ORIGINAL ARTICLE

A Phase 1/2 Study of Lazertinib 240 mg in Patients With Advanced *EGFR* T790M-Positive NSCLC After Previous EGFR Tyrosine Kinase Inhibitors

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ABSTRACT

Introduction: This integrated analysis of a phase 1/2 study (NCT03046992) evaluated the efficacy and safety of lazertinib, a third-generation EGFR tyrosine kinase inhibitor (TKI), in patients with advanced *EGFR* T790M-positive NSCLC after previous EGFR TKI therapy.

Methods: Adults with *EGFR* mutation-positive NSCLC that progressed after prior EGFR-directed TKIs received once daily oral lazertinib 240 mg continuously until disease progression. Prior TKIs to treat T790M-positive NSCLC were prohibited. Primary endpoints were safety and objective response rate (ORR). Secondary endpoints included progression-free survival, overall survival, and intracranial ORR.

Results: A total of 78 patients received lazertinib 240 mg at 17 centers in South Korea. Among patients with T790M-positive tumors at baseline (N = 76), one (1.3%) had a complete response and 41 (53.9%) had partial responses, giving an ORR of 55.3% (95% confidence interval [CI]: 44.1–66.4). Median progression-free survival was 11.1 months (95% CI: 5.5–16.4). Median overall survival was not reached (median follow-up = 22.0 mo). In patients with measurable intracranial lesions (n = 7), one (14.3%) had a complete intracranial response and five (71.4%) had partial responses, giving an intracranial ORR of 85.7% (95% CI: 59.8%–100.0%). The most common treatment-emergent adverse events were rash (37.2%), pruritus (34.6%), and paresthesia (33.3%); most were mild to moderate in severity. Serious drug-related adverse events occurred in three patients (gastritis, pneumonia, pneumonitis). The major mechanism of resistance was *EGFR* T790M loss.

Conclusions: Lazertinib 240 mg/d has a manageable safety profile with durable antitumor efficacy, including brain metastases, in patients with advanced T790M-positive NSCLC after previous EGFR TKI therapy.

Keywords: Lazertinib; Epidermal growth factor receptor (EGFR); Tyrosine kinase inhibitor (TKI); EGFR T790M-positive non-small cell lung cancer (NSCLC)

Introduction

Among patients with advanced EGFR mutation-positive NSCLC, acquired *EGFR* T790M mutations are the most common cause of resistance after treatment with first- or second-generation tyrosine kinase inhibitors (TKIs).[1–4] The focus of recent research has been to identify third-generation agents that selectively inhibit *EGFR* and T790M resistance mutations, without inhibiting the wild-type receptor.[5] Efficient penetration of the blood-brain barrier is also important, as more than 50% of patients develop brain metastases within 5 years of diagnosis despite treatment with early generation EGFR TKIs.[6]

Lazertinib (YH25448, JNJ-73841937) is a potent, irreversible, brain-penetrant, mutant-selective, but wild-type–sparing, third-generation EGFR TKI.[7] In preclinical studies, lazertinib had improved activity compared with osimertinib in *EGFR* single- and double-mutant patient-

derived cell lines and good blood-brain barrier penetration and antitumor activity in a brain metastasis model.[7] In a first-in-human phase 1/2 study (LASER201), lazertinib had promising clinical activity and a manageable safety profile in patients with advanced *EGFR* mutation-positive NSCLC who had previously received EGFR TKIs.[8]

We present a preplanned integrated analysis of the efficacy and safety of lazertinib in patients with advanced T790M-positive NSCLC from the LASER201 study. We focus specifically on the 240 mg dose of lazertinib, which is currently being investigated in phase 3 trials and has recently been approved for use in South Korea.[9] Translational data to explore possible mechanisms of lazertinib resistance are also reported.

Materials and Methods

Study Design

This multicenter, open-label, phase 1/2 study was conducted to evaluate lazertinib in patients with advanced *EGFR* mutation-positive NSCLC; the methods have been described previously.[8] The study is composed of four parts (Supplementary Fig. 1). Part A (dose-escalation), part B (dose-expansion), and part C (dose-extension in first-line and second-line cohorts) were conducted at 17 centers in South Korea (ClinicalTrials.gov identifier: NCT03046992). Part D is being conducted outside Korea (ClinicalTrials.gov identifier: NCT04075396). This article focuses on a protocol-defined integrated analysis of patients from parts A, B, and C (second-line cohort).

