ORIGINAL ARTICLE

Lazertinib Versus Gefitinib Tyrosine Kinase Inhibitors in Treatment-Naíve Patients With *EGFR*-Mutated Advanced NSCLC: Analysis of the Asian Subpopulation in LASER301

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ABSTRACT

Introduction: Lazertinib is a third-generation central nervous system–penetrant tyrosine kinase inhibitor targeting mutant EGFR in NSCLC. Lazertinib exhibited improved efficacy versus gefitinib in the LASER301 study; this subset analysis compared lazertinib with gefitinib among Asian patients.

Methods: The phase 3 LASER301 study evaluated lazertinib efficacy and safety in treatment-naive patients with *EGFR*-mutated (exon 19 deletion or L858R) locally advanced or metastatic NSCLC. Patients were randomized one-to-one and received either lazertinib or gefitinib. The primary end point was investigator-assessed progression-free survival using Response Evaluation Criteria in Solid Tumors version 1.1. Secondary end points included overall survival, objective response rate, duration of response, and safety.

Results: Between February 13, 2020, and July 29, 2022, among 258 patients of Asian descent, the median progression-free survival was significantly longer with lazertinib than gefitinib (20.6 versus 9.7 mo; hazard ratio: 0.46; 95% confidence interval [CI]: 0.34–0.63, $p < 0.001$), and the benefit was consistent across predefined subgroups (exon 19 deletion, L858R, baseline central nervous system metastases). Objective response rate and disease control rates were similar between treatment groups. The median duration of response was 19.4 months (95% CI: 16.6–24.9) versus 9.6 months (95% CI: 6.9–12.4) in the lazertinib versus gefitinib group. Adverse event rates in Asian patients were comparable with the overall LASER301 population. Adverse events leading to discontinuation in the lazertinib and gefitinib groups were 13% and 12%, respectively.

Conclusions: In LASER301, efficacy and safety results in Asian patients were consistent with the overall population. Lazertinib exhibited better efficacy than gefitinib in Asian patients with a tolerable safety profile.

Keywords: Asian subpopulation; CNS; Lazertinib; NSCLC; TKI

Introduction

NSCLC is frequently associated with *EGFR*-activating mutations, specifically exon 19 deletion (Ex19del) and L858R mutations. These mutations account for nearly 90% of all *EGFR*-activating mutations and frequently drive cases of NSCLC.[1,2] The rate of *EGFR*-mutant (*EGFR*m) NSCLC is highest in the Asia-Pacific region at approximately 47%, highlighting a therapeutic need within this population that is crucial to address.[3]

Whereas the introduction of the first- and second-generation EGFR tyrosine kinase inhibitors (TKIs), such as erlotinib, gefitinib, dacomitinib, and afatinib, revolutionized the treatment of advanced *EGFR*m NSCLC, tumors invariably acquire resistance to these drugs.[1] Thus, the development of third-generation EGFR TKIs has focused on improved selectivity for targeting *EGFR* TKI sensitizing and resistance mutations over the wild-type EGFR.[4] In addition, the frequent development of central nervous system (CNS) metastases, despite treatment with early-generation TKIs, underscores the need to improve blood-brain barrier penetration of new TKIs.[5]

Lazertinib, a third-generation, potent, CNS-penetrant TKI, has been noted for its selectivity for mutant *EGFR*.[6,7] Lazertinib targets both T790M and sensitizing mutations while sparing wild-type EGFR.[6,8] Lazertinib also has exhibited efficacy against intracranial lesions.[9,10] A phase 1/2 study of 240 mg/d lazertinib revealed durable antitumor activity in patients with NSCLC after treatment of other EGFR TKIs.[10] The phase 3 LASER301 study reported significantly improved efficacy versus the first-generation TKI gefitinib, along with a tolerable safety profile.[11] Both Asian and non-Asian patients were enrolled in LASER301 to achieve a better representation of the global burden of *EGFR*m NSCLC. Longer progression-free survival (PFS) rates were observed in the Asian and L858R subgroups (20.6 mo and 17.8 mo, respectively) in LASER301 compared with that observed with the third-generation EGFR TKI osimertinib in the Asian and L858R subsets of the FLAURA study (16.5 mo and 14.4 mo, respectively).[12,13] The current study presents an in-depth efficacy and safety analysis among Asian patients enrolled in LASER301.

