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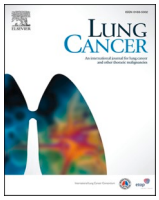

Lazertinib as a frontline treatment in patients with *EGFR*-mutated advanced non-small cell lung cancer: Long-term follow-up results from LASER201

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ABSTRACT

Objective: This analysis of the first-line cohort of LASER201 study evaluated the efficacy and safety of lazertinib 240 mg as a frontline therapy for epidermal growth factor receptor (*EGFR*)-mutated locally advanced or metastatic non–small cell lung cancer (NSCLC).

Methods: A total of 43 patients, with *EGFR* mutation-positive (Exon19Del, n = 24; L858R, n = 18; G719X, n = 1) locally advanced or metastatic NSCLC who had not previously received EGFR tyrosine kinase inhibitor (EGFR TKI) therapy, received once-daily lazertinib 240 mg. *EGFR* mutation status was confirmed by local or central testing. The primary endpoint was objective response rate (ORR) assessed by blinded independent central review. Secondary efficacy endpoints included duration of response (DoR), disease control rate (DCR), progression-free survival (PFS), tumor shrinkage, and overall survival (OS).

Results: At the primary data cut-off (DCO; January 8, 2021), the ORR was 70 % (95 % confidence interval [CI]: 56.0–83.5), DCR was 86 % (95 % CI: 75.7–96.4) and the median DoR was 23.5 (95 % CI: 12.5–not reached) months. The median PFS was 24.6 (95 % CI: 12.2–30.2) months. At the final DCO (March 30, 2023), the median OS was not estimable and the median follow-up duration for OS was 55.2 [95 % CI: 22.8–55.7] months. OS rates at 36 months and 54 months were 66 % (95 % CI: 47.5–79.3 %) and 55 % (95 % CI: 36.6–70.7 %), respectively. The most commonly reported TEAEs were rash (54 %), diarrhea (47 %), pruritus (35 %), and paresthesia (35 %). No drug-related rash or pruritus TEAEs of grade 3 or higher were reported. Diarrhea and paresthesia of grade 3 or higher were reported in 3 (7 %) and 1 (2 %) patients, respectively.

Conclusion: This analysis demonstrated long-term clinical benefit with lazertinib 240 mg in patients with *EGFR*-mutated NSCLC who had not previously received EGFR TKIs. The safety profile for lazertinib was tolerable and consistent with that previously reported.

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1. Introduction

Targeted treatment with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) is the current standard of care for *EGFR*-mutated advanced/metastatic non-small cell lung cancer (NSCLC), which typically exhibits a five-year survival rate of 25–30 % [1,2]. Notably, in Asia, nearly half of the patients diagnosed with lung adenocarcinoma harbor classical activating *EGFR* mutations (exon 19 deletions [Ex19Del] and L858R point mutation in exon 21 [3]. Patients with these mutations were found to exhibit favorable clinical responses to first-generation EGFR TKIs [4]. Consequently, these inhibitors have been widely used as the first-line therapy for *EGFR*-mutated advanced/metastatic NSCLC [5], resulting in a median progression-free survival (PFS) of approximately 9–13 months [6]. However, a significant challenge emerges as nearly all patients who initially respond to first- or second-generation EGFR TKIs eventually develop resistance [6]. To address this, third-generation EGFR TKIs were developed, aiming to counteract acquired resistance following first- and second-generation EGFR TKI therapy, primarily attributed to T790M mutation [7]. Currently, clinical practice guidelines from the European Society for Medical Oncology, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network recommend a third-generation EGFR TKI (osimertinib) as the preferred first-line treatment option [8–10]. Moreover, half of patients with NSCLC harboring *EGFR* mutations develop brain metastasis (BM) within 3 years of diagnosis [11]. The challenge of rapid BM development, together with the limited blood–brain barrier (BBB) penetration of first-generation EGFR TKIs, further motivated the development of next-generation EGFR TKIs. These newer agents exhibit enhanced BBB penetration and improved clinical efficacy in NSCLC patients with brain metastases [12,13].

