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CNS Response to Osimertinib Versus Standard Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients With Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

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ABSTRACT

Purpose

We report CNS efficacy of osimertinib versus standard epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors (TKIs) in patients with untreated *EGFR*-mutated advanced non–small-cell lung cancer from the phase III FLAURA study.

Patients and Methods

Patients (N = 556) were randomly assigned to osimertinib or standard EGFR-TKIs (gefitinib or erlotinib); brain scans were not mandated unless clinically indicated. Patients with asymptomatic or stable CNS metastases were included. In patients with symptomatic CNS metastases, neurologic status was required to be stable for ≥ 2 weeks after completion of definitive therapy and corticosteroids. A preplanned subgroup analysis with CNS progression-free survival as primary objective was conducted in patients with measurable and/or nonmeasurable CNS lesions on baseline brain scan by blinded independent central neuroradiologic review. The CNS evaluable-for-response set included patients with ≥ one measurable CNS lesion.

Results

Of 200 patients with available brain scans at baseline, 128 (osimertinib, n = 61; standard EGFR-TKIs, n = 67) had measurable and/or nonmeasurable CNS lesions, including 41 patients (osimertinib, n = 22; standard EGFR-TKIs, n = 19) with ≥ one measurable CNS lesion. Median CNS progression-free survival in patients with measurable and/or nonmeasurable CNS lesions was not reached with osimertinib (95% CI, 16.5 months to not calculable) and 13.9 months (95% CI, 8.3 months to not calculable) with standard EGFR-TKIs (hazard ratio, 0.48; 95% CI, 0.26 to 0.86; $P = .014$ [nominally statistically significant]). CNS objective response rates were 91% and 68% in patients with ≥ one measurable CNS lesion (odds ratio, 4.6; 95% CI, 0.9 to 34.9; $P = .066$) and 66% and 43% in patients with measurable and/or nonmeasurable CNS lesions (odds ratio, 2.5; 95% CI, 1.2 to 5.2; $P = .011$) treated with osimertinib and standard EGFR-TKIs, respectively. Probability of experiencing a CNS progression event was consistently lower with osimertinib versus standard EGFR-TKIs.

Conclusion

Osimertinib has CNS efficacy in patients with untreated *EGFR*-mutated non–small-cell lung cancer. These results suggest a reduced risk of CNS progression with osimertinib versus standard EGFR-TKIs.

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INTRODUCTION

Metastatic disease in the CNS is common in patients with advanced non–small-cell lung cancer (NSCLC) and has a negative impact on survival and quality of life (QOL).[1,2] For patients with epidermal growth factor receptor (*EGFR*)–mutated advanced NSCLC, treatment with first- or second-generation EGFR-tyrosine kinase inhibitors (TKIs) can reduce the risk of CNS progression compared with chemotherapy.[3] However, the CNS activity of these agents is suboptimal; preclinical models and clinical studies

ASSOCIATED CONTENT

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have shown that first- and second-generation EGFR-TKIs have limited ability to cross the blood–brain barrier,[4-6] allowing the CNS to emerge as a sanctuary site for metastatic spread.[7] The CNS is a common site of treatment failure after initial response to EGFR-TKI treatment,[8,9] and because patients with *EGFR*-mutated disease have extended survival compared with patients with *EGFR* wild-type disease,[10] up to 40% of patients with *EGFR*-mutated NSCLC develop CNS metastases over the course of the disease, despite treatment with EGFR-TKIs.[11] Therefore, the evaluation of therapies that may offer improved CNS disease control is an important clinical priority.

Osimertinib is a potent, oral, irreversible EGFR-TKI selective for both EGFR-TKI sensitizing (*EGFR*m) and *EGFR* T790M resistance mutations,[12] approved in patients with T790M-positive advanced NSCLC whose disease has progressed during or after EGFR-TKI therapy.[13,14] Preclinical studies have shown osimertinib to be highly distributed in the nonhuman primate brain, with greater exposure than gefitinib or erlotinib.[4,15] Furthermore, clinical CNS activity of osimertinib has been demonstrated in patients with *EGFR* T790M-positive NSCLC who have progressed during prior EGFR-TKI treatment: CNS objective response rate (ORR) was 54% (27 of 50; 95% CI, 39% to 68%) in a pooled analysis of two phase II studies and 70% (21 of 30; 95% CI, 51% to 85%) from the phase III (AURA3) study.[16,17]

The phase III, randomized, double-blind FLAURA study compared osimertinib with standard EGFR-TKIs (gefitinib or erlotinib) as first-line therapy in patients with *EGFR*m (exon 19 deletion [Ex19del] or L858R) advanced NSCLC. Median progression-free survival (PFS) was significantly longer with osimertinib versus standard EGFR-TKIs (18.9 *v* 10.2 months; hazard ratio, 0.46; 95% CI, 0.37 to 0.57; $P < .001$).[18] Systemic responses and number of CNS progression events (by investigator) in patients with and without known or treated CNS metastases at study entry in the overall FLAURA population have previously been reported.[18] Here we report the CNS efficacy of osimertinib versus standard EGFR-TKIs (including CNS PFS, CNS ORR, and CNS duration of response [DoR]) in a subset of patients from the FLAURA study who had CNS metastases documented on baseline brain scans, as assessed by neuroradiologic blinded independent central review (BICR).