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*m (Ex19del or L858R mutation) locally advanced or metastatic NSCLC who had not previously received any line of therapy for NSCLC. Full details of the methodology are presented in the article reporting results from the overall LASER301 population.[11]

Patients of Asian descent included in this subset analysis were enrolled at sites in Korea, Malaysia, Thailand, Singapore, the Philippines, Taiwan, and Australia. No patients of non-Asian descent were enrolled in Asian countries. Patients were randomized one-to-one to receive oral lazertinib (240 mg/d, which could be reduced to 160 mg/d when toxicity was reported) or oral gefitinib (250 mg/d). Patients were allowed to crossover from the gefitinib group to receive open-label lazertinib if they demonstrated objective progressive disease confirmed by blinded independent central review (BICR) and postprogression T790M-positive status confirmed locally or centrally by plasma or tissue testing.

Patients

Eligible patients were 18 years of age and older, had *EGFR* mutations determined by tissue biopsy, and were treatment-naive for locally advanced or metastatic NSCLC, although treatment for early-stage disease more than 12 months before randomization was permitted. 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. Exclusion criteria included symptomatic or unstable brain metastases, leptomeningeal metastases, and a history of interstitial lung disease (ILD).

Protocol Approval

This clinical trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization. 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 was PFS assessed by investigators per Response Evaluation Criteria in Solid Tumors version 1.1. In a sensitivity analysis, PFS was also assessed by BICR. Secondary end points included overall survival (OS), objective response rate (ORR), disease control rate (DCR), duration of response (DoR), and safety. Several exploratory end points were also investigated in patients who had a brain scan during screening or at baseline and identified as having brain disease in the Asian subset, including the depth of intracranial response, intracranial PFS, intracranial ORR (iORR), intracranial DCR (iDCR), and intracranial DoR (iDoR). Intracranial efficacy results and scans were assessed by BICR and by neurologists.

During the screening period, patients were assessed for eligibility up to 28 days before randomization. Tumor and efficacy assessments were performed every 6 weeks for the first 18 months, then every 12 weeks after randomization until disease progression. Patients who discontinued treatment were assessed for survival, disease progression, and poststudy cancer treatment every 6 weeks until loss to follow-up, consent withdrawal, or

death. 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 Asian patient was given the initial dose on February 13, 2020, and the data cutoff was July 29, 2022. The Asian subset was a subgroup of the overall population for which there was no formal sample size or power calculations. All efficacy outcomes were analyzed in Asian patients in the full analysis set (all randomized patients; intent-to-treat). All safety outcomes were analyzed in Asian patients in the safety analysis set (all patients who received at least one dose of study treatment).

The PFS was analyzed by the Kaplan-Meier method by treatment group, 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. All patients who undertook a brain scan in the screening or baseline period and had measurable or nonmeasurable brain disease at baseline were included in the intracranial full analysis set (a subset of the full analysis set).

The pharmacokinetic analysis was performed on Asian patients in the pharmacokinetic analysis set, which comprised patients who had at least one measurable concentration of lazertinib collected postdose in the lazertinib group.

Results

Patients

Of the 393 patients enrolled in LASER301, 258 were of Asian descent (129 received lazertinib, 129 received gefitinib) (Supplementary Fig. 1). All enrolled patients received at least one dose of the study drug. The median (range) duration of study treatment for lazertinib and gefitinib groups were 78.0 weeks (0.9–126.0) and 46.0 weeks (0.3–120.3), respectively (Supplementary Table 1). For the overall population in LASER301, the mean relative dose intensity (RDI) was 96.11% and 100.00% for lazertinib and gefitinib, respectively.

