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ORIGINAL ARTICLE

COMPEL: osimertinib plus platinum-based chemotherapy in patients with EGFR-mutated advanced NSCLC and progression on first-line osimertinib

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Available online 8 September 2025

Background: COMPEL (NCT04765059) was a global, randomized, double-blind study that evaluated osimertinib plus chemotherapy versus placebo plus chemotherapy in patients with epidermal growth factor receptor (EGFR)-mutated advanced non-small-cell lung cancer (NSCLC) following non-central nervous system (CNS) progression on first-line osimertinib.

Patients and methods: Patients were randomly assigned to receive osimertinib 80 mg, or placebo, once daily (o.d.) in combination with chemotherapy [cisplatin 75 mg/m^2 or carboplatin area under the curve 5 plus pemetrexed 500 mg/m^2 every 3 weeks (q3w) for four cycles], followed by osimertinib 80 mg, or placebo, o.d. in combination with maintenance pemetrexed (500 mg/m^2 q3w) until progression. The primary endpoint was investigator-assessed progression-free survival (PFS). Secondary endpoints included CNS PFS according to CNS metastases status at baseline and overall survival (OS).

Results: Ninety-eight patients were randomly assigned (49 per arm). Median PFS in all patients was 8.4 months [95% confidence interval (CI) 5.7-11.8 months] with osimertinib plus chemotherapy versus 4.4 months (95% CI 3.5-5.6 months) with placebo plus chemotherapy [hazard ratio (HR) 0.43, 95% CI 0.27-0.70]. CNS PFS was longer with osimertinib plus chemotherapy versus placebo plus chemotherapy (HR 0.56, 95% CI 0.27-1.13) in patients without baseline CNS metastases ($n = 75$). Median OS in all patients was 15.9 months (95% CI 12.4-20.8 months) with osimertinib plus chemotherapy versus 9.8 months (95% CI 8.4-17.2 months) with placebo plus chemotherapy (HR 0.71, 95% CI 0.42-1.23). Grade $\geq$3 adverse events occurred more frequently with osimertinib plus chemotherapy (63%) than placebo plus chemotherapy (46%).

Conclusions: In patients with non-CNS progression on first-line osimertinib, osimertinib plus chemotherapy was associated with improved PFS and longer OS compared with placebo plus chemotherapy. These findings support osimertinib as a backbone treatment for EGFR-mutated advanced NSCLC through lines of therapy.

Key words: EGFR-mutated, non-small-cell lung cancer, EGFR-TKI, osimertinib, chemotherapy

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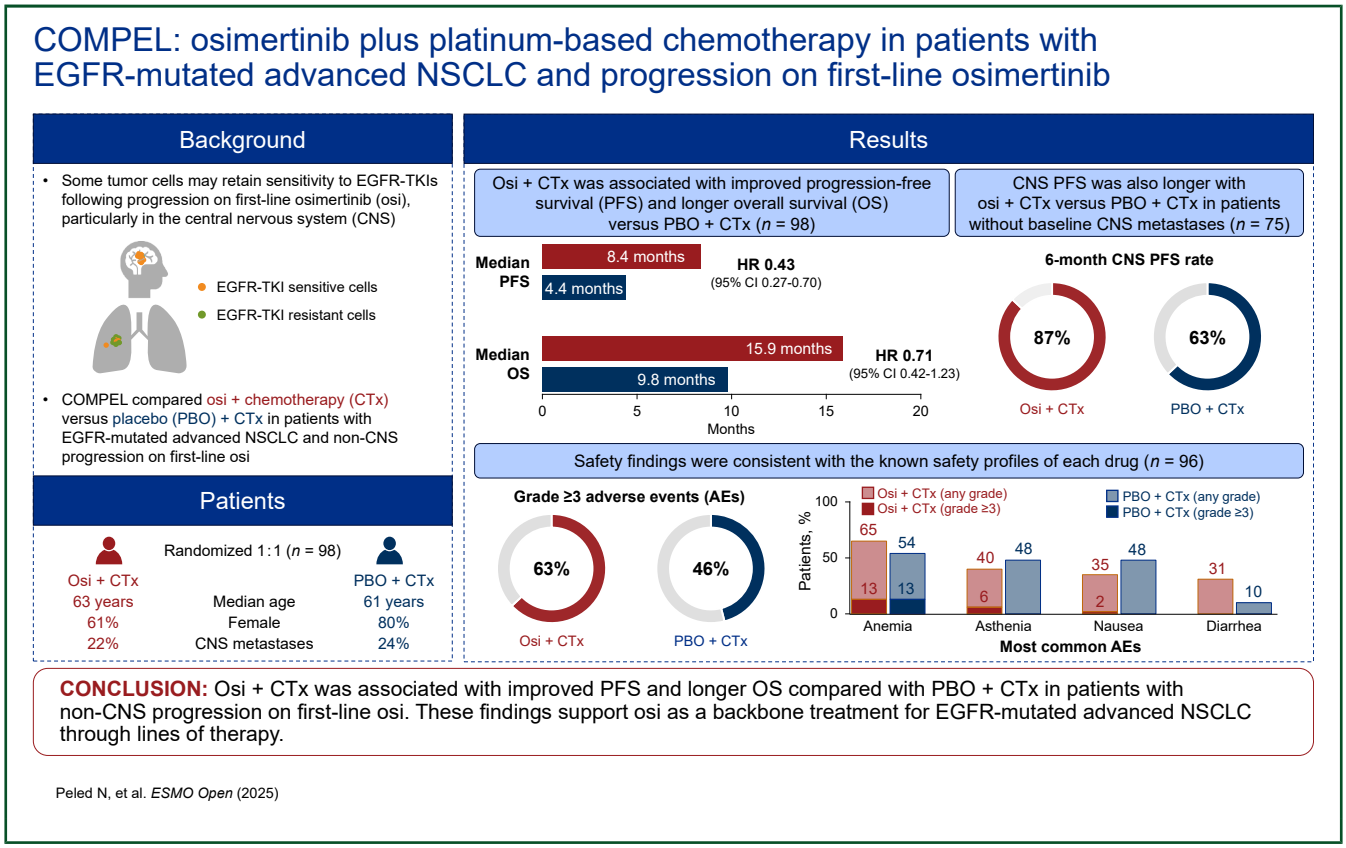
GRAPHICAL ABSTRACT