The study was performed in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. The protocol and any amendments were approved by institutional review boards at participating centers. Patients provided written informed consent before study participation.

Patients

Patients were at least 20 years of age with histologically or cytologically confirmed NSCLC harboring an activating *EGFR* mutation (L858R, exon 19 deletion, G719X, or L861Q) and measurable disease at baseline. Patients had disease progression after prior therapy with an EGFR TKI. Central confirmation of T790M mutation status (part A) or T790M-positive status (parts B and C second-line cohort) in a tumor sample taken after progression was required using the cobas EGFR Mutation Test v2 (Roche Diagnostics International AG, Rotkreuz, Switzerland). Prior therapy with EGFR TKIs to treat T790M-positive NSCLC was not allowed.

Patients with asymptomatic brain metastasis were eligible, but patients with brain metastases and symptoms and/or requiring emergency treatment, symptomatic spinal cord compression, intracranial hemorrhage, central nervous system (CNS) complications requiring neurosurgical intervention, or leptomeningeal metastasis were excluded; steroid treatment was permitted if completed at least 2 weeks before initiating study treatment. Other exclusion criteria were a history of interstitial lung disease (ILD), clinically active or drug-induced ILD, radiation pneumonitis requiring steroid treatment, or any cardiovascular disease.

Treatment

Patients received oral lazertinib 20 to 320 mg (parts A and B) or 240 mg (part C) once daily continuously until disease progression, unacceptable toxicity, or other discontinuation criteria were met. Patients were permitted to continue therapy beyond progression if they derived ongoing clinical benefit as judged by the investigator.

In cases of grade greater than or equal to three or other unacceptable toxicities, treatment was interrupted, and supportive therapy was administered in accordance with local practice. If toxicity resolved to grade less than or equal to two within 21 days and the patient was having clinical benefit, treatment was restarted at the same or reduced dose. If toxicity did not resolve to grade less than or equal to two after 21 days, the patient was withdrawn from the study.

Assessments

Computed tomography or magnetic resonance imaging of the chest and abdomen was performed at baseline and every 6 weeks until disease progression and assessed by investigators and an independent central review (ICR) (Bioclinica, Princeton, NJ) using Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1.[10] After treatment discontinuation, patients completed a 28-day follow-up visit, with further follow-up in parts B and C every 6 weeks (or 12 wk after primary database lock) until death, loss to follow-up, or consent withdrawal. Brain computed tomography or magnetic resonance imaging at baseline was mandatory (parts B and C) or was performed if brain metastases were suspected (part A) and repeated every 6 weeks. Intracranial lesions were assessed by investigators and ICR using RECIST v1.1.[10] In patients with intracranial disease and progression of extracranial lesions only, assessments were continued for intracranial lesions every 6 weeks until progression.

Patients were monitored for adverse events until 28 days after the last dose of study treatment. Adverse events were graded according to the National Cancer

Institute Common Terminology Criteria for Adverse Events v4.03. Serial assessments of left ventricular ejection fraction (LVEF) by echocardiography or multiple-gated acquisition scan and electrocardiograms (read centrally by a cardiologist) were performed.

Cell-Free DNA Analysis

Patients from parts A, B, and C (second-line cohort) who received lazertinib doses greater than or equal to 120 mg were included in the cell-free DNA (cfDNA) analysis. Patients provided mandatory plasma samples (10–20 mL) for analysis of circulating tumor DNA (ctDNA) at baseline and at disease progression. cfDNA next-generation sequencing analysis was performed at Guardant Health, Inc. (Redwood City, CA), a clinical laboratory improvement amendments–certified, College of American Pathologists–accredited, New York State Department of Health–approved laboratory using Guardant360. Guardant360 is validated to detect single-nucleotide variants (SNVs) and indels in 74 genes, copy number alterations in 18 genes, and fusions in six genes, with reportable ranges of greater than or equal to 0.01%, greater than or equal to 0.01%, greater than or equal to 2.14 copies, and greater than or equal to two molecules, respectively, and detects high microsatellite instability as described previously.[11–13] Patients with detectable plasma *EGFR* Ex19del or L858R at screening who also had ctDNA results at progression were included for mechanism of resistance (MoR) analysis. Acquired, nonsynonymous, characterized mutations detected in a sample at disease progression, but not in the screening sample, were considered putative MoR, excluding aneuploidy and genes and/or alterations with unknown clinical or functional significance.