Table 1. Demographics and Baseline Disease Characteristics

Demographic or Characteristic	Lazertinib (n = 129)	Gefitinib (n = 129)
Age		
Median	66.0	64.0
Range	34.0-86.0	40.0-85.0
Age group, y, n (%)		
<65	55 (43)	67 (52)
≥65	74 (57)	62 (48)
Sex, n (%)		
Male	49 (38)	57 (44)
Female	80 (62)	72 (56)
Smoking status, n (%)		
Never	86 (67)	95 (74)
Ever	43 (33)	34 (26)
Current	7 (5)	5 (4)
Former	36 (28)	29 (22)
WHO performance status, n (%)		
0	30 (23)	31 (24)
1	99 (77)	98 (76)
CNS metastases at study entry,[a] n (%)	39 (30)	31 (24)
Overall disease classification, n (%)		
Metastatic	126 (98)	126 (98)
Locally advanced	3 (2)	3 (2)
Histology, n (%)		
Adenocarcinoma	129 (100)	129 (100)
Other[b]	1 (1)	0
EGFR mutation at randomization,[c] n (%)		
Ex19del	77 (60)	77 (60)
L858R	52 (40)	52 (40)

[a]CNS metastases were determined from NSCLC history.
[b]Squamous cell carcinoma was also confirmed in one patient; however, all the predominant histology was adenocarcinoma.
[c]Local or central test.
CNS, central nervous system; Ex19del, exon 19 deletion mutation.

For the Asian subset analysis, the mean RDI was 95.25% and 100.00% for lazertinib and gefitinib, respectively. The median RDI was 100.00% for both treatment groups in the overall population and the Asian subset. RDI is the ratio of the actual dose intensity to the planned dose intensity. Demographics and baseline disease characteristics were generally balanced between treatment groups (Table 1). Approximately 60% of patients had Ex19del mutations and 40% of patients had L858R mutations in each treatment group. Among patients with CNS metastases at study entry, 30% were in the lazertinib group and 24% were in the gefitinib group.

Efficacy

All Asian patients in the full analysis set were included in the Asian subgroup efficacy analysis set. Among these Asian patients, 62 patients (48%) in the lazertinib group and 24 patients (19%) in the gefitinib group were receiving ongoing treatment.

The median PFS determined by investigator assessment was significantly longer in the lazertinib group at 20.6 months versus 9.7 months in the gefitinib group (HR: 0.46, 95% CI: 0.34–0.63, $p < 0.001$) (Fig. 1*A*). The median follow-up for PFS was 23.3 months in both treatment groups (interquartile range: 19.4–26.0 in the lazertinib group and 18.4–26.1 in the gefitinib group). The PFS values among predefined subgroups favored lazertinib more than gefitinib (Fig. 1*B*). Among Asian patients with CNS metastases at baseline, the median PFS was 20.7 months in the lazertinib group versus 9.5 months in the gefitinib group (HR: 0.33, 95% CI: 0.18–0.58, $p < 0.001$) (Fig. 1*C*). Among patients with Ex19del, the median PFS was 20.8 months in the lazertinib group versus 12.3 months in the gefitinib group (HR: 0.47, 95% CI: 0.31–0.71, $p < 0.001$) (Fig. 1*D*). Among patients with L858R, the median PFS was 16.7 months in the lazertinib group versus 9.6 months in the gefitinib group (HR: 0.44, 95% CI: 0.28–0.71, $p = 0.002$) (Fig. 1*E*).

The PFS estimated by BICR was similar to that of the investigator assessment, with a median PFS of 17.8 months in the lazertinib group and 8.3 months in the gefitinib group (HR: 0.53, 95% CI: 0.39–0.72, $p < 0.001$) (Supplementary Fig. 2).

The OS data were at 28% maturity at the time of this analysis. The median OS was not reached (NR) in either group (HR: 0.89, 95% CI: 0.57–1.40, $p = 0.617$) (Fig. 2). A total of 41 patients (32%) in the gefitinib group crossed over to the lazertinib group.