INTRODUCTION

Osimertinib is a third-generation, irreversible, oral, epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) that selectively inhibits both EGFR-TKI-sensitizing and *EGFR T790M* resistance mutations with demonstrated efficacy in EGFR-mutated NSCLC.[1-11] Based on findings from the phase III FLAURA study, in which osimertinib demonstrated superior progression-free survival (PFS) and overall survival (OS) compared with first-generation EGFR-TKIs,[3,7] osimertinib is a preferred first-line treatment for patients with EGFR-mutated advanced NSCLC.[12-14] Osimertinib has demonstrated efficacy for the treatment of central nervous system (CNS) metastases in the advanced NSCLC setting[5,6,9,10,15] and may protect against the development of CNS metastases.[15,16]

Most patients who receive osimertinib in the first-line setting eventually experience disease progression.[17] Although the treatment landscape is evolving, options for second-line treatment following progression on first-line osimertinib remain limited, with platinum-based chemotherapy remaining a standard treatment for most patients.[12-14] Progression on first-line osimertinib is spatially and temporally diverse, with some clonal tumor cells maintaining EGFR-signaling dependence.[18] In particular, data suggest that clonal evolution of CNS metastases may differ from non-CNS sites.[19] Reasons for this are unclear, but may relate to differing drug exposures between these sites due to the blood—brain barrier.[19,20] For example, lower therapeutic exposure in the CNS may reduce the evolution of resistant clones in the CNS site. As such, there may be a role for continued osimertinib treatment with the addition of chemotherapy following progression on first-line osimertinib, particularly among patients with CNS disease control and non-CNS progression. Reassuringly, the combination of osimertinib with chemotherapy has demonstrated a manageable safety profile in other studies and has been approved as first-line treatment for patients with EGFR-mutated advanced NSCLC.[21-24]

The COMPEL study (NCT04765059) was conducted to assess the benefit of continuing osimertinib with the addition of chemotherapy compared with the use of chemotherapy alone in patients with EGFR-mutated advanced NSCLC and non-CNS (extracranial) progression on first-line osimertinib. Here, we report efficacy and safety data from COMPEL.

PATIENTS AND METHODS

Study design and patients

COMPEL (NCT04765059) was designed as a phase III, global, randomized, double-blind study of osimertinib plus chemotherapy versus placebo plus chemotherapy in patients with EGFR-mutated advanced NSCLC who had non-CNS disease progression following first-line osimertinib

(Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105807).

Eligible patients were ≥18 years of age with locally advanced, metastatic, or recurrent NSCLC with or without stable CNS metastases (based on CNS RECIST version 1.1 assessments of baseline brain scans). Patients had evidence of radiological non-CNS progression following investigator-assessed response (complete or partial) or stable disease for a duration of at least 6 months on first-line osimertinib and had not received any subsequent treatment. Patients had tumors harboring *EGFR* exon 19 deletions (Ex19del) or L858R mutations, either alone or in combination with other EGFR mutations, and had measurable disease per RECIST version 1.1. A World Health Organization performance status of 0 or 1 at study entry was required.

Patients were randomly assigned 1 : 1 to receive either oral osimertinib 80 mg once daily (o.d.) or placebo o.d. in combination with intravenous platinum—pemetrexed chemotherapy [cisplatin 75 mg/m^2 or carboplatin area under the curve 5 (AUC5) plus pemetrexed 500 mg/m^2 every 3 weeks (q3w) for four cycles], followed by osimertinib 80 mg o.d. or placebo o.d. in combination with maintenance pemetrexed (500 mg/m^2 q3w); the platinum agent was chosen by the investigator before randomization. Randomization was stratified by baseline CNS metastases status at study entry (CNS metastases on baseline brain scan versus no CNS metastases). Patients were randomly assigned to receive their first dose of study treatment within a maximum of 4 weeks following their last dose of first-line osimertinib (no interruption in daily osimertinib dosing between first-line treatment and study treatment was required). Randomized treatment continued until RECIST version 1.1—or CNS RECIST version 1.1—defined progression or another discontinuation criterion was met. Patients could continue to receive study treatment beyond progression if they were obtaining clinical benefit (as judged by the investigator) and did not meet any other discontinuation criteria. Patients in the placebo plus chemotherapy arm who experienced CNS progression as their first progression event were permitted to undergo unblinding and receive open-label osimertinib 80 mg o.d. at the investigator's discretion.

The protocol was approved by relevant institutional review boards or ethics committees. The study was conducted in accordance with the provisions of the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, International Council for Harmonization Good Clinical Practice guidelines, and applicable regulatory requirements. All patients provided written informed consent before participating in the study.

Endpoints and assessments

The primary endpoint was investigator-assessed PFS. Secondary endpoints included investigator-assessed CNS PFS in patients with and without baseline CNS metastases, non-CNS PFS, and OS. A *post hoc* exploratory analysis of non-CNS tumor response [including objective response rate (ORR), best objective response, and duration of response] was carried out. Safety was also assessed.

PFS was defined as the time from randomization until disease progression (CNS or non-CNS progression, whichever occurred first, per CNS RECIST version 1.1 and RECIST version 1.1, respectively) or death due to any cause. CNS PFS was defined as time from randomization until CNS progression, per CNS RECIST version 1.1, or death from any cause. Non-CNS PFS was defined as time from randomization until non-CNS progression, per RECIST version 1.1, or death from any cause. OS was defined as time from randomization until death from any cause. Non-CNS tumor response was defined as complete or partial non-CNS response per RECIST version 1.1 in the absence of CNS progression per CNS RECIST version 1.1. Additional details on efficacy assessments, including use of CNS RECIST version 1.1, are provided in Supplementary Methods, available at https://doi.org/10.1016/j.esmoop.2025.105807.

