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Updated overall survival and ctDNA analysis in patients with *EGFR* T790M-positive advanced non-small cell lung cancer treated with lazertinib in the phase 1/2 LASER201 study

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Abstract

Background Lazertinib is a potent, irreversible, third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) with significant efficacy in patients with *EGFR* T790M-mutated non-small cell lung cancer (NSCLC). This is the final overall survival (OS) report from the phase 1/2 LASER201 study in patients with advanced NSCLC with disease progression on or after prior EGFR TKI therapy.

Methods Eligible patients were aged ≥ 20 years, with advanced *EGFR*-mutated NSCLC and previous therapy with EGFR TKI. Patients in this integrated analysis received oral lazertinib 240 mg/day. Endpoints included efficacy and safety; exploratory analyses included associations between circulating *EGFR*-mutant tumor DNA (ctDNA) and efficacy parameters.

Results This integrated analysis included 78 patients in Korea who received second- or later-line lazertinib. The median OS was 38.9 months; estimated survival rates at 12, 24, and 36 months were 89.5%, 73.9%, and 52.8%, respectively. The cumulative 12-month incidence of central nervous system progression was 9.4%. *EGFR*-mutant ctDNA was detected in 46 patients (62.2%) at baseline. The presence of ctDNA at baseline significantly predicted progression-free survival (PFS), disease control rate (DCR), and OS. PFS, response rate, and DCR were significantly associated with *EGFR*-mutant ctDNA clearance at cycle 3; PFS and OS were significantly associated with ctDNA clearance at cycle 5. The safety profile of lazertinib 240 mg/day was consistent with previous findings.

Conclusions Lazertinib is a promising treatment option for patients with *EGFR* T790M-positive NSCLC following disease progression on prior *EGFR*-directed TKIs. Patients in LASER201 experienced prolonged OS, regardless of their *EGFR* mutation, brain metastases, or prior brain radiation status. Clearance of plasma *EGFR* mutations after lazertinib was associated with patient outcomes.

Trial registration ClinicalTrials.gov identifier NCT03046992.

Keywords ctDNA, Lazertinib, NSCLC, TKI, Overall survival

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Background

The Thr790Met (T790M) gatekeeper mutation is the dominant mechanism of acquired resistance to first- and second-generation tyrosine kinase inhibitors (TKIs) in patients with advanced epidermal growth factor receptor (*EGFR*) mutation-positive non-small cell lung cancer (NSCLC) [1, 2]. Third-generation *EGFR*-directed TKIs were designed to overcome T790M-mediated resistance while retaining activity against common activating *EGFR* mutations (e.g., exon 19 deletion (Ex19Del), L858R). Osimertinib, a third-generation TKI, is standard of care for the treatment of patients with *EGFR* T790M-positive NSCLC [3, 4]. Other third-generation TKIs are either in late-stage clinical development or have been recently approved in Asia [5]. Beyond the TKIs, agents such as MET inhibitors and antibody–drug conjugates are currently under investigation, as are combinations of chemotherapy, immunotherapy, and antiangiogenic therapy [6–10]; clinical trials investigating these strategies are underway [10].

Lazertinib (YH25448, JNJ-73841937) is an oral, potent, irreversible, third-generation *EGFR* TKI. It has similar or greater inhibitory potency than osimertinib against mutated *EGFR*, including T790M, Ex19Del, and L858R, but less activity than osimertinib against wild-type *EGFR* [11]. Lazertinib demonstrated good blood–brain barrier penetration in a brain metastasis xenograft model [11].

In January 2021, lazertinib was approved in the Republic of Korea as a second-line treatment for patients with *EGFR* T790M-positive locally advanced or metastatic NSCLC previously treated with *EGFR* TKIs [12]. Approval was based on the phase 1/2 LASER201 study [13, 14], which showed that lazertinib was effective, had evidence of intracranial efficacy based on an independent central review, and had a manageable safety profile at the recommended therapeutic dose of 240 mg/day [15]. Median overall survival (OS) was not reached at the time of analysis (23.7% maturity) [15]. In June 2023, lazertinib was approved by the Ministry of Food and Drug Safety in the Republic of Korea as a first-line treatment for *EGFR*-mutated non-small cell lung cancer [12]. We now report an updated analysis of OS and safety of lazertinib 240 mg/day in patients with advanced *EGFR* T790M-positive NSCLC previously treated with *EGFR* TKIs from the LASER201 study, as well as the results of circulating tumor DNA (ctDNA) analyses, which were undertaken to identify potential associations between changes in detected *EGFR* mutations and patient outcomes.