PATIENTS AND METHODS

Trial Design and Treatment

This was a preplanned, exploratory analysis of the CNS efficacy of osimertinib versus standard EGFR-TKIs in the phase III, double-blind, randomized FLAURA study. Details of the methodology of this study have been published previously.[18] Patients enrolled in FLAURA were stratified by tumor *EGFR* mutation status (Ex19del or L858R) and race (Asian or non-Asian) before being randomly assigned at a one-to-one ratio. Treatment continued until disease progression as defined by Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1), unacceptable toxicity, or withdrawal of consent; patients with disease progression could continue to receive treatment as long as the investigator judged continued clinical benefit.

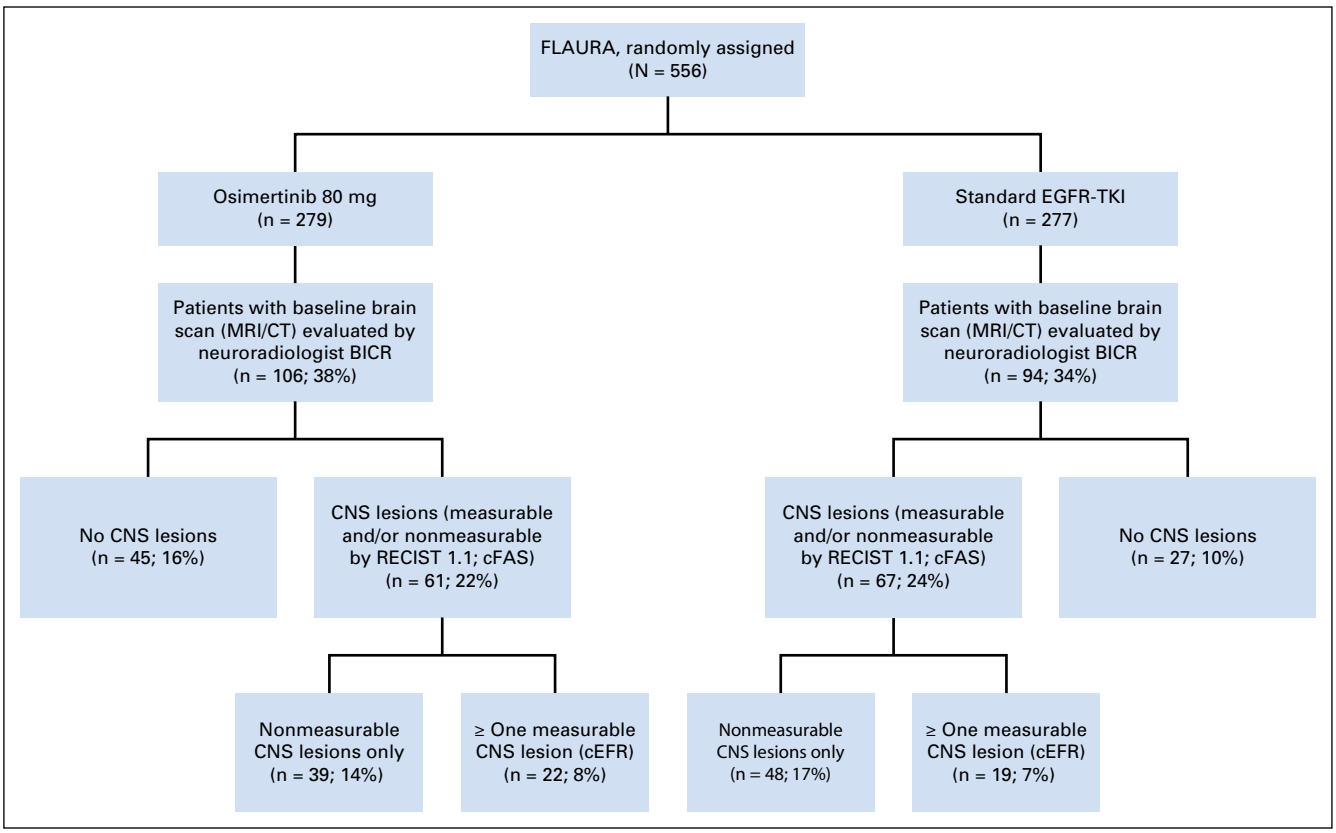

Fig 1. CONSORT diagram. Patient disposition. BICR, blinded independent central review; cEFR, CNS evaluable-for-response set; cFAS, CNS full-analysis set; CT, computed tomography; EGFR, epidermal growth factor receptor; MRI, magnetic resonance imaging; TKI, tyrosine kinase inhibitor.