Tumor assessments of the chest and abdomen (by computed tomography preferred), as well as the brain (by magnetic resonance imaging preferred), were carried out at baseline, then every 6 weeks (q6w; ±1 week) for the first 13 cycles, and every 12 weeks (q12w; ±1 week) thereafter. The tumor assessment schedule was the same for all patients, irrespective of baseline CNS metastases status. Non-CNS tumor assessments continued until radiological non-CNS progression, per RECIST version 1.1, or the end of survival follow-up. CNS tumor assessments continued until radiological CNS progression, per CNS RECIST version 1.1, or the end of survival follow-up, except for patients in the placebo plus chemotherapy arm who received open-label osimertinib following initial CNS progression; these patients continued CNS assessments q6w (±1 week) until the second CNS progression.

Safety was assessed throughout the study based on physical examinations, vital signs, laboratory assessments, and adverse events (AEs). AEs were graded per the National Cancer Institute Common Terminology Criteria for AEs version 5.0.

Statistical analysis

Efficacy analyses were conducted in the full analysis set, which included all randomly assigned patients. Safety was summarized in the safety analysis set, comprising all randomly assigned patients who received at least one dose of study treatment, according to the actual treatment received.

At study initiation, ∼204 patients were planned to be randomly assigned; however, the number was reduced to 80 patients due to treatment landscape changes, which outpaced study recruitment. The data cut-off for PFS was planned to occur when ∼60 PFS events had occurred (∼75% maturity). Due to the reduced sample size, the study was no longer powered to carry out a formal hypothesis test and a descriptive analysis for all efficacy

endpoints was carried out. The hazard ratio (HR) and 95% confidence interval (CI) were calculated without hypothesis testing. The data cut-off was 28 October 2024.

RESULTS

Patients and treatment

Between 10 October 2021 and 27 February 2024, 98 patients from six countries (China, Germany, Israel, Italy, Spain, and the USA) were randomly assigned 1 : 1 to receive osimertinib plus chemotherapy ($n = 49$) or placebo plus chemotherapy ($n = 49$); 96 of these patients started study treatment ($n = 48$ per treatment arm; Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2025.105807). At the data cut-off, seven patients (15%) were still receiving osimertinib treatment and six patients (13%) were still receiving pemetrexed maintenance in the osimertinib plus chemotherapy arm; meanwhile, four patients (8%) were still receiving placebo treatment and four patients (8%) were still receiving pemetrexed maintenance in the placebo plus chemotherapy arm. One patient in the placebo plus chemotherapy arm received open-label osimertinib following progression.

Baseline characteristics were generally well balanced between the two treatment arms. There was a lower proportion of female patients in the osimertinib plus chemotherapy arm (61%) than the placebo plus chemotherapy arm (80%; Table 1). In addition, a higher proportion of patients had tumors harboring *EGFR* Ex19del mutations in the osimertinib plus chemotherapy arm (65%) than the placebo plus chemotherapy arm (55%).

At the data cut-off, 27% and 29% of all randomly assigned patients had received subsequent anticancer therapy after discontinuing study treatment in the osimertinib plus chemotherapy and placebo plus chemotherapy arms, respectively. Subsequent treatments received following discontinuation of study treatment are summarized in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105807.

Table 1. Baseline patient demographics and disease characteristics (full analysis set)

Characteristic	Osimertinib + platinum–pemetrexed ($n = 49$)	Placebo + platinum–pemetrexed ($n = 49$)
Age (years)		
Median (range)	63 (37-85)	61 (42-88)
Sex, *n* (%)		
Female	30 (61)	39 (80)
Male	19 (39)	10 (20)
Race, *n* (%)		
Asian	6 (12)	9 (18)
White	39 (80)	38 (78)
Other	1 (2)	1 (2)
Not reported	3 (6)	1 (2)
Smoking status, *n* (%)		
Never	32 (65)	33 (67)
Current	4 (8)	2 (4)
Former	13 (27)	14 (29)
WHO PS, *n* (%)		
0	22 (45)	24 (49)
1	26 (53)	25 (51)
2	1 (2)	0
AJCC stage at study entry, *n* (%)		
IIIB	0	1 (2)
IV	49 (100)	48 (98)
Metastatic sites at study entry (*n*)		
Median (range)	2 (1-6)	2 (1-7)
CNS metastases at study entry, *n* (%)	11 (22)	12 (24)
EGFR mutation type,[a] *n* (%)		
Ex19del	32 (65)	27 (55)
L858R	17 (35)	22 (45)
Duration of first-line osimertinib treatment (months)[b]		
Median (range)	21.3 (3.2-51.3)	19.6 (7.4-52.3)

Data cut-off: 28 October 2024.
AJCC, American Joint Committee on Cancer; CNS, central nervous system; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; L858R, exon 21 p.Leu858Arg point mutation; WHO PS, World Health Organization performance status.
[a]Pre-existing local EGFR mutation test results; mutation testing was not mandated following progression on first-line osimertinib.
[b]Summary does not include missing data for 9 patients in the osimertinib plus platinum–pemetrexed arm and 11 patients in the placebo plus platinum–pemetrexed arm (the end date of first-line osimertinib treatment was not recorded for these patients).

