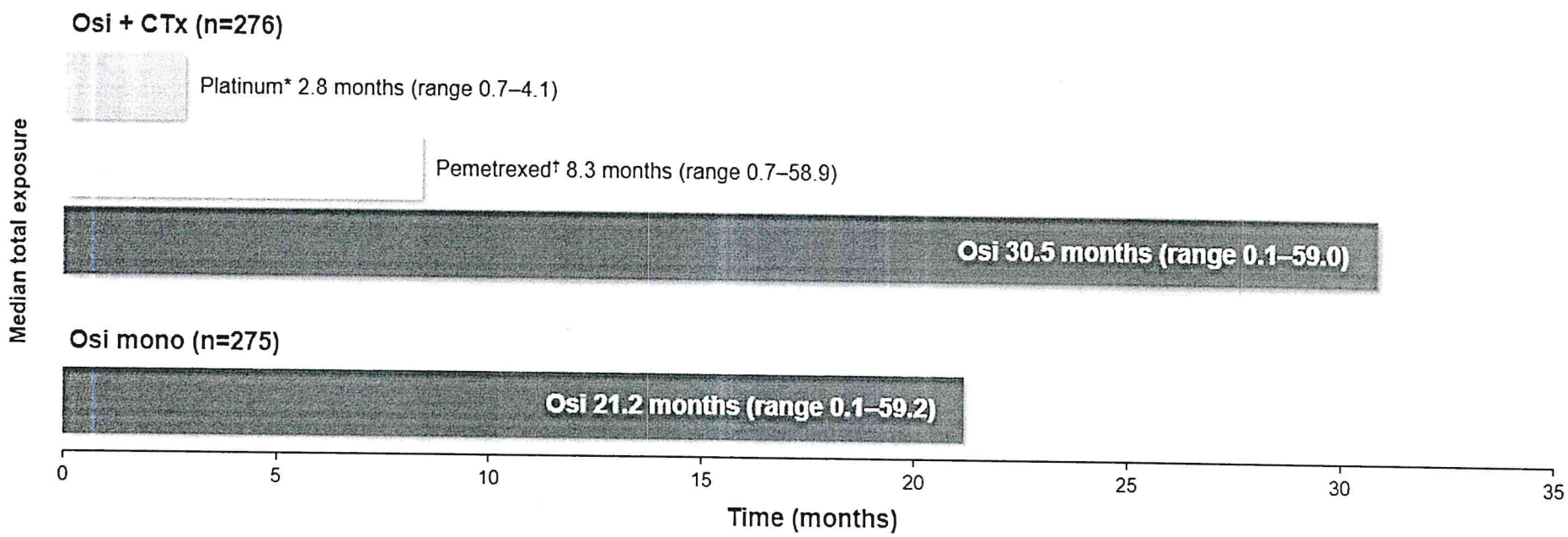
OS benefit was consistent across predefined subgroups

D. Planchard. First-line Osimertinib + Chemotherapy Versus Osimertinib Monotherapy in EGFRm Advanced NSCLC: FLAURA2 Final Overall Survival

Data cut-off: 12 June 2025

*Two additional subgroups performed to fulfil regulatory requirements for diagnostics are not included. EGFR mutations by central cobas® tissue test and EGFR mutations by central cobas® ctDNA test
†Race was reported by the patient. ‡For EGFR mutation type, patients with both Ex19del and L858R were included in the Ex19del group
CI, confidence interval; CNS, central nervous system; ctDNA, circulating tumour DNA; CTx, chemotherapy; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; HR, hazard ratio; mets, metastases; mono, monotherapy; OS, overall survival; osi, osimertinib; PH, proportional hazard; WHO PS, World Health Organization performance status

Exposure



The osi + CTx arm had a long CTx-free period – median exposure to osi vs pem was 30.5 vs 8.3 months