Lazertinib is a potent irreversible, brain-penetrant, third-generation EGFR TKI exhibiting high selectivity for both activating and T790M *EGFR* resistance mutations while reducing the common drug-related treatment-emergent adverse events (TEAEs) (such as rash and diarrhea) associated with inhibition of wild-type (WT) *EGFR* activity [14,15]. Clinical trials, including the first-in-human Phase 1/2 study (LASER201) [14], the Phase 3 LASER301 study [16], and the Phase 3 MARIPOSA study [17], have provided evidence of the clinical efficacy and tolerable safety profile of lazertinib. As a first-line therapy in patients with *EGFR*-mutated NSCLC, lazertinib was associated with a significantly longer median PFS than gefitinib [16]. Lazertinib has received approval in Korea for use in both first-line and subsequent lines of therapy for patients with locally advanced or metastatic *EGFR*-mutant NSCLC [18]. Furthermore, the activity of lazertinib within the central nervous system (CNS) is well established through clinical and preclinical investigations [14,15]. Unlike osimertinib, lazertinib is not a substrate of breast cancer resistance protein (BCRP), and only a weak substrate of multidrug resistance protein 1 (MDR1) [19,20]. These transport proteins are responsible for drug efflux at the BBB, and this difference may contribute to lazertinib's anti-tumor activity within the CNS [15].

This analysis of the first-line cohort within LASER201 provides additional insights into the long-term clinical outcomes associated with lazertinib as front-line therapy, complementing the recently published data from the LASER301 Phase 3 study.

2. Materials and methods

2.1. Study design

The LASER201 multicenter, open-label, Phase 1/2 study evaluated lazertinib therapy in patients with locally advanced or metastatic *EGFR*-mutated NSCLC with or without stable brain lesions (ClinicalTrials.gov identifier: NCT03046992). The overall study design and methods have been described previously [21]. The present analysis focuses on the first-line cohort of patients in LASER201 (Part C, dose extension cohort; **Supplementary** Fig. 1). The study was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The protocol and its amendments were approved by the institutional review boards of participating centers. Patients provided written informed consent before study participation.

2.2. Patients

Eligible patients were 20 years of age or older, diagnosed with locally advanced or metastatic NSCLC, had not previously received treatment for advanced disease, had not previously received EGFR TKIs, and were eligible to receive first-line treatment with lazertinib. Local or central confirmation of an activating *EGFR* mutation (Ex19Del, L858R, G719X, or L861Q) was required. Central testing of *EGFR* mutation status was performed using the cobas EGFR mutation test (version 2; Roche, Basel, Switzerland). Patients with brain metastases were eligible if their condition was neurologically stable; they had to have at least one measurable extracranial lesion and be suitable for repeated measurement during the study period. In addition to these criteria, patients who had received radiotherapy with a wide field within 4 weeks or radiotherapy with a limited field within 1 week prior to the first dose of study treatment were not eligible. Patients who were administered any cytotoxic chemotherapy or other anticancer drugs for the treatment of advanced NSCLC from a previous treatment regimen within 14 days prior to the first dose of study treatment were not eligible for this study. The tumor tissue sample collected prior to initiation of the study treatment had to be submitted for central confirmation.

2.3. Treatment

Patients received 240 mg of oral lazertinib once daily continuously until disease progression, occurrence of unacceptable toxicity, death, or other discontinuation criteria were met (**Supplementary** Fig. 2) [14,21]. Patients were allowed to continue the treatment beyond progression if they were experiencing clinical benefit as judged by the investigator. According to the general dose modification guidelines for this study, if a patient experienced any Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 toxicity or unacceptable toxicity not attributable to the disease, dosing was temporarily interrupted and supportive therapy was administered in accordance with local practice. If the toxicity resolved or reverted to grade 2 or lower within 21 days of onset and the patient was showing clinical benefit, lazertinib treatment could be restarted at the same dose or one dose level lower after appropriate discussion and agreement with the sponsor study physician or delegated study physician. If the toxicity did not resolve to grade ≤ 2 after 21 days, the patient was withdrawn from the study.

2.4. Assessments and endpoints

In this single-arm study, disease response was primarily assessed by blinded independent central review (BICR) using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients were followed up every 6 weeks until death, loss to follow-up, or consent withdrawal. In patients with intracranial disease and progression of extra-cranial lesions, assessments were continued for intracranial lesions every 6 weeks until intracranial progression.

After the primary database lock, patients were followed up every 12 weeks for survival. Unless patients withdrew consent, safety monitoring continued until 28 days after the last dose of study treatment. Adverse events (AEs) were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, CTCAE version 4.03. In the event of serious or study drug-related toxicities, patients were followed until AE resolution or stabilization. The primary endpoint for Part C (dose extension) was BICR-assessed objective response rate (ORR), defined as the percentage of patients with confirmed partial or complete responses. Secondary efficacy endpoints included duration of

response (DoR), disease control rate (DCR), PFS, tumor shrinkage, and overall survival (OS).

