ORIGINAL ARTICLE

Central Nervous System Outcomes of Lazertinib Versus Gefitinib in *EGFR*-Mutated Advanced NSCLC: A LASER301 Subset Analysis

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ABSTRACT

Introduction: Lazertinib, a third-generation mutant-selective EGFR tyrosine kinase inhibitor, improved progression-free survival compared with gefitinib in the phase 3 LASER301 study (ClinicalTrials.gov Identifier: NCT04248829). Here, we report the efficacy of lazertinib and gefitinib in patients with baseline central nervous system (CNS) metastases.

Methods: Treatment-naive patients with *EGFR*–mutated advanced NSCLC were randomized one-to-one to lazertinib (240 mg/d) or gefitinib (250 mg/d). Patients with asymptomatic or stable CNS metastases were included if any planned radiation, surgery, or steroids were completed more than 2 weeks before randomization. For patients with CNS metastases confirmed at screening or subsequently suspected, CNS imaging was performed every 6 weeks for 18 months, then every 12 weeks. End points assessed by blinded independent central review and Response Evaluation Criteria in Solid Tumors version 1.1 included intracranial progression-free survival, intracranial objective response rate, and intracranial duration of response.

Results: Of the 393 patients enrolled in LASER301, 86 (lazertinib, n = 45; gefitinib, n = 41) had measurable and or nonmeasurable baseline CNS metastases. The median intracranial progression-free survival in the lazertinib group was 28.2 months (95% confidence interval [CI]: 14.8–28.2) versus 8.4 months (95% CI: 6.7–not reached [NR]) in the gefitinib group (hazard ratio = 0.42, 95% CI: 0.20–0.89, $p = 0.02$). Among patients with measurable CNS lesions, the intracranial objective response rate was numerically higher with lazertinib (94%; n = 17) versus gefitinib (73%; n = 11, $p = 0.124$). The median intracranial duration of response with lazertinib was NR (8.3–NR) versus 6.3 months (2.8–NR) with gefitinib. Tolerability was similar to the overall LASER301 population.

Conclusions: In patients with CNS metastases, lazertinib significantly improved intracranial progression-free survival compared with gefitinib, with more durable responses.

Keywords: CNS; Lazertinib; NSCLC; TKI

Introduction

Up to 30% of patients with *EGFR*-mutated NSCLC present with brain metastasis at initial diagnosis, and the risk may increase over time to 50% within 3 years of diagnosis, contributing to the morbidity, mortality, and deterioration in the quality of life associated with NSCLC.[1–3] The introduction of the first- and second-generation EGFR tyrosine kinase inhibitors (TKIs) revolutionized the treatment of advanced *EGFR*-mutated NSCLC, with better efficacy against central nervous

system (CNS) disease compared with chemotherapy.[4] However, currently available first- and second-generation EGFR TKIs still exhibit suboptimal efficacy for the treatment of brain metastasis, with intracranial progression typically occurring within 10 months, likely owing to their limited blood-brain barrier penetration.[4–10] Thus, investigation of agents with improved CNS activity for the treatment of patients with *EGFR*-mutated NSCLC with brain metastases is warranted.

Lazertinib is a potent, CNS-penetrant, mutant-selective, third-generation TKI that targets EGFR T790M and sensitizing mutations while sparing wild-type EGFR.[11,12] In the phase 1/2 LASER201 trial (ClinicalTrials.gov identifier: NCT03046992), oral lazertinib 240 mg daily was associated with an objective response rate of 55%, median progression-free survival (PFS) of 11.1 months, and median overall survival (OS) of 38.9 months in 76 patients with *EGFR* mutation–positive (T790M+) NSCLC previously treated with early-generation TKIs; no differences in OS were seen between patients with or without CNS metastases.[13,14]

The global, phase 3 LASER301 study compared lazertinib versus gefitinib in 393 treatment-naïve patients with *EGFR*-mutated locally advanced or metastatic NSCLC and found a significantly longer median PFS with lazertinib than with gefitinib (20.6 versus 9.7 mo, $p < 0.001$). The PFS benefit of lazertinib over gefitinib was consistent across all predefined subgroups, including patients with or without known or treated brain metastases at the study baseline.[15] The current analysis presents an in-depth analysis of CNS efficacy among patients enrolled in LASER301 who had brain metastases identified on baseline brain scans by blinded independent central review (BICR).