Overall response, ORR, DCR, and DoR, are summarized in Table 2. The number of patients who had a response of stable disease or better was 120 (93%) in the lazertinib group and 122 (95%) in the gefitinib group. The ORR and DCR were not significantly different between the treatment groups. The median DoR from the onset of response was 19.4 months (95% CI: 16.6–24.9) and 9.6 months (95% CI: 6.9–12.4) among patients receiving lazertinib and gefitinib, respectively. The best percentage change from baseline in lesion size per patient and by response category is displayed as a waterfall plot by treatment group in Supplementary Figure 3 and Supplementary Table 2.

Intracranial efficacy results were evaluated by neuroradiologic BICR assessment (Supplementary Table 3). A total of 27 patients had measurable brain disease determined by brain scan during screening or at baseline; 13 of these patients received lazertinib and 14 received gefitinib. All patients receiving lazertinib experienced a best intracranial response of complete response or partial response, resulting in an iORR and iDCR of 100% (95% CI: 75.3–100) each. Of those receiving gefitinib, 10 experienced complete or partial response, three had stable disease, and one was not evaluable, resulting in an iORR of 71% (95% CI: 42.9–91.6) and iDCR of 93% (95% CI: 66.1–99.8). The median iDoR was NR in the lazertinib group (95% CI: 8.31–NR), and the median iDoR in the gefitinib group was 6.3 months (95% CI: 2.8–NR). The median best percentage change from baseline in target lesion size among patients with CNS metastases at baseline is presented in Supplementary Table 4 and Supplementary Figure 4.

A total of 40 patients (31%) in the lazertinib group and 83 patients (64%) in the gefitinib group underwent a subsequent line of therapy after treatment in this study (Supplementary Table 5). The most common poststudy treatment was cytotoxic chemotherapy (16%) in the lazertinib group and a third-generation TKI (39%; osimertinib, lazertinib, or with chemotherapy combination) in the gefitinib group.

Safety

Among Asian patients within the safety analysis set, the rates of AEs were similar overall between the two treatment groups. No AEs of grade 4 or 5 were reported in this population (Table 3). The rates of AEs, related AEs, AE grades greater than or equal to 3, and related serious AEs were also similar for each study group between the Asian population and the overall LASER301 population. AEs leading to treatment interruption, reduction, or discontinuation of the study drug, respectively, were reported in 38%, 25%, and 13% of patients in the lazertinib group and 32%, 16%, and 12% in the gefitinib group. AEs ultimately resulting in death were reported in 5% of patients receiving lazertinib and in 3% of patients receiving gefitinib; no treatment-related deaths were reported in either treatment group.