Baseline brain scans by magnetic resonance imaging (MRI) or computed tomography (CT) were mandated only in patients with known or suspected CNS metastases, but they may have been performed in patients without known or suspected CNS metastases according to local medical practice. All submitted baseline brain CT or MRI scans were assessed by an independent neuroradiologist (neuroradiologic BICR) in a single-read model (ie, no double read or adjudication was performed). Single–time point scans were first reviewed individually and then chronologically by the same independent neuroradiologist. The independent neuroradiologist received prior CNS radiotherapy reports where applicable. Patients with measurable and/or nonmeasurable lesions on available baseline brain scans were included in this analysis of CNS response by neuroradiologic BICR. Patients with leptomeningeal metastases (LMs) were not specifically excluded; however, LMs were assessed as nontarget lesions (NTLs) because of their mostly diffuse radiologic appearance.

Follow-up brain scans for patients with evidence of CNS metastases were performed at the same time as other RECIST assessments: every 6 weeks for 18 months, then every 12 weeks until systemic disease progression. Per protocol, patients were assessed at follow-up using the same imaging modality as the baseline assessment. All subsequent CNS scans (including those at unscheduled visits) were assessed by neuroradiologic BICR.

Participants

Patients were age ≥ 18 years with Ex19del or L858R (locally or centrally confirmed) locally advanced or metastatic NSCLC. Patients could not have received prior systemic therapy for advanced disease. Patients with asymptomatic or stable CNS metastases were included; patients with symptomatic or unstable CNS metastases were only included if stable for ≥ 2 weeks after completion of definitive therapy and corticosteroids.

Ethics

FLAURA was approved by the institutional review board or independent ethics committee of each study center. The study was performed in accordance with ethical principles originating in the Declaration of Helsinki and consistent with the International Conference on Harmonisation/Good Clinical Practice, applicable regulatory requirements, and the AstraZeneca policy on bioethics. Informed consent was obtained from all patients before enrollment. The trial was designed by the sponsor, AstraZeneca, and the study investigators.

Table 1. Patient Demographic and Baseline Clinical Characteristics

Characteristic	No. (%)			
	cFAS (n = 128)		Overall FLAURA Population (n = 556)	
	Osimertinib (n = 61)	Standard EGFR-TKIs (n = 67)	Osimertinib (n = 279)	Standard EGFR-TKIs (n = 277)
Sex				
Male	23 (38)	26 (39)	101 (36)	105 (38)
Female	38 (62)	41 (61)	178 (64)	172 (62)
Age, years				
Median	63	63	64	64
Range	34-83	39-85	26-85	35-93
Race				
White	21 (34)	28 (42)	101 (36)	100 (36)
Asian	40 (66)	37 (55)	174 (62)	173 (62)
Other*	0	2 (3)	4 (1)	4 (1)
WHO performance status†				
0	16 (26)	27 (40)	112 (40)	116 (42)
1	45 (74)	39 (58)	167 (60)	160 (58)
EGFR mutation‡				
Ex19del	40 (66)	45 (67)	175 (63)	174 (63)
L858R	21 (34)	22 (33)	104 (37)	103 (37)
Histology				
Adenocarcinoma	61 (100)	67 (100)	275 (99)	272 (98)
Other§	0	0	4 (1)	5 (2)
Prior brain radiotherapy	15 (25)	16 (24)	8 (3)	7 (3)
Baseline CNS target lesion size, mm¶			NA	NA
Median	16	29		
Range	11-66	10-90		
Baseline CNS target lesion size category, mm¶			NA	NA
< 40	16 (73)	13 (68)		
40-79	6 (27)	3 (16)		
80-119	0	3 (16)		
CNS lesions, No.			NA	NA
1-3	47 (77)	49 (73)		
> 3	14 (23)	18 (27)		

Abbreviations: cFAS, CNS full-analysis set; *EGFR*, epidermal growth factor receptor; NA, not applicable; TKI, tyrosine kinase inhibitor.
*Includes black, American Indian, Alaska Native, or missing.
†Missing for one patient in the standard EGFR-TKI arm in the overall population and the cFAS.
‡*EGFR* mutations based on the test (local or central) used to determine random assignment strata.
§Includes large-cell carcinoma (osimertinib, n = 2; standard EGFR-TKIs, n = 3), adenosquamous carcinoma (osimertinib, n = 1; standard EGFR-TKIs, n = 2), and carcinoid tumors (osimertinib, n = 1).
¶No. of patients with measurable disease used as the denominator. Baseline CNS target lesion size is the sum of target lesions; up to five target lesions could be selected.

Assessments

The primary objective for this preplanned CNS analysis was CNS PFS by neuroradiologic BICR. Additional objectives included CNS ORR, CNS DoR, CNS disease control rate (DCR), CNS tumor shrinkage, and competing risk analysis of CNS progression. CNS efficacy was assessed according to RECIST (version 1.1). In contrast to the primary analysis of the overall FLAURA population (in which CNS lesions were designated NTLs for response assessment), CNS metastases identified on MRI and/or CT scans that were ≥ 10 mm in longest diameter or ≥ two times the slice thickness or reconstruction interval were considered measurable lesions and could be selected as target lesions (TLs; up to a maximum of five). All other lesions, including suspected LMs, were considered NTLs. Patients with measurable and/or nonmeasurable CNS metastases on available baseline brain scans were included in the CNS full-analysis set (cFAS). The CNS evaluable-for-response set (cEFR) included only patients with ≥ one measurable CNS lesion.

