CNS Efficacy of Osimertinib With or Without Chemotherapy in Epidermal Growth Factor Receptor–Mutated Advanced Non–Small-Cell Lung Cancer

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ABSTRACT

PURPOSE We report CNS efficacy of first-line osimertinib plus chemotherapy versus osimertinib monotherapy in patients with epidermal growth factor receptor (*EGFR*)–mutated advanced non–small-cell lung cancer (NSCLC) from the phase III FLAURA2 study according to baseline CNS metastasis status.

METHODS Patients were randomly assigned to osimertinib plus platinum-pemetrexed (combination) or osimertinib monotherapy until disease progression or discontinuation. Brain scans were performed in all patients at baseline and progression and at scheduled assessments until progression for patients with baseline CNS metastases; scans were assessed by neuroradiologist CNS blinded independent central review (BICR).

RESULTS On the basis of baseline CNS BICR, 118 of 279 (combination) and 104 of 278 (monotherapy) randomly assigned patients had ≥one measurable and/or nonmeasurable CNS lesion and were included in the CNS full analysis set (cFAS); 40 of 118 and 38 of 104 had ≥one measurable target CNS lesion and were included in the post hoc CNS evaluable-for-response set (cEFR). In the cFAS, the hazard ratio (HR) for CNS progression or death was 0.58 (95% CI, 0.33 to 1.01). In patients without baseline CNS metastases, the HR for CNS progression or death was 0.67 (95% CI, 0.43 to 1.04). In the cFAS, CNS objective response rates (ORRs; 95% CI) were 73% (combination; 64 to 81) versus 69% (monotherapy; 59 to 78); 59% versus 43% had CNS complete response (CR). In the cEFR, CNS ORRs (95% CI) were 88% (73 to 96) versus 87% (72 to 96); 48% versus 16% had CNS CR.

CONCLUSION Osimertinib plus platinum-pemetrexed demonstrated improved CNS efficacy compared with osimertinib monotherapy, including delaying CNS progression, irrespective of baseline CNS metastasis status. These data support this combination as a new first-line treatment for patients with *EGFR*-mutated advanced NSCLC, including those with CNS metastases.

ACCOMPANYING CONTENT

Appendix

Protocol

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INTRODUCTION

CNS metastases negatively affect patient quality of life (QoL) and prognosis[1,2] and are common in patients with epidermal growth factor receptor (*EGFR*)–mutated advanced non–small-cell lung cancer (NSCLC). Approximately 30%-50% of these patients develop CNS metastases within 5 years of diagnosis,[3-5] and the incidence is rising owing to improved survival and enhanced detection.[2,6] Treatment is challenging as many drugs cannot cross the blood-brain barrier or are effluxed, making the CNS a sanctuary site for metastases and limiting the ability of systemic treatments to affect intracranial disease.[2]

EGFR-tyrosine kinase inhibitors (EGFR-TKIs) are the recommended first-line treatment for certain patients with *EGFR*-mutated advanced NSCLC and brain metastases; some guidelines specifically recommend osimertinib.[7-9]

CONTEXT

Key Objective

Is treatment with osimertinib plus platinum-pemetrexed associated with better CNS efficacy versus osimertinib monotherapy in patients with epidermal growth factor receptor–mutated advanced non–small-cell lung cancer, including those with CNS metastases?

Knowledge Generated

This phase III study of osimertinib plus platinum-pemetrexed (combination) versus osimertinib monotherapy included mandatory brain scans at baseline and progression, allowing systematic evaluation of CNS efficacy. In patients with baseline CNS metastases, the combination demonstrated a clinically meaningful improvement in CNS progression-free survival (PFS) versus monotherapy (42% reduction in the risk of CNS progression or death); 59% versus 43% achieved complete response. CNS PFS benefit was also seen in patients without baseline CNS metastases.

Relevance *(T.E. Stinchcombe)*

The additional data about the CNS activity of osimertinib and chemotherapy may assist in the selection of patients for the combination therapy.*

*Relevance section written by *JCO* Associate Editor Thomas E. Stinchcombe, MD.

Osimertinib is a third-generation, irreversible, oral EGFR-TKI that potently and selectively inhibits both EGFR-TKI sensitizing and T790M resistance mutations, with demonstrated efficacy in *EGFR*-mutated NSCLC, including CNS metastases.[10-21] Osimertinib was associated with a 52% reduction in the risk of CNS progression or death from any cause versus comparator EGFR-TKIs (erlotinib or gefitinib) in a subgroup analysis of the FLAURA trial in patients with untreated *EGFR*-mutated advanced NSCLC and baseline CNS metastases.[15]

Despite the observed CNS efficacy with osimertinib, outcomes for patients with baseline CNS metastases remain poorer than for those without.[12] Improved outcomes with carboplatin-pemetrexed plus gefitinib versus gefitinib alone have been shown in *EGFR*-mutated advanced NSCLC, including in patients with baseline CNS metastases.[22,23] The GAP BRAIN phase III trial, conducted in China, showed improved intracranial efficacy for platinum-pemetrexed plus gefitinib versus gefitinib alone as a first-line treatment for patients with *EGFR*-mutated NSCLC with brain metastases.[24] These data support the possibility that adding chemotherapy to osimertinib may further improve outcomes compared with osimertinib monotherapy, including in patients with baseline CNS metastases.

FLAURA2, a phase III randomized trial in patients with *EGFR*-mutated advanced NSCLC, showed that first-line osimertinib plus platinum-pemetrexed was associated with a statistically significant and clinically meaningful improvement in investigator-assessed systemic progression-free survival (PFS) compared with osimertinib monotherapy (hazard ratio [HR], 0.62 [95% CI, 0.49 to 0.79]; $P < .001$).[25] Investigator-assessed systemic PFS was also improved with osimertinib plus platinum-pemetrexed versus osimertinib monotherapy in the subgroup analyses of patients with and without baseline CNS metastases (median PFS, 24.9 *v* 13.8 months; HR, 0.47 [95% CI, 0.33 to 0.66] and 27.6 *v* 21.0 months; HR, 0.75 [95% CI, 0.55 to 1.03], respectively).[25] Brain scans were performed in all randomly assigned patients at baseline and at progression in FLAURA2, allowing systematic evaluation of the CNS efficacy of osimertinib both with and without platinum-pemetrexed. We report the CNS efficacy (including CNS PFS) of osimertinib plus platinum-pemetrexed (combination arm) versus osimertinib monotherapy (monotherapy arm) in patients from FLAURA2 according to baseline CNS metastases status, as assessed by neuroradiologist CNS blinded independent central review (BICR).

METHODS

Trial Design

FLAURA2 (ClinicalTrials.gov identifier: NCT04035486) was a phase III, international, open-label, randomized trial conducted in patients with *EGFR*-mutated advanced NSCLC untreated for advanced disease (Appendix Fig A1, online only). Full trial design details have been published previously.[25] Eligible patients were randomly assigned 1:1 to receive osimertinib plus platinum-pemetrexed or osimertinib monotherapy (further details on eligibility and treatment are provided in Appendix 1). Random assignment was stratified by race (Chinese/Asian *v* non-Chinese/Asian *v* non-Asian), WHO performance status (PS; 0 *v* 1), and *EGFR* mutation tissue testing method (central *v* local). Treatment continued until investigator-assessed, RECIST 1.1-defined progression, unacceptable toxicity, or another discontinuation criterion. Treatment beyond progression

was permitted if the investigator judged the patient had continued clinical benefit.

Relevant institutional review boards or ethics committees approved the Protocol. The trial was performed in accordance with the provisions of the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, International Council for Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. All patients provided written, informed consent.

End Points

This preplanned analysis of exploratory end points by CNS BICR included evaluation of CNS PFS, CNS objective response rate (ORR), CNS duration of response (DoR), CNS disease control rate (DCR), and CNS tumor shrinkage in patients with baseline CNS metastases. CNS efficacy of osimertinib (prevention of CNS metastases) with and without platinum-pemetrexed was also assessed in patients without baseline CNS metastases.

Assessments

Brain scans were performed in all patients at baseline and at progression (Appendix Fig A1). Patients with CNS metastases identified at baseline scan, or with a history of CNS metastases, had brain scans at each tumor assessment (baseline, 6 weeks, 12 weeks, and then every 12 weeks) until disease progression. For patients without CNS metastases, no scheduled brain imaging was required, unless clinically indicated and/or until disease progression by RECIST 1.1 per investigator assessment. All CNS scans were evaluated by independent neuroradiologist review (CNS BICR) per modified RECIST 1.1 guidelines. CNS metastases measuring ≥10 mm (longest diameter) or ≥two times the slice thickness or reconstruction interval, and which could be measured reproducibly, were considered measurable lesions and could be selected as target lesions (maximum five lesions). All other lesions, including leptomeningeal disease, were considered nontarget lesions. Available prior radiotherapy was shared with readers; lesions within prior radiotherapy sites were considered nontarget lesions. Response criteria were derived per RECIST 1.1.

Patients with ≥one measurable and/or nonmeasurable baseline CNS lesion by neuroradiologist CNS BICR were included in the CNS full analysis set (cFAS); the CNS evaluable-for-response set (cEFR) included only those with ≥one measurable target CNS lesion.