PFS and patterns of progression

At the data cut-off, PFS events were reported in 32 patients (65%) in the osimertinib plus chemotherapy arm and 42 patients (86%) in the placebo plus chemotherapy arm (PFS maturity: 76%). In both treatment arms, PFS was primarily driven by RECIST progression (with 28 progression events reported in the osimertinib plus chemotherapy arm and 39 progression events reported in the placebo plus chemotherapy arm). Median follow-up for PFS in censored patients was 5.4 months (range <0.1-24.9 months) and 5.5 months (range <0.1-11.1 months) for the osimertinib plus chemotherapy and placebo plus chemotherapy arms, respectively. Median PFS was 8.4 months (95% CI 5.7-11.8 months) with osimertinib plus chemotherapy versus 4.4 months (95% CI 3.5-5.6 months) with placebo plus chemotherapy (HR 0.43, 95% CI 0.27-0.70; Figure 1); the PFS rates at 6 months were 64% (95% CI 48% to 77%) and 32% (95% CI 19% to 46%) for each treatment arm, respectively. PFS results for predefined subgroups are reported in Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2025.105807.

Overall, 18 patients (37%) in the osimertinib plus chemotherapy arm had new lesions at the time of progression versus 25 patients (51%) in the placebo plus chemotherapy arm (Table 2). New brain lesions occurred in 5 patients (10%) in the osimertinib plus chemotherapy arm and 13 patients (27%) in the placebo plus chemotherapy arm.

CNS PFS in patients without and with baseline CNS metastases

At baseline, 38 patients in the osimertinib plus chemotherapy arm and 37 patients in the placebo plus chemotherapy arm did not have CNS metastases. Among these patients, CNS PFS events were reported in 14 patients (37%)

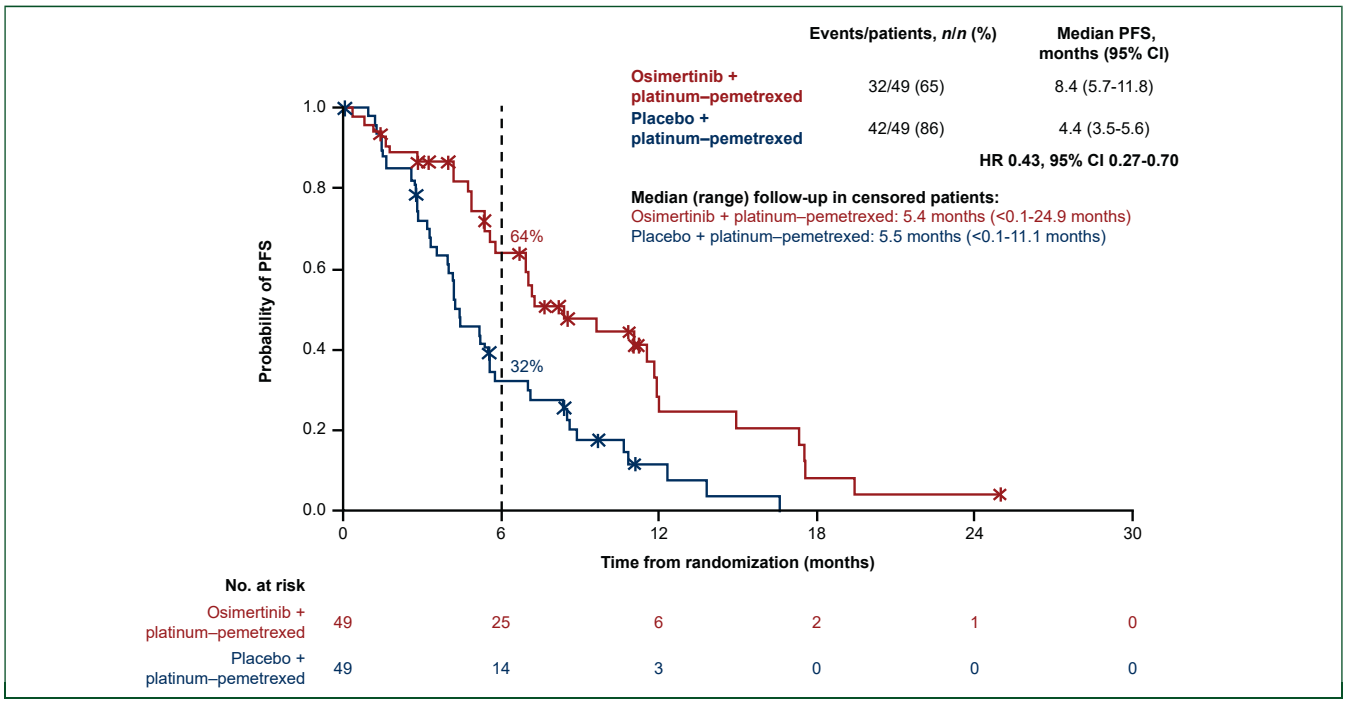


Figure 1. Kaplan–Meier curve of progression-free survival (PFS) (full analysis set). Data cut-off: 28 October 2024. The crosses indicate censored observations. Progression events that did not occur within two missed visits of the last evaluable assessment were censored. The hazard ratio (HR) and confidence interval (CI) were calculated using a log-rank test.

with osimertinib plus chemotherapy and 18 patients (49%) with placebo plus chemotherapy (CNS PFS maturity: 43%). Median follow-up for CNS PFS in censored patients was 5.5 months (range <0.1-23.6 months) and 5.6 months (range <0.1-13.8 months) for the osimertinib plus chemotherapy and placebo plus chemotherapy arms, respectively. Median CNS PFS was 15.9 months (95% CI 7.9-18.6 months) with osimertinib plus chemotherapy and 8.6 months (95% CI 5.6-19.4 months) with placebo plus chemotherapy (HR 0.56, 95% CI 0.27-1.13; Figure 2A); the CNS PFS rates at 6 months were 87% (95% CI 68% to 95%) and 63% (95% CI 43% to 78%) for each treatment arm, respectively.