Statistical Methods

The data cutoff (DCO) was June 12, 2017. A hierarchic procedure was used to adjust for multiplicity in testing the key end points of PFS and overall survival (OS) in the overall FLAURA population and CNS PFS in the cFAS. To provide strong control for the type I error rate (5% two sided), the primary end point of PFS and end points of OS and CNS PFS were tested sequentially. Statistical significance testing of CNS PFS was only to be performed if the OS analysis was statistically significant at the time of the PFS (interim OS) analysis or final OS analysis. If the OS analysis was not statistically significant at this time, formal significance testing of CNS PFS would not be performed, and the *P* value for the statistical analyses would be classed as nominally significant.

CNS PFS was defined as the time from random assignment until date of objective CNS progression or death resulting from any cause. CNS ORR was defined as the number and percentage of patients with a CNS response of complete response (CR) or partial response (PR); confirmation of response was not required, per RECIST (version 1.1) guidance on randomized studies. CNS response in TLs was classed as CR, PR, stable disease, progressive disease (PD), or not evaluable. Response in NTLs was classed as CR, non-CR, non-PD, PD, or not evaluable. CNS DCR was defined as the percentage of patients who had a best overall response of CR, PR, or stable disease ≥ 6 weeks before any PD event. CNS DoR was defined as the time from first documented response until date of documented PD or death. The competing risk analysis was an estimation of the cumulative incidence for the event of interest (CNS progression) in the presence of two competing risk events (non-CNS progression and death) using a semiparametric Fine and Gray model. Event time was the occurrence of the earliest of the three events, or patients were censored at the time of their last evaluable assessment. SAS statistical software (version .9.4; SAS Institute, Cary, NC) was used for the analysis.

RESULTS

Patients

Of 556 patients randomly assigned to study treatment, 200 (36%) had a baseline CNS scan available for evaluation by neuroradiologic BICR. Of these, 128 patients (osimertinib, n = 61; standard EGFR-TKIs, n = 67) were included in the cFAS and 41 patients (osimertinib, n = 22; standard EGFR-TKIs, n = 19) in the cEFR (Fig 1). Median sum of baseline CNS TL size was numerically larger in the standard EGFR-TKI arm (29 *v* 16 mm in the osimertinib arm), because three patients in the standard EGFR-TKI arm had a large (80 to 119 mm) baseline total CNS TL size. The proportion of patients presenting with between one and three CNS lesions was similar between treatment arms: 77% in the osimertinib arm and 73% in the standard EGFR-TKI arm. Seven patients had radiologic evidence suggestive of LMs at baseline: five in the osimertinib arm and two in the standard EGFR-TKI arm. Demographics were generally well balanced between the treatment arms and consistent with the overall FLAURA population (Table 1). Stratification was mostly preserved, although the proportion of Asian patients was higher in the osimertinib arm compared with the standard EGFR-TKI arm. Fifteen patients (25%) in the osimertinib arm and 16 patients (24%) in the standard EGFR-TKI arm received prior brain radiotherapy, all within 6 months of study entry. The overlap between the cFAS and patients in the overall FLAURA population with known or treated CNS metastases at study entry, for whom the systemic response to osimertinib has previously been reported,[18] is detailed in the Data Supplement.

Efficacy

CNS PFS and risk of progression. Median follow-up for systemic PFS in the overall FLAURA study population was 15.0 months in the osimertinib arm and 9.7 months in the standard EGFR-TKI arm. Median follow-up for CNS PFS was 12.4 months in the osimertinib arm and 7.0 months in the standard EGFR-TKI arm. In the cFAS, median CNS PFS was not reached (NR) with osimertinib (95% CI, 16.5 months to not calculable [NC]) versus 13.9 months (95% CI, 8.3 months to NC) with standard EGFR-TKIs (Table 2; Fig 2A). This difference was nominally statistically significant (hazard ratio, 0.48; 95% CI, 0.26 to 0.86%; $P = .014$). CNS progression was reported in 20% (12 of 61) of patients in the osimertinib arm versus 39% (26 of 67) of patients in the standard EGFR-TKI arm. CNS progression resulted from new CNS lesions in 12% (seven of 61) of patients in the osimertinib arm and 30% (20 of 67) of patients in the standard

Table 2. CNS PFS and Reasons for CNS Progression (cFAS)