Adverse events (AEs) were reported according to the National Cancer Institute Common Terminology Criteria for AEs, version 5.0.

Statistical Methods

The CNS analysis was conducted at the time of the primary PFS data cutoff (April 3, 2023). Analysis in the cFAS was prespecified; we also performed a post hoc analysis in the cEFR. All reported *P* values are nominal.

CNS PFS was defined as the time from random assignment until the date of objective CNS progression or death resulting from any cause in the absence of known CNS progression. Other end point definitions are provided in Appendix 1.

CNS PFS was evaluated using Kaplan-Meier methodology and analyzed by a stratified (cFAS; by race, WHO PS, and method used for tissue testing) or unstratified (cEFR) log-rank test. Patients who had not progressed in the CNS or died at the time of analysis were censored at their last evaluable brain scan. CNS ORR and CNS DCR by CNS BICR were analyzed using logistic regression with a factor for treatment.

A post hoc competing risk analysis of CNS progression was performed to estimate the cumulative incidence for the event of interest (defined as CNS progression) with competing risks of non-CNS progression or death. Event time was the occurrence of the earliest of the three events. Patients who were alive and without CNS or non-CNS progression were censored at the time of their last evaluable assessment. The results of this analysis were presented by treatment arm using cumulative incidence curves.

RESULTS

Patients

All 557 patients randomly assigned to treatment had baseline brain scans: 470 (84%) by magnetic resonance imaging (MRI) and 87 (16%) by computed tomography (CT); 118 of 279 patients in the combination arm and 104 of 278 in the monotherapy arm were included in the cFAS, and 40 and 38 patients, respectively, were included in the cEFR (Fig 1). Overlap between patients with CNS metastases at baseline per investigator and those identified by CNS BICR (cFAS) is illustrated in Appendix Fig A2.

Demographics in the cFAS were generally well balanced between the treatment arms and consistent with the overall FLAURA2 population (Table 1). Sixty-five patients (55%) in the combination arm and 59 patients (57%) in the monotherapy arm had >one CNS lesion at baseline, including 34 (29%) and 27 (26%), respectively, with ≥four CNS lesions (Appendix Table A1). Sixteen patients (14%) in the combination arm and 18 (17%) in the monotherapy arm had received prior brain radiotherapy.

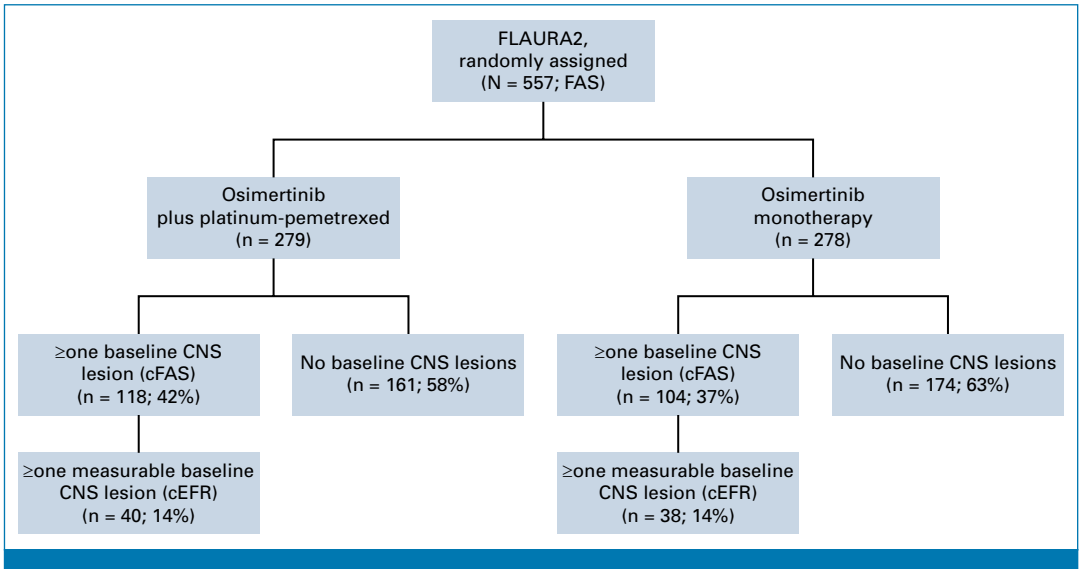

FIG 1. CONSORT diagram, patient disposition. Data cutoff: April 3, 2023. Neuroradiologist CNS BICR was evaluated on the basis of data derived from the brain scans (MRI or computed tomography) of all patients in the FAS. The cFAS included patients with ≥one CNS lesion (measurable and/or nonmeasurable) on CNS scans assessed by neuroradiologist BICR. The cEFR included only patients with ≥one measurable CNS lesion at baseline, on CNS scans assessed by neuroradiologist BICR. BICR, blinded independent central review; cEFR, CNS evaluable-for-response set; cFAS, CNS full analysis set; FAS, full analysis set; MRI, magnetic resonance imaging.

Efficacy

CNS PFS

The median (range) follow-up for CNS PFS in the cFAS was 20.1 (0-33.3) months in the combination arm and 13.9 (0-33.1) months in the monotherapy arm. The CNS PFS data maturity was 27% (59 of 222 events across both arms); CNS progression status by CNS BICR assessment and reasons for CNS progression are shown in Table 2.

The HR for CNS progression or death was 0.58 (95% CI, 0.33 to 1.01; nominal *P* value .0548; Fig 2A; CNS PFS in cEFR shown in Fig 2B; HR, 0.40 [95% CI, 0.19 to 0.84]). In the combination arm, the median CNS PFS was 30.2 months (95% CI, 28.4 months to not calculable [NC]) versus 27.6 months (95% CI, 22.1 months to NC) in the monotherapy arm. On the basis of a competing risk analysis, the estimated probability of observing a CNS progression event (in the absence of a non-CNS progression event or death) at 24 months was 9% (95% CI, 4 to 16) with osimertinib plus platinum-pemetrexed versus 23% (95% CI, 14 to 33) with osimertinib monotherapy (Fig 2C).

In patients without baseline CNS metastases per CNS BICR, the HR for CNS progression or death was 0.67 (95% CI, 0.43 to 1.04; nominal *P* value .0769; Appendix Fig A3); the data maturity was 26% (87 of 335 events across both arms).

A longitudinal analysis of CNS lesion status at baseline and at data cutoff according to baseline CNS metastases status per CNS BICR was conducted in the overall FLAURA2 population (Fig 2D). In patients with CNS metastases at baseline, fewer patients had CNS lesions at data cutoff in the combination arm (45 of 118 [38%]) than in the monotherapy arm (58 of 104 [56%]). Among those without baseline CNS metastases, very few patients in either treatment arm had new CNS lesions at data cutoff (combination arm, 6 of 161 [4%]; monotherapy arm, 8 of 174 [5%]).

CNS Tumor Response

In the cFAS, CNS ORRs were 73% in the combination arm (86 of 118; 95% CI, 64 to 81) versus 69% (72 of 104; 95% CI, 59 to 78) in the monotherapy arm (odds ratio [OR], 1.19 [95% CI, 0.67 to 2.14]; Table 3). In the combination arm, 59% of patients achieved CNS complete response (CR) compared with 43% of patients in the monotherapy arm (Table 3). CNS ORRs in patients without prior brain radiotherapy were 78% with osimertinib plus platinum-pemetrexed and 71% with osimertinib monotherapy (Appendix Table A2).

In the cEFR, the CNS ORR was 88% with osimertinib plus platinum-pemetrexed and 87% with osimertinib monotherapy (OR, 1.06 [95% CI, 0.28 to 4.00]; Table 3). Almost half of the patients (48%) in the combination arm had a CNS CR compared with 16% of patients in the monotherapy arm

TABLE 1. Baseline Patient Demographics and Disease Characteristics

Characteristic	cFAS (n = 222)		Overall FLAURA2 Population[25] (N = 557)	
	Osimertinib Plus Platinum-Pemetrexed (n = 118)	Osimertinib Monotherapy (n = 104)	Osimertinib Plus Platinum-Pemetrexed (n = 279)	Osimertinib Monotherapy (n = 278)
Sex, No. (%)				
Male	36 (31)	38 (37)	106 (38)	109 (39)
Female	82 (69)	66 (63)	173 (62)	169 (61)
Age, years				
Median (range)	60 (34-82)	61 (30-84)	61 (26-83)	62 (30-85)
Race (self-reported), No. (%)				
Asian	79 (67)	68 (65)	179 (64)	176 (63)
White	30 (25)	28 (27)	74 (27)	83 (30)
Other	9 (8)	8 (8)	26 (9)	19 (7)
WHO PS, No. (%)				
0	38 (32)	25 (24)	104 (37)	102 (37)
1	79 (67)	79 (76)	174 (62)	176 (63)
2	1 (1)	0	1 (<1)	0
Histology, No. (%)				
Adenocarcinoma	118 (100)	103 (99)	275 (99)	275 (99)
Adenosquamous	0	0	2 (1)	0
Other	0	1 (1)	2 (1)	3 (1)
EGFR mutation at random assignment, No. (%)[a]				
Ex19del	74 (63)	59 (57)	169 (61)	168 (60)
L858R	42 (36)	42 (40)	106 (38)	107 (38)
Both Ex19del and L858R	1 (1)	1 (1)	3 (1)	1 (<1)
Unknown	1 (1)	2 (2)	1 (<1)	2 (1)

Abbreviations: cFAS, CNS full analysis set; *EGFR*, epidermal growth factor receptor; Ex19del, exon 19 deletion; PS, performance status.
[a]On the basis of central or local testing. Overall FLAURA2 population data taken from N Engl J Med, Planchard D, Jänne PA, Cheng Y, et al., Osimertinib with or without Chemotherapy in *EGFR*-Mutated Advanced NSCLC, 389:1935-1948. Copyright © (2023) Massachusetts Medical Society. Reprinted with permission.