Endpoints

Primary endpoints were safety and objective response rate (ORR), defined as the percentage of patients with confirmed partial or complete responses according to RECIST v1.1 by ICR. Secondary efficacy endpoints included duration of response, disease control rate, progression-free survival, and overall survival. Intracranial outcomes (intracranial ORR, duration of intracranial response, and intracranial progression-free survival) were evaluated in patients with brain metastases. Definitions for all efficacy endpoints are provided in Supplementary Table 1.

Statistical Analysis

An integrated analysis of patients receiving lazertinib from parts A, B, and C (second-line cohort) was performed. Predefined subgroup analyses by T790M mutation status were performed for efficacy endpoints. Data cutoff for the present analysis was January 8, 2021.

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	Lazertinib 240 mg (N = 78)
Age, median (range), y	62 (33-82)
Race, no. (%)	
Asian	78 (100.0)
Sex, no. (%)	
Male	40 (51.3)
Female	38 (48.7)
ECOG performance status, no. (%)	
0	20 (25.6)
1	58 (74.4)
Tumor histological type, no. (%)	
Adenocarcinoma	74 (94.9)
Adenosquamous carcinoma	2 (2.6)
Other	2 (2.6)
Stage (AJCC seventh edition), no. (%)	
III	3 (3.8)
IV	75 (96.2)
Brain metastases at baseline,[a] no. (%)	40 (51.3)
EGFR mutation status,[b] no. (%)	
Positive	77 (98.7)
L858R	23 (29.5)
Exon19Del	53 (67.9)
L861Q	1 (1.3)
Negative	1 (1.3)
T790M status,[b] no. (%)	
Positive	76 (97.4)
Negative	2 (2.6)
Previous lines of systemic therapy, no. (%)	
1	50 (64.1)
≥2	28 (35.9)
Number of previous EGFR TKI, median (range), no. (%)	1 (1-3)
Previous EGFR TKI,[c] no. (%)	78 (100.0)
Afatinib	28 (35.9)
Erlotinib	16 (20.5)
Gefitinib	40 (51.3)

Note: Some totals do not add up to 100% owing to rounding.
[a]Investigator assessment.
[b]By central testing.
[c]Patients may have received more than one previous EGFR TKI.
AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; Exon19Del, exon 19 deletion; TKI, tyrosine kinase inhibitor.

The safety analysis population included all patients who received at least one dose of lazertinib. The evaluable for response population included patients in the safety population who had a baseline tumor assessment and centrally confirmed *EGFR* T790M mutation status. Data were analyzed by descriptive statistical methods. Time-to-event endpoints were evaluated using the Kaplan-Meier method. All analyses were performed using SAS v9.4 (SAS Institute Inc., Cary, NC).

Results

Patients and Treatment

Between February 15, 2017 and May 10, 2019, a total of 181 patients were enrolled in parts A, B, and C and

received lazertinib as second-line or later therapy. Of these, 78 patients received lazertinib 240 mg and were evaluable for response and safety (Supplementary Fig. 2). All patients were Asian and had received at least one EGFR TKI previously, most often gefitinib (51.3%) (Table 1). *EGFR* T790M was detected by central confirmation at baseline in 76 patients (97.4%).

At the time of data cutoff, the median duration of lazertinib treatment was 13.3 (range: 0.3–37.4) months. Mean (SD) relative dose intensity was 95.5% (9.6). Of 78 patients, 19 remained on treatment and 59 had discontinued therapy, most often because of disease progression (Supplementary Fig. 2).

Efficacy

T790M-Positive Subgroup. Among T790M-positive patients (N = 76, by central confirmation in the tissue), one (1.3%) had a complete response and 41 (53.9%) had partial responses by ICR with lazertinib 240 mg, giving an ORR of 55.3% (95% confidence interval [CI]: 44.1–66.4) (Table 2). The median duration of response was 17.7 months (95% CI: 9.9–not reached); 21 patients (27.6%) responded to lazertinib for 12 months or more. Disease control was achieved in 68 patients (89.5%; 95% CI: 82.6–96.4). Mean best percentage change in tumor size from baseline was −50.4% (SD = 30.5).