Methods

Study design

LASER201 was a multicenter, open-label, phase 1/2 study conducted to evaluate the safety, tolerability, and efficacy of lazertinib in patients with locally advanced or metastatic *EGFR*-mutated NSCLC (ClinicalTrials.gov identifier: NCT03046992). The study methodology has been described previously [13]. This report focuses on a protocol-defined integrated analysis of patients who received the 240 mg dose of lazertinib as second- or later-line therapy.

ctDNA clearance analysis

All patients in parts A, B, and C (the second-line cohort) of the study (Fig. 1A) provided mandatory plasma samples for analysis of ctDNA until the primary database lock at screening, and every two cycles thereafter until disease progression as per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.

Plasma samples of 10 ml were collected in EDTA tubes and centrifuged at 3000×g for 10 min at 4 °C. Plasma was isolated within 4 h and stored at – 80 °C until the time of DNA extraction. Plasma cell-free DNA was extracted from 2 ml of the plasma using the QIAamp DSP Circulating NA Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions.

EGFR-mutated ctDNA analysis (Ex19Del/L858R/L861Q/G724S) was conducted in plasma samples with valid ctDNA results by droplet digital polymerase chain reaction (ddPCR) using a ddPCR system (QX200 Droplet Digital PCR System; Bio-Rad, Hercules, CA, USA) and *EGFR* mutation analysis kit (Droplex *EGFR* Mutation Test v2; Gencurix, Seoul, South Korea) as per the manufacturer's recommended protocol. If *EGFR* mutations were no longer detectable, the sample was defined as “cleared.” If any of the *EGFR* mutations were still detectable, the sample was defined as “not cleared.” Detectability of *EGFR*-mutated ctDNA at baseline (cycle 1 day 1), and its clearance at weeks 6 (cycle 3 day 1) and 12 (cycle 5 day 1)—specifically in patients with detectable *EGFR*-mutated ctDNA at baseline—were analyzed in relation to progression-free survival (PFS) per independent central review (according to RECIST version 1.1), OS, objective response rate (ORR), and disease control rate (DCR).

Recognizing the clinical significance of the T790M mutation, particularly in the context of resistance to *EGFR*-targeted therapy, we conducted an additional supplementary analysis to incorporate mutation status using the Guardant 360 test [14]. This analysis aimed to provide further insights into the genetic landscape of patients undergoing lazertinib treatment and its potential