Materials and Methods

Trial Design and Treatment

LASER301 (ClinicalTrials.gov identifier: NCT04248829) is a randomized, double-blind, multinational phase 3 study that evaluated the efficacy and safety of lazertinib among patients with *EGFR*-mutated (exon 19 deletion or L858R mutation) locally advanced or metastatic NSCLC who had not previously received any line of therapy for NSCLC. Full details of the study methods are presented in the article reporting results from the overall LASER301 population.[15] This subset analysis included patients enrolled in LASER301 who had measurable and or non-measurable brain metastases by study BICR at the study baseline. Response Evaluation Criteria in Solid Tumors version 1.1 criteria were used, with no study-specific criteria to define measurable and non-measurable brain lesions.

Patients were randomized one-to-one to receive either oral lazertinib (240 mg/d, which could be reduced to 160 mg/d if toxicity was reported) or oral gefitinib (250 mg/d). Patients were allowed to cross over from the gefitinib arm to receive open-label lazertinib when they exhibited objective progressive disease confirmed by BICR and postprogression T790M-positive status confirmed locally or centrally by plasma or tissue testing. Surgery during the study was not permitted, and radiation therapy was permitted only for non-target lesions.

Patients

Eligible patients were at least 18 years of age, had *EGFR* mutations determined by tissue biopsy, and were treatment-naïve for locally advanced or metastatic NSCLC, although treatment for early-stage disease more than 12 months before randomization was permitted.

Baseline brain imaging was not mandatory and only performed for patients with previously confirmed or suspected brain metastases. Neurologically stable patients with CNS metastases were allowed, provided any definitive treatment or steroids were completed for more than 2 weeks before randomization and the patient remained asymptomatic. Patients with leptomeningeal metastases or symptomatic or unstable CNS metastases were excluded. Irradiated CNS lesions were not eligible as target lesions.

Protocol Approval

This clinical trial was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation. Written informed consent was provided by all who participated in the trial, and at each clinical site, the study protocol was approved by an independent ethics committee or institutional review board.

End Points and Assessments

The primary end point of this analysis was intracranial progression-free survival (iPFS) according to Response Evaluation Criteria in Solid Tumors version 1.1 by neuroradiologic BICR and investigator assessment and defined as the time from randomization until the date of objective intracranial disease progression or death, whichever came first. If intracranial progression did not occur but death occurred before two cycles after the last assessment, the event was counted as "death," whereas if both intracranial progression and death did not occur, the event was counted as "no progression." Other end points included intracranial objective response rate (iORR), intracranial disease control rate (iDCR), and intracranial duration of response (iDoR). In

addition, the depth of intracranial response was assessed among patients with measurable intracranial disease at baseline and was derived at each visit by the percent change in the sum of the diameters of the intracranial target lesions in the absence of new intracranial lesions or progression of intracranial non-target lesions compared with baseline.

Patients with confirmed brain metastases at screening were followed up with repeated imaging assessment (magnetic resonance imaging or computed tomography) by BICR. Imaging was performed at screening, every 6 weeks for 18 months, then every 12 weeks relative to randomization, using the same modality at each follow-up.

Adverse events (AEs) were collected throughout the study up to 28 days after the last dose, graded according to Common Terminology Criteria for Adverse Events version 5.0, and presented as single preferred terms.

Statistical Methods

The first dosing date for patients in the CNS subset was January 4, 2021, and the data cutoff was July 29, 2022. The intracranial full analysis set comprised all randomized patients who underwent a brain scan in the screening or baseline period and had measurable and or non-measurable brain disease at baseline by BICR; analyses of iPFS and response were conducted in this analysis set. The safety analysis set comprised all patients who received greater than or equal to one dose of the study treatment. The iPFS was analyzed by the Kaplan-Meier method, with medians, 95% confidence intervals (CIs), and the number of events summarized. Hazard ratios (HRs) and their corresponding 95% CIs were calculated from a stratified Cox model. A competing risk analysis was conducted as an estimate of the cumulative incidence for the event (CNS progression) in the presence of two competing risk events (non-CNS progression and death). Event time was defined as the occurrence of the earliest of the three events, or patients were censored at the time of the last evaluable assessment. All analyses were performed using Statistical Analysis System version 9.3 (SAS Institute, Cary, NC).

Results

Patients

Of the 393 patients enrolled in LASER301, 283 patients with previously confirmed or suspected brain metastases had a baseline brain scan evaluated. Of these, 86 patients found to have brain metastases at baseline were eligible for this analysis (45 receiving lazertinib and 41 receiving gefitinib), 33 of whom had at least one measurable CNS lesion (18 receiving lazertinib and 15 receiving gefitinib), whereas 53 had non-measurable lesions only (27 receiving lazertinib and 26 receiving gefitinib). Of the patients with baseline brain scans, 197 had no baseline CNS lesion (Fig. 1). A total of 77 patients overlapped between the group of 99 patients with known or treated CNS metastases status at study entry and the 86 patients with at least one measurable or non-measurable CNS lesion on baseline brain scan by BICR (Supplementary Fig. 1). All enrolled patients received one or more doses of the study drug. Of the 41 patients randomized to receive gefitinib, 9 (22%) crossed over to receive lazertinib.