At data cutoff, 49 of 76 patients (64.5%) had progressed or died after a median follow-up of 20.8 months (interquartile range: 17.7–28.8). Median progression-free survival was 11.1 months (95% CI: 5.5–16.4) (Fig. 1*A*). Estimated progression-free survival rates at 6, 12, and 18 months were 59.3% (95% CI: 46.9–69.8), 48.0% (95% CI: 35.6–59.3), and 38.0% (95% CI: 26.3–49.6), respectively. CNS progression occurred in seven patients (9.2%); new CNS lesions were documented in two cases. Median overall survival was not reached after a median follow-up of 22.0 months (interquartile range: 15.4–28.3) (Fig. 1*B*). Estimated overall survival rates at 12 and 24 months were 89.5% (95% CI: 79.2–94.9) and 72.7% (95% CI: 58.2–82.9), respectively. Results by investigator assessment are presented in Supplementary Table 2.

T790M-Negative Subgroup. Among T790M-negative patients (n = 2), one had a confirmed partial response lasting for 30.4 months with lazertinib 240 mg by ICR assessment. The other patient had stable disease. Mean best percentage change in tumor size from baseline was −21.6% (SD = 45.8).

Intracranial Efficacy

Among T790M-positive patients with measurable intracranial lesions evaluated by ICR (n = 7), one (14.3%) had a complete intracranial response and five (71.4%) had partial responses with lazertinib 240 mg (Supplementary Table 3). The confirmed intracranial ORR was 85.7% (95% CI: 59.8%–100.0%), and intracranial disease control rate was 100.0% (95% CI: 100.0%–100.0%). Median duration of intracranial response was 15.1 months (95% CI: 2.8–not reached). Median intracranial progression-free survival was 26.0 months (95% CI: 5.4–not reached) (Fig. 1*C*).

Table 2. Efficacy Analysis in Patients With T790M-Positive Tumors by Independent Central Review

Parameter	Lazertinib 240 mg (N = 76)
Objective response rate, no. (%)	42 (55.3)
95% CI	44.1-66.4
Complete response	1 (1.3)
Partial response	41 (53.9)
Stable disease	26 (34.2)
Progressive disease	6 (7.9)
Not evaluable	2 (2.6)
Duration of response, mo	
Median (95% CI)	17.7 (9.9-NR)
Disease control rate, no. (%)	68 (89.5)
95% CI	82.6-96.4
Progression-free survival, mo	
Median (95% CI)	11.1 (5.5-16.4)
Progression-free survival rate (95% CI), %	
6 mo	59.3 (46.9-69.8)
12 mo	48.0 (35.6-59.3)
18 mo	38.0 (26.3-49.6)

CI, confidence interval; NR, not reached.

Safety

Among patients who received lazertinib 240 mg (N = 78), 76 (97.4%) reported at least one treatment-emergent adverse event that was deemed to be drug related by the investigator in 69 cases (88.5%) (Supplementary Table 4). The most common treatment-emergent adverse events of any grade were rash (37.2%), pruritus (34.6%), paresthesia (33.3%), headache (28.2%), and muscle spasms (28.2%); most events were mild to moderate in severity (Table 3). Grade greater than or equal to three treatment-emergent adverse events were reported in 27 patients (34.6%). Grade three events were considered to be drug related in 11 patients (14.1%). No drug-related grade four or five events were reported. Serious drug-related adverse events with lazertinib 240 mg occurred in three patients (3.8%; gastritis, n = 1; pneumonia, n = 1; pneumonitis, n = 1). Apart from one case of pneumonitis, there were no other reports of ILD with lazertinib 240 mg. Drug-related QT prolongation (grade 1) was reported in three patients (3.8%), but no patient had a Fridericia's-