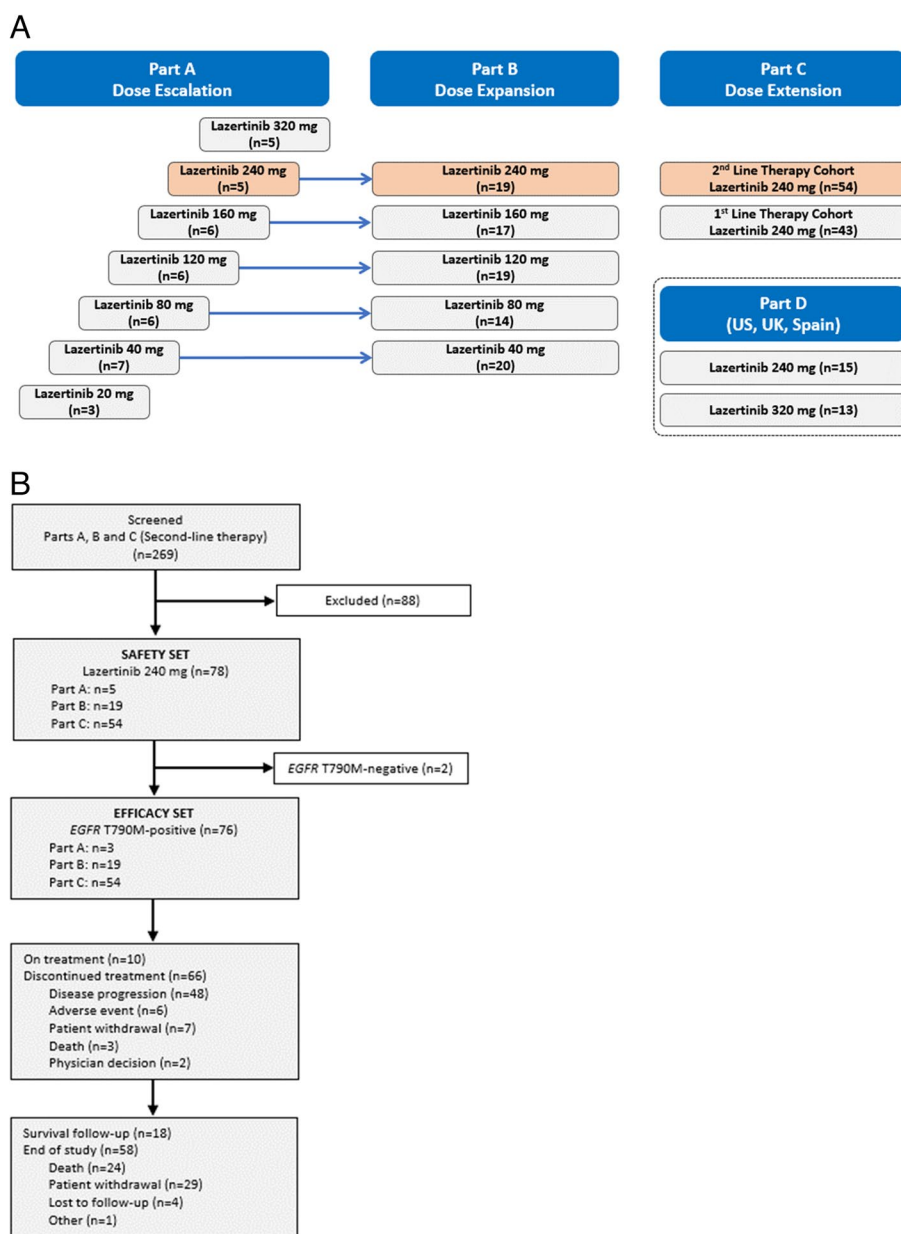


Fig. 1 Study design (A) and patient disposition (B). Data cut-off: April 8, 2022. Orange shading in top panel shows the patient subgroup included in the present integrated analysis. *EGFR* epidermal growth factor receptor

implications for treatment response and resistance mechanisms.

Statistical analysis

An integrated analysis of patients receiving lazertinib from parts A, B, and C of the study was performed per protocol. The data cut-off dates for PFS and OS assessments were January 8, 2021, and April 8, 2022, respectively. The data cut-off date for safety assessment was

March 30, 2023. The safety set included all patients who received at least one dose of lazertinib. Safety data were analyzed by descriptive statistical methods.

The efficacy set included patients in the safety set who had baseline RECIST (version 1.1) assessment and whose tumor *EGFR* mutation status was centrally confirmed. Kaplan–Meier methods were used to evaluate OS and to estimate the proportion of patients without an event, with 95% confidence intervals (CIs), at 12, 24, and 36 months.

Exploratory analyses included: subgroup analyses of OS according to baseline characteristics; time to first subsequent therapy or death and time to second subsequent therapy or death, which were defined as the interval from the first multiple-dose date (cycle 1 day 1) to start date of first/second subsequent anticancer therapy (excluding radiotherapy) following study treatment discontinuation or death, whichever was earlier. All analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

Cell-free DNA next-generation sequencing was conducted by Guardant Health, Inc. (Redwood City, CA) using Guardant 360, as previously described [14]. The baseline genetic alteration status determined by the Guardant 360 test was further analyzed according to ctDNA cleared or not cleared at cycle 3, which was confirmed by ddPCR and tumor shrinkage.

Results

Patient population

Between February 15, 2017, and May 10, 2019, 224 patients were enrolled in study parts A, B, and C (Fig. 1A). For the present integrated analysis, 78 patients received lazertinib 240 mg/day as second- or later-line therapy and were included in the safety set. All patients were Asian and had received at least one prior EGFR TKI (Table 1). The median duration of lazertinib treatment was 13.3 months (range, 0.3–50.3 months; Additional file 1: Table S1). Seventy-six patients had *EGFR* T790M-positive disease by central testing at baseline and constituted the efficacy set. At data cut-off (April 8, 2022), 10 of 76 patients remained on treatment and 66 had discontinued treatment, primarily because of disease progression (Fig. 1B).

Overall survival

The median duration of follow-up for OS was 27.7 months (interquartile range, 15.4–41.7 months); 24 of 76 patients (31.6%) had died at the time of analysis. Median OS was 38.9 months (95% CI 30.2–not reached [NR]) (Fig. 2). Survival rates at 12, 24, and 36 months were 89.5% (95% CI 79.2–94.9), 73.9% (95% CI 60.1–83.5), and 52.8% (95% CI 37.0–66.3), respectively.