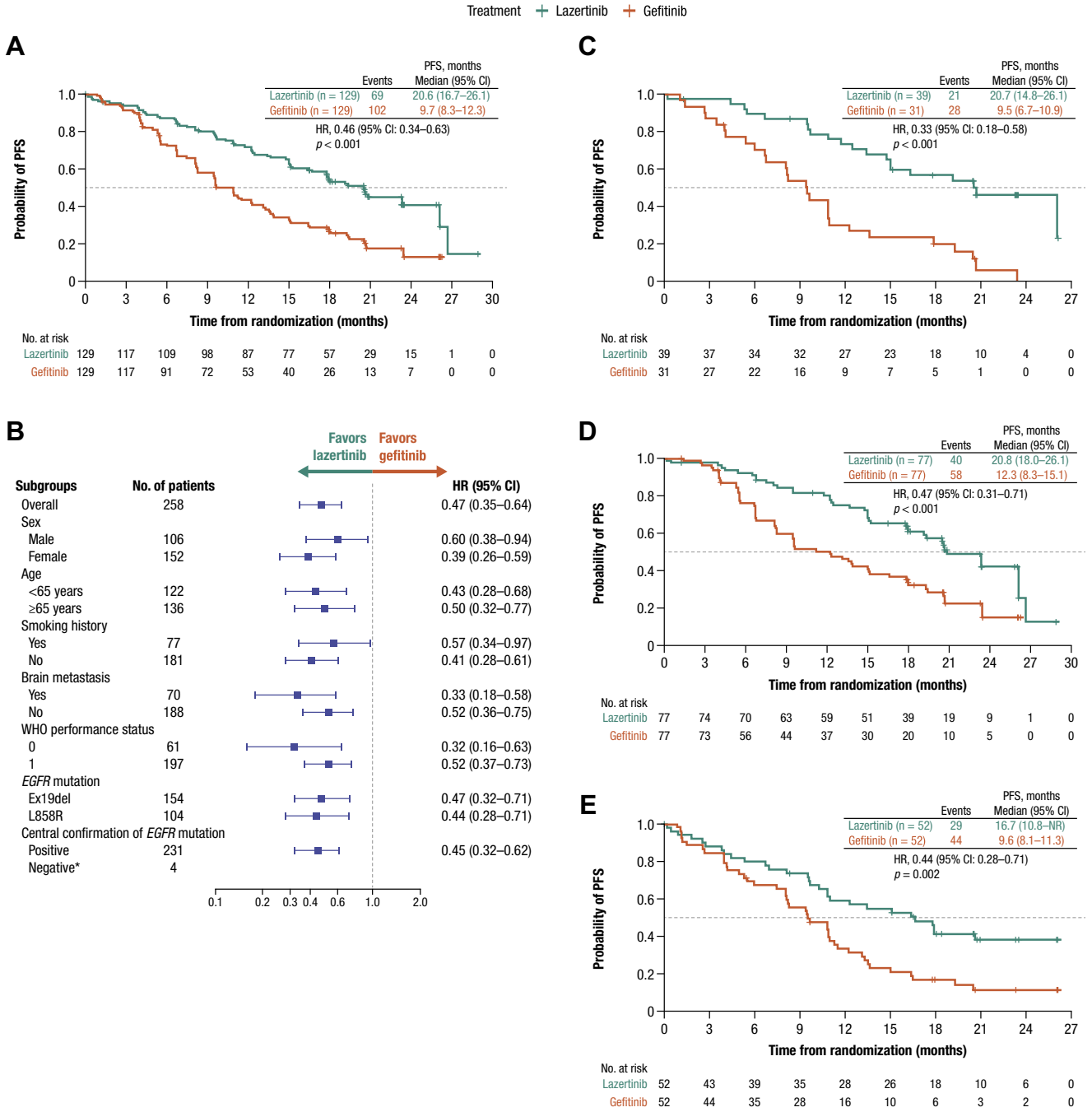

Figure 1. PFS estimates in Asian patients in LASER301 (*A*), including among patients in predefined subgroups (*B*), those with CNS metastases at study entry (*C*), those with Ex19del mutations (median follow-up: lazertinib, 23.3 mo, gefitinib, 23.5 mo) (*D*), and those with L858R mutations (median follow-up: 23.3 mo in both groups) (*E*). *Subgroups with fewer than 20 events were excluded and not analyzed. CI, confidence interval; Ex19del, exon 19 deletion mutation; HR, hazard ratio; mets, metastases; PFS, progression-free survival.

The most often reported AEs in the lazertinib group were paresthesia (46%), rash (42%), and pruritus (37%), whereas the most often reported AEs in the gefitinib group were rash (47%), diarrhea (44%), and increased alanine aminotransferase (33%). Most AEs in each treatment group were grade 1 or 2 (Table 4). Treatment-related AEs occurring with a frequency of at least 10% in the lazertinib group are included in Supplementary Table 6; the most frequently reported were rash (42%), paresthesia (40%), and pruritis (37%) in the lazertinib group and rash (44%), diarrhea (40%), and increased alanine aminotransferase (29%) in the gefitinib group. The most often reported grade 3 or higher treatment-related AEs were paresthesia (3%) and diarrhea (3%)