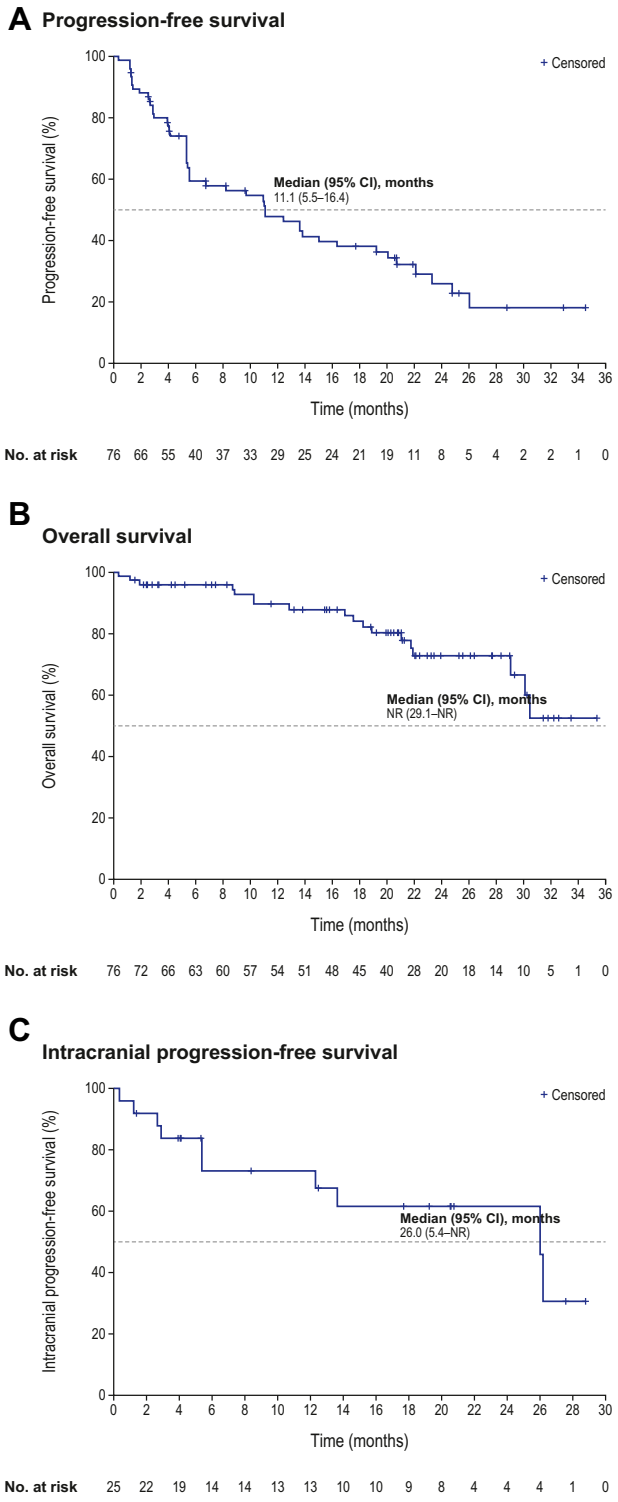

Figure 1. Progression-free survival, overall survival, and intracranial progression-free survival in patients with T790M-positive tumors assessed by independent central review. CI, confidence interval; NR, not reached.

corrected QT interval exceeding 500 msec or Fridericia's-corrected QT interval increase from baseline exceeding 60 msec. No clinically meaningful changes in LVEF were reported. Dose reductions, dose interruptions, and drug withdrawal because of adverse events were required in 13 (16.7%), 17 (21.8%), and six (7.7%) patients receiving lazertinib 240 mg, respectively.

ctDNA Analysis

Among 79 patients with baseline and progression plasma samples available for next-generation sequencing analysis (Supplementary Fig. 3), the median plasma volume provided was 2.1 mL (range: 1–4 mL) and median cfDNA extracted was 20.6 ng (range: 2.9–507.5 ng). All screening samples were successfully sequenced; two progression samples failed. Of 79 screening samples successfully sequenced, ctDNA was detected in 75 (94.9%). Of 77 progression samples successfully sequenced, ctDNA was detected in 69 (89.6%).

Among patients with ctDNA detected, *EGFR* Ex19del or L858R was detected at screening in 63 of 75 patients (84.0%). Patients with no *EGFR* driver detected at both screening and progression (n = 7) had low maximum variant allele fraction (median = 0.17%), indicating low tumor shedding. Of these seven patients, six had no putative MoR at progression; one had both T790M and C797S at progression.

Of the 63 patients with *EGFR* Ex19del or L858R detected at screening, 56 (89%) had ctDNA detected at progression and were included in the MoR analysis (Supplementary Fig. 3). *EGFR* T790M was detected at screening in 45 of 56 patients (80.4%). Samples without T790M at screening had lower median cfDNA input (18.3 ng versus 23.7 ng; two-sided *t* test $p = 0.09$) and median maximum variant allele fraction (1.0% versus 8.2%; $p = 0.13$) than those with T790M detected.