Subgroup analyses

Subgroup analyses of OS by baseline characteristics are presented in Additional file 2: Fig. S1. When analyzed by *EGFR* mutation type at baseline, median OS was NR (95% CI 30.5–NR) in patients harboring an Ex19Del ($n=53$) and 29.1 months (95% CI 10.3–NR) in patients with L858R mutations ($n=22$) (Additional file 2: Fig. S1A).

Table 1 Baseline demographics and disease characteristics (safety set)

Characteristic	Lazertinib 240 mg ($n=78$)
Age, median (range), years	62 (33–82)
Race, n (%)	
Asian	78 (100.0)
Sex, n (%)	
Male	40 (51.3)
Female	38 (48.7)
ECOG performance status, n (%)	
0	20 (25.6)
1	58 (74.4)
Tumor histology, n (%)	
Adenocarcinoma	74 (94.9)
Adeno-squamous carcinoma	2 (2.6)
Other	2 (2.6)
Stage (AJCC 7th edition), n (%)	
III	3 (3.8)
IV	75 (96.2)
Brain metastases at baseline (investigator assessment), n (%)	40 (51.3)
<i>EGFR</i> mutation status (central testing), n (%)	
Exon19Del	53 (67.9)
L858R	23 (29.5)
L861Q	1 (1.3)
Negative (T790M-positive only)	1 (1.3)
T790M status (central testing), n (%)	
Positive	76 (97.4)
Negative	2 (2.6)
Prior lines of systemic therapy, n (%)	
1	50 (64.1)
≥ 2	28 (35.9)
Number of prior EGFR TKIs, median (range)	1 (1–3)
Prior EGFR TKI, ^a n (%)	78 (100.0)
Gefitinib	40 (51.3)
Afatinib	28 (35.9)
Erlotinib	16 (20.5)

Note: Some totals do not add up to 100% due to rounding

AJCC American Joint Committee on Cancer, *EGFR* epidermal growth factor receptor, ECOG Eastern Cooperative Oncology Group, TKI tyrosine kinase inhibitor

^a Patients may have received more than one prior EGFR TKI

When analyzed by the presence or absence of brain metastases at baseline, median OS was NR (95% CI 21.1–NR) in patients with brain metastases ($n=25$) and 38.9 months (95% CI 30.1–NR) in patients without brain metastases ($n=51$) (Additional file 2: Fig. S1B).

Lazertinib showed consistent efficacy regardless of brain metastasis status (Additional file 2: Fig. S1B) and prior brain radiation therapy status (Additional file 2: Fig.

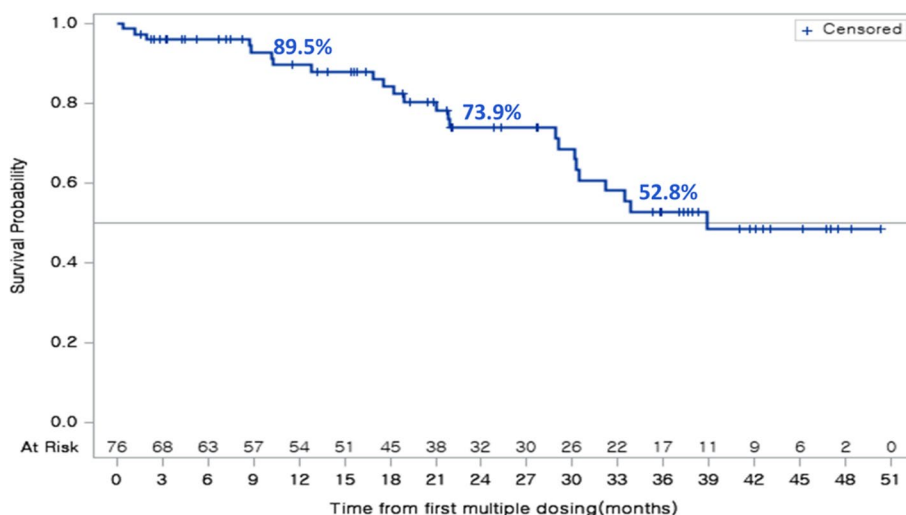


Fig. 2 Overall survival in patients with *EGFR* T790M-positive tumors (efficacy set). Data cut-off: April 8, 2022. CI confidence interval, *EGFR* epidermal growth factor receptor, NR not reached

S1C). For patients with baseline central nervous system (CNS) metastases, the cumulative incidence rate of CNS progression at 12 months was 9.4% (Additional file 2: Fig. S2).