(Table 3); no patients with CR had received prior brain radiotherapy (Figs 3A and 3B).

In the cFAS, the median time to response was 11.8 weeks (IQR, 6.3-24.3 weeks) in the combination arm and 8.4 weeks (IQR, 6.1-23.9 weeks) in the monotherapy arm. Median CNS DoR was not reached in the combination arm and was 26.2 months in the monotherapy arm (Table 3). The median best percentage change from baseline in CNS target lesion size was −94% (range, −100% to +7%) with osimertinib plus platinum-pemetrexed and −61% (range, −100% to +68%) with osimertinib monotherapy (Figs 3A and 3B). MRI scans from two patients receiving osimertinib plus platinum-pemetrexed who had CNS CR are shown in Appendix Fig A4.

The overall concordance (responders and nonresponders) between CNS and systemic response to osimertinib plus platinum-pemetrexed (cEFR) was 95% (38 of 40 patients; 35 of 40 [88%] had both CNS and systemic responses) versus 87% (33 of 38 patients; 30 of 38 [79%] had both CNS and systemic responses) in the monotherapy arm (Appendix Table A3). Only two (5%) patients in each arm had discordance where CNS disease remained stable while systemic disease responded.

Patients With Leptomeningeal Metastases

Thirteen patients (11%) in the combination arm and five patients (5%) in the monotherapy arm had baseline leptomeningeal metastases (Appendix Table A1). The median duration of total treatment exposure in these patients was 25.2 months in the combination arm and 12.0 months in the monotherapy arm. Eight of 13 patients (62%) in the combination arm and 0 of 5 (0%) in the monotherapy arm were alive and progression-free, with 10 of 13 (77%) and 3 of 5 (60%) still in follow-up for survival. Nine of 13 patients (69%) in the combination arm and 2 of 5 (40%) in the monotherapy arm achieved a CNS response, with CNS CR in 5 of 13 (38%) and 1 of 5 (20%) patients, respectively (Table 4).

Safety

Overall AE rates were similar between the cFAS and the overall FLAURA2 study population (Appendix Table A4).

TABLE 2. CNS Progression Status by BICR Assessment and Reasons for CNS Progression (cFAS and cEFR)

	FLAURA2 cFAS (n = 222)		FLAURA2 cEFR (n = 78)	
Progression Status	Osimertinib Plus Platinum-Pemetrexed (n = 118)	Osimertinib Monotherapy (n = 104)	Osimertinib Plus Platinum-Pemetrexed (n = 40)	Osimertinib Monotherapy (n = 38)
CNS progression, No. (%)	28 (24)	31 (30)	11 (28)	18 (47)
CNS RECIST progression[a]	11 (9)	20 (19)	5 (13)	13 (34)
In existing target CNS lesions[b]	2 (2)	7 (7)	2 (5)	7 (18)
In existing nontarget CNS lesions[b]	0	4 (4)	0	3 (8)
In new CNS lesions[b]	9 (8)	12 (12)	3 (8)	6 (16)
Death in the absence of CNS progression	17 (14)	11 (11)	6 (15)	5 (13)
No CNS progression, No. (%)	90 (76)	73 (70)	29 (73)	20 (53)
Censored CNS RECIST progression because of missing visits[c]	1 (1)	0	0	0
Censored death because of missing visits[c]	13 (11)	16 (15)	8 (20)	4 (11)
CNS progression-free at time of analysis	71 (60)	55 (53)	20 (50)	14 (37)
Withdrawn consent	4 (3)	2 (2)	1 (3)	2 (5)
Discontinued study because of other reasons	1 (1)	0	0	0
Median CNS PFS, months (95% CI)	30.2 (28.4 to NC)	27.6 (22.1 to NC)	NR (23.0 to NC)	17.3 (13.9 to NC)
Hazard ratio (95% CI)	0.58 (0.33 to 1.01)		0.40 (0.19 to 0.84)	
Nominal two-sided *P*	*P* = .0548		*P* = .0157	

Abbreviations: BICR, blinded independent central review; cEFR, CNS evaluable-for-response set; cFAS, CNS full analysis set; NC, not calculable; NR, not reached; PFS, progression-free survival.

[a]Only includes CNS progression events that occurred within two consecutive scheduled visits (plus visit window) of the last CNS assessment or random assignment.

[b]Progression in target lesions, nontarget lesions, and new lesions were not necessarily mutually exclusive.

[c]RECIST CNS progression or death occurred in >two consecutive scheduled visits (plus visit window) after previous CNS RECIST assessment or after baseline if there was no CNS postbaseline assessment. Patients were censored at the previous evaluable CNS RECIST assessment or random assignment date.

DISCUSSION

This preplanned subgroup analysis of FLAURA2 assessed the CNS efficacy of osimertinib plus platinum-pemetrexed versus osimertinib monotherapy as first-line treatment in patients with *EGFR*-mutated NSCLC according to baseline CNS metastases status. All randomly assigned patients in FLAURA2 had brain scans at baseline, performed predominantly using MRI (84%), which is a more sensitive assessment than CT.[26] Furthermore, scans were assessed by neuroradiologist BICR. These results, therefore, provide a comprehensive, high-quality, robust data set to assess CNS outcomes.

Patient baseline characteristics were balanced; approximately 55% of patients in each treatment arm had >one CNS lesion, and the proportion of patients who received prior brain radiotherapy, which could potentially confound interpretation of CNS response data, was low at approximately 15% per arm.

Among 222 patients with baseline CNS metastases, osimertinib plus platinum-pemetrexed demonstrated a clinically meaningful improvement in CNS PFS compared with osimertinib monotherapy, with a 42% reduction in the risk of CNS progression or death. Fewer patients had CNS progression with osimertinib plus platinum-pemetrexed than with osimertinib monotherapy (9% *v* 19%), and in the small number of patients with baseline leptomeningeal metastases, 8 of 13 in the combination arm remained alive and CNS progression-free versus none in the monotherapy arm. Moreover, the probability of observing CNS progression while adjusting for the presence of competing risk events (non-CNS progression or death) was consistently lower with osimertinib plus platinum-pemetrexed versus osimertinib monotherapy; at 24 months, it was 9% versus 23%, respectively.

As expected, given that patients received osimertinib in both treatment arms,[15] CNS ORRs were high and similar in both treatment arms (approximately 70%). However, the proportion of patients achieving CNS CR was numerically higher in the combination arm (59%) compared with the monotherapy arm (43%). The difference in CNS CR between arms was even more pronounced in patients with ≥one measurable CNS lesion at baseline (48% *v* 16%); no patients with a CNS CR had received prior brain radiotherapy. Although CNS responses were durable across both treatment arms, DoR was improved among those patients receiving combination therapy (93% *v* 81% with osimertinib plus