2.5. Statistical analysis

The data cut-off date for the analysis of the primary efficacy endpoint was January 8, 2021. For analyses of overall survival and safety, the data cut-off date was March 30, 2023. Time-to-event endpoints were evaluated using the Kaplan-Meier method. All analyses were performed using SAS v9.4 (SAS Institute Inc., Cary, NC). Analyses were conducted in NSCLC patients harboring locally or centrally confirmed activating *EGFR* mutations (Ex19Del, L858R, G719X, or L861Q) at baseline (n = 43), and additionally conducted in 35 patients who had centrally confirmed classical *EGFR* mutations (Ex19Del or L858R). Intracranial response and intracranial PFS (iPFS) were assessed in patients who had BM at baseline.

3. Results

3.1. Patients

All 43 patients with locally/centrally confirmed *EGFR*-mutated NSCLC received lazertinib 240 mg once daily. Patient demographics and other baseline characteristics are presented in Table 1. At the final data cut-off (March 30, 2023), 10 of 43 patients were still receiving study treatment.

At the final data cut-off, 33 (77 %) patients had discontinued study treatment: 23 (53 %) as a result of progressive disease, seven (16 %) as a result of AEs, and one (2 %) as a result of death, one (2 %) as a result of the physician's decision and one (2 %) as a result of withdrawal of consent (Supplementary Table 1). The median (Q1, Q3) duration of RECIST follow-up at primary data cut-off was 28.8 (17.8, 28.9) months and median duration of OS follow-up at the final data cut-off was 55.2 (95 % CI: 22.8–55.7) months. The median (Q1, Q3) total treatment duration was 16.7 (5.5, 54.5) months.

Table 1
Patient demographics and clinical characteristics at baseline.

Characteristics	Lazertinib 240 mg (N = 43)
Age in years, median (range)	61 (45, 82)
Male, n (%)	20 (47)
ECOG performance status, n (%)	
0	6 (14)
1	37 (86)
Adenocarcinoma, n (%)	42 (98)
AJCC stage, n (%)	
IIIB	2 (5)
IV	41 (95)
Smoking status, n (%)	
Never	21(49)
Former	18 (42)
Current	4 (9)
Brain metastasis at baseline, n (%)	22 (51)
EGFR mutation status (local or central[a] testing), n (%)	
Ex19Del[b]	24 (56)
L858R	18 (42)
G719X	1 (2)
T790M positive, n (%)	2 (5)
Prior lines of systemic chemotherapy, n (%)	
1	2 (5)
≥2	2 (5)
Previous brain radiotherapy, n (%)	5 (12)

ECOG: Eastern Cooperative Oncology Group; AJCC: American Joint Committee on Cancer, 7th edition
Percentages are calculated based on the number of patients in the safety analysis population who received at least one dose of lazertinib; Note: Some totals do not add up to 100% owing to rounding.
[a] Central testing was not performed in 1 patient, and central testing results were negative (n = 4) or unknown (n = 2) in 6 patients (14 %), attributed to inadequate quantity or quality of tissue samples.
[b] One patient had both Ex19Del and Exon 20 insertion mutations.

3.2. Efficacy

Efficacy analysis was conducted on 43 patients harboring an activating *EGFR* mutation (Ex19Del, L858R, or G719X). A separate analysis focusing on a subset of 35 patients who had centrally confirmed classical *EGFR* mutations (Ex19Del or L858R) was also conducted. Table 2 summarizes the results for the anti-tumor efficacy endpoints. The confirmed ORR was 70 % (95 % CI: 56.0–83.5 %), including 14 % who achieved complete response and 56 % who achieved partial response. The disease control rate was 86 % (95 % CI: 75.7–96.4 %) and the median DoR was 23.5 (95 % CI: 12.5–NR) months. For BICR-assessed tumor shrinkage, the median (range) of best percent change from baseline was −41 % (-100–85 %). The median PFS was 24.6 (95 % CI: 12.2–30.2) months (Fig. 1A), which was consistent with results for the subset of patients harboring a centrally confirmed classical *EGFR* mutation (Fig. 1B) and for investigator-assessed PFS (**Supplementary Fig. 2**).