In the intracranial full analysis set, demographic and baseline disease characteristics were generally balanced between treatment groups, apart from a greater

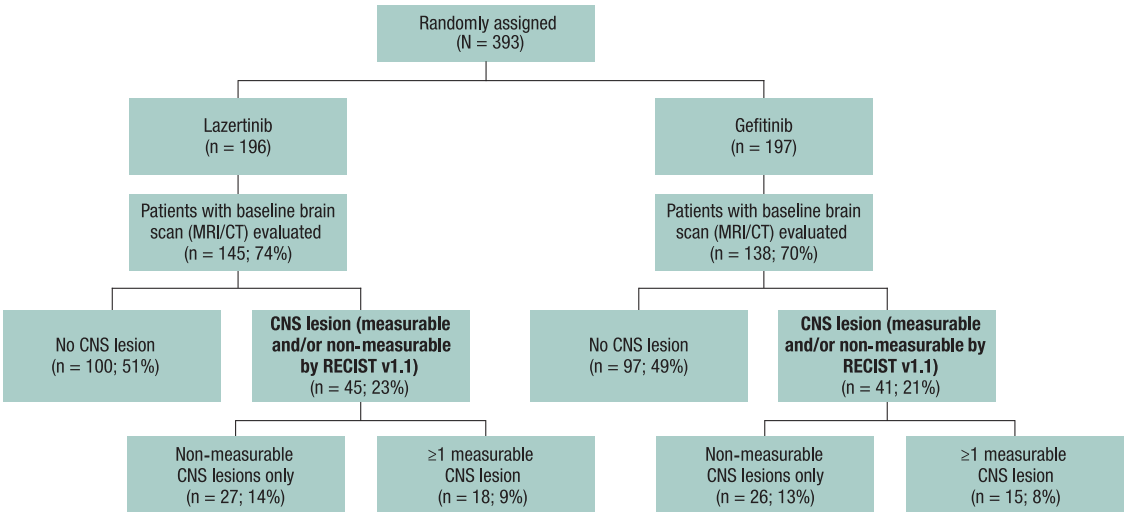

Figure 1. CONSORT diagram of patient disposition. CNS, central nervous system; CT, computed tomography; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 1. Demographic and Baseline Disease Characteristics

Demographic/ Characteristic	Lazertinib (n = 45)	Gefitinib (n = 41)
Age (y)		
Median	66.0	59.0
Range	37.0-86.0	40.0-85.0
Age group, n (%)		
<65 y	19 (42)	28 (68)
≥65 y	26 (58)	13 (32)
Sex, n (%)		
Male	14 (31)	17 (41)
Female	31 (69)	24 (59)
Race, n (%)		
Asian	36 (80)	29 (71)
Korean	28 (62)	20 (49)
Chinese	3 (7)	5 (12)
Other	5 (11)	4 (10)
White	9 (20)	12 (29)
EGFR mutation at randomization, n (%)		
Ex19del	25 (56)	23 (56)
L858R	20 (44)	18 (44)
Patients with target lesion of brain tumors at baseline, n (%)	18 (40)	15 (37)
Baseline target lesion size of brain tumor (mm)[a]		
Median	20.0	16.0
Range	10.3-65.2	10.1-53.6
WHO performance status, n (%)		
0	8 (18)	12 (29)
1	37 (82)	29 (71)
Prior radiotherapy to the brain, n (%)		
Yes	11 (24)	11 (27)
≤6 mo before randomization	11 (24)	11 (27)
No	34 (76)	30 (73)
Number of brain lesions at baseline, n (%)		
1–3	41 (91)	34 (83)
>3	4 (9)	7 (17)
Brain imaging assessment method, n (%)		
MRI	40 (89)	32 (78)
CT	5 (11)	8 (20)
MRI and CT	0	1 (2)

Note: The baseline CNS target lesion is the sum of the target lesions; up to five target lesions could be selected.

[a]The baseline CNS target lesion is the sum of the target lesions; up to 5 target lesions could be selected.