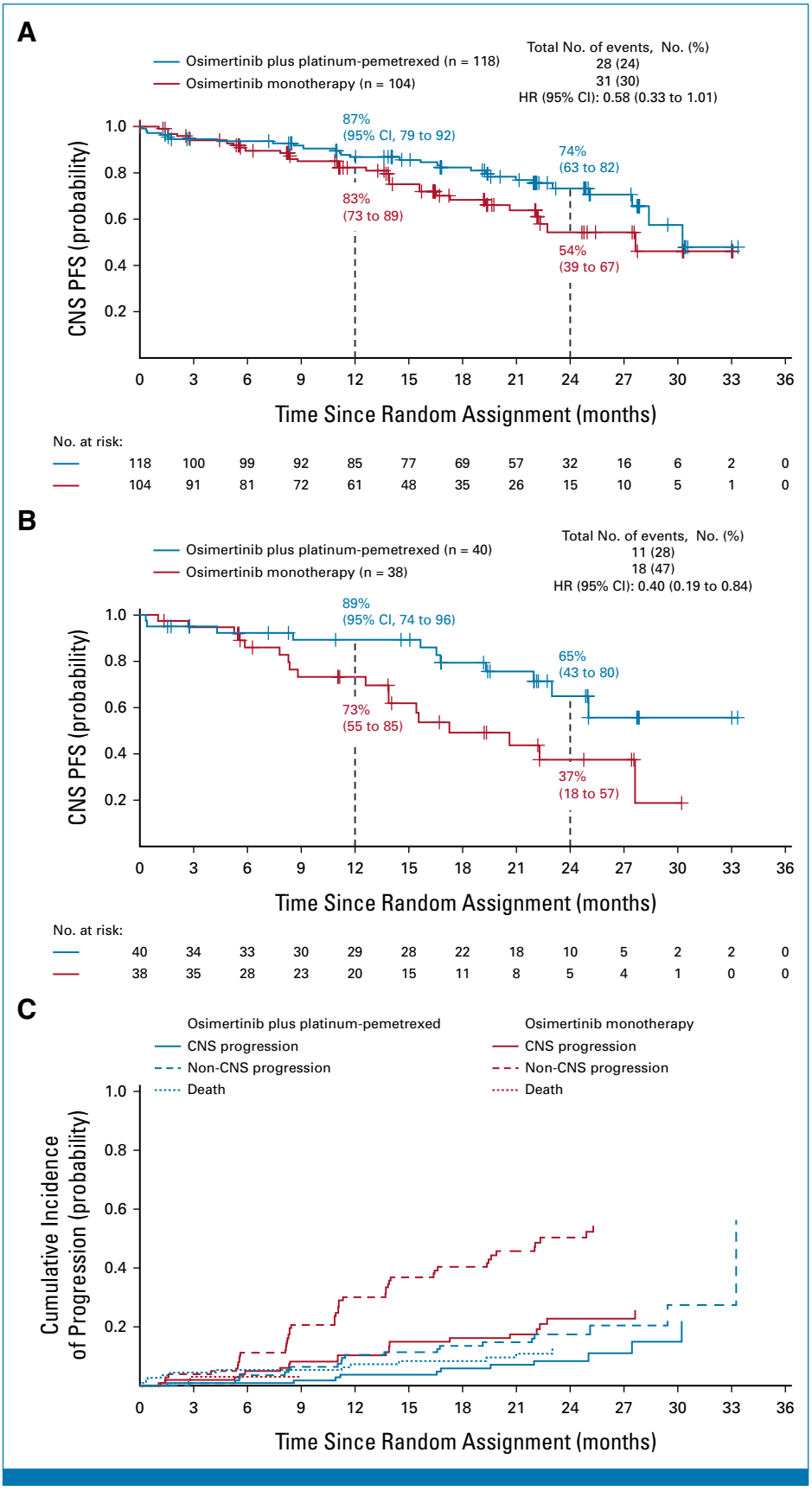

FIG 2. CNS PFS in (A) cFAS and (B) cEFR. (C) Cumulative incidence of CNS progression, taking into account competing risks of non-CNS progression and death resulting from any cause, in cFAS. (D) Analysis of CNS lesion status at data cutoff by study BICR (continued on following page)

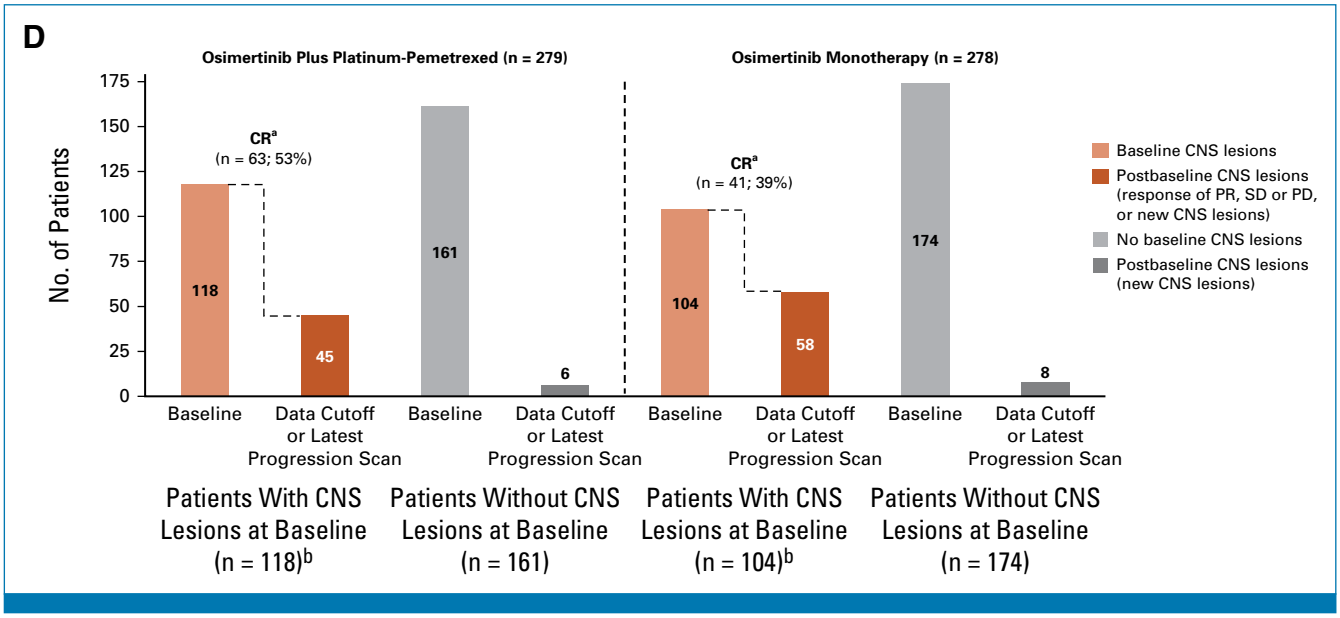

FIG 2. (Continued). in the overall FLAURA2 study population. (A): The median CNS PFS was 30.2 months (95% CI, 28.4 months to NC) with osimertinib plus platinum-pemetrexed and 27.6 months (95% CI, 22.1 months to NC) with osimertinib monotherapy. Censored data are indicated by tick marks. (C): CNS progression included patients who experienced progression in the CNS (by CNS BICR) and in other anatomies at the same overall visit; non-CNS progression included those with radiological documentation of progression outside the CNS only (overall study BICR); death included patients who died in the absence of radiological confirmed CNS or non-CNS progression. On the basis of this competing risk analysis, the estimated 24-month cumulative incidence rates with osimertinib plus platinum-pemetrexed versus osimertinib monotherapy were CNS progression, 9% versus 23% and non-CNS progression, 17% versus 50%. The 24-month cumulative incidence rates for death were NC (as seen in the figure, no death events at 24 months or later contributed to the competing risk analysis for the CNS PFS). [a]CR indicates those patients with a CR that was maintained at the time of data cutoff. [b]Among patients included in the cFAS (ie, those with ≥one BICR CNS lesion at baseline), 10 patients in the osimertinib plus platinum-pemetrexed arm and five patients in the osimertinib monotherapy arm had no post-baseline assessment by BICR. BICR, blinded independent central review; cEFR, CNS evaluable-for-response set; cFAS, CNS full analysis set; CR, complete response; HR, hazard ratio; NC, not calculable; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

platinum-pemetrexed *v* osimertinib monotherapy estimated remaining alive and in CNS response at 12 months). Furthermore, patients in the combination arm had a greater depth of response compared with those in the monotherapy arm (median best percentage change from baseline in CNS target lesion size −94% *v* −61%).

There was high (>85%) concordance between CNS and systemic response in both treatment arms; only two patients in each arm experienced CNS nonresponse (stable disease) with an overall systemic response. This suggests that CNS treatment failure with osimertinib is unlikely in patients with systemic disease control. Moreover, results for CNS PFS assessed by BICR were consistent with the analysis of systemic PFS in the overall FLAURA2 population, including the subgroup analysis of patients with CNS metastases at baseline on the basis of investigator assessment (as opposed to assessment by neuroradiologist BICR as used in the current analysis).[25]

CNS efficacy for the monotherapy arm in FLAURA2 was consistent with that observed in the subgroup analysis of FLAURA in patients with baseline brain scans; CNS PFS rates with osimertinib monotherapy at 12 and 24 months were 83% and 54% in FLAURA2 and 77% and 58% in FLAURA, respectively.[15] In the GAP BRAIN phase III trial, similar to our results, gefitinib plus platinum-pemetrexed was associated with improved intracranial ORR versus gefitinib monotherapy (85% *v* 63%, respectively). Intracranial median PFS was 15.6 months with gefitinib plus platinum-pemetrexed and 9.1 months with gefitinib alone.[24]

Osimertinib penetrates the blood-brain barrier and has shown activity in patients with *EGFR*-mutated NSCLC and brain metastases.[15,21,27,28] Conversely, pharmacokinetic studies have suggested only limited CNS penetration for cisplatin, carboplatin, and pemetrexed.[29,30] Nevertheless, chemotherapy has shown efficacy in the brain; in a subgroup analysis of patients with CNS metastases at baseline in the AURA3 study, a CNS ORR of 17% was seen in the platinum-pemetrexed arm.[14] Furthermore, cisplatin plus pemetrexed was associated with a CNS ORR of 42% in a single-arm phase II trial in 43 patients with NSCLC with brain metastases.[31] It is possible that the presence of CNS metastases might facilitate brain penetration of chemotherapy owing to disruption of the blood-brain barrier,[32] thus contributing to the observed