Time to first or second subsequent therapy or death

Thirteen (17.1%) and 15 (19.7%) of the 76 patients received osimertinib and a platinum doublet, respectively, as subsequent therapy. Kaplan–Meier curves for time to first or second subsequent therapy or death in patients with *EGFR* T790M-positive tumors are presented in Additional file 2: Fig. S3. Median time to first subsequent therapy or death was 21.0 months (95% CI 13.8–32.2). Median time to second subsequent therapy or death was 29.1 months (95% CI 22.0–38.9).

Safety

In the safety set of patients who received lazertinib 240 mg/day ($n=78$), 76 (97.4%) reported at least one treatment-emergent adverse event (Table 2). Treatment-emergent adverse events were considered to be drug-related by the investigator in 69 patients (88.5%). The most common drug-related treatment-emergent adverse events of any grade were rash ($n=29$; 37.2%), paresthesia ($n=26$; 33.3%), pruritus ($n=25$; 32.1%), and muscle spasms ($n=21$; 26.9%) (Additional file 1: Table S2). Drug-related grade 3 treatment-emergent adverse events were reported in 11 patients (14.1%). No drug-related grade 4 or 5 events were reported.

Serious adverse events were reported in 21 patients (26.9%); these were considered drug-related in three patients (3.8%), one with gastritis, one with pneumonia, and one with pneumonitis. Drug-related QT interval

prolongation (grade 1) was reported in three patients (3.8%).

Dose reductions, interruptions, and discontinuation because of adverse events were required in 13 (16.7%), 17 (21.8%), and 6 (7.7%) patients who received lazertinib 240 mg/day, respectively. Adverse events leading to drug discontinuation were pneumonitis ($n=1$), pulmonary embolism ($n=1$), peripheral neuropathy ($n=1$), herpes zoster and aspiration pneumonia ($n=1$), cerebellar infarction ($n=1$), and drug intoxication due to pesticide ($n=1$).

ctDNA clearance analysis

Among the 74 patients who received lazertinib 240 mg/day and who had a sample for ctDNA analysis, *EGFR*-mutated ctDNA was detected in 46 patients (62.2%) at baseline and not detected in 27 patients (36.5%); one patient had an invalid result (Additional file 2: Fig. S4). Among patients who had cleared ctDNA by cycles 3 and 5, seven patients had continued treatment for longer than 2 years (21.2% and 22.6%, respectively); all patients who did not have ctDNA clearance had a treatment duration of less than 2 years (Additional file 1: Table S1).

Overall, the “cleared” group showed a better prognostic trend in terms of key anti-tumor efficacy endpoints, including ORR, DCR, PFS, and OS, compared with the “not cleared” group at baseline, cycle 3, and cycle 5. In particular, significant prognostic superiority was observed for PFS, ORR, and DCR at cycle 3 (Table 3; Additional file 2: Fig. S5).

Genetic mutations related to the mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K), and cyclic adenosine monophosphate signaling

Table 2 Summary of treatment-emergent adverse events (safety set; n = 78)

Parameter	No. of patients (%)	
TEAE	76 (97.4)	
Drug-related TEAE	69 (88.5)	
Serious TEAE	21 (26.9)	
Drug-related serious TEAE	3 (3.8)	
Grade ≥ 3 TEAE	28 (35.9)	
Drug-related grade ≥ 3 TEAE	11 (14.1)	
TEAE leading to death	3 (3.8)	
Drug-related TEAE leading to death	0	
TEAE leading to dose reduction	13 (16.7)	
TEAE leading to temporary drug interruption	17 (21.8)	
TEAE leading to permanent drug withdrawal	6 (7.7)	
TEAEs occurring in ≥ 10% of patients	All grades	Grade ≥ 3
Rash	29 (37.2)	1 (1.3)
Paresthesia	28 (35.9)	2 (2.6)
Pruritus	27 (34.6)	0
Headache	22 (28.2)	0
Muscle spasms	22 (28.2)	0
Diarrhea	21 (26.9)	1 (1.3)
Decreased appetite	20 (25.6)	0
Cough	16 (20.5)	0
Paronychia	16 (20.5)	1 (1.3)
Constipation	15 (19.2)	0
Nausea	13 (16.7)	0
Fatigue	12 (15.4)	0
Aspartate aminotransferase increased	11 (14.1)	0
Alanine aminotransferase increased	10 (12.8)	0
Myalgia	10 (12.8)	0
Pulmonary embolism	10 (12.8)	5 (6.4)
Dizziness	10 (12.8)	0
Dyspepsia	9 (11.5)	0
Stomatitis	9 (11.5)	0
Blood creatinine increased	9 (11.5)	0
Vomiting	8 (10.3)	1 (1.3)
Dry skin	8 (10.3)	0

Note: Data cut-off: March 30, 2023. Patients with two or more adverse events with the same term were counted only once for that adverse-event term

TEAE treatment-emergent adverse event

pathways showed a tendency to be more frequently detected at baseline in the not cleared group compared with the cleared group. This suggests that components in these pathways may be associated with lazertinib resistance mechanisms (Additional file 2: Fig. S6).