Table 3 summarizes the OS results. The median OS was not reached (Fig. 2A). OS rates at 36 months and 54 months were 66 % (95 % CI: 47.5–79.3 %) and 55 % (95 % CI: 36.6–70.7 %), respectively. These results were consistent with OS in the subset of patients with a centrally confirmed classical *EGFR* mutation (Fig. 2B).

In the subset of patients with BM at baseline, the median OS was not reached (95 % CI: 35.9–NR) months (**Supplementary Fig. 3**). The median iPFS was not reached in patients with BM at baseline based on either BICR or investigator assessment: BICR, NR (95 % CI: 4.1–NR)

Table 2
Anti-tumor efficacy by blinded independent central review.

	Patients harboring an activating *EGFR* mutation (Ex19Del, L858R, or G719X) (N = 43)	Patients harboring a centrally confirmed classical *EGFR* mutation (Ex19Del, L858R) (N = 35)
Objective response rate (ORR)[a]		
n (%), [95 % CI]	30 (70), [56.0–83.5]	27 (77), [63.2–91.1]
Complete response, n (%)	6 (14)	6 (17)
Partial response, n (%)	24 (56)	21 (60)
Disease control rate (DCR)[b]		
n (%), [95 % CI]	37 (86), [75.7–96.4]	33 (94), [86.6–100]
Duration of response (DoR)[c]		
months, median [95 % CI][d]	23.5 [12.5–NR]	23.5 [11.0–NR]
Progression-free survival (PFS)[e]		
Number of event (s), n (%)	23 (53)	18 (51)
months, median [95 % CI][d]	24.6 [12.2–30.2]	24.9 [13.6–NR]

All analyses were conducted using the primary data cut-off date (January 8, 2021).
CI, confidence interval; DCO, data cut-off; NR, not reached. Percentages are calculated based on the number of evaluable patients. Includes patients who received at least one dose of lazertinib 240 mg and had a baseline RECIST 1.1 assessment.
[a] Objective response rate is the proportion of subjects who have a confirmed best overall response of complete response or partial response.
[b] Disease control rate is the proportion of subjects who have a confirmed best overall response of complete response or partial response or stable disease.
[c] Duration of response is confirmed CR or PR until objective tumor progression or death, whichever occurs first.
[d] Median and 95 % CI are calculated using Kaplan-Meier estimate.
[e] Progression free survival is measured from the first lazertinib dose until objective tumor progression or death, whichever occurs first.

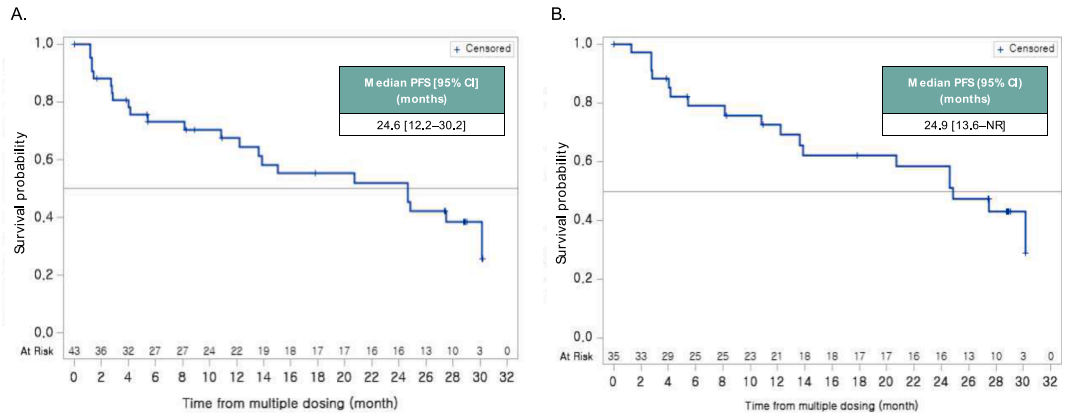

Fig.1. Progression-free survival (PFS) assessed by blinded independent central review. A. PFS in patients harboring an activating *EGFR* mutation (Ex19Del, L858R, or G719X) (n = 43); B. PFS in patients harboring a centrally confirmed classical *EGFR* mutation (Ex19Del, L858R) (n = 35). Data cut-off: January 8, 2021. PFS: progression-free survival; CI: confidence interval; NR: not reached.

Table 3
Overall survival.