TABLE 3. CNS Response by BICR Assessment to Osimertinib Plus Platinum-Pemetrexed Versus Osimertinib Monotherapy (cFAS and cEFR)

	cFAS (n = 222)		cEFR (n = 78)	
Response	Osimertinib Plus Platinum-Pemetrexed (n = 118)	Osimertinib Monotherapy (n = 104)	Osimertinib Plus Platinum-Pemetrexed (n = 40)	Osimertinib Monotherapy (n = 38)
CNS best objective response, No. (%)[a]	86 (73)	72 (69)	35 (88)	33 (87)
CR	70 (59)	45 (43)	19 (48)	6 (16)
PR	16 (14)	27 (26)	16 (40)	27 (71)
CNS ORR, % (95% CI)	73 (64 to 81)	69 (59 to 78)	88 (73 to 96)	87 (72 to 96)
OR (95% CI)	1.19 (0.67 to 2.14)		1.06 (0.28 to 4.00)	
Nominal two-sided *P*	*P* = .5492		*P* = .9308	
CNS DCR, % (95% CI)	91 (84 to 95)	93 (87 to 97)	95 (83 to 99)	97 (86 to 100)
OR (95% CI)	0.70 (0.26 to 1.88)		0.51 (0.04 to 5.91)	
Nominal two-sided *P*	*P* = .4781		*P* = .5827	
Responders who subsequently CNS progressed or died, No. (%)	17 (20)	19 (26)	8 (23)	13 (39)
Median CNS DoR, months (95% CI)[b]	NR (23.8 to NC)	26.2 (19.4 to NC)	NR (21.6 to NC)	20.9 (12.6 to NC)
Estimated percent remaining in response, % (95% CI)[b]				
At 6 months	99 (92 to 100)	87 (75 to 93)	100 (100 to 100)	78 (57 to 90)
At 12 months	93 (85 to 97)	81 (68 to 89)	93 (75 to 98)	74 (53 to 87)
At 18 months	82 (70 to 90)	73 (58 to 83)	80 (58 to 91)	58 (36 to 76)
At 24 months	62 (40 to 77)	57 (38 to 72)	57 (27 to 78)	45 (22 to 65)

Abbreviations: BICR, blinded independent central review; cEFR, CNS evaluable-for-response set; cFAS, CNS full analysis set; CR, complete response; DCR, disease control rate; DoR, duration of response; NC, not calculable; NR, not reached; OR, odds ratio; ORR, objective response rate; PR, partial response.

[a]Responses did not require confirmation, per RECIST guidance on randomized studies.

[b]Kaplan-Meier estimates.

synergistic effect of platinum-pemetrexed on the CNS efficacy of osimertinib.

Among patients without baseline CNS metastases in FLAURA2, the proportion of patients who experienced CNS progression (ie, new CNS lesions) was very low and similar between treatment arms (4% with osimertinib plus platinum-pemetrexed and 5% with osimertinib monotherapy). Osimertinib can penetrate the intact blood-brain barrier in healthy volunteers[33] and can also cross the blood-brain barrier in patients with *EGFR*-mutated advanced NSCLC and brain metastases.[34] In the adjuvant setting, where patients were disease-free after surgical resection, patients from ADAURA who received osimertinib had fewer CNS disease recurrence events than those who received placebo.[35] CNS efficacy with osimertinib has also been shown in patients with *EGFR*-mutated advanced NSCLC and brain metastases.[15] Considered together, these data support that the ability of osimertinib to penetrate the blood-brain barrier[34] may offer a protective effect against the development of CNS metastases.

CNS metastases negatively affect cognition and QoL.[1] Moreover, local therapy for CNS metastases, such as neurosurgery or radiotherapy, may also have a long-term cognitive detriment.[36,37] As such, the improved efficacy observed with osimertinib plus platinum-pemetrexed supports deferring local therapies in patients with asymptomatic brain metastases, thus potentially preserving neurocognition and maintaining or improving QoL. Given that the median overall survival with osimertinib in FLAURA was 38.6 months,[16] there is a need for studies to evaluate neurocognition over a number of years to understand the true long-term impact of contemporary treatment strategies.

The potential benefits of using osimertinib plus platinum-pemetrexed in patients with baseline CNS metastases highlights the need to identify such patients. Mandatory baseline brain scans in FLAURA2 enabled an accurate reflection of the proportion of patients with baseline CNS metastases. The observed rate of baseline CNS metastases, on the basis of neuroradiologist BICR, in FLAURA2 was 40% (222 of 557 patients), almost double that observed in FLAURA (23%; 128 of 556),[15] where baseline brain scans were not mandated. However, the rate is similar to that reported in other studies in *EGFR*-mutated advanced NSCLC that have mandated baseline brain scans, including OPAL (33%)[5] and LASER201 (51%).[4] This suggests that a substantial proportion of patients may have occult asymptomatic CNS

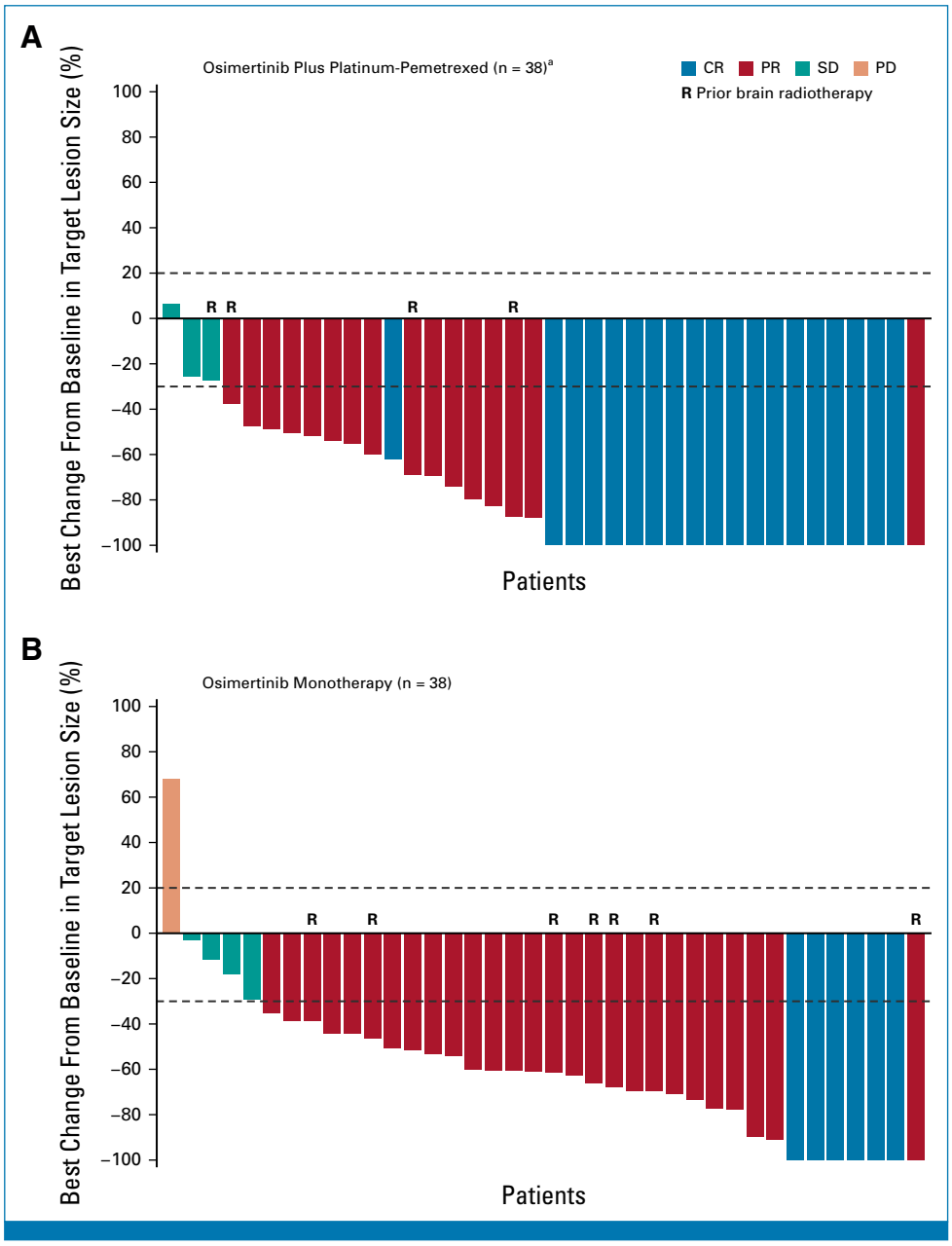

FIG 3. Best percentage change from baseline in CNS target lesion size with (A) osimertinib plus platinum-pemetrexed and (B) osimertinib monotherapy (cFAS). [a]Two patients had ≥one measurable CNS lesion at baseline by CNS BICR but died before the follow-up CNS BICR scan. (A) and (B): This evaluation only includes patients with measurable (≥10 mm) baseline CNS lesions and ≥one follow-up assessment. BICR, blinded independent central review; cFAS, CNS full analysis set; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

metastases at baseline and reinforces the need to consider CNS imaging for all patients with *EGFR*-mutated advanced NSCLC, regardless of symptoms. This approach is in line with clinical guidelines[38] and may help to guide optimal treatment choice.