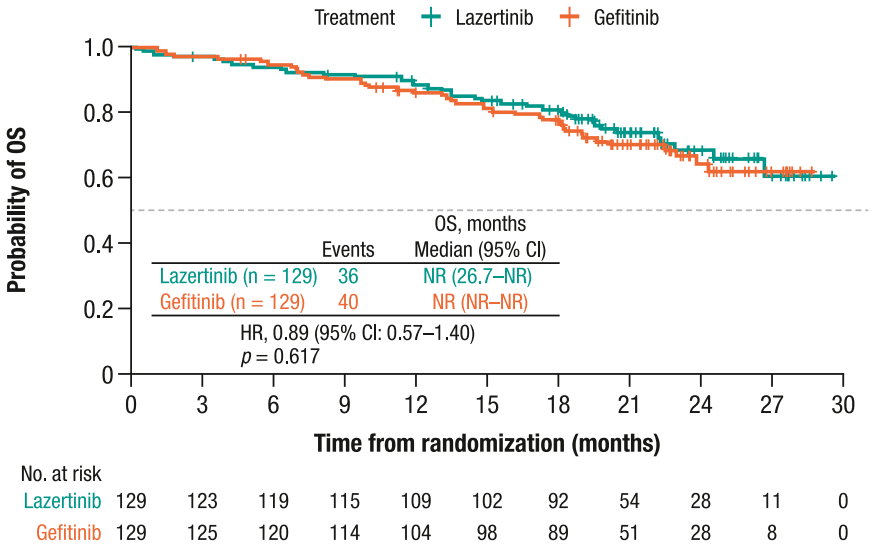

Figure 2. Kaplan-Meier estimates of OS. CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival.

in the lazertinib group and alanine aminotransferase increase (11%) and aspartate aminotransferase increase (9%) in the gefitinib group (Supplementary Table 6).

Treatment-related AEs resulting in dose interruption, reduction, and discontinuations, respectively, were reported in 27%, 24%, and 8.5% of patients receiving lazertinib, respectively, and 26%, 14%, and 11% of patients receiving gefitinib, respectively. The treatment-related AEs most frequently resulting in dose reduction were paresthesia (8%) and maculopapular rash (2%) in the lazertinib group, and rash (5%) and alanine aminotransferase increase (4%) in the gefitinib group.

Table 2. Secondary Efficacy End Points

End Point	Lazertinib (n = 129)	Gefitinib (n = 129)
Best overall response, n (%)		
CR	1 (1)	1 (1)
PR	100 (78)	101 (78)
Stable disease	19 (15)	20 (16)
PD	4 (3)	5 (4)
NE	5 (4)	2 (2)
ORR[a], n (%)	101 (78)	102 (79)
95% CI for ORR[b]	70.2-85.1	71.0-85.7
OR (95% CI), *p* value[c]	0.95 (0.52-1.75), $p = 0.877$	
DCR[d], n (%)	120 (93)	122 (95)
95% CI for DCR[b]	87.2-96.8	89.1-97.8
OR (95% CI), *p* value[c]	0.76 (0.27-2.14), $p = 0.600$	
Duration of response from the onset of response (mo)[e]		
Median	19.4	9.6
95% CI for median	16.6-24.9	6.9-12.4
Estimated percentage remaining in response, mo		
6	92	66
12	76	42
18	56	24
24	45	13

Notes: Response does not require confirmation. RECIST version 1.1.
[a]ORR is defined as the percentage of patients with measurable disease with at least one visit response of CR or PR.
[b]95% exact CI using the Clopper-Pearson method.
[c]ORR and DCR were analyzed using logistic regression models stratified by mutation type.
[d]DCR is defined as the percentage of patients who have a best overall response of CR or PR or stable disease (stable disease at ≥ 6 weeks, before any PD event). The 6-week time point will allow for a visit window and be defined as on or after study day 35 (allowing for the visit window).
[e]The median duration and 95% CI were calculated from Kaplan-Meier estimates.
CI, confidence interval; CR, complete response; DCR, disease control rate; NE, not evaluable; OR, odds ratio; ORR, objective response rate; PD, progression disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 3. Summary of Overall AEs

AE, n (%)	Lazertinib (n = 129)	Gefitinib (n = 129)
Any AEs	129 (100)	128 (99)
Any related AE	120 (93)	118 (91)
Any AE grade ≥3	61 (47)	63 (49)
Any AE grade 4 or 5	0	0
Any related AE grade ≥3	32 (25)	35 (27)
Any serious AE	41 (32)	32 (25)
Any related serious AE	8 (6)	6 (5)
Any AE with outcome of death	7 (5)	4 (3)
Any related AE with outcome of death	0	0
Any AEs leading to:		
Temporary drug interruption	49 (38)	41 (32)
Dose reduction	32 (25)	20 (16)
Permanent discontinuation	17 (13)	16 (12)

AE, adverse event.