Progression	Osimertinib (n = 61)	Standard EGFR-TKIs (n = 67)
Total No. of events (CNS progression or death), No. (%)*	18 (30)	30 (45)
CNS progression other than death	12 (20)	26 (39)
Death resulting from progression	6 (10)	4 (6)
Median CNS PFS (95% CI)†	NR (16.5 to NC)	13.9 (8.3 to NC)
Progression free at 6 months, %	87 (74 to 94)	71 (57 to 81)
Progression free at 12 months, %	77 (62 to 86)	56 (42 to 68)
Progression free at 18 months, %	58 (40 to 72)	40 (25 to 55)
Any progression, No. (%)‡		
In target CNS lesions	4 (7)	2 (3)
In nontarget CNS lesions	1 (2)	5 (7)
In new CNS lesions	7 (12)	20 (30)
Unknown reason for CNS progression§	2 (3)	1 (1)

Abbreviations: cFAS, CNS full-analysis set; *EGFR*, epidermal growth factor receptor; NC, not calculable; NR, not reached; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

*Progression events that did not occur within two scheduled visits (plus visit window) of the last evaluable assessment (or random assignment) were censored and therefore excluded in the No. of events.

†Calculated using the Kaplan-Meier technique.

‡Target lesions, nontarget lesions, and new lesions were not necessarily mutually exclusive categories.

§Patients were identified as having progression, but their first lesion progression could not be determined.

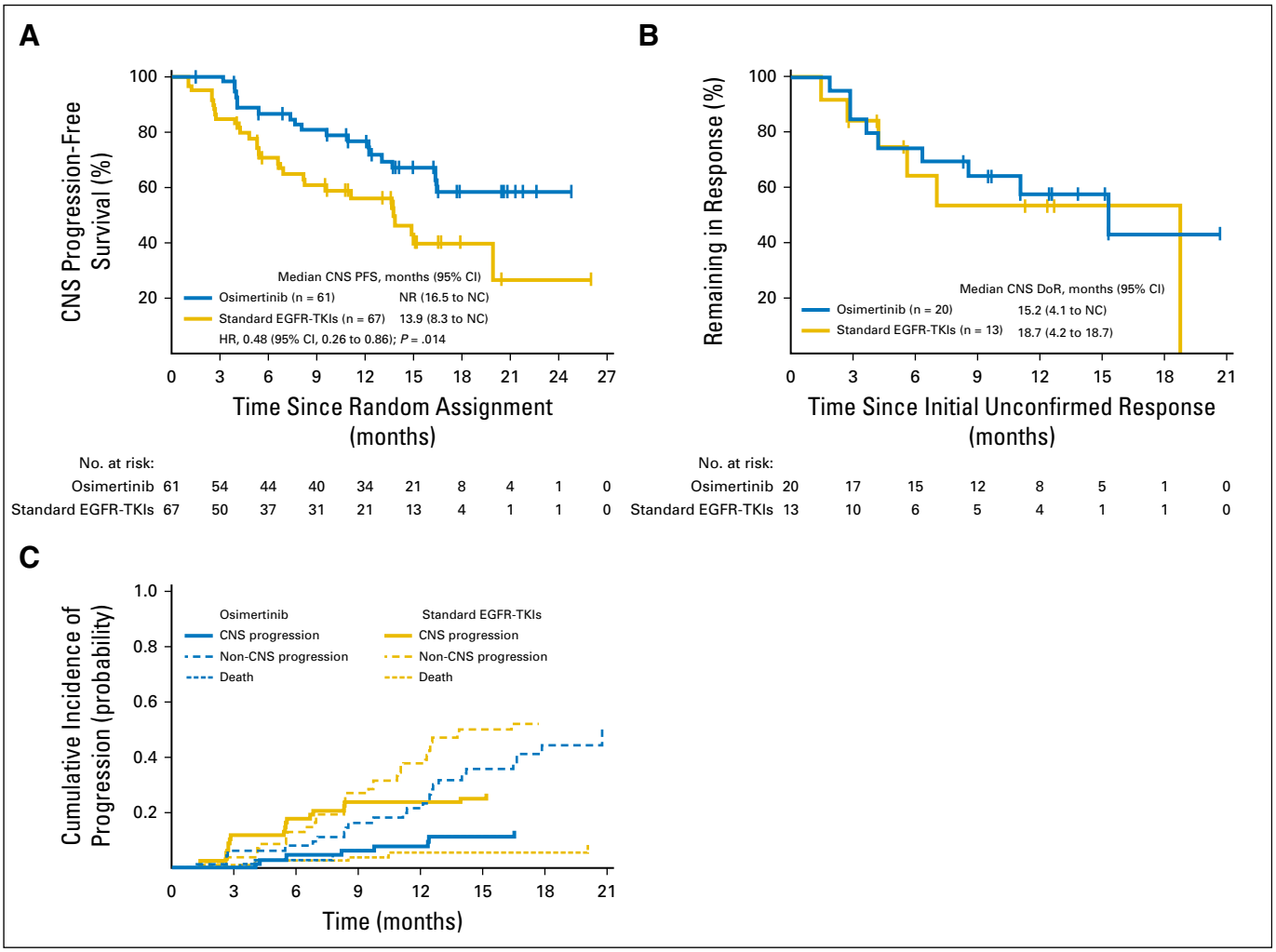

Fig 2. (A) CNS progression-free survival (PFS) in CNS full-analysis set (cFAS). (B) Duration of CNS response (DoR) in CNS evaluable-for-response set. (C) Cumulative incidence of CNS progression, taking into account competing risks of non-CNS progression and death resulting from any cause (cFAS). *EGFR*, epidermal growth factor receptor; HR, hazard ratio; NC, not calculable; TKI, tyrosine kinase inhibitor.