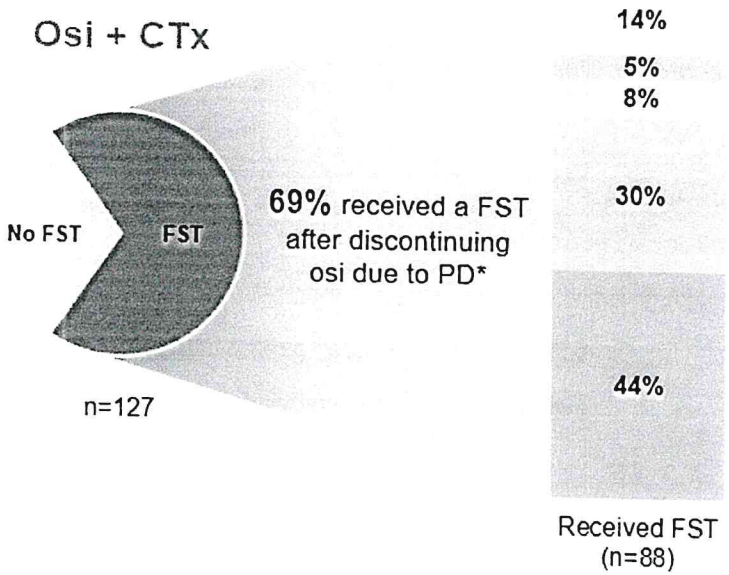
D. Planchard. First-line Osimertinib + Chemotherapy Versus Osimertinib Monotherapy in EGFRm Advanced NSCLC: FLAURA2 Final Overall Survival

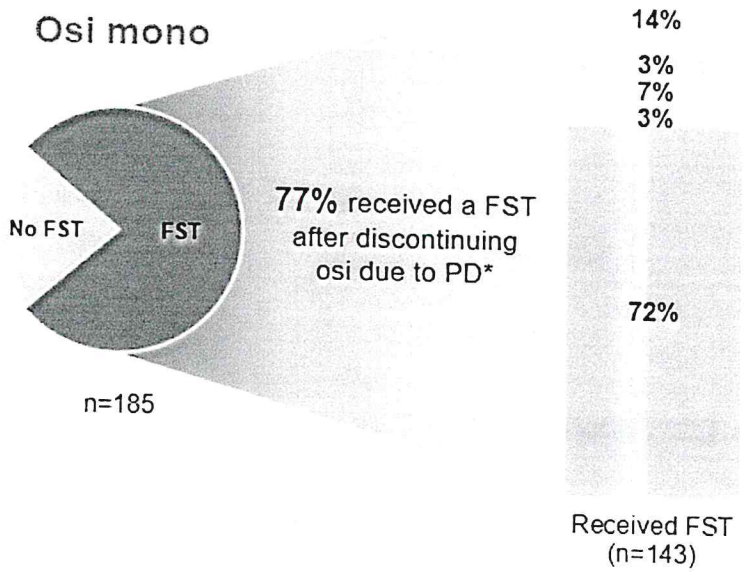
Data cut off: 12 June 2025
*Median (range) total exposure to platinum CTx in cycles was 4 (1–6). †Median (range) total exposure to pemetrexed in cycles was 11 (1–67)
CTx, chemotherapy; mono, monotherapy; osi, osimertinib; pem, pemetrexed

First subsequent treatment (FST)

CTx was the most common FST (74%) after osi + CTx – 44% of FSTs were rechallenge with platinum CTx

OS benefit with osi + CTx was observed despite SoC CTx being the most common FST after osi mono





Platinum-based CTx | Non-platinum-based CTx | EGFR targeted therapy (other than osi), mono or combo | Osi + targeted agent / investigational drug (no CTx) | Other†