Table 2. Sites of new lesions at progression (full analysis set)

	Osimertinib + platinum–pemetrexed (n = 49)	Placebo + platinum–pemetrexed (n = 49)
Patients with no new lesions, n (%)	31 (63)	24 (49)
Patients with new lesions,[a] n (%)	18 (37)	25 (51)
Brain	5 (10)	13 (27)
Liver	6 (12)	7 (14)
Lung	6 (12)	3 (6)
Bone	2 (4)	4 (8)
Adrenal gland	1 (2)	2 (4)
Pleural effusion	1 (2)	2 (4)
Regional lymph node	1 (2)	1 (2)
Kidney	1 (2)	1 (2)
Other	1 (2)	1 (2)
Pleura	0	2 (4)
Distant lymph nodes	0	1 (2)
Pancreas	0	1 (2)
Peritoneum	0	1 (2)
Missing	1 (2)	0

Data cut-off: 28 October 2024.
[a]New lesions were not necessarily mutually exclusive; a patient could report new lesions at more than one site.

At baseline, 11 patients in the osimertinib plus chemotherapy arm and 12 patients in the placebo plus chemotherapy arm had stable CNS metastases following first-line osimertinib treatment. Among these patients, CNS PFS events were reported in five patients (45%) in the osimertinib plus chemotherapy arm and four patients (33%) in the placebo plus chemotherapy arm (CNS PFS maturity: 39%). Median follow-up for CNS PFS in censored patients was 7.1 months (range 1.4-24.9 months) and 4.7 months (range <0.1-11.1 months) for the osimertinib plus chemotherapy and placebo plus chemotherapy arms, respectively. The Kaplan–Meier curve for CNS PFS in patients with baseline CNS metastases is shown in Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2025.105807; due to the low number of events (n = 9), the HR was not calculated. The CNS PFS rate at 6 months was 82% (95% CI 45% to 95%) with osimertinib plus chemotherapy and 56% (95% CI 20% to 80%) with placebo plus chemotherapy, although the sample size for this analysis was limited (n = 23).

Non-CNS PFS

Among all randomly assigned patients, non-CNS PFS events were reported in 31 patients (63%) in the osimertinib plus chemotherapy arm and 41 patients (84%) in the placebo plus chemotherapy arm (non-CNS PFS maturity: 73%). Median follow-up for non-CNS PFS in censored patients

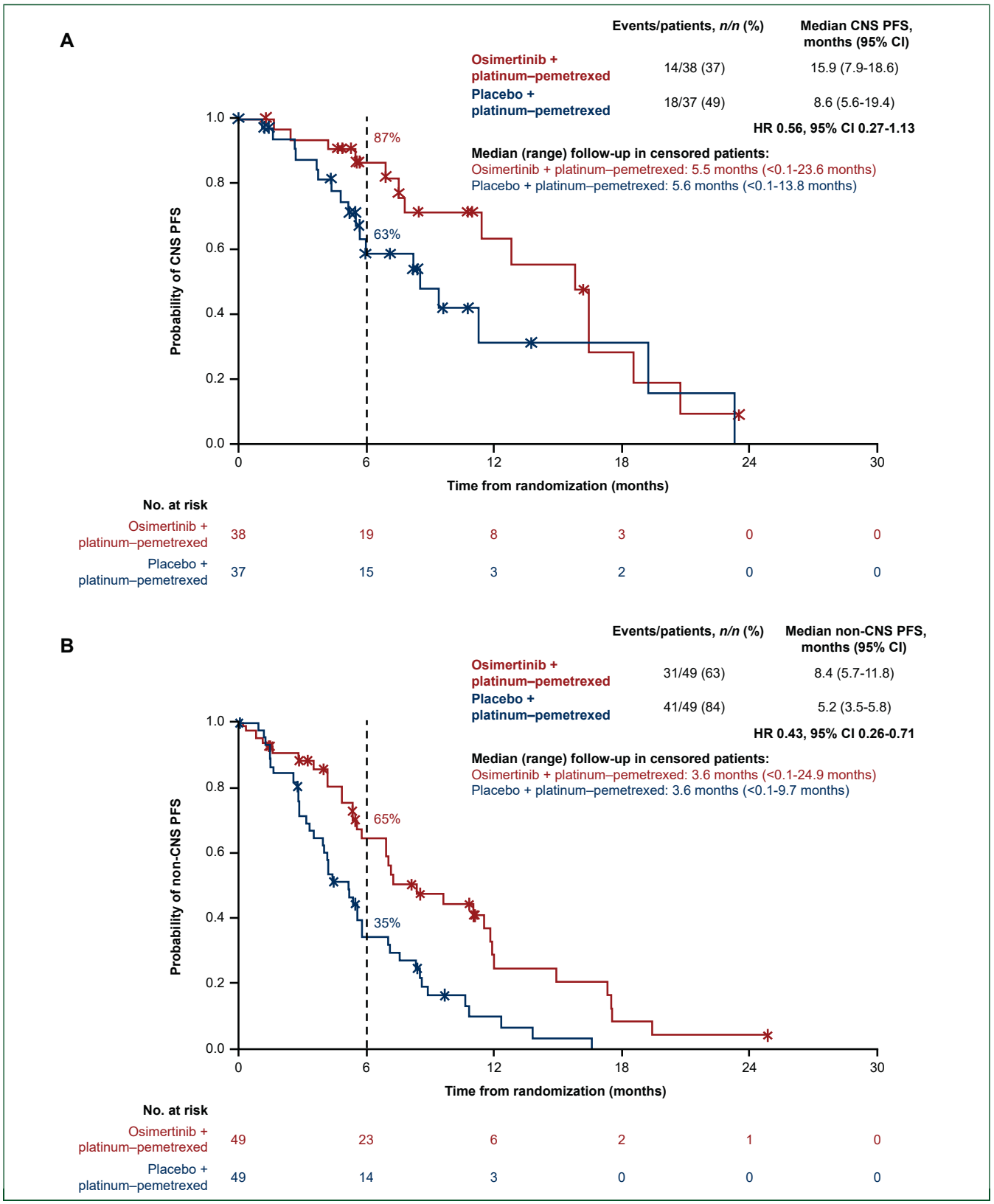


Figure 2. Central nervous system (CNS) and non-CNS progression-free survival (PFS). Shown are Kaplan–Meier curves of (A) CNS PFS in patients without CNS metastases at baseline and (B) non-CNS PFS in all patients (full analysis set). Data cut-off: 28 October 2024. The crosses indicate censored observations. The hazard ratios (HRs) and confidence intervals (CIs) were calculated using a log-rank test.

was 3.6 months (range <0.1-24.9 months) and 3.6 months (range <0.1-9.7 months) for the osimertinib plus chemotherapy and placebo plus chemotherapy arms, respectively.