Our analysis was limited by low CNS PFS data maturity (27%); of note, there were low numbers at risk after 24 months in both treatment arms (combination arm, 32 patients; monotherapy arm, 15 patients). Furthermore, a small number of patients in the cFAS had baseline CNS metastases by neuroradiologist BICR, but not according to investigator assessment (33 of 222; Appendix Fig A2). These patients were not required to have further brain imaging until investigator-assessed RECIST progression, unless clinically indicated, thus asymptomatic CNS progression would only be detected at the time of systemic disease progression in these patients.

TABLE 4. Characteristics, CNS PFS, and CNS Objective Response Rates in Patients With Leptomeningeal Metastases at Baseline

Characteristic or Outcome	Osimertinib Plus Platinum-Pemetrexed (n = 13)	Osimertinib Monotherapy (n = 5)
Age, years, median	57	54
Baseline WHO PS, No. (%)		
0	6 (46)	2 (40)
1	7 (54)	3 (60)
EGFR mutation, No. (%)		
Ex19del	10 (77)	3 (60)
L858R	3 (23)	2 (40)
Total exposure, months, median	25.2	12.0
CNS PFS event or censoring description, No. (%)		
RECIST progression	3 (23)	5 (100)
Alive and progression-free	8 (62)	0
Censored death	1 (8)	0
Death	1 (8)	0
Best objective CNS response, No. (%)		
Patients with response	9 (69)	2 (40)
CR	5 (38)	1 (20)
PR	4 (31)	1 (20)
Patients without response	4 (31)	3 (60)
SD	2 (15)	2 (40)
NE	2 (15)	0
PD	0	1 (20)

NOTE. Percentages may not equal 100 because of rounding.
Abbreviations: CR, complete response; *EGFR*, epidermal growth factor receptor; Ex19del, exon 19 deletion; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; PR, partial response; PS, performance status; SD, stable disease.

Overall, in patients with *EGFR*-mutated advanced NSCLC and baseline CNS metastases, osimertinib plus platinum-pemetrexed was associated with a high rate of CNS responses (including CRs) and improved depth and DoR in the CNS, driving a clinically meaningful reduction in the risk of CNS progression compared with osimertinib monotherapy. The safety profile of osimertinib plus platinum-pemetrexed in patients with CNS metastases was consistent with the overall FLAURA2 population. Osimertinib plus platinum-pemetrexed is a first-line treatment option in this patient population with high unmet need and poor prognosis.

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CNS Efficacy of Osimertinib With or Without Chemotherapy in Epidermal Growth Factor Receptor–Mutated Advanced Non–Small-Cell Lung Cancer

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APPENDIX 1. SUPPLEMENTARY METHODS

Eligibility

Eligible patients (age 18 years or older or 20 years or older in Japan) had locally advanced or metastatic non–small-cell lung cancer (NSCLC) and had not received previous systemic treatment for advanced disease. Nonsquamous NSCLC was pathologically confirmed with locally or centrally confirmed epidermal growth factor receptor (*EGFR*) exon 19 deletion (Ex19del) or L858R, either alone or in combination with other *EGFR* mutations. Patients had a WHO performance status (PS) of 0 or 1. Patients with asymptomatic CNS metastases (not requiring immediate treatment) and those with stable CNS metastases (stable neurological status for ≥2 weeks after completion of local treatment and steroids) were eligible.

Treatment

Treatment in the combination arm was with oral osimertinib 80 mg once daily plus intravenous pemetrexed 500 mg/m^2 with either cisplatin 75 mg/m^2 or carboplatin AUC5 (platinum-based treatments administered on day 1 of 21-day cycles [once every 3 weeks] for four cycles), followed by osimertinib 80 mg once daily plus maintenance with pemetrexed 500 mg/m^2 once every 3 weeks. Treatment in the monotherapy arm was with oral osimertinib 80 mg once daily.

End Point Definitions

CNS response in target lesions was classed as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or not evaluable. CNS response in nontarget lesions was classed as CR, non-CR/non-PD, PD, or not evaluable. CNS objective response rate was defined as the percentage of patients who had ≥one visit with a CNS response of PR or CR by CNS blinded independent central review (BICR) assessment. CNS duration of response was defined as the time of first documented CNS response (by CNS BICR) until the date of objective CNS progression or death from any cause. CNS disease control rate was defined as the percentage of patients who had a best CNS BICR response of CR, PR, SD (for ≥5 weeks), or non-CR/non-PD by CNS RECIST 1.1. Best percentage change in CNS target lesion tumor size was calculated on the basis of the relative change in the sum of the longest diameters of target lesions at the nadir, in the absence of new lesions or progression of nontarget lesions, compared with baseline.

APPENDIX 2. SUPPLEMENTARY RESULTS

The brain magnetic resonance imaging (MRI) scans in Appendix Fig A4A are from a 49-year-old, Asian, female patient (never-smoker, WHO PS 1) with stage IVB (T3N0M1c) *EGFR*-mutated (Ex19del) NSCLC, with metastatic disease present in the brain, bone, bilateral lung, and left pleura at baseline. The patient had not received prior systemic or local therapy for lung cancer. The patient was randomly assigned to the osimertinib plus platinum-pemetrexed arm, completed four cycles of carboplatin-pemetrexed, and has continued with osimertinib plus pemetrexed for more than 2.5 years without any dose modifications; the patient was ongoing on study treatment at data cutoff.

Brain MRI at baseline showed leptomeningeal disease and seven parenchymal lesions distributed in bilateral cerebral hemispheres and posterior fossa, including three target lesions (15.6, 14.7, and 14.1 mm). Most lesions had areas of central necrosis and heterogeneous enhancement and were associated with mild perilesional edema with some mass effect but without herniation. Baseline images show three lesions in the right precentral gyrus with associated vasogenic edema. Leptomeningeal disease was most prominent in the posterior fossa evidenced by enhancement in the bilateral cerebellar subarachnoid spaces. At week 6, a >90% reduction in tumor size, resolution of vasogenic edema, and reduction in leptomeningeal enhancement was observed. By week 12, CR was recorded in the brain (not shown). Images at week 108 (>2 years) showed that CR was maintained until data cutoff. Simultaneously, her disease response in the body was a PR in her left lung lesion from baseline (33.8-9.3 mm at data cutoff).