Subsequent treatment was per investigator choice

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Data cut off: 12 June 2025

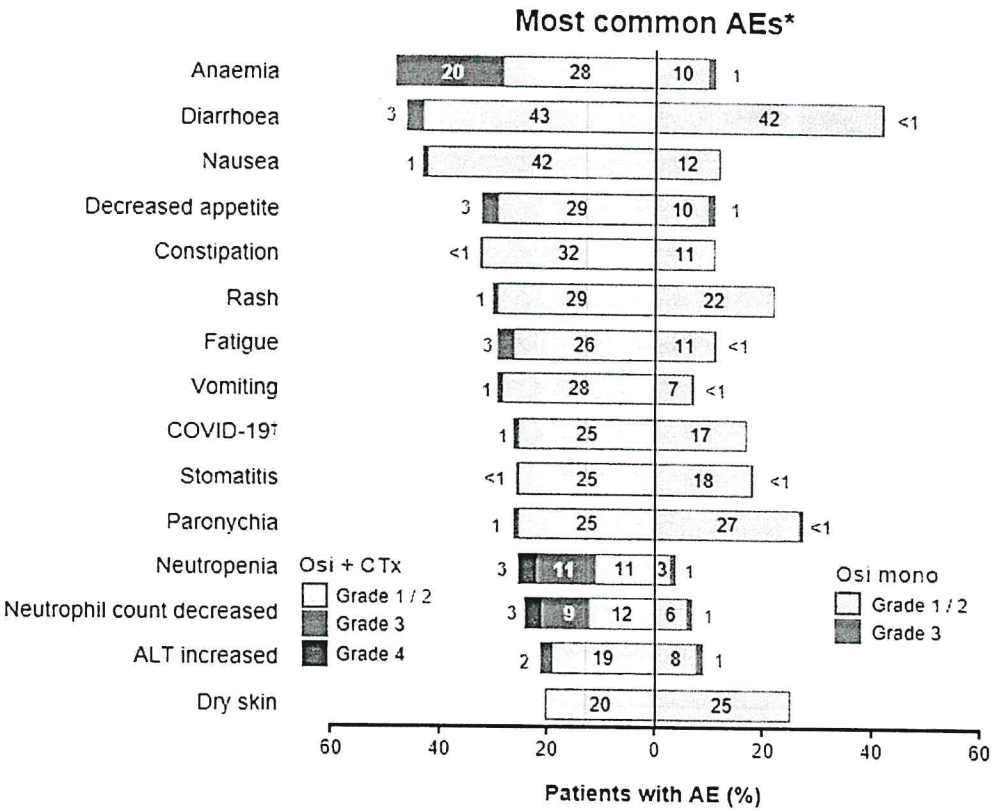
*Denominator (127 for osi + CTx and 185 for osi mono) is the number of patients who discontinued osimertinib due to progression. †Other included ADCs, immunotherapies [PD-(L)1 inhibitors], other investigational anticancer therapies, antiangiogenic therapies [VEGF(R) inhibitors], catequentinib hydrochloride, salvaluma, and unspecified herbal and traditional anti-cancer medicines. ADCs, antibody drug conjugates; CTx, chemotherapy; combo, combination; EGFR, epidermal growth factor receptor; FST, first subsequent treatment; mono, monotherapy; OS, overall survival; osi, osimertinib; PD, progressive disease; PD-(L)1, programmed cell death (ligand) 1; SoC, standard of care; VEGF(R), vascular endothelial growth factor (receptor)

Safety

Since the primary analysis[1] (>2 years additional follow-up):

- No new safety signals observed
- AEs leading to discontinuation of osi remained low
- No new treatment-related deaths observed with osi + CTx (vs 1 with osi mono)

AE summary	Osi + CTx (n=276)	Osi mono (n=275)
AE any cause, n (%)		
Any grade	276 (100)	269 (98)
Grade ≥3	193 (70)	94 (34)
Serious	126 (46)	75 (27)
Outcome of death	22 (8)	10 (4)
Considered possibly related to treatment	5 (2)	2 (1)
Leading to discontinuation of osi	34 (12)	20 (7)
Leading to discontinuation of pemetrexed	137 (50)	NA
Leading to discontinuation of platinum	46 (17)	NA



D. Planchard. First-line Osimertinib + Chemotherapy Versus Osimertinib Monotherapy in EGFRm Advanced NSCLC: FLAURA2 Final Overall Survival