Among patients in the cleared group (n = 21), baseline genetic alterations related to cell cycle and DNA repair were observed relatively more frequently in patients with significant tumor shrinkage (≥ 50%) than in those with shrinkage of less than 10%. In the not cleared group,

genetic alterations in *BRAF* and *MAPK1* in the MAPK signaling pathway were more frequent in patients with less tumor shrinkage at cycle 3 (Additional file 2: Fig. S7).

Discussion

The first reported analysis of the LASER201 study established the efficacy and safety of lazertinib 240 mg/day in patients with advanced *EGFR* T790M-positive NSCLC who had progressed on prior therapy with *EGFR*-directed TKIs [14]. OS data were not mature at that time. We now report updated findings from the same integrated analysis after a median follow-up of 27.7 months. At this time, the median OS with lazertinib 240 mg/day was 38.9 months (95% CI 30.2–NR), with an estimated survival rate of 52.8% at 36 months. These findings compare favorably with those reported for osimertinib from a pooled analysis of the AURA extension and AURA2 studies (median OS, 26.8 months; 36-month survival rate, 37%) and from the phase 3 AURA3 study (median OS, 26.8 months; 36-month survival rate, 30%) in a similar patient population [16, 17]. Median times to first subsequent therapy and second subsequent therapy or death with lazertinib in LASER201 (21.0 and 29.1 months, respectively) were also consistent with the AURA3 findings for osimertinib (16.0 and 20.0 months, respectively) [17].

The median OS was relatively longer in patients harboring an Ex19Del (NR; 95% CI 30.5–NR) in patients with L858R mutations (29.1 months; 95% CI 10.3–NR). This observation is aligned with multiple reports suggesting that outcomes with *EGFR* TKIs can be influenced by *EGFR* mutation type. For example, median OS following treatment with osimertinib was 29.1 months in patients with *EGFR* T790M-positive NSCLC with Ex19Del versus 21.4 months in patients with L858R mutations [16].

We investigated the dynamics of *EGFR* mutations in ctDNA to predict outcomes in lazertinib-treated patients in LASER201. Patients who were identified as ctDNA cleared at cycle 3 had better outcomes in the key anti-tumor efficacy endpoints of PFS, ORR, and DCR than those in the not cleared group. Numerous studies have explored the association of ctDNA clearance with clinical outcomes for first-, second-, and third-generation TKIs [18–20]. Recently, much effort has been invested in the evaluation and validation of ctDNA as a prognostic biomarker to guide clinical conversations around expected treatment outcomes across various advanced cancers, including NSCLC, and colorectal, breast, and pancreatic cancers [21–23]. Our data provide additional evidence for this approach, although further confirmatory studies are needed.

Several factors likely contributed to the favorable outcomes observed in LASER201. Lazertinib had a high

Table 3 Analysis of non-clearance or clearance of plasma *EGFR* mutations

Variable	Baseline ctDNA			Cycle 3 ctDNA clearance			Cycle 5 ctDNA clearance		
	Yes (n = 46)	No (n = 27)	P-value	Cleared (n = 33)	Not cleared (n = 11)	P-value	Cleared (n = 31)	Not cleared (n = 5)	P-value
ORR ^a , n (%)	24 (52.2)	16 (59.3)	0.5571	21 (63.6)	3 (27.3)	0.0359	22 (71.0)	2 (40.0)	0.3074
DCR ^b , n (%)	38 (82.6)	27 (100.0)	0.0226	32 (97.0)	6 (54.5)	0.0022	30 (96.8)	4 (80.0)	0.2619
Median PFS ^c , months [95% CI] ^d	5.6 [4.1–11.1]	23.3 [15.0–NR]	0.0002 ^e	11.1 [5.4–13.6]	5.4 [1.3–8.2]	0.0012 ^e	11.0 [5.5–13.6]	4.0 [1.3–NR]	0.0037 ^e
Hazard ratio [95% CI]	0.30 [0.15–0.59]		0.0004	0.28 [0.12–0.64]		0.0026			0.0087
Median OS ^f , months [95% CI] ^d	32.2 [21.8–NR]	NR [30.5–NR]	0.0235 ^e	33.4 [21.1–NR]	29.6 [28.9–NR]	0.8447 ^e	33.4 [21.8–NR]	NR [8.8–NR]	0.0151 ^e
Hazard ratio [95% CI]	0.35 [0.14–0.90]			0.86 [0.19–3.95]					