CNS, central nervous system; CT, computed tomography; Ex19del, exon 19 deletion; MRI, magnetic resonance imaging; WHO, World Health Organization.

proportion of patients in the lazertinib group being 65 years of age or older (58% versus 32% in the gefitinib group) (Table 1). Exon 19 deletion and L858R mutations were found in 56% and 44% of patients in each treatment group, respectively. Most patients had 1 to 3 brain lesions at baseline; whereas a greater proportion of patients in the gefitinib group had greater than three brain lesions (17% versus 9% in the lazertinib group), most lesions in this group were less than 20 mm in size. A total of 11 patients in each treatment group had received previous brain radiotherapy (all >14 d before study entry) and six patients had previous brain surgery or procedure, all of whom were randomized to receive lazertinib.

Efficacy

At the data cutoff, 18 patients in the lazertinib group and six in the gefitinib group were receiving ongoing treatment. No patients underwent brain surgery during the study; however, five patients (one in the lazertinib group and four in the gefitinib group) received palliative radiotherapy while on treatment.

Intracranial efficacy is presented in Table 2. After a median (interquartile range) follow-up of 17.8 months (9.6–20.7) in the lazertinib group and 12.2 months (8.5–17.9) in the gefitinib group, median iPFS was significantly longer in the lazertinib group (28.2 mo [95% CI: 14.8–28.2]) compared with the gefitinib group (8.4 mo [95% CI: 6.7–not reached (NR)]; HR = 0.42, 95% CI: 0.2–0.89, $p = 0.020$) (Fig. 2*A*). CNS progression or death was reported in 31% (14 of 45) of patients in the lazertinib group versus 51% (21 of 41) of patients in the gefitinib group. CNS progression resulted from new CNS lesions in 11% (5 of 45) of patients in the lazertinib group and 20% (8 of 41) of patients in the gefitinib group.

The response rates among the 33 patients with at least one measurable brain lesion at baseline are detailed in Table 3. Although not statistically significant, a numerically higher iORR was observed in the lazertinib group compared with the gefitinib group (94.4% versus 73.3%, respectively; OR = 6.18, 95% CI: 0.61–62.83, $p = 0.124$), and similar iDCR rates were observed in the two treatment groups (94.4% and 93.3%, respectively; OR = 1.21, 95% CI: 0.07–21.22, $p = 0.894$). The median time to intracranial response was 5.6 weeks (95% CI: 5.29–12.00) in the lazertinib group versus 5.9 weeks (95% CI: 5.14–12.00) in the gefitinib group (Table 3). The median iDoR (Fig. 2*B*) was NR (95% CI: 8.31–NR) in the lazertinib group versus 6.3 months (95% CI: 2.79–NR) in the gefitinib group. At 6 and 12 months, respectively, an estimated 84.4% and 73.9% of patients in the lazertinib group and 50% and 40% in the gefitinib group remained in response (Table 3). The median (range) best percent change from baseline in lesion size was –57% (–100% to –38.9%) in the lazertinib group and –47% (–100% to –1.8%) in the gefitinib group, respectively (Supplementary Fig. 2*A* and *B*).

A longitudinal analysis of the status of CNS lesions assessed by study BICR at baseline and the data cutoff in the overall LASER301 study population is illustrated in

Table 2. Intracranial Efficacy End Points

End Point	Lazertinib (n = 45)	Gefitinib (n = 41)
Intracranial progression or death, n (%)	14 (31)	21 (51)
Intracranial progression	10 (22)	15 (37)
Death[a]	4 (9)	6 (15)
Median iPFS (mo)[b]	28.2	8.4
95% CI for iPFS	14.8-28.2	6.7-NR
HR (95% CI), *p* value[c]	0.42 (0.2-0.89), $p = 0.020$	
Intracranial progression-free rate, % (95% CI)		
6 mo	90.3 (76.1-96.2)	71.9 (53.9-83.8)
12 mo	68.8 (50.4-81.6)	39.6 (22.7-56.1)
18 mo	61.3 (42.1-75.8)	29.7 (11.2-51.0)
Any progression, n (%)[d]	10 (22)	15 (37)
In target CNS lesions	2 (4)	2 (5)
In non-target CNS lesions	3 (7)	5 (12)
In new CNS lesions	5 (11)	8 (20)

[a]Death in the absence of intracranial progression.
[b]Median and 95% CI were calculated using Kaplan-Meier estimates.
[c]*p* value was calculated using log-rank test stratified by mutation type (Ex19del, L858R) and race (Asian, non-Asian).
[d]Target lesions, non-target lesions, and new lesions were not necessarily mutually exclusive categories.
CI, confidence interval; CNS, central nervous system; Ex19del, exon 19 deletion; HR, hazard ratio; iPFS, intracranial progression-free survival; NR, not reached.