Data cut off: 12 June 2025
1. Planchard D, et al. N Engl J Med 2023;389:1935-1948
*Reported in ≥20% of patients in either treatment arm. †One Grade 5 AE of COVID-19 was reported in the osi + CTx arm
AE, adverse event; ALT, alanine aminotransferase; CTx, chemotherapy; mono, monotherapy; NA, not applicable; osi, osimertinib

Conclusions

- First-line osimertinib plus chemotherapy demonstrated superior overall survival versus osimertinib monotherapy
  - OS HR: 0.77 (95% CI: 0.61, 0.96); p=0.02
  - Median OS with osimertinib plus chemo was 47.5 months – the longest in a global phase III study showing OS benefit in this population[1–5]
  - Observed OS benefit was consistent across predefined subgroups

- The combination arm had a long chemo-free period – median exposure for osimertinib vs pemetrexed was 30.5 vs 8.3 months

- Chemotherapy was the most common first subsequent treatment in both arms
  - Chemo rechallenge, primarily with platinum doublet, was the most common first subsequent treatment in the combination arm
  - OS benefit in the combination arm was observed despite SoC platinum doublet being the most common treatment in the monotherapy arm

- With over 2 years additional follow-up since the primary analysis, the safety profiles remained as expected and manageable

These compelling OS results from FLAURA2 confirm osimertinib plus chemotherapy as a first-line standard of care in EGFRm advanced NSCLC

1. Ramalingam S, et al. N Engl J Med 2020;382:41–50. 2. Yang J, C H, et al. J Thorac Oncol 2026;20:S6–6. 3. Nakagawa K, et al. J Thorac Oncol 2025;20:497–99. 4. Miyauchi E, et al. J Clin Oncol 2022;40:3567–92. 5. Zhao H, et al. J Thorac Oncol 2015;10:655–64.
Note: A two-sided p value of <0.04953 was considered to indicate statistical significance at the final OS analysis
Chemo, chemotherapy; CI, confidence interval; EGFRm, epidermal growth factor receptor mutated; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; SoC, standard of care

Acknowledgements

- We thank all patients and their families, staff at each study site, and all FLAURA2 investigators and study members
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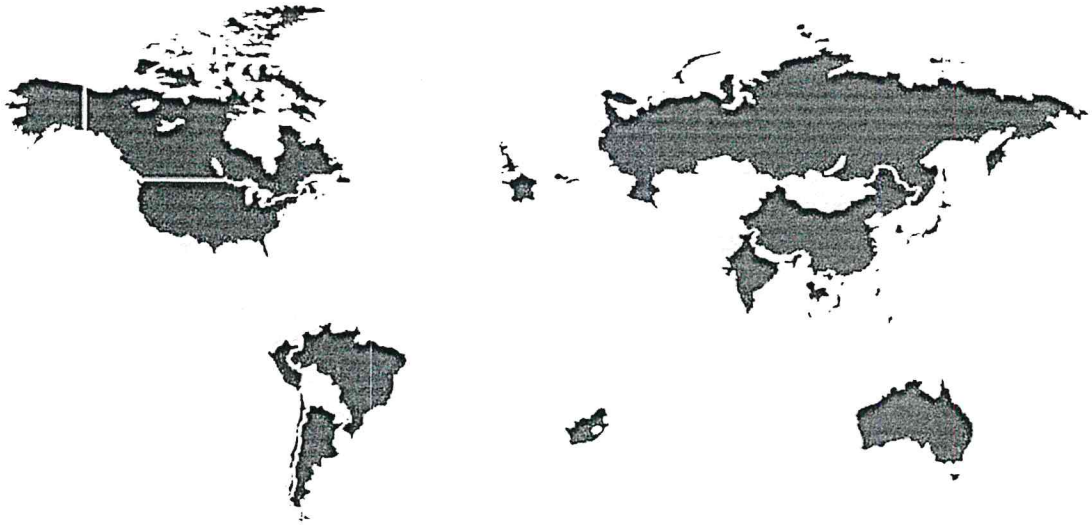
- We thank Azura Evans, Elena Armenteros-Monterroso, Dana Ghiorghiu, Dakshayini Kulkarni and Neha Amin for their contributions to this work
- The FLAURA2 study (NCT04035486) was funded by AstraZeneca, Cambridge, UK
- The authors would like to acknowledge Eric C. Exner, MD, PhD, of Ashfield MedComms, an Inizio company, for medical writing support that was funded by AstraZeneca in accordance with Good Publications Practice (GPP) guidelines (https://www.ismpp.org/gpp-2022)