Acquired Putative Mechanisms of Resistance

Genomic modifiers of response by individual patient are found in Figure 2, and details of all alterations detected at screening and progression by individual patient are presented in Supplementary Table 5. At progression, *EGFR* T790M was detected in 13 of 56 patients (23.2%), 12 of whom also had T790M detected at screening. In the remaining 33 of 45 patients (73.3%) with T790M present at screening, T790M was not detected at progression. The most frequent acquired putative MoRs were *MET* focal amplifications and *PIK3CA* mutations, each detected in five of 56 patients (8.9%) at progression. Other putative off-target MoR were found in 28.6% (16 of 56) of patients, including the following: *BRAF* 5.4% (3 of 56), *GNAS* 5.4% (3 of 56), *ERBB2* 3.6% (2 of 56), *KRAS* 3.6% (2 of 56), and *ARID1A* 3.6% (2 of 56).

In the 13 patients with T790M at progression, on-target acquired MoR (*EGFR* C797S/G, T854A,

Table 3. Treatment-Emergent Adverse Events (>10% of Patients)

	Lazertinib 240 mg (N = 78)			
Adverse Event	All Grades	Grade 3	Grade 4	Grade 5
Patient with at least one TEAE	76 (97.4)	21 (26.9)	3 (3.8)	3 (3.8)
Rash	29 (37.2)	1 (1.3)	0	0
Pruritus	27 (34.6)	0	0	0
Paresthesia	26 (33.3)	2 (2.6)	0	0
Headache	22 (28.2)	0	0	0
Muscle spasms	22 (28.2)	0	0	0
Diarrhea	21 (26.9)	1 (1.3)	0	0
Decreased appetite	20 (25.6)	0	0	0
Paronychia	16 (20.5)	1 (1.3)	0	0
Cough	16 (20.5)	0	0	0
Constipation	15 (19.2)	0	0	0
Nausea	13 (16.7)	0	0	0
Fatigue	12 (15.4)	0	0	0
Aspartate aminotransferase increased	11 (14.1)	0	0	0
Dizziness	10 (12.8)	0	0	0
Alanine aminotransferase increased	10 (12.8)	0	0	0
Myalgia	10 (12.8)	0	0	0
Dyspepsia	9 (11.5)	0	0	0
Stomatitis	9 (11.5)	0	0	0
Blood creatinine increased	9 (11.5)	0	0	0
Dry skin	8 (10.3)	0	0	0
Vomiting	8 (10.3)	1 (1.3)	0	0
Pulmonary embolism	8 (10.3)	1 (1.3)	1 (1.3)	1 (1.3)

Note: Data expressed as number of patients (%).
TEAE, treatment-emergent adverse event.

amplification) were detected in seven patients (53.8%). All C797S/G mutations (5 of 5) were in cis with T790M. Putative off-target MoR were also found among these 13 patients in *MET* 23.0% (3 of 13), *KRAS* 15.4% (2 of 13), *GNAS* 15.4% (2 of 13), *ERBB2* 7.7% (1 of 13), *PIK3CA* 7.7% (1 of 13), *CCND1* 7.7% (1 of 13), and *CCNE1* 7.7% (1 of 13).

In the 33 patients with T790M loss, acquired *PIK3CA* 9.1% (3 of 33), *BRAF* 9.1% (3 of 33), *MET* 6.0% (2 of 33), *ERBB2* 3.0% (1 of 33), *FGFR1* 3.0% (1 of 33), *BRCA2* 3.0% (1 of 33), and *GNAS* 3.0% (1 of 33) alterations were found.

Discussion

In this integrated analysis of a phase 1/2 study, lazertinib 240 mg was associated with a response rate of 55% in patients with advanced T790M-positive NSCLC who had progressed on prior therapy with first-generation (erlotinib, gefitinib) or second-generation (afatinib) TKIs. All patients were positive for a sensitizing *EGFR* mutation and T790M at baseline. The median duration of response was approximately 18 months, with a median progression-free survival of 11.1 months. This analysis provides a more robust estimate of the efficacy of lazertinib 240 mg in patients with T790M-positive NSCLC after an additional 2 years of follow-up, and the results are consistent with the initial analysis of this study (ORR = 57% across all lazertinib doses).[8] These observations are also in line with phase 2 studies of osimertinib in a similar patient population (ORR, 61%–70%; median progression-free survival, 9.6–12.3 mo).[14–16] At data cutoff, the analysis of overall survival was not mature, and more than three-quarters of the patients remain alive after almost 2 years of follow-up.