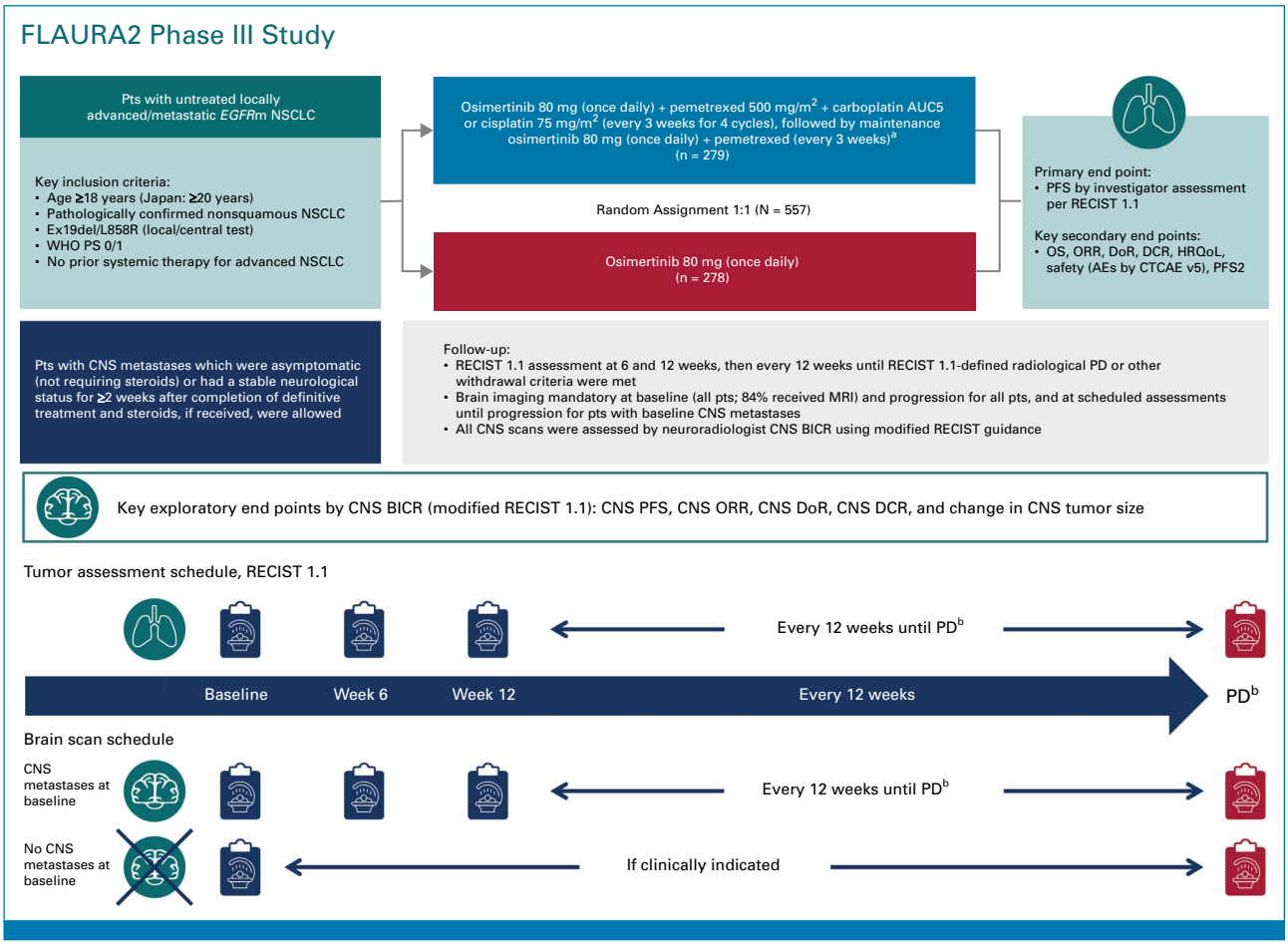

FIG A1. FLAURA2 study schema and scan schedule. The FLAURA2 study schema for the overall population (full analysis set) is shown, including key inclusion criteria, randomly assigned treatment, and primary and key secondary end points. Additional detail on inclusion criteria for patients with CNS metastases is provided, alongside details on follow-up. The tumor assessment schedule per RECIST 1.1 for systemic assessments in all patients is shown. The brain scan schedule is shown for patients with and without CNS metastases at baseline (as assessed by investigator). Brain scans were subsequently assessed by neuroradiologist BICR per modified RECIST 1.1. [a]Pemetrexed maintenance continued until a discontinuation criterion was met. [b]RECIST 1.1-defined radiological PD was by investigator assessment. AE, adverse event; BICR, blinded independent central review; CNS, central nervous system; CTCAE, Common Terminology Criteria for AEs; DCR, disease control rate; DoR, duration of response; *EGFR*, epidermal growth factor receptor; *EGFR*m, EGFR-mutated; Ex19del, exon 19 deletion; HRQoL, health-related quality of life; MRI, magnetic resonance imaging; NSCLC, non–small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, second progression-free survival; PS, performance status; pts, patients.

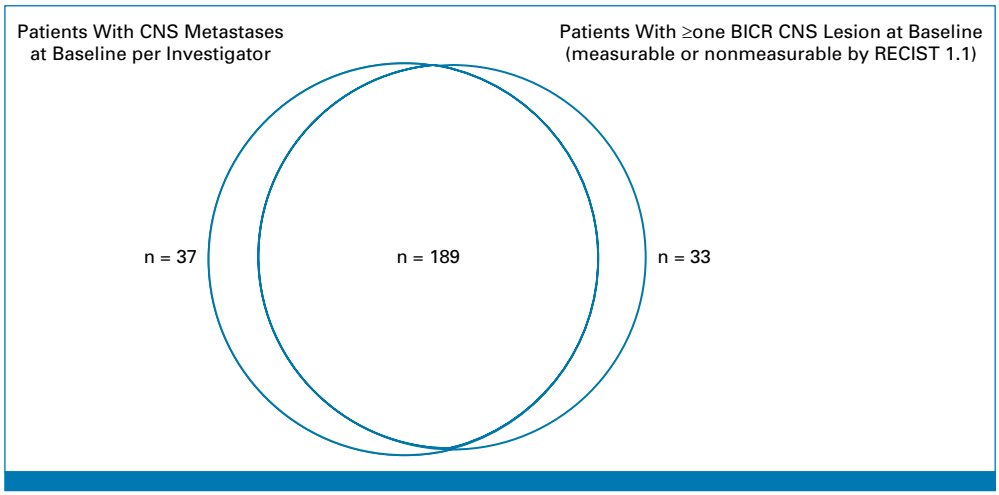

FIG A2. Overlap between patients with CNS metastases at baseline per investigator and those included in the cFAS (≥one BICR CNS lesion at baseline) in the overall FLAURA2 population. Most patients with CNS metastases at baseline per investigator were also included in the cFAS. Thirty-seven patients were not included in the cFAS but did have CNS metastases at baseline per investigator. Thirty-three patients were included in the cFAS but did not have CNS metastases at baseline per investigator. BICR, blinded independent central review; cFAS, CNS full analysis set.

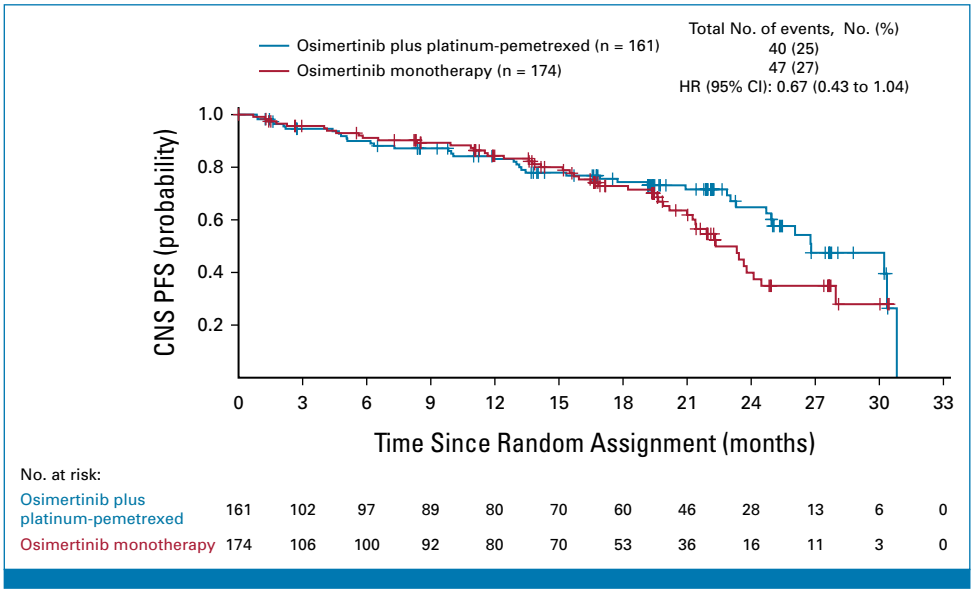

FIG A3. CNS PFS in patients without CNS metastases at baseline by BICR. Censored data are indicated by tick marks. BICR, blinded independent central review; HR, hazard ratio; PFS, progression-free survival.