887 patients enrolled from 153 sites across 21 countries / regions that participated in FLAURA2

Plain language summary

Osimertinib plus chemotherapy significantly improved overall survival compared with osimertinib alone as first-line treatment of epidermal growth factor receptor (EGFR)-mutated advanced non-small cell lung cancer (NSCLC)

Why did we perform this research?

- EGFR is a protein that regulates cell growth and division.[1] Osimertinib is a drug that can block the activity of the mutated form of EGFR on cancer cells, reducing their growth and spread[2]
- Osimertinib is recommended as an initial (first-line) treatment for patients with advanced NSCLC that has a mutation in the EGFR gene (known as EGFR-mutated advanced NSCLC)[3,4]
- The FLAURA2 study assessed if giving chemotherapy with osimertinib could improve patient outcomes compared with osimertinib alone when given as first-line treatment for patients with EGFR-mutated advanced NSCLC[5]
- In previous results from FLAURA2, patients who received osimertinib plus chemotherapy were alive, without the cancer growing or spreading, for longer than patients who received osimertinib alone (known as progression-free survival)[5]
- Here, we present results from FLAURA2 showing how long patients stayed alive for after starting treatment (known as overall survival)

How did we perform this research?

- In total, 557 patients with previously untreated EGFR-mutated advanced NSCLC were randomly assigned to receive osimertinib plus chemotherapy or osimertinib alone. Treatment was planned to continue until the cancer grew or spread, the patient died, or the patient stopped due to another reason, such as side effects

What were the findings of this research?

- Overall survival was significantly longer with osimertinib plus chemotherapy than osimertinib alone. Half of the patients in the osimertinib plus chemotherapy group were alive at 47.5 months (known as median overall survival). Median overall survival was 37.6 months in the osimertinib alone group
- At 3 years, more patients in the osimertinib plus chemotherapy group were alive (63%) compared with the osimertinib alone group (51%)
- Overall survival benefit with osimertinib plus chemotherapy versus osimertinib alone was consistent regardless of factors such as patient age, sex and EGFR mutation type
- With prolonged treatment, the side effects of each treatment were as expected and manageable

What are the implications of this research?

- Osimertinib plus chemotherapy prolonged the time that patients were alive after starting treatment compared with osimertinib alone. These results confirm osimertinib plus chemotherapy as an important first-line treatment for EGFR-mutated advanced NSCLC