Note: Data cut-off: January 8, 2021 (PFS), and April 8, 2022 (OS). Percentages are calculated based on number of evaluable patients

^a ORR is the proportion of patients with a confirmed best overall response of CR or PR

^b DCR is the proportion of patients who have a best overall response of CR or PR or SD (SD at ≥ 5 weeks)

^c PFS is measured from the first multiple-dose date (cycle 1 day 1) until objective tumor progression or death, whichever occurs first

^d Median and 95% CI are calculated using Kaplan–Meier estimates

^e Log-rank test

^f OS is measured from the first multiple-dose date (cycle 1 day 1) until death due to any cause or date of last known alive

CI confidence interval, CR complete response, ctDNA circulating tumor DNA, DCR disease-control rate, NR not reached, ORR objective response rate, OS overall survival, PFS progression-free survival, PR partial response, SD stable disease

clearance rate for *EGFR* mutations, with ctDNA clearance in 33 of 46 patients (71.7%) at cycle 3 and in 31 of 46 patients (67.4%) after cycle 5. In AURA3, 83 of 189 patients (43.9%) with baseline *EGFR* mutations and evaluable plasma samples at week 6 had detectable *EGFR* mutations [24]. The intracranial efficacy of lazertinib, evidenced by the median intracranial PFS of 26.0 months [14], may also contribute to the observed favorable OS. Furthermore, lazertinib showed consistent efficacy regardless of brain metastasis status and prior brain radiation therapy. For patients with baseline CNS metastases, the cumulative incidence rate of CNS progression at 12 months was 9.4%, which is lower than the 16% previously reported in AURA3 [25], although cross-trial comparisons are made with caution.

The updated safety analysis was consistent with earlier reports [13, 14] and supports the long-term safety of lazertinib 240 mg/day, with no new safety signals. Median time on treatment was more than 1 year (13 months), with some patients receiving lazertinib for up to 4 years. The most common drug-related adverse events with lazertinib 240 mg/day were skin toxicities (rash, pruritus) and paresthesia, which were typically mild or moderate in severity. The risk of cardiac events with lazertinib 240 mg/day, including corrected QT interval prolongation or reduced left ventricular ejection fraction, was low after extended follow-up. These findings align with a detailed cardiac safety assessment by Jang and colleagues, which suggests that lazertinib is not associated with an increased cardiac risk and has a small predicted

magnitude of Fridericia’s corrected QT interval increase (2.2 ms) at maximum steady-state plasma concentration when dosed at 240 mg/day [26].

This was a single-arm study with a small sample size in a Korean patient population. Two ongoing international phase 3 trials involving lazertinib in patients with metastatic *EGFR*-mutated NSCLC are currently in progress. LASER301 compared lazertinib with gefitinib as first-line therapy in advanced *EGFR*-mutated NSCLC (ClinicalTrials.gov identifier: NCT04248829) [15]. Median PFS was statistically significantly longer with lazertinib versus gefitinib (20.6 vs 9.7 months; HR 0.45; 95% CI 0.34–0.58; $p < 0.001$). A similar result was observed in the subpopulation of Asian patients [27]. MARIPOSA, a study comparing lazertinib plus amivantamab versus osimertinib as first-line treatment in advanced *EGFR*-mutated NSCLC, included lazertinib monotherapy to assess the contribution of components (Clinicaltrials.gov identifier NCT04487080). With a median follow-up of 22 months, the median PFS was numerically longer with lazertinib (18.5 months; 95% CI 14.8–20.1) compared with osimertinib (16.6 months; 95% CI 14.8–18.5) [28].

Some limitations of this study warrant consideration. The proportion of patients with invalid results increased as treatment progressed, which may have been a result of treatment interventions impacting on the quality and quantity of ctDNA that was collected as previously reported [29]. There was an incomplete pairing of ctDNA and Guardant 360 results, as not all patients had ctDNA and Guardant 360 results, thus limiting comprehensive

paired analysis. A more in-depth assessment of treatment response and mutation status would have been possible if matched ctDNA and Guardant 360 results had been available for each patient. In total, 29 analysis sets included both ctDNA analysis and Guardant 360 results, so interpretation of these results must be approached cautiously.