Median non-CNS PFS was 8.4 months (95% CI 5.7-11.8 months) with osimertinib plus chemotherapy and 5.2 months (95% CI 3.5-5.8 months) with placebo plus

chemotherapy (HR 0.43, 95% CI 0.26-0.71; Figure 2B); the non-CNS PFS rates at 6 months were 65% (95% CI 48% to 77%) and 35% (95% CI 21% to 49%) for each treatment arm, respectively.

Non-CNS tumor response

Non-CNS ORR was 35% (95% CI 22% to 50%) in the osimertinib plus chemotherapy arm and 29% (95% CI 17% to 43%) in the placebo plus chemotherapy arm (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105807). No patients in either treatment arm had a complete response. Best percentage change from baseline in target lesion size for non-CNS progression in each arm is shown in Supplementary Figure S5, available at https://doi.org/10.1016/j.esmoop.2025.105807. Among patients with a non-CNS response, 11 of 17 (65%) in the osimertinib plus chemotherapy arm and 11 of 14 (79%) in the placebo plus chemotherapy arm had subsequently progressed or died at the data cut-off. The median duration of non-CNS response was 8.2 months (interquartile range 4.4-12.2 months) in the osimertinib plus chemotherapy arm and 4.2 months (interquartile range 3.1-7.6 months) in the placebo plus chemotherapy arm.

OS

At the data cut-off, 26 patients (53%) in the osimertinib plus chemotherapy arm and 28 patients (57%) in the placebo plus chemotherapy arm had died (OS maturity: 55%). Median follow-up for OS in censored patients was 12.0 months (range 4.2-36.0 months) and 11.1 months (range 0.8-34.5 months) for the osimertinib plus chemotherapy and placebo plus chemotherapy arms, respectively. Median OS was 15.9 months (95% CI 12.4-20.8 months) with osimertinib plus chemotherapy and 9.8 months (95% CI 8.4-17.2 months) with placebo plus chemotherapy (HR 0.71, 95% CI 0.42-1.23; Supplementary Figure S6, available at https://doi.org/10.1016/j.esmoop.2025.105807); the OS rates at 12 months were 67% (95% CI 52% to 79%) and 47% (95% CI 31% to 61%) for each treatment arm, respectively.

Safety

Overall, 96 patients received at least one dose of study treatment (48 per treatment arm). In the osimertinib plus chemotherapy arm, the median total duration of treatment with platinum therapy, pemetrexed, and osimertinib was 2.8 months, 6.1 months, and 6.7 months, respectively. In the placebo plus chemotherapy arm, the median total duration of treatment with platinum therapy, pemetrexed, and placebo was 2.8 months, 5.1 months, and 5.1 months, respectively.

AEs of any grade and cause were reported in 47 patients (98%) in each treatment arm. The most reported AEs of any grade and cause with osimertinib plus chemotherapy versus placebo plus chemotherapy were anemia (65% versus 54%), asthenia (40% versus 48%), nausea (35% versus 48%), and diarrhea (31% versus 10%) (Table 3).

Table 3. All-causality adverse events (any grade events occurring in ≥10% of patients in either treatment arm; safety analysis set)

	Osimertinib + platinum–pemetrexed (n = 48)		Placebo + platinum–pemetrexed (n = 48)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Patients with any AE, *n* (%)	47 (98)	30 (63)	47 (98)	22 (46)
Anemia	31 (65)	6 (13)	26 (54)	6 (13)
Asthenia	19 (40)	3 (6)	23 (48)	0
Nausea	17 (35)	1 (2)	23 (48)	0
Diarrhea	15 (31)	0	5 (10)	0
Vomiting	13 (27)	2 (4)	9 (19)	1 (2)
Constipation	11 (23)	0	11 (23)	1 (2)
Neutropenia	11 (23)	7 (15)	9 (19)	2 (4)
Platelet count decreased	10 (21)	3 (6)	4 (8)	3 (6)
Alanine aminotransferase increased	9 (19)	2 (4)	9 (19)	1 (2)
Neutrophil count decreased	9 (19)	5 (10)	12 (25)	3 (6)
Decreased appetite	8 (17)	1 (2)	9 (19)	0
Aspartate aminotransferase increased	8 (17)	2 (4)	7 (15)	0
Blood creatinine increased	8 (17)	0	4 (8)	0
Conjunctivitis	7 (15)	0	2 (4)	0
White blood cell count decreased	6 (13)	5 (10)	9 (19)	2 (4)
Edema peripheral	6 (13)	0	4 (8)	0
Pyrexia	6 (13)	0	4 (8)	0
COVID-19	6 (13)	0	5 (10)	1 (2)
Stomatitis	5 (10)	0	4 (8)	0
Rash	5 (10)	0	5 (10)	0
Fatigue	5 (10)	2 (4)	3 (6)	1 (2)
Back pain	5 (10)	1 (2)	2 (4)	0
Abdominal pain	5 (10)	0	2 (4)	0
Cough	4 (8)	0	7 (15)	0
Dyspnea	4 (8)	2 (4)	6 (13)	2 (4)
γ-Glutamyltransferase increased	3 (6)	1 (2)	5 (10)	3 (6)
Hyponatremia	2 (4)	0	5 (10)	1 (2)
Blood alkaline phosphatase increased	1 (2)	0	5 (10)	0

Data cut-off: 28 October 2024. Includes AEs with an onset or worsening date on or after the date of first dose and up to and including 28 days following the date of last dose of study medication and before start of a new anticancer treatment.
AE, adverse event; COVID-19, coronavirus disease 2019.