Supplementary Figure 3. In the lazertinib arm, fewer patients had CNS lesions at the data cutoff compared with baseline (median follow-up for OS = 21.0 mo). In contrast, in the gefitinib arm, more patients had CNS lesions at the data cutoff compared with baseline (median follow-up for OS = 22.1 mo). Among the 35 patients with baseline CNS lesions in the lazertinib group, 11 had a complete response. Six patients in the lazertinib group with no CNS lesion at baseline developed new CNS lesions by the data cutoff date. In the gefitinib group, fewer patients with baseline CNS lesions had a complete response at the data cutoff (8 of 35 patients), and more patients with no CNS lesion at baseline went on to develop new CNS lesions (14 patients).

Among patients who had previously received radiotherapy (11 patients in each group), the median iPFS was NR (95% CI: 4.2–NR) in the lazertinib group and 8.4 months (95% CI: 1.9–NR) in the gefitinib group (HR = 0.31, 95% CI: 0.08–1.22, $p = 0.0766$) (Supplementary Table 1 and Supplementary Fig. 4*A* and *B*). For those who did not previously receive radiotherapy (34 and 30 patients, respectively), the median iPFS was significantly longer in the lazertinib group compared with the gefitinib group (28.2 mo [95% CI: 10.9–NR] and 8.2 mo [95% CI: 5.5–NR]; HR = 0.43; 95% CI: 0.19–0.98, $p = 0.0387$).

In a competing risk analysis, the estimated probability of observing a CNS progression event in the absence of death or a non-CNS progression event at 6 months was 5% (95% CI: 1%–14%) with lazertinib versus 18% (95% CI: 8%–32%) with gefitinib. At 12 months, the probability was 17% (95% CI: 7%–30%) with lazertinib versus 26% (95% CI: 13%–40%) with gefitinib, and at 18 months, the probability was 17% (95% CI: 7%–30%) with lazertinib versus 30% (95% CI: 15%–47%) with gefitinib (Fig. 2*C*).

Safety

In the safety analysis set, the rates of AEs were similar overall between the two treatment groups (Table 4) and were similar to those observed in the overall LASER301 study population.[15] The rates of treatment-related AEs, grade 3 or higher–related AEs, and related serious AEs were also similar for each study group in the CNS analysis population and comparable to those in the overall LASER301 population. The most treatment-related AEs in each treatment group were grade 3 or less. AEs leading to treatment interruption, treatment reduction, or discontinuation of the study drug, respectively, were reported in 44%, 18%, and 13% of patients in the lazertinib group and 39%, 7%, and 10% in the gefitinib group. AEs ultimately resulting in death were reported in 7% of patients receiving lazertinib and 5% of patients receiving gefitinib; one death was considered treatment-related (interstitial lung disease [ILD] in the lazertinib group).

The most often reported AEs in the lazertinib group were paresthesia (51%), pruritus (31%), rash (29%), and anemia (29%), whereas, in the gefitinib group, the most common AEs were rash (37%), diarrhea (34%), and alanine aminotransferase increased (29%) (Supplementary Table 2). Paresthesia was more common in the lazertinib group (51%) than in the gefitinib group (10%).

AEs that have been frequently reported with other EGFR TKIs include rash, diarrhea, ILD, and QTc prolongation. Diarrhea was reported by 27% of patients in the lazertinib group and 34% in the gefitinib group. ILD was reported by 4% of patients in the lazertinib group and 2% in the gefitinib group. QTc prolongation was reported by 9% of patients in the lazertinib group and 2% of patients in the gefitinib group.

Discussion

Our analysis of phase 3 LASER301 study revealed that, among patients with CNS metastases identified by BICR at baseline, lazertinib significantly improved iPFS compared with gefitinib, and had more durable responses. In this CNS subset, the median iPFS in the