Patients with asymptomatic or stable brain metastases were eligible to enroll in the present study. Although patient numbers were small, lazertinib was found to have promising activity with a confirmed intracranial ORR of 86% in patients with measurable brain metastasis according to central review and a median intracranial progression-free survival of more than 2 years, which is remarkable. These findings are supported by preclinical research, which revealed that lazertinib inhibited intracranial tumor growth in an *EGFR*-mutant brain metastasis model and achieved good penetration of the blood-brain barrier with a brain-to-plasma ratio of 0.9 and intracranial tumor-to-plasma ratio of 7.0.[7] Lazertinib is not a substrate for BCRP and only a weak substrate of MDR1 (P-glycoprotein) according to in vitro assays,[7] suggesting it may be minimally affected by efflux transporters in the blood-brain barrier.

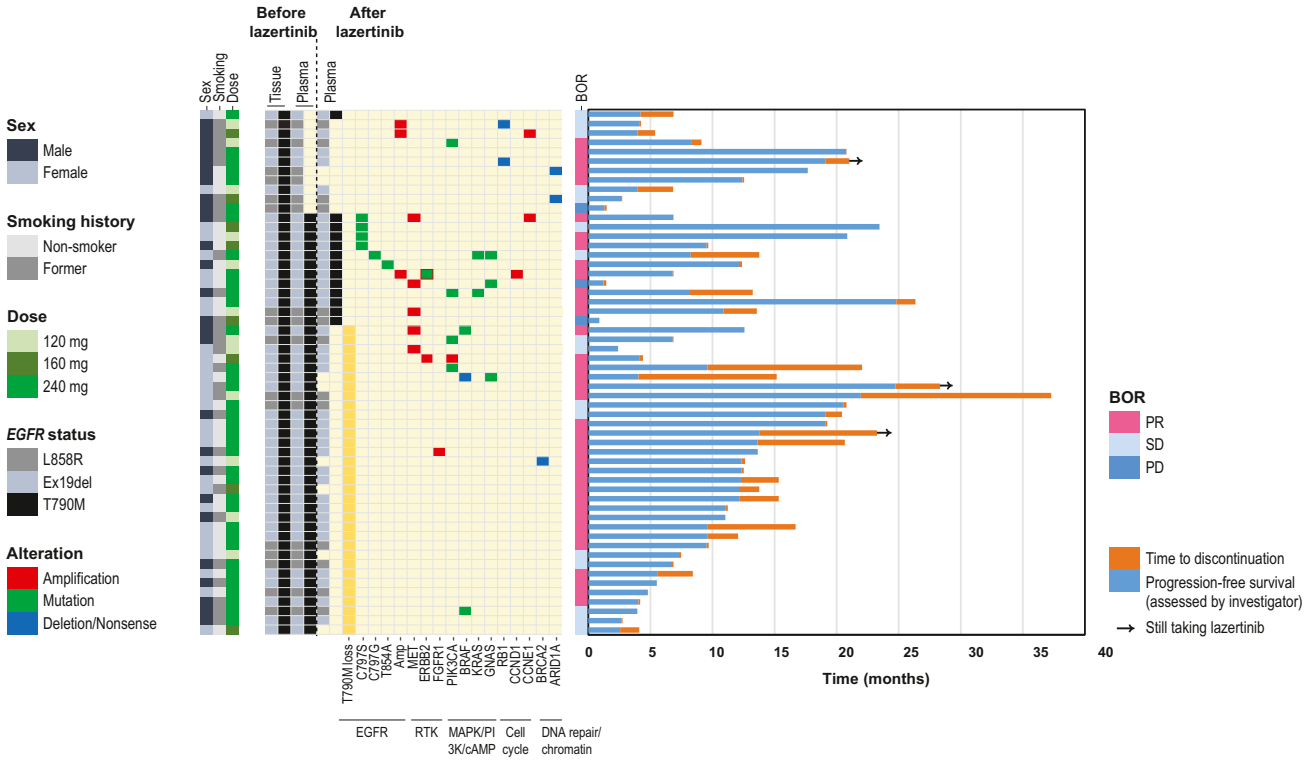

Figure 2. Genomic modifiers of response by treatment duration: mechanism of resistance analysis (n = 56). Note: The alterations exclude aneuploid amplifications, synonymous alterations, suspected clonal hematopoiesis, and SNVs/indels of unknown functional/clinical significance in *MET*, *EGFR*, *MAPK3*, *ARID1A*, *ERBB2*, *NOTCH1*, *BRAF*, *CCNE1*, *TP53*, *APC*, *PIK3CA*, *RHOA*, *ATM*, *KRAS*, *MTOR*, *FGFR2*, *PTEN*, *GNAS*, *ALK*, *NTRK1*, *FGFR1*, *CCND1*, *RB1*, *AR*, *FBXW7*, *BRCA2*, *DDR2*, and *CDK12*. BOR, best overall response; Indels, insertion and deletion; PD, progressive disease; PR, partial response; RTK, receptor tyrosine kinase; SD, stable disease; SNV, single-nucleotide variant.

Inhibition of wild-type EGFR in normal epithelial cells can lead to toxicities of the skin (rash, paronychia) and gastrointestinal tract (diarrhea). These events are typically dose limiting, and their occurrence and severity are associated with potency of EGFR inhibition.[17] ILD and liver function abnormalities are less common, but potentially serious, consequences of EGFR inhibition.[17] The most common adverse events with lazertinib 240 mg were skin toxicities (rash, pruritus) and paresthesia. Notably, no dose-limiting toxicities were documented with lazertinib at doses of up to 320 mg,[8] and toxicities with the 240 mg dose were typically mild or moderate in severity. With the exception of one case of pneumonitis, there were no reports of ILD with lazertinib 240 mg. The risk of QTc prolongation or reduced LVEF with lazertinib 240 mg was also low. This is consistent with a more detailed cardiac safety assessment, which suggested no or minimal cardiac safety risk with lazertinib.[18]