Grade ≥3 AEs of any cause were reported in 30 patients (63%) with osimertinib plus chemotherapy and 22 patients (46%) with placebo plus chemotherapy. The most reported grade ≥3 AEs of any cause were neutropenia (15%) and anemia (13%) in the osimertinib plus chemotherapy arm, and anemia (13%) in the placebo plus chemotherapy arm (Table 3). AEs of any grade considered causally related to osimertinib or placebo occurred in 33 patients (69%) with osimertinib plus chemotherapy and 30 patients (63%) with placebo plus chemotherapy. AEs of any grade considered causally related to platinum therapy and pemetrexed were reported in 42 patients (88%) and 44 patients (92%), respectively, with osimertinib plus chemotherapy and in 45 patients (94%) and 46 patients (96%), respectively, with placebo plus chemotherapy.

AEs of special interest were reported in 39 patients (81%) with osimertinib plus chemotherapy and 35 patients (73%) with placebo plus chemotherapy. All AEs of special

interest were hematological toxic effects (reported as a grouped term) apart from one event of grade 2 interstitial lung disease or pneumonitis (grouped term) reported in the placebo plus chemotherapy arm.

Serious AEs were reported in 18 patients (38%) with osimertinib plus chemotherapy and 15 patients (31%) with placebo plus chemotherapy. AEs leading to death occurred in one patient in each treatment arm [pulmonary embolism in the osimertinib plus chemotherapy arm and coronavirus disease 2019 (COVID-19) pneumonia in the placebo plus chemotherapy arm; neither was considered causally related to any of the study treatments]. In the osimertinib plus chemotherapy arm, AEs leading to discontinuation of platinum therapy and osimertinib were reported in six patients (13%) each, and AEs leading to discontinuation of pemetrexed were reported in nine patients (19%). The most common AE leading to discontinuation of osimertinib was anemia (two patients; 4%). In the placebo plus chemotherapy arm, AEs leading to discontinuation of placebo and pemetrexed were reported in one patient (2%) each; no patients discontinued platinum therapy due to an AE in the placebo plus chemotherapy arm.

DISCUSSION

Results from COMPEL showed that continuing osimertinib treatment beyond progression, with the addition of chemotherapy, was associated with improved PFS and longer OS compared with placebo plus chemotherapy in patients with EGFR-mutated advanced NSCLC and non-CNS progression on first-line osimertinib. Overall, the combination of osimertinib plus chemotherapy had a manageable safety profile that was consistent with previously reported data.[21]

Platinum-based chemotherapy remains a standard treatment for most patients with progression on first-line osimertinib.[12-14] Median PFS with chemotherapy alone was ∼4 months in COMPEL, consistent with outcomes from previous studies of patients who progressed on or after EGFR-TKI therapy.[2,25] This highlights the unmet need to improve outcomes in the second-line setting. Median PFS was approximately twice as long with continued use of osimertinib in combination with chemotherapy in COMPEL, suggesting that progression on first-line osimertinib is spatially and temporally diverse, with some clonal tumor cells maintaining sensitivity to osimertinib beyond the first progression. Other studies also support continued use of EGFR inhibitors in combination with platinum-based chemotherapy in the relapsed setting. In the phase III MARIPOSA-2 study of patients with EGFR-mutated advanced NSCLC and progression on osimertinib, PFS was significantly longer among patients receiving amivantamab (an EGFR-MET bispecific inhibitor) plus chemotherapy versus chemotherapy alone (median 6.3 months versus 4.2 months; HR 0.48, 95% CI 0.36-0.64, $P < 0.001$).[25] Based on these results, the combination of amivantamab with chemotherapy is another treatment option following progression on osimertinib.[12-14]

Osimertinib crosses the blood—brain barrier and has shown activity in patients with EGFR-mutated NSCLC who have CNS metastases.[6,26,27] While some studies suggest that chemotherapy agents such as cisplatin, carboplatin, and pemetrexed only have limited CNS penetration,[28,29] these agents have shown efficacy in the brain.[5] Furthermore, findings from the phase III FLAURA2 study showed that the combination of osimertinib and chemotherapy, as first-line therapy, delayed CNS progression in patients with EGFR-mutated NSCLC versus osimertinib alone, regardless of baseline CNS metastasis status, suggesting that the addition of chemotherapy may maximize the protective CNS effects of osimertinib.[15] Consistent with FLAURA2, osimertinib plus chemotherapy in COMPEL was associated with longer CNS PFS versus placebo plus chemotherapy in patients without CNS metastases at baseline [HR 0.56, 95% CI 0.27-1.13; owing to the limited sample size ($n = 23$), there were too few events to present the HR for CNS PFS for the subgroup of patients with CNS metastases at baseline]. There were also fewer patients with new brain lesions at the time of progression in the osimertinib plus chemotherapy arm (10%) compared with the placebo plus chemotherapy arm (27%). These findings add to the growing body of evidence supporting the robust CNS efficacy of osimertinib and show a continued protective effect with osimertinib, even after non-CNS progression on first-line osimertinib. Osimertinib plus chemotherapy was also associated with longer non-CNS PFS than placebo plus chemotherapy in COMPEL (HR 0.43, 95% CI 0.26-0.71), suggesting that the protective effects of this combination in the relapsed setting extend beyond the CNS. Together, these results support osimertinib as a backbone treatment for EGFR-mutated advanced NSCLC,[30] with benefits beyond the first-line setting.