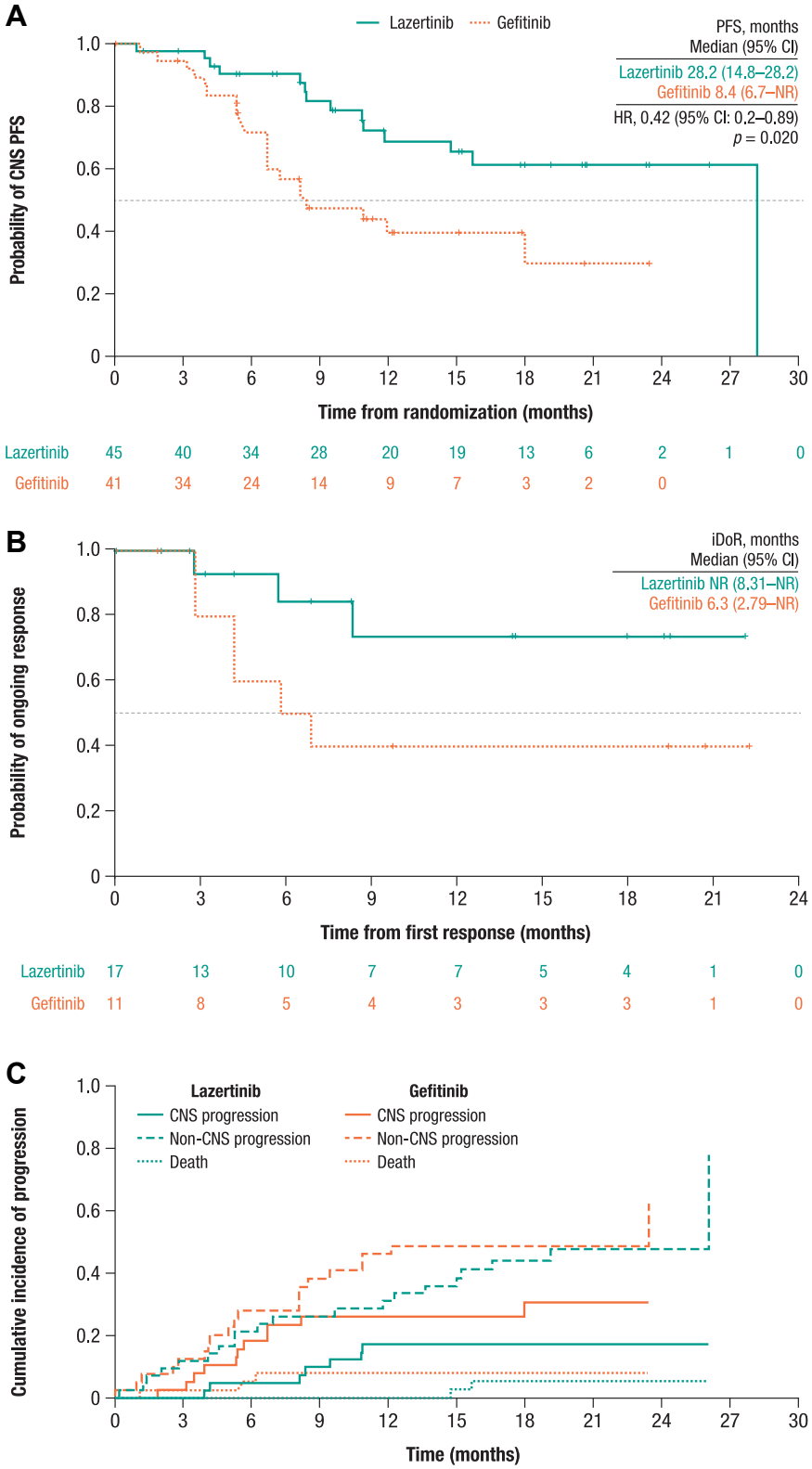

Figure 2. Intracranial efficacy outcomes by BICR in the iFAS, including (*A*) iPFS, (*B*) iDoR, and (*C*) cumulative incidence of CNS progression. BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; iDoR, intracranial duration of response; iFAS, intracranial full analysis set; iPFS, intracranial progression-free survival; NR, not reached.

Table 3. Intracranial Efficacy End Points in Patients With Target Lesion of Brain Tumors at Baseline

End Point	Lazertinib (n = 18)	Gefitinib (n = 15)
iORR,[a] n (%)	17 (94.4)	11 (73.3)
95% CI for iORR[b]	72.7-99.9	44.9-92.2
OR (95% CI), *p* value[c]	6.18 (0.61-62.83), $p = 0.124$	
iDCR,[d] n (%)	17 (94.4)	14 (93.3)
95% CI for iDCR[b]	72.7-99.9	68.1-99.8
OR (95% CI), *p* value[c]	1.21 (0.07-21.22), $p = 0.894$	
Duration of response from onset of intracranial response (mo)[e,f]		
Median	NR	6.3
95% CI for median	8.31-NR	2.79-NR
Estimated percentage remaining in intracranial response, % (95% CI)[a,e]		
6 mo	84.4 (50.4-95.9)	50.0 (18.4-75.3)
12 mo	73.9 (37.9-91.0)	40.0 (12.3-67.0)
18 mo	73.9 (37.9-91.0)	40.0 (12.3-67.0)
24 mo	73.9 (37.9-91.0)	40.0 (12.3-67.0)
Time to response from randomization of intracranial response (wk)[e]		
Median	5.6	5.9
95% CI for median	5.29-12.00	5.14-12.00