Interpretation of results such as these requires careful consideration because of the heterogeneity in patients' response to treatment, which is attributed to inherent biological differences, disease characteristics, and other unidentified factors.

Conclusions

In summary, lazertinib is a promising treatment option for patients with *EGFR* T790M-positive NSCLC following *EGFR*-directed TKIs. Patients experienced prolonged OS, regardless of brain metastases or prior brain radiation, with a median OS of over 3 years. The safety profile of lazertinib 240 mg/day was consistent with previous findings and supportive of the long-term safety of lazertinib in this patient population. The ctDNA analyses suggest that clearance of plasma *EGFR* mutations has the potential to predict clinical outcomes in patients with *EGFR*-mutated NSCLC, although further confirmatory studies are needed.

Abbreviations

CI	Confidence interval
CNS	Central nervous system
ctDNA	Circulating tumor DNA
DCR	Disease-control rate
ddPCR	Droplet digital polymerase chain reaction
EGFR	Epidermal growth factor receptor
Ex19Del	Exon 19 deletion
MAPK	Mitogen-activated protein kinase
NR	Not reached
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase chain reaction
PFS	Progression-free survival
PI3K	Phosphoinositide 3-kinase
RECIST	Response Evaluation Criteria in Solid Tumours
TKI	Tyrosine kinase inhibitor

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12916-024-03620-8>.

Additional file 1: Table S1. Duration of lazertinib treatment in ctDNA Cleared group and Not Cleared group. Table S2. Drug-related treatment-emergent adverse events occurring in $\geq 10\%$ of patients. Table S3. Ethics committee approvals.

Additional file 2: Fig. S1. Subgroup analyses of overall survival by I mutation type, brain metastases, and brain radiotherapy. Fig. S2. Cumulative incidence rate of CNS progression in lazertinib-treated patients in the LASER201 trial. Fig. S3. Time to first or second subsequent therapy or death in patients with *EGFR* T790M-positive non-small cell lung cancer. Data cut-off April 8, 2022. Fig. S4. Patient disposition for ctDNA analysis. Patients

were categorized based on their clearance status as determined by ddPCR. Fig. S5. Analysis of plasma *EGFR* mutations at baseline, cycle 3, and cycle 5 in patients with a valid ctDNA sample at baseline and cycle 3 and/or cycle 5. Kaplan–Meier estimates showing OS and independent central review-assessed PFS according to the presence of ctDNA at baseline, cycle 3, and cycle 5. Fig. S6. Resistance mechanism with ctDNA clearance. Fig. S7. Summary of baseline genetic alterations at screening by ctDNA clearance at cycle 3 or not.

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Authors' contributions

J-YH: conceptualization, investigation, methodology, data curation, writing—review and editing. BCC: data curation, resources, investigation, writing—review and editing. M-JA: data curation, resources, investigation, writing—review and editing. KHL: data curation, resources, investigation, writing—review and editing. Y-GL: data curation, resources, investigation, writing—review and editing. D-WK: data curation, resources, investigation, writing—review and editing. YJM: data curation, resources, investigation, writing—review and editing. S-WK: data curation, resources, investigation, writing—review and editing. EKC: data curation, resources, investigation, writing—review and editing. J-HK: data curation, resources, investigation, writing—review and editing. G-WL: data curation, resources, investigation, writing—review and editing. SSL: data curation, resources, investigation, writing—review and editing. NML: data curation, software, validation, formal analysis, visualization, writing—review and editing. HH: data curation, software, validation, formal analysis, visualization, writing—review and editing. HWJ: resources; writing—review and editing. HP: visualization, writing—original draft, writing—review and editing. JL: visualization, writing—original draft, writing—review and editing. All authors read and approved the final manuscript.

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Availability of data and materials

Deidentified participant data will be made available when all endpoints 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.

Declarations

Ethics approval and consent to participate

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 (Additional file 1: Table S3). Patients provided written informed consent before study participation.

Consent for publication

Not applicable.

Competing interests

Ji-Youn Han reports: grants or contracts from Takeda, Ono, Roche, and Pfizer; consulting fees from AstraZeneca, Takeda, Amgen, Janssen, Merck, Novartis, J INTS Bio, Oncobix, and Daiichi Sancho; payments or honoraria for lectures, presentations, speakers' bureaux, or writing from AstraZeneca, Takeda, Janssen, Pfizer, Merck, Novartis, and Yuhan; payment for expert testimony from AstraZeneca; payment for participating in data safety monitoring boards or advisory boards for AstraZeneca, Janssen, J INTS Bio, and Abion; leadership or fiduciary role in Health Insurance Review and Assessment.

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