COMPEL was designed to assess the benefit of continuing osimertinib treatment with the addition of chemotherapy in patients with EGFR-mutated advanced NSCLC and non-CNS progression on first-line osimertinib. As such, the study population included patients who had stable CNS metastases at baseline as well as patients without CNS metastases. Randomization was stratified according to the presence or absence of CNS metastases at baseline, and patients had regular systemic and CNS scans throughout treatment regardless of their CNS metastases status at baseline. The primary PFS endpoint considered both non-CNS and CNS progression events (whichever occurred first), and secondary non-CNS PFS and CNS PFS endpoints were included to evaluate the contribution of CNS metastases to progression in this population. Despite these strengths, the results should be considered in the context of the lower than planned sample size and subsequent lack of formal statistical testing, which prevents definitive conclusions.

The treatment landscape for EGFR-mutated NSCLC continues to evolve. Further studies are evaluating novel

combinations with osimertinib as a backbone treatment in the second-line setting. The combination of osimertinib with savolitinib (a MET-TKI) showed promising activity in patients with high levels of MET overexpression and/or amplification following progression on first-line osimertinib in the phase II SAVANNAH study (median PFS 7.4 months, 95% CI 5.5-7.6 months).[31] Complementing these findings, the phase III SACHI study demonstrated superior PFS with osimertinib plus savolitinib versus platinum-based chemotherapy in patients with MET amplification following progression on first-line EGFR-TKI therapy.[32]

The TROP2-directed antibody—drug conjugate datopotamab deruxtecan (Dato-Dxd), was recently approved by the United States Food and Drug Administration for patients previously treated for EGFR-mutated NSCLC.[33] Recent findings from the phase II ORCHARD platform study demonstrated promising activity with osimertinib plus Dato-Dxd in patients who progressed on first-line osimertinib (median PFS for the 6 mg/kg Dato-Dxd cohort: 11.7 months, 95% CI 8.3 months-not calculable).[34] The ongoing, phase III TROPION-Lung15 study is evaluating the efficacy and safety of Dato-Dxd, alone and in combination with osimertinib, versus platinum-based chemotherapy in patients with EGFR-mutated NSCLC and progression on first-line osimertinib.[35]

In conclusion, the findings of COMPEL show that continuing osimertinib, with the addition of chemotherapy, is associated with improved PFS and longer OS compared with placebo plus chemotherapy in patients with non-CNS progression on first-line osimertinib. This supports osimertinib as a backbone treatment for patients with EGFR-mutated advanced NSCLC through lines of therapy. These findings may help inform future treatment decisions based on individual patient characteristics.

ACKNOWLEDGEMENTS

The authors would like to thank all the patients involved in the COMPEL study and their families, the study investigators, and the team at AstraZeneca. The study was funded by AstraZeneca. The authors would like to acknowledge Caroline Allinson, BSc (as contracted), and Aaron Korpal, PhD, of Ashfield MedComms, an Inizio company, for medical writing support that was funded by AstraZeneca, in accordance with Good Publications Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

FUNDING

This work (NCT04765059) was supported by AstraZeneca (no grant number).

DISCLOSURE

NP reports receiving grants/contracts from AstraZeneca, Bayer, Bristol Myers Squibb (BMS), Merck, Merck Sharp & Dohme (MSD), Novartis, Pfizer, and Roche; receiving consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Eli Lilly, Imagine, Guardant360, Imagene, Merck, MSD, Novartis, Pfizer, Renium, Roche, and Takeda; receiving honoraria from AstraZeneca, BMS, Guardant360, Merck, MSD, Pfizer, Renium, Roche, and Takeda; and stock ownership with Imagine Ltd. AT reports receiving honoraria from Lilly, Pfizer, Novartis, AstraZeneca, Amgen, Celgene, Takeda, Janssen, Roche, MSD, BMS, and Boehringer Ingelheim; and employment with LMU University Hospital of Munich. GP reports receiving grants/contracts from MSD and Roche; receiving consulting fees from MSD, AstraZeneca, BMS, Roche, Pfizer, Novartis, Johnson & Johnson, Amgen, and Lilly; receiving honoraria from MSD, AstraZeneca, BMS, Roche, Pfizer, Novartis, Johnson & Johnson, Amgen, and Lilly; and advisory board/committee participation for AstraZeneca, Pfizer, Roche, and Amgen. LA reports receiving honoraria from AstraZeneca, Roche, Astellas, Novartis, MSD, BMS, Ipsen, Merck Serono, Amgen, and Bayer; travel support from AstraZeneca, Novartis, Ipsen, Merck Serono, and Amgen; advisory board/committee participation for Abbott and Pharmacosmos; and research funding to institution from AstraZeneca and Novartis. SMV reports receiving travel support from AstraZeneca, MSD, BMS, Pfizer, and Janssen. MM reports receiving grants/contracts from Roche; honoraria from MSD, AstraZeneca, Viatris, Servier, Ipsen, and Janssen; travel support from AstraZeneca; and advisory board/committee participation for Novartis and Oncosil. PMM reports receiving payment for expert testimony from Pfizer and Pierre Fabre; and receiving travel support from MSD, AstraZeneca, Pfizer, and Takeda. IBA reports receiving grants/contracts from Amgen, AstraZeneca, Takeda, Roche, MSD, and Pfizer; travel support from Roche and PharmaMar; and advisory board/committee participation with AstraZeneca and BeiGene. NVP reports receiving payment for expert testimony from AstraZeneca and Pfizer. EB reports receiving grants/contracts from AstraZeneca and Roche; travel support from MSD and Roche; advisory board/committee participation for MSD, Pfizer, Novartis, BMS, AstraZeneca, Roche, Amgen, and Celltrion. LS, RP, and AAG report employment and stock ownership with AstraZeneca. JZ reports advisory board/committee participation for AstraZeneca, BeONE, Novartis, and Pfizer. All other authors have declared no conflicts of interest.

DATA SHARING

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

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