	Patients harboring an activating *EGFR* mutation (Ex19Del, L858R, or G719X) (N = 43)	Patients harboring a centrally confirmed classical *EGFR* mutation (Ex19Del, L858R) (N = 35)
Death(s), n(%)	15 (35)	12 (34)
Overall survival[a]		
months, median [95 % CI][b]	NR [35.9–NR]	NR [38.3–NR]
Overall survival rate [95 % CI]		
at 12 months	82 [66.5–91.2]	89 [72.4–95.5]
at 24 months	79 [62.5–89.1]	85 [67.5–93.5]
at 36 months	66 [47.5–79.3]	71 [51.2–83.8]
at 42 months	59 [40.3–73.7]	63 [43.4–78.0]
at 54 months	55 [36.6–70.7]	59 [39.3–74.8]

All analyses were conducted using the final data cut-off date (March 30, 2023). CI, confidence interval; NR, not reached. Percentages are calculated based on the number of evaluable patients. Includes patients who received at least one dose of lazertinib 240 mg had a baseline RECIST 1.1 assessment.

[a] The interval between the date of first dose and the date of patient death due to any cause.

[b] Median and 95 % CI are calculated using Kaplan-Meier estimate.

months; investigator-assessed, NR (95 % CI: 18.0–NR) months (Supplementary Fig. 4).

3.3. Safety

The safety analysis set consisted of patients who received at least one dose of lazertinib. All patients reported at least one treatment-emergent adverse event (TEAE) (Table 4). Drug-related TEAEs were reported in 41 (95 %) patients. Grade ≥ 3 TEAEs were reported in 22 (51 %) patients. Grade ≥ 3 TEAEs that were considered drug-related were reported in six (14 %) patients (Supplementary Table 2). Serious drug-related TEAEs were reported in two (5 %) patients; one patient reported diarrhea and one reported acute pyelonephritis. TEAEs leading to dose reduction occurred in 10 (23 %) patients, and TEAEs leading to temporary drug interruption occurred in 13 (30 %) patients. Seven (16 %) patients had TEAEs leading to permanent drug discontinuation. Of these, paresthesia and rash erythematous, in one patient each, were considered possibly related to the study drug. No drug-related TEAEs led to death.

The most commonly reported TEAEs were rash (23 patients; 54 %), followed by diarrhea (20 patients; 47 %), pruritus (20 patients; 47 %) and paresthesia (15 patients; 35 %). There were no cases of interstitial lung disease (ILD). Pneumonitis (not drug-related) was reported in one patient (2 %). No clinically relevant cardiac events were reported, including significant QT prolongation or decrease in left ventricular ejection fraction (LVEF).

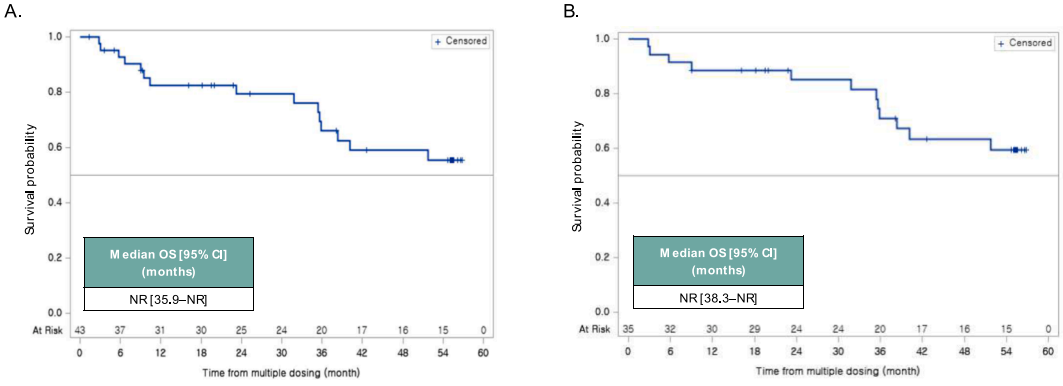

Fig.2. Overall survival in A. Patients harboring an activating *EGFR* mutation (Ex19Del, L858R, or G719X) (n = 43); B. Patients harboring a centrally confirmed classical *EGFR* mutation (Ex19Del, L858R) (n = 35). Data cut-off: March 30, 2023. OS: overall survival; CI: confidence interval; NR: not reached.

Table 4
Summary of adverse events.