Treatment-related AEs that have been frequently reported with the use of other EGFR TKIs include rash, diarrhea, ILD, and QTc prolongation. Treatment-related diarrhea of any grade was numerically lower in the lazertinib group than in the gefitinib group (23% versus 40%). ILD, which included pneumonitis, was reported by 2% of patients in both treatment groups. QTc prolongation was reported by 5% of patients in the lazertinib group and 2% of patients in the gefitinib group.

Pharmacokinetics

The plasma concentration-time profile in Asian patients receiving lazertinib 240 mg/d is illustrated in Supplementary Figure 5. In Asian patients, lazertinib plasma concentrations remained similar from cycle 2 to cycle 13, with a geometric mean range of trough concentrations of 213.2 to 228.1 ng/mL. This indicates that lazertinib steady state was achieved by cycle 2 day 1.

Discussion

The results of the efficacy study for Asian patients in the phase 3 LASER301 trial were consistent with the overall study population. Importantly, a consistent, significantly higher median PFS ($p < .001$) and DoR in the lazertinib group versus the gefitinib group was observed in both the overall LASER301 population and in Asian patients, including among Asian patients in predefined subgroups with Ex19del and L858R

Table 4. AEs Occurring in Greater Than or Equal to 10% of Patients in the Lazertinib Group

	Lazertinib (n = 129)				Gefitinib (n = 129)			
Preferred Term, n (%)	Any Grade	Grade 1	Grade 2	Grade 3[a]	Any Grade	Grade 1	Grade 2	Grade 3[a]
Paresthesia	59 (46)	32 (25)	23 (18)	4 (3)	7 (5)	7 (5)	0	0
Rash	54 (42)	25 (19)	27 (21)	2 (2)	60 (47)	27 (21)	28 (22)	5 (4)
Pruritus	48 (37)	29 (22)	18 (14)	1 (1)	35 (27)	22 (17)	13 (10)	0
Diarrhea	39 (30)	28 (22)	7 (5)	4 (3)	57 (44)	39 (30)	18 (14)	0
Paronychia	31 (24)	17 (13)	14 (11)	0	32 (25)	13 (10)	18 (14)	1 (1)
Stomatitis	30 (23)	23 (18)	7 (5)	0	15 (12)	12 (9)	2 (2)	1 (1)
Decreased appetite	25 (19)	16 (12)	7 (5)	2 (2)	24 (19)	12 (9)	11 (9)	1 (1)
Constipation	23 (18)	11 (9)	12 (9)	0	18 (14)	10 (8)	8 (6)	0
Anemia	22 (17)	4 (3)	12 (9)	6 (5)	11 (9)	2 (2)	4 (3)	5 (4)
Dry skin	22 (17)	18 (14)	4 (3)	0	17 (13)	16 (12)	1 (1)	0
Muscle spasms	20 (16)	17 (13)	3 (2)	0	4 (3)	4 (3)	0	0
Nausea	19 (15)	15 (12)	4 (3)	0	7 (5)	3 (2)	4 (3)	0
Dermatitis acneiform	17 (13)	11 (9)	4 (3)	2 (2)	19 (15)	11 (9)	7 (5)	1 (1)
ALT increased	17 (13)	12 (9)	3 (2)	2 (2)	43 (33)	15 (12)	12 (9)	16 (12)
AST increased	14 (11)	11 (9)	2 (2)	1 (1)	37 (29)	17 (13)	9 (7)	11 (9)

Notes: Patients with two or more AEs with the same AE term are counted only once for that AE term. AEs are presented in descending frequency by any grade in the lazertinib group.