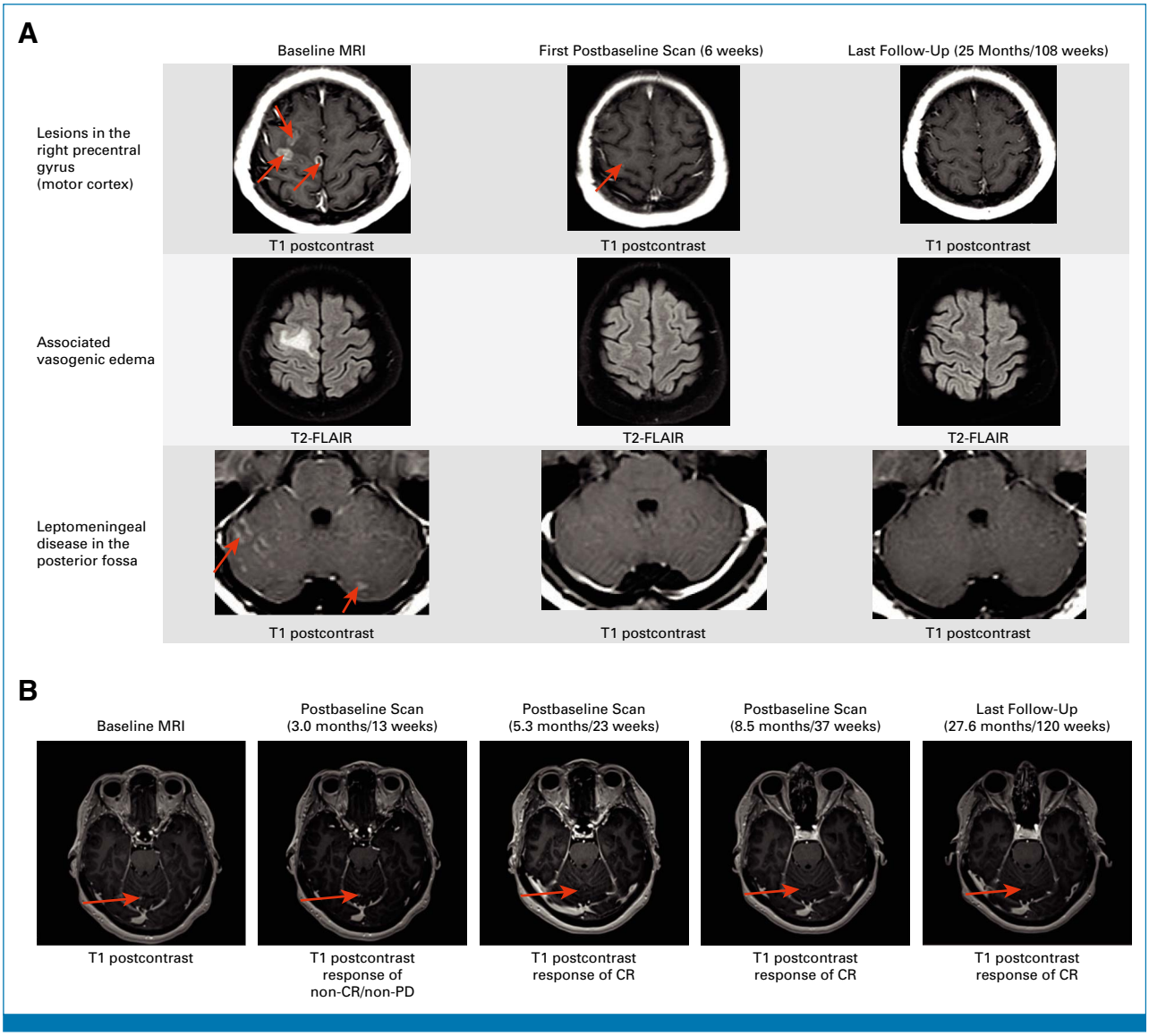

FIG A4. Brain MRI scans from two patients receiving osimertinib plus carboplatin-pemetrexed who had durable CNS CRs in the brain. (A) Baseline images show three lesions in the right precentral gyrus with associated vasogenic edema. Leptomeningeal disease was most prominent in the posterior fossa evidenced by enhancement in the bilateral cerebellar subarachnoid spaces. At week 6, a >90% reduction in tumor size, resolution of vasogenic edema, and reduction in leptomeningeal enhancement was observed. By week 12, CR was recorded in the brain (not shown). Images at week 108 (>2 years) showed CR was maintained until data cutoff. Additional details for this patient are provided in Appendix 2. (B) The baseline image shows an enhancing nodule (<10 mm) in the right cerebellar subarachnoid space, indicating leptomeningeal disease; this was considered a nontarget lesion. The image at 3.0 months/13 weeks shows that the lesion had not increased in size; as a nontarget lesion, this was classed as a response of non-CR/non-PD. The image at 5.3 months/23 weeks shows that the lesion had resolved because there was no residual enhancing lesion; this was classed as a CR. The images at 8.5 months/37 weeks and 27.6 months/120 weeks (>2 years; last follow-up) show that the lesion remained resolved as there was no recurrent enhancing lesion; the response was classed as a CR. CR, complete response; MRI, magnetic resonance imaging; PD, progressive disease.

TABLE A1. Prior Therapy and Baseline CNS Lesion Characteristics

Characteristic	cFAS	
	Osimertinib Plus Platinum-Pemetrexed (n = 118)	Osimertinib Monotherapy (n = 104)
Patients with prior brain radiotherapy and/or prior brain surgery, No. (%)	17 (14)	24 (23)
Patients with prior brain radiotherapy, No. (%)	16 (14)	18 (17)
Whole-brain radiotherapy	8 (7)	9 (9)
Partial-brain[a] radiotherapy	8 (7)	8 (8)
Unknown	0	1 (1)
Patients with prior brain surgery, No. (%)	1 (1)	7 (7)
Patients with leptomeningeal metastases, No. (%)	13 (11)	5 (5)
Patients with CNS lesions, No. (%)	118 (100)	104 (100)
1 lesion	53 (45)	45 (43)
2-3 lesions	31 (26)	32 (31)
4-10 lesions	33 (28)	26 (25)
>10 lesions	1 (1)	1 (1)

	cEFR	
	Osimertinib Plus Platinum-Pemetrexed (n = 118)	Osimertinib Monotherapy (n = 104)
Patients with ≥one measurable CNS lesion, No. (%)	40 (34)	38 (37)
CNS target lesion size (sum of longest diameters), mm, median (range)	20 (11-88)	20 (10-65)
CNS target lesion size category (sum of longest diameters), mm, No. (%)[b]		
<20	22 (55)	18 (47)
20-40	12 (30)	13 (34)
>40	6 (15)	7 (18)

Abbreviations: cEFR, CNS evaluable-for-response set; cFAS, CNS full analysis set.
[a]Included stereotactic and/or other cranial irradiation that did not cover the whole brain.
[b]Percentages calculated using the No. of patients with target lesions in each arm as the denominators.

TABLE A2. CNS ORRs by Prior Brain Radiotherapy Status

Response by Prior Radiotherapy Status	cFAS		cEFR	
	Osimertinib Plus Platinum-Pemetrexed (n = 118)	Osimertinib Monotherapy (n = 104)	Osimertinib Plus Platinum-Pemetrexed (n = 40)	Osimertinib Monotherapy (n = 38)
Prior radiotherapy, No.	16	18	4	7
CNS response, No. (%)	6 (38)	11 (61)	3 (75)	7 (100)
CNS ORR, % (95% CI)	38 (15 to 65)	61 (36 to 83)	75 (19 to 99)	100 (59 to 100)
No prior radiotherapy, No.	102	86	36	31
CNS response, No. (%)	80 (78)	61 (71)	32 (89)	26 (84)
CNS ORR, % (95% CI)	78 (69 to 86)	71 (60 to 80)	89 (74 to 97)	84 (66 to 95)

NOTE. Analysis performed using logistic regression with a factor for treatment.
Abbreviations: cEFR, CNS evaluable-for-response set; cFAS, CNS full analysis set; ORR, objective response rate.

TABLE A3. Concordance Between CNS ORR and Systemic RECIST ORR by BICR Assessment (cEFR)

Concordance	CNS Response, No. (%)			CNS Nonresponse, No. (%)			
	Total	CR	PR	Total	SD	PD	NE
Osimertinib plus platinum-pemetrexed (n = 40)							
Systemic response							
Total	**35 (88)**	19 (48)	16 (40)	**2 (5)**	2 (5)	0	0
CR	0	0	0	0	0	0	0
PR	35 (88)	19 (48)	16 (40)	2 (5)	2 (5)	0	0
Systemic nonresponse							
Total	**0**	0	0	**3 (8)**	1 (3)	2 (5)	0
SD	0	0	0	0	0	0	0
PD	0	0	0	2 (5)	0	2 (5)	0
NE	0	0	0	1 (3)	1 (3)	0	0
Osimertinib monotherapy (n = 38)							
Systemic response							
Total	**30 (79)**	5 (13)	25 (66)	**2 (5)**	2 (5)	0	0
CR	0	0	0	0	0	0	0
PR	30 (79)	5 (13)	25 (66)	2 (5)	2 (5)	0	0
Systemic nonresponse							
Total	**3 (8)**	1 (3)	2 (5)	**3 (8)**	2 (5)	1 (3)	0
SD	2 (5)	1 (3)	1 (3)	2 (5)	2 (5)	0	0
PD	1 (3)	0	1 (3)	1 (3)	0	1 (3)	0
NE	0	0	0	0	0	0	0

NOTE. Responses did not require confirmation, per RECIST guidance on randomized studies. The denominator used in the calculation of the percentages is the total overall sample size in a treatment. Values shown in bold indicate the total number (percentage) of patients with each category of CNS/systemic response or nonresponse.
Abbreviations: BICR, blinded independent central review; cEFR, CNS evaluable-for-response set; CR, complete response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

TABLE A4. Adverse Events in the cFAS and the Overall FLAURA2 Population

AE Category	cFAS (n = 222), No. (%)		Overall FLAURA2 Population[a] (n = 551), No. (%)	
	Osimertinib Plus Platinum-Pemetrexed (n = 118)	Osimertinib Monotherapy (n = 104)	Osimertinib Plus Platinum-Pemetrexed (n = 276)	Osimertinib Monotherapy (n = 275)
Any AE	116 (98)	102 (98)	276 (100)	268 (97)
Any possibly causally related AE[b]	112 (95)	92 (88)	269 (97)	241 (88)
Any AE of grade ≥3	75 (64)	30 (29)	176 (64)	75 (27)
Any possibly causally related AE of grade ≥3[b]	58 (49)	14 (13)	146 (53)	29 (11)
Fatal AEs	7 (6)	3 (3)	18 (7)	8 (3)
Possibly causally related fatal AEs[b]	2 (2)	0	5 (2)	1 (<1)
Serious AEs	44 (37)	23 (22)	104 (38)	53 (19)
Possibly causally related serious AEs[b]	20 (17)	9 (9)	52 (19)	15 (5)
AEs leading to treatment discontinuation	53 (45)	6 (6)	132 (48)	17 (6)
Leading to osimertinib discontinuation	12 (10)	6 (6)	30 (11)	17 (6)
Leading to chemotherapy discontinuation	50 (42)	NA	125 (45)	NA
Leading to carboplatin/cisplatin discontinuation	20 (17)	NA	46 (17)	NA
Leading to pemetrexed discontinuation	47 (40)	NA	119 (43)	NA

NOTE. Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

Abbreviations: AE, adverse event; cFAS, CNS full analysis set; NA, not applicable.

[a]Safety analysis set. Some of the data for the overall population have previously been published (Planchard et al[25]).

[b]As assessed by the investigator; causally related to any study drug.