	Lazertinib 240 mg (N = 43)	
At least one TEAE	43 (100)	
Drug-related TEAEs	41 (95)	
Serious TEAEs	16 (37)	
Drug-related serious TEAEs	2 (5)	
TEAEs of grade ≥ 3	22 (51)	
Drug-related TEAEs of grade ≥ 3	6 (14)	
TEAEs leading to death	1 (2)	
Drug-related TEAEs leading to death	0	
TEAEs leading to dose reduction	10 (23)	
TEAEs leading to temporary drug interruption	13 (30)	
TEAEs leading to permanent drug withdrawal	7 (16)	
TEAEs with frequency ≥ 10 % by PT	Any grade	Grade ≥ 3
Rash	23 (54)	0
Diarrhea	20 (47)	3 (7)
Pruritus	20 (47)	0
Paresthesia	15 (35)	1 (2)
Decreased appetite	14 (33)	2 (5)
Alanine aminotransferase increased	12 (28)	2 (5)
Constipation	12 (28)	0
Muscle spasms	11 (26)	0
Aspartate aminotransferase increased	10 (23)	1 (2)
Insomnia	9 (21)	0
Nausea	9 (21)	0
Paronychia	9 (21)	0
Arthralgia	8 (19)	0
Asthenia	8 (19)	3 (7)
Cough	8 (19)	0
Stomatitis	8 (19)	0
Dizziness	7 (16)	0
Headache	7 (16)	0
Fatigue	6 (14)	1 (2)
Upper respiratory tract infection	6 (14)	0
Dermatitis acneiform	5 (12)	0
Dyspepsia	5 (12)	0
Productive cough	5 (12)	0
Pyrexia	5 (12)	0

TEAE, treatment-emergent adverse event; PT, preferred term.
Percentages are calculated based on the number of evaluable patients. If a subject had multiple occurrences of an adverse event (AE), the subject is presented only once in the respective subject count column (n) for the corresponding AE.
Adverse events were coded using MedDRA version 26.0. Data cut-off date: March 30, 2023.

4. Discussion

This analysis of the first-line cohort of LASER201 focused on the long-term efficacy and safety of lazertinib as front-line therapy in locally advanced or metastatic NSCLC patients with *EGFR* mutations. The high ORR (≥70 %) included some complete responses and the disease control rate exceeded 85 %. Patients treated with lazertinib as front-line therapy experienced a long duration of response (median DoR was 23.5 months), and the median progression-free survival (PFS) exceeded two years. These results align with recent findings from the Phase 3 LASER301 trial, which evaluated lazertinib as front-line treatment and reported an ORR of 76 % (95 % CI: 69.4–81.8) and a median PFS of 20.6 months (95 % CI: 17.8–26.1) [16]. The only other approved third-generation EGFR TKI, osimertinib, showed median PFS of 18.9 months (95 % CI: 15.2–21.4) in the first-line setting, which is similar to that reported for lazertinib in this analysis [22]. With a median PFS of 9–13 months reported with the first- and second-generation EGFR TKIs, this analysis along with the LASER301 trial demonstrated that lazertinib has meaningful clinical activity in patients with locally advanced/metastatic *EGFR*-mutated NSCLC who had not previously been treated with EGFR TKIs [6].

Patients in the first-line cohort of LASER201 continued lazertinib treatment for an average of 25 months, demonstrating sustained benefit from lazertinib for two years or more. Although direct comparisons are not appropriate due to the different study designs, we note that the 3-year survival rate of 66 % in this cohort appears comparable with first-line osimertinib in the Phase 3 FLAURA trial (3-year survival rate: 54 %) [23]. Similarly, the interim data (18-month OS rate) from the larger Phase 3 LASER301 trial also aligns with that reported in the present analysis [16]. This analysis is currently the first to report longer-term outcomes (55 months of follow-up) with lazertinib as first-line therapy. With a 54-month overall survival rate of 55 % (95 % CI: 36.6–70.7 %), these data add to existing evidence for lazertinib by highlighting the possibility of long-term efficacy in patients with advanced/metastatic *EGFR*-mutated NSCLC.

Brain metastasis is commonly seen in patients with *EGFR*-mutated NSCLC, with approximately 25 % of patients presenting with BM at initial diagnosis and approximately half of patients developing BM within three years of receiving targeted therapy [13]. The LASER201 first-line cohort included 22 patients who had neurologically stable BM at baseline (five patients with prior brain radiotherapy), and lazertinib showed anti-tumor activity in these patients with baseline BM. The median iPFS (BICR) was not reached (95 % CI: 4.1–NR). Over half of patients with BM at baseline (n = 22) were still alive at 54 months, with a 3-year survival rate of 59 %.