[a]iORR is defined as the percentage of patients who have ≥1 CR or PR in intracranial lesion according to RECIST version 1.1 before disease progression in patients who have ≥1 measurable intracranial lesion at baseline.
[b]95% exact CI using the Clopper−Pearson method.
[c]iORR and iDCR are analyzed on the basis of a fitted logistic regression.
[d]iDCR is defined as the percentage of patients who have a best intracranial overall response of CR or PR or SD in patients who have ≥1 measurable intracranial lesion at baseline.
[e]Median and 95% CI were calculated using Kaplan-Meier estimates.
[f]Duration of response is the time from the first documentation of CR or PR until the date of progression or death in the absence of disease progression.
CI, confidence interval; CR, complete response; iDCR, intracranial disease control rate; iORR, intracranial objective response rate; NR, not reached; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Table 4. Summary of Overall TEAEs

AE, n (%)	Lazertinib (n = 45)	Gefitinib (n = 41)
Any TEAE	44 (98)	40 (98)
Any related TEAE	40 (89)	33 (80)
Any TEAE grade ≥3	19 (42)	20 (49)
Any TEAE grade 4	4 (9)	2 (5)
Any TEAE grade 5	3 (7)	2 (5)
Any related AE grade ≥3	11 (24)	11 (27)
Serious TEAE	15 (33)	11 (27)
Related serious TEAE	3 (7)	3 (7)
Any TEAE with outcome of death	3 (7)	2 (5)
Any related TEAE with outcome of death	1[a] (2)	0
Any TEAE leading to:		
Temporary drug interruption	20 (44)	16 (39)
Dose reduction	8 (18)	3 (7)
Permanent discontinuation	6 (13)	4 (10)
Related AEs leading to:		
Permanent discontinuation	4 (9)	3 (7)

[a]ILD.
AE, adverse event; ILD, interstitial lung disease; TEAE, treatment-emergent adverse event.

lazertinib group was 28.2 months compared with 8.4 months in the gefitinib group ($p = 0.02$), whereas the median iDoR was NR in the lazertinib group compared with 6.3 months in the gefitinib group. The iPFS rate was notably higher in the lazertinib group compared with the gefitinib group at multiple time points up to 18 months (61% versus 30%). The probability of CNS progression occurring, without death or non-CNS progression, was lower for patients receiving lazertinib versus gefitinib. CNS progression was primarily observed as new lesions for both the lazertinib and gefitinib groups, but fewer patients developed new lesions in the lazertinib group (11%; 5 of 45) compared with the gefitinib group (20%; 8 of 41). A statistically nonsignificant improvement with lazertinib compared with gefitinib treatment was observed in iORR (94% versus 73%, respectively), whereas iDCR was similar in the treatment groups (94% versus 93%, respectively). The comparison of efficacy depending on prior brain radiotherapy, which did not allow for statistical comparison of iORR and iPFS between groups by previous treatment; however, CNS response to lazertinib was observed irrespective of previous brain radiotherapy.

The efficacy results of this subset analysis are consistent with those seen in the overall LASER301 study population, with significantly improved outcomes in the lazertinib versus gefitinib group.[15] Specifically, the significant improvements in iPFS and iDoR with lazertinib versus gefitinib mirror those of PFS and duration of response in the overall study population. Notably, in patients with baseline brain metastases, more patients in the lazertinib group experienced a complete CNS response (11 patients) compared with the gefitinib group (8 patients). These results, along with an investigator assessment of CNS progression, suggest strong outcomes for the CNS efficacy of lazertinib. In the overall LASER301 population, the incidence of CNS progression events, as assessed by the investigators, was reduced with lazertinib versus gefitinib, regardless of the presence or absence of known or treated CNS metastases at study entry.[15] A lower rate of CNS progression was observed among patients with (14% versus 42%) or without (3% versus 5%) known or treated CNS metastases at study entry for lazertinib versus gefitinib, respectively. More importantly, a previous phase 2 study

involving 40 patients with NSCLC with asymptomatic or mildly symptomatic brain metastases after disease progression on or after EGFR TKI treatment, revealed a cerebrospinal fluid penetration rate (cerebrospinal fluid/free plasma concentration rate) for lazertinib of 46.2%,[16] which is substantially greater than that previously exhibited for first-generation TKIs.[7,17,18] Breast cancer resistance protein and multidrug resistance-1/P-glycoprotein are efflux transporters that prevent molecules from penetrating the blood-brain barrier. In a preclinical study, lazertinib was not a substrate of breast cancer resistance protein and was a weak substrate of multidrug resistance-1, which may indicate that lazertinib is minimally affected by efflux transporters that reduce a drug's ability to penetrate the CNS.[12]