EGFR-TKI 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 6 months was 5% (95% CI, 1% to 13%) with osimertinib versus 18% (95% CI, 10% to 28%) with standard EGFR-TKIs. At 12 months, it was 8% (95% CI, 3% to 16%) with osimertinib versus 24% (95% CI, 15% to 35%) with standard EGFR-TKIs (Fig 2C).

CNS response. In the cFAS, CNS ORR was 66% (40 of 61; 95% CI, 52% to 77%) with osimertinib versus 43% (29 of 67; 95% CI, 31% to 56%) with standard EGFR-TKIs (odds ratio [OR], 2.5; 95% CI, 1.2 to 5.2; $P = .011$). In the cEFR, CNS ORR was 91% (20 of 22; 95% CI, 71% to 99%) with osimertinib and 68% (13 of 19; 95% CI, 43% to 87%) with standard EGFR-TKIs (OR, 4.6; 95% CI, 0.9 to 34.9; $P = .066$). In the osimertinib arm, 23% of patients had a CR compared with no patients in the standard EGFR-TKI arm (cEFR; Table 3). A sensitivity analysis of CNS ORR in patients with a confirmed response (CR or PR documented on a subsequent scan performed at least 4 weeks after first documentation of response) confirmed these results (Data Supplement). Benefit with osimertinib was seen irrespective of prior brain radiotherapy (Fig 3; Data Supplement). Of the 20 patients in the cEFR who responded to osimertinib, non-CNS tissue samples were positive for L858R in nine patients and Ex19del in 11 patients. Of the 13 patients in the cEFR who responded to standard EGFR-TKIs, non-CNS tissue samples were positive for L858R in three patients and Ex19del in 10 patients. Five patients in the osimertinib arm had suspected LMs, four of whom had a complete radiographic response and one of whom had radiographic non-CR, non-PD (Table 4). Two patients in the standard EGFR-TKI arm had suspected LMs; one patient had non-CR, non-PD, and the other had no CNS follow-up.

In the cEFR, median time to response was 6 weeks in both arms; median CNS DoR was 15.2 months (95% CI, 4.1 months to NC) with osimertinib versus 18.7 months (95% CI, 4.2 to 18.7 months) with standard EGFR-TKIs (Table 3; Fig 2B). CNS DCR in the cEFR was 95% with osimertinib (95% CI, 77% to 100%) versus 89% with standard EGFR-TKIs (95% CI, 67% to 99%; OR, 2.5 (95% CI, 0.2 to 55.8; $P = .462$). Median best percentage change from baseline in CNS TL size was −64% (range, −100% to +20%) with osimertinib and −45% (range, −100% to +20%) with standard EGFR-TKIs (cEFR; Fig 3).

Table 3. CNS Response to Osimertinib Versus Standard EGFR-TKIs

Response	cFAS (n = 128)		cEFR (n = 41)	
	Osimertinib (n = 61)	Standard EGFR-TKIs (n = 67)	Osimertinib (n = 22)	Standard EGFR-TKIs (n = 19)
CNS ORR, No. (%)*	40 (66)	29 (43)	20 (91)	13 (68)
CR	25 (41)	16 (24)	5 (23)	0
PR	15 (25)	13 (19)	15 (68)	13 (68)
SD ≥ 6 weeks†	15 (25)	27 (40)	1 (5)	4 (21)
PD	0	5 (7)	0	2 (11)
Not evaluable	6 (10)	6 (9)	1 (5)	0
CNS DCR, No. (%)	55 (90)	56 (84)	21 (95)	17 (89)
95% CI‡	80 to 96	73 to 92	77 to 100	67 to 99
OR§	1.8		2.5	
95% CI	0.6 to 5.5		0.2 to 55.8	
P¶	.269		.462	
Median time to response, weeks (interquartile range)	6 (6-12)	12 (6-18)	6 (6-6)	6 (6-12)
Median CNS DoR, months (95% CI)	NR (11.9 to NC)	14.4 (7.0 to 18.7)	15.2 (4.1 to NC)	18.7 (4.2 to 18.7)
Estimated % remaining in response (95% CI)*‖				
At 3 months	92 (77 to 97)	89 (71 to 97)	85 (60 to 95)	85 (51 to 96)
At 6 months	86 (70 to 94)	76 (55 to 89)	75 (50 to 89)	65 (30 to 85)
At 9 months	80 (63 to 90)	67 (43 to 82)	65 (40 to 81)	54 (21 to 78)
At 12 months	65 (46 to 79)	67 (43 to 82)	58 (33 to 77)	54 (21 to 78)