In the analysis of plasma ctDNA from patients receiving lazertinib, the distribution of acquired resistance mechanisms was consistent with previous studies of osimertinib.[19–21] The major mechanism was loss of *EGFR* T790M. Alternative resistance mechanisms involving receptor tyrosine kinase amplification, the MAPK-PI3K pathway, and cell cycle or DNA repair genes occurred in the analyzed groups regardless of loss or maintenance of *EGFR* T790M, but most patients with *EGFR* T790M loss did not seem to have other established mechanisms of resistance. Among the group with alternative resistance mechanisms, there was a trend toward shorter progression-free survival or time to discontinuation (data not shown).

We acknowledge that further clinical experience with lazertinib 240 mg is required in a larger number of patients and in populations outside of Korea. Two international phase 3 trials of lazertinib are currently in progress. LASER301 is comparing lazertinib with gefitinib in the first-line treatment of advanced *EGFR* mutation-positive NSCLC (ClinicalTrials.gov Identifier: NCT04248829), and MARIPOSA is comparing lazertinib alone or in combination with amivantamab, an EGFR-MET bispecific antibody, versus osimertinib as first-line therapy in approximately 1000 patients with advanced *EGFR*-mutated NSCLC (Clinicaltrials.gov identifier: NCT04487080).[22] We suggest that our findings are likely to be generalizable to other populations with advanced T790M-positive NSCLC, but the relevance of our results

after previous use of osimertinib or other third-generation agents is unknown.

In conclusion, this analysis revealed that lazertinib 240 mg/d had durable antitumor efficacy, with clinically meaningful activity against brain metastases in patients with advanced or metastatic T790M-positive NSCLC who had previously received EGFR TKIs. Lazertinib had a mild and manageable safety profile, with limited skin and gastrointestinal toxicities.

CrediT Authorship Contribution Statement

Byoung Chul Cho: Had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Byoung Chul Cho, Myung-Ju Ahn, Ji-Youn Han, Sang-We Kim, Ki Hyeong Lee, Dong-Wan Kim: Conceptualization, Methodology.

All authors: Investigation, Writing – review & editing.

Ji Ah Kang, NaMi Lee, Mi-Jung Kwon, Carin Espenschied, Arielle Yablonovitch: Writing – original draft.

Mi-Jung Kwon, Carin Espenschied: Visualization.

NaMi Lee, Arielle Yablonovitch: Formal analysis.

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Data Sharing Statement

Deidentified participant data will be made available when all endpoints of all trial 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.2021.11.025].

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