The tolerability profile of lazertinib in the CNS subset was similar to that observed in the overall LASER301 population, with no apparent differences in the incidence of AEs. The overall rate of AEs in the CNS subset was similar in the lazertinib and gefitinib treatment groups, with similar proportions in each group interrupting or discontinuing treatment owing to AEs. These observations were consistent with the tolerability profile observed in the overall LASER301 population.[15] Of the individual AEs reported in the lazertinib group, paresthesia in the CNS subset (51%) occurred more frequently compared with the overall LASER301 population (39%); however, the overall analysis revealed that most paresthesia events are manageable, reversible, and symptomatically relieved with dose interruption or reduction.[15] Hepatotoxic AEs (i.e., increases in alanine aminotransferase and aspartate aminotransferase) were lower in the lazertinib group than in the gefitinib group in both the CNS subset and the overall study population. Reports of related AEs of special interest (ILD and electrocardiogram QTc prolongation) were low and generally similar between the lazertinib and gefitinib groups in the CNS and overall populations. Whereas this subset population is small, overall, no new safety signals were identified.

Another third-generation TKI, osimertinib, has also revealed efficacy in patients with *EGFR*-mutated NSCLC with CNS metastases in an exploratory analysis of the phase 3 FLAURA study.[19] In that analysis, in which serial brain imaging was not conducted in all patients, median iPFS with osimertinib (NR after a median follow-up of 12.4 mo) was considered to be nominally statistically significantly longer than that with first-generation TKIs erlotinib or gefitinib (iPFS of 13.9 mo after a median follow-up of 7.0 mo; HR = 0.48, 95% CI: 0.26–0.86, $p = 0.014$). In patients with measurable CNS lesions, there were statistically nonsignificant improvements in the osimertinib group compared with the erlotinib or gefitinib group in iORR (91% versus 68%, respectively, $p = 0.066$) and iDCR (95% versus 89%, respectively, $p = 0.462$). A similar analysis of patients with baseline brain metastases enrolled in the FURLONG trial in the People's Republic of China comparing the third-generation TKI furmonertinib with gefitinib revealed a significantly improved iPFS with furmonertinib (20.8 mo) versus gefitinib (9.8 mo; HR = 0.40, 95% CI: 0.23–0.71, $p = 0.0011$).[20] In patients with measurable lesions, iORR was significantly greater with furmonertinib (91%) versus gefitinib (65%; OR = 6.82, 95% CI: 1.23–37.67, $p = 0.0277$). Whereas direct comparison of our results with those from the FLAURA and FURLONG analyses is not possible owing to inherent differences in the enrolled populations and assessments, lazertinib seems to provide iPFS benefits over gefitinib at least as favorable as those seen with other third-generation TKIs.

The strengths of the overall LASER301 study include a double-blind, double-dummy design, multinational patient enrollment across Asia-Pacific and Europe, the option for crossover to lazertinib, and mandatory scheduled brain imaging. Limitations of the study include the lack of comparison with other first- and second-generation TKIs, such as afatinib or erlotinib, or with other approved third-generation TKIs, such as osimertinib. The current CNS subset analysis limited the patient population to only those who had CNS metastases at baseline by BICR. Baseline brain imaging was not mandatory for all patients, which could lead to potential selection bias. In addition, the small number of patients with one or more measurable intracranial lesions at baseline or who had previously received radiotherapy, and the lack of study-specific criteria defining measurable and non-measurable lesions, limits the interpretation of these results. Finally, OS data are not sufficiently mature (29% in the overall population) at this time to allow comparison between treatment groups in patients with baseline CNS metastases.

In conclusion, for patients with baseline CNS metastases in the LASER301 study, lazertinib significantly improved iPFS versus gefitinib, with more durable responses and a tolerable safety profile, suggesting that lazertinib has the potential to improve CNS outcomes in patients with *EGFR*-mutated NSCLC.

CRediT Authorship Contribution Statement

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Data Sharing Statement

Deidentified participant data will be made available when all end points of all trials have been evaluated. Any requests for trial data and supporting material (data dictionary and statistical analysis plan) will be reviewed by the trial management group in the first instance. Only requests that have a methodologically sound proposal and whose proposed use of the data has been approved by the independent trial steering committee will be considered. Proposals should be directed to the corresponding author in the first instance; to gain access, data requesters will need to sign a data access agreement.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2023.08.017.

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