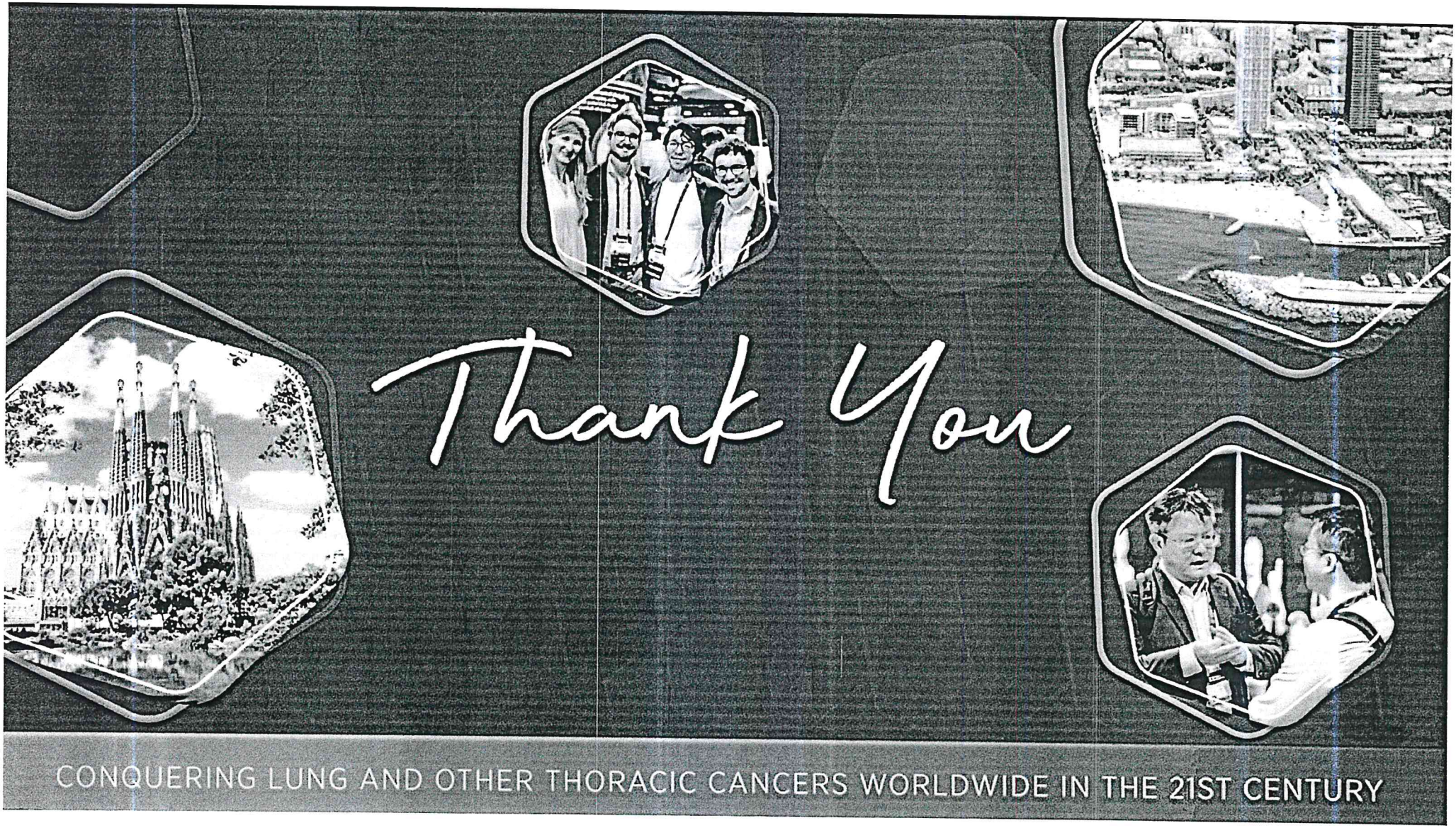
Where can I access more information?

- More information on the FLAURA2 study can be found on ClinicalTrials.gov (NCT04035486); https://clinicaltrials.gov/study/NCT04035486; the previously published results are freely available online[5–7]

D. Planchard, First-line Osimertinib + Chemotherapy Versus Osimertinib Monotherapy in EGFRm Advanced NSCLC: FLAURA2 Final Overall Survival

This study was funded by AstraZeneca. Presented at the World Conference on Lung Cancer 2025. By: David Planchard

1. Bethune G, et al. J Thorac Dis 2010;2:48–51. 2. Cross DAE, et al. Cancer Discov 2014;4:1046–1061. 3. Owen DH, et al. J Clin Oncol 2025;43:e2–e16. 4. Bazhenova L, et al. J Clin Oncol 2024;42:e72–e86. 5. Planchard D, et al. N Engl J Med 2023;389:1935–1948. 6. Planchard D, et al. Future Oncol 2025;21:903–915. 7. Jänne PA, et al. Future Oncol 2025;21:917–926.


Thank You
CONQUERING LUNG AND OTHER THORACIC CANCERS WORLDWIDE IN THE 21ST CENTURY