The study also indicated a tolerable toxicity profile for lazertinib. Most drug-related AEs were grades 1–2 and were skin-related or gastrointestinal-related, consistent with EGFR inhibition. Paresthesia was reported in 35 % of patients, although the majority of events were grade 1 or 2. Although it is uncommon, paresthesia has been reported in anti-tumor treatment with other TKIs [24,25]. The underlying mechanisms of lazertinib-associated paresthesia and related sensory abnormalities are not yet well-characterized, although a recent *in vivo* mechanistic study showed that lazertinib treatment elicits long-lasting spontaneous calcium channel responses and hyperexcitability in nociceptive sensory neurons, but did not cause neuronal cell death [26]. Mechanistically, lazertinib-associated paresthesia thus appears distinct from chemotherapy-induced peripheral neuropathy, which is caused by damage to peripheral nerves, and which can be disabling and persistent [27]. Further research is required to understand the mechanism of action for paresthesia and its associated risk factors. Seven patients withdrew permanently from the study treatment due to AEs, and of these, paresthesia and rash erythematous, in one patient each, were reported to have a possible relationship to lazertinib. The safety findings were consistent with previous reports [14,16,21]. No patients reported TEAEs of ILD or drug-related ILD and no clinically relevant cardiac AEs were reported. Additionally, there were no drug-related TEAEs leading to death. Taken together, the safety results of the first line cohort are consistent with the earlier cardiac safety analysis of the LASER201 trial data [28], which indicates that lazertinib is unlikely to be associated with clinically meaningful increase in cardiac AEs.

Lazertinib, a novel third-generation EGFR TKI, has emerged as a promising treatment option for *EGFR*-mutated NSCLC, demonstrating at least a comparable efficacy and safety profile when compared to the other available third-generation EGFR TKI, osimertinib. The LASER301 study reported extended PFS with lazertinib in both the overall and Asian populations, with a median PFS of 20.6 months [16,29]. The overall and Asian populations in the FLAURA study of osimertinib showed median PFS durations of 18.9 months and 16.5 months, respectively [22,30]. In addition, the Phase 3 MARIPOSA study reported a median PFS of 18.5 months with lazertinib compared with 16.6 months for the comparator [17].

Our present analysis reveals that lazertinib treatment offers substantial long-term clinical benefits, exemplified by its 54-month overall survival rate. The 2-year survival rate in this study aligns with the outcomes observed in the ongoing LASER301 trial thus far [16]. While our analysis may be viewed as providing support to the results from the Phase 3 LASER301 trial, further alignment and discussion of these results will be of great interest when the eventual OS data from the LASER301 trial matures. As we await conclusive data from LASER301,

this analysis provides a preliminary window into the potential long-term clinical advantages offered by lazertinib. We acknowledge the limitations of our study, particularly the relatively small cohort size and the uncontrolled nature of the study design, even as our results add support to other lazertinib study findings.

5. Conclusion

The findings in this first-line cohort analysis of the LASER201 study align with the efficacy demonstrated in the recent randomized controlled Phase 3 study, LASER301. The results provide support for the long-term clinical efficacy and tolerable safety profile of lazertinib as a front-line therapy for patients with locally advanced/metastatic *EGFR*-mutated NSCLC.

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CRediT authorship contribution statement

Byoung Chul Cho: Writing – review & editing, Methodology, Investigation, Conceptualization. **Ji-Youn Han:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Ki Hyeong Lee:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Yun-Gyoo Lee:** Writing – review & editing, Investigation. **Dong-Wan Kim:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Young Joo Min:** Writing – review & editing, Investigation. **Sang-We Kim:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Eun Kyung Cho:** Writing – review & editing, Investigation. **Joo-Hang Kim:** Writing – review & editing, Investigation. **Gyeong-Won Lee:** Writing – review & editing, Investigation. **Sung Sook Lee:** Writing – review & editing, Investigation. **NaMi Lee:** Writing – review & editing, Formal analysis. **Jang Young Wang:** Writing – review & editing, Investigation. **Hyejoo Park:** Writing – review & editing, Investigation. **Myung-Ju Ahn:** Writing – review & editing, Methodology, Investigation, Conceptualization.

Declaration of competing interest

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Appendix A. Supplementary data

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