[a]No grade 4 or 5 AEs were reported in the Asian subset analysis.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

mutations, and with CNS metastases at study entry. These consistent benefits of lazertinib in Asian patients with either of the common mutations of *EGFR* or with CNS metastases are noteworthy, considering Asian patients receiving osimertinib in the FLAURA study revealed a numerically shorter overall PFS (16.5 mo) compared with the overall FLAURA population (18.9 mo). In addition, within the FLAURA Asian subset, osimertinib did not exhibit a consistent benefit versus standard of care (gefitinib or erlotinib) across these subgroups; for example, although significant benefits were seen in subgroups with Ex19del and L858R mutations, the PFS benefit was not significant in patients with CNS metastases.[12]

The safety profile assessed in this study confirmed the tolerability of lazertinib, similar to that of the overall LASER301 population, with no new safety signals reported and similar rates of discontinuation (10% in the overall population versus 13% in Asian patients).

The OS data remain immature in the current analysis (28% maturity), limiting the comparison between lazertinib and gefitinib within this study and with other studies involving third-generation TKIs in Asian patients. Additional follow-up is needed before the OS efficacy among Asian patients can be fully interpreted in LASER301. The high number of patients who crossed over from the gefitinib group to the lazertinib group (n = 41 of 129, 32%), and patients who crossed over to other non–protocol-specified third-generation TKIs, may be confounding factors for a potential OS benefit. However, the favorable PFS result in Asian patients overall and among Asian patients with L858R mutations may suggest that OS could be favorable with additional follow-up.

The prevalence of *EGFR*m NSCLC among patients of Asian descent and the reduced efficacy of osimertinib observed among Asian patients in the FLAURA study highlighted a need to demonstrate the efficacy of a third-generation TKI in Asian populations. In the LASER301 study, both Asian and non-Asian patients were enrolled, making the study more representative of the worldwide population, which contrasts with previous studies of the TKIs aumolertinib and furmonertinib, which enrolled patients across the People's Republic of China.[14,15] Up to 50% of patients with NSCLC develop CNS metastases, which are a major source of declining quality of life and mortality for those with this disease.[16] As new third-generation TKIs are developed, these therapies must exhibit efficacy against CNS progression. Approximately 30% of Asian patients enrolled in LASER301 had CNS metastases at baseline, but lazertinib treatment exhibited favorable outcomes among intracranial-specific end points, including DoR (NR in the lazertinib group versus 6.3 mo in the gefitinib group), iPFS, and iORR. Lazertinib treatment also substantially reduced CNS lesion size among Asian patients with measurable disease.

Results from the overall LASER301 population indicated that paresthesia was the most common AE reported among patients receiving lazertinib (39%).[11] Treatment-related paresthesia rates among Asian patients enrolled in LASER301 receiving lazertinib (40%) were comparable with the overall population and higher than the rates among patients receiving gefitinib (5%). However, this AE was manageable and reversible and often relieved with an interruption or reduction in lazertinib dosage. Hepatotoxic AEs (i.e., increases in alanine aminotransferase and aspartate aminotransferase) in the lazertinib group were comparable to the overall LASER301 population and lower than for gefitinib among both Asian patients and the overall study population. Reports of related AEs of special interest (ILD, QTc prolongation in electrocardiogram) were low ($\leq$5%) and similar between the lazertinib and gefitinib groups.

Our study must be interpreted within its limitations. Lazertinib was compared only with gefitinib, rather than with other first- and second-generation TKIs, such as afatinib and erlotinib. In addition, among Asian patients, the number of patients who had CNS metastases at baseline was low (n = 27); the small sample size limits the definitive interpretation of the intracranial efficacy results.

In conclusion, analysis of Asian patients with *EGFR*m advanced NSCLC in LASER301 revealed that lazertinib elicited better efficacy than gefitinib in this population, including among Asian patients with Ex19del or L858R mutations, or with CNS metastases at baseline. The safety and tolerability of lazertinib in Asian patients are notable for their similarity to the LASER301 overall population.

CrediT Authorship Contribution Statement

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SeokYoung Choi: Data Curation, Formal analysis, Software, Validation, Visualization, Writing – original draft, Writing – review and editing.

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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 requestors 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.2023.06.016.

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