Abbreviations: cEFR, CNS evaluable-for-response set; cFAS, CNS full-analysis set; CR, complete response; DCR, disease control rate; DoR, duration of response; *EGFR*, epidermal growth factor receptor; NC, not calculable; NR, not reached; OR, odds ratio; ORR, objective response rate; PR, partial response; PD, progressive disease; SD, stable disease; TKI, tyrosine kinase inhibitor.
*Responses did not require confirmation, per RECIST 1.1 guidance on randomized studies.
†Includes non-CR, non-PD in patients with nontarget lesions only.
‡Calculated using Clopper-Pearson exact method for binomial proportions.
§This analysis was performed using logistic regression with a factor for treatment; CI was calculated using profile likelihood. An OR > 1 favors osimertinib.
¶The *P* value was calculated based on the likelihood ratio test, which compared two models (one model with the intercept only and a second model including the treatment factor).
‖Calculated using Kaplan-Meier technique.

The overall concordance between CNS and systemic response to osimertinib in the cEFR was 77%. Of 22 patients in the osimertinib arm, 16 (73%) had both CNS and systemic objective responses and one (5%) had neither CNS nor systemic response (Data Supplement). The overall concordance between CNS and systemic response to standard EGFR-TKIs in the cEFR was 63%; of 19 patients in the standard EGFR-TKI arm, 11 (58%) had both CNS and systemic objective responses and one (5%) had neither CNS nor systemic response.

A longitudinal analysis of CNS lesion status at baseline and at DCO in the overall FLAURA study population, assessed by study BICR, is presented in the Data Supplement. In the osimertinib arm, there were fewer patients with CNS lesions at DCO compared with baseline (median follow-up for OS, 18.6 months). In the standard EGFR-TKI arm, there were more patients with CNS lesions at DCO compared with baseline (median follow-up for OS, 17.4 months).

Safety

Overall, the rates of adverse events were similar between the cFAS and the overall FLAURA study population (Data Supplement).

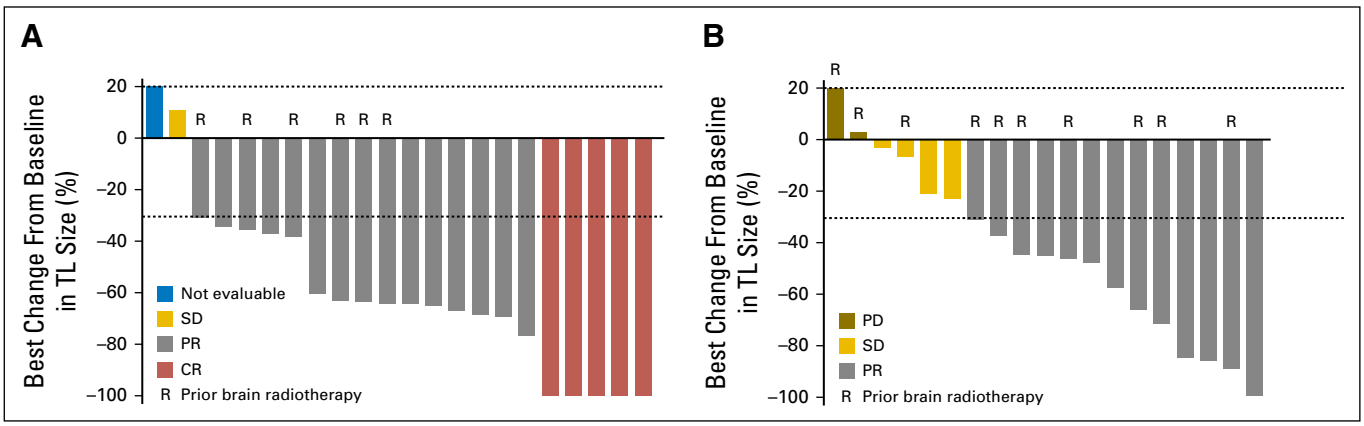

Fig 3. Best percentage change from baseline in CNS target lesion (TL) size (cEFR) with (A) osimertinib and (B) standard epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs).

Table 4. Responses in Patients With Suspected LM*

Treatment Arm	Highest Response		Best Objective Response	
	LM	TL	CNS	Systemic
Osimertinib	CR	PR	PR	PR
Osimertinib	Non-CR, non-PD	No TL	SD	PR
Osimertinib	CR	No TL	CR	PR
Osimertinib	CR	No TL	SD	PR
Osimertinib	CR	CR	CR	PR
Standard EGFR-TKIs	Non-CR, non-PD	No TL	SD	PR
Standard EGFR-TKIs	Baseline only	No TL	NE	PR

Abbreviations: CR, complete response; *EGFR*, epidermal growth factor receptor; LM, leptomeningeal metastases; NE, nonevaluable; PD, progressive disease; PR, partial response; SD, stable disease; TL, target lesion; TKI, tyrosine kinase inhibitor.
*LM, TL and CNS responses were assessed by CNS BICR; systemic response was assessed by study BICR.

DISCUSSION

Osimertinib demonstrated a nominally statistically significant and clinically meaningful improvement in CNS PFS over standard EGFR-TKIs in the first-line treatment of patients with CNS metastases from *EGFR*m NSCLC, with a 52% reduction in the risk of CNS progression. These results are consistent with the analysis of PFS in the overall FLAURA population.[18] The probability of experiencing a CNS progression event, in the absence of non-CNS progression or death, was consistently lower with osimertinib versus standard EGFR-TKIs. CNS progression events mainly resulted from new lesions in both treatment arms; however, there were fewer new lesions with osimertinib compared with standard EGFR-TKIs.

This analysis adds to the growing evidence for the CNS efficacy of osimertinib in advanced NSCLC. A pooled analysis of two phase II studies of osimertinib in patients with T790M-positive NSCLC who had experienced progression during prior EGFR-TKI treatment found a CNS ORR of 54% and CNS DCR of 92%.[16] Similarly, analysis of the phase III AURA3 study found a CNS ORR of 70% with osimertinib versus 31% with platinum plus pemetrexed (OR, 5.13; 95% CI, 1.44 to 20.64; $P = .015$) in patients with previously treated T790M-positive NSCLC (cEFR).[17] These data, together with preclinical data showing osimertinib to be highly distributed in the nonhuman primate brain, with greater exposure than gefitinib or erlotinib (CSF/brain-to-blood ratio of exposure in cynomolgus monkeys was 2.62 for [^{11}C]osimertinib and 0.28 for [^{11}C]gefitinib),[4,15] support osimertinib as an EGFR-TKI with CNS efficacy. Osimertinib is recommended in the National Comprehensive Cancer Network guidelines for NSCLC for the treatment of patients with CNS metastases from *EGFR*m NSCLC, including those patients with LMs. Although only a small number of patients with suspected LMs were identified in our study, osimertinib activity in these patients was encouraging.

In the cFAS, there was a lower rate of CNS progression resulting from new lesions with osimertinib compared with standard EGFR-TKIs (seven [12%] of 61 *v* 20 [30%] of 67). A limitation of this analysis is that brain scans were only carried out if patients had known or treated CNS metastases at study entry or as part of local practice before initiation of first-line therapy; therefore, the analysis may have excluded some patients with asymptomatic CNS metastases. In the overall FLAURA study population, the incidence of CNS progression events was reduced with osimertinib (17 [6%] of 279) versus standard EGFR-TKIs (42 [15%] of 277), irrespective of presence or absence of known or treated CNS metastases at study entry.[18] Taken together, the consistent CNS efficacy observed across analyses in the FLAURA study, assessed by investigator in the overall FLAURA population and by BICR in the CNS analysis, provides strong evidence for the CNS efficacy of osimertinib. The lower frequency of CNS progression with osimertinib compared with standard EGFR-TKIs (seven [3%] of 226 *v* 15 [7%] of 214) in the subgroup of patients without known or treated CNS metastases at study entry[18] may indicate a protective effect of osimertinib against the development of CNS metastases. Previous reports have suggested an increase in CNS metastases over time in patients with *EGFR*-mutated NSCLC receiving treatment.[11] This was observed in the standard EGFR-TKI arm of the overall FLAURA study population. However, in the osimertinib arm, there was a lower proportion of patients with CNS metastases at DCO compared with baseline. The development of CNS metastases often has an important adverse impact on QOL.[1] A more effective TKI therapy may defer the need for whole-brain radiotherapy, which is associated with adverse effects[19] and may not improve survival or QOL.[20]

CNS ORR was higher with osimertinib compared with standard EGFR-TKIs, with more patients achieving a CR. The small number of patients did not allow for comparison of CNS ORR between groups by prior brain radiotherapy; however, CNS response to osimertinib was observed irrespective of prior brain radiotherapy. Although median CNS DoR in the cEFR was longer in the standard EGFR-TKI arm compared with the osimertinib arm (15.2 *v* 18.7 months, respectively), the point estimates for patients remaining in response at 6 and 12 months favored osimertinib. This difference may be attributable to the small patient numbers in the cEFR. There was good concordance between CNS and systemic response to osimertinib, with a higher level of agreement observed compared with standard EGFR-TKIs. The higher level of agreement with osimertinib was driven by a lower CNS response in the standard EGFR-TKI arm. Although the EGFR-mutation status of patients' CNS disease was not assessed in this study, substantial concordance has been demonstrated between primary tumors and CNS metastases with respect to *EGFR*m.[21] However, the emergence of the *EGFR* T790M resistance mutation is comparatively rare in the CNS, suggesting that divergent evolution and alternative mechanisms of resistance may occur.[22-24] In conclusion, these data show improved CNS efficacy with osimertinib in patients with untreated *EGFR*m advanced NSCLC and suggest a reduced risk of CNS progression with osimertinib compared with standard EGFR-TKIs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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