Original Article

Lazertinib versus Gefitinib as First-line Treatment for EGFR-mutated Locally Advanced or Metastatic NSCLC: LASER301 Korean Subset

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Running Title: First-line lazertinib for metastatic EGFR-mutated NSCLC

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Abstract

Purpose

This subgroup analysis of the Korean subset of patients in the Phase 3 LASER301 trial evaluated the efficacy and safety of lazertinib versus gefitinib as first-line therapy for epidermal growth factor receptor mutated (EGFRm) non-small cell lung cancer (NSCLC).

Materials and Methods

Patients with locally advanced or metastatic EGFRm NSCLC were randomised 1:1 to lazertinib (240 mg/day) or gefitinib (250 mg/day). The primary endpoint was investigator-assessed progression-free survival (PFS).

Results

In total, 172 Korean patients were enrolled (lazertinib, N=87; gefitinib, N=85). Baseline characteristics were balanced between the treatment groups. One-third of patients had brain metastases (BM) at baseline. Median PFS was 20.8 months (95% confidence interval [CI]: 16.7–26.1) for lazertinib and 9.6 months (95% CI: 8.2–12.3) for gefitinib (hazard ratio [HR] 0.41, 95% CI: 0.28–0.60). This was supported by PFS analysis based on blinded independent central review. Significant PFS benefit with lazertinib was consistently observed across pre-defined subgroups, including patients with BM (HR 0.28, 95% CI: 0.15–0.53) and those with L858R mutations (HR 0.36, 95% CI: 0.20–0.63). Lazertinib safety data were consistent with its previously reported safety profile. Common adverse events (AEs) in both groups included rash, pruritus and diarrhoea. Numerically fewer severe AEs and severe treatment-related AEs occurred with lazertinib than gefitinib.

Conclusion

Consistent with results for the overall LASER301 population, this analysis showed significant PFS benefit with lazertinib versus gefitinib with comparable safety in Korean patients with
untreated $EGFR_m$ NSCLC, supporting lazertinib as a new potential treatment option for this patient population.

**Key words** Non-small cell lung cancer, Lazertinib, $EGFR$ mutation
Introduction

In Korea, lung cancer is reported to be the most commonly diagnosed cancer, after thyroid cancer, and the leading cause of cancer-related deaths [1-3]. Similar to global disease trends, non-small cell lung cancer (NSCLC), particularly adenocarcinoma, has become the most common type of lung cancer in Korea, replacing squamous cell carcinoma as the dominant histologic subtype since 2011 [2]. NSCLC is associated with various somatic driver mutations in the epidermal growth factor receptor gene (EGFR) and other genes. The most common EGFR activating mutations, deletions in EGFR exon 19 (Ex19del) and the Leu858Arg (L858R) point mutation in exon 21, result in constitutively active EGFR tyrosine kinase signalling, contributing to tumour growth and development [4].

The development of EGFR tyrosine kinase inhibitors (EGFR TKIs) capable of targeting activating EGFR mutations changed the paradigm of care for patients with NSCLC. This has been especially relevant for Korean and other Asian populations, wherein the prevalence of EGFR activating mutations is much higher (30–60%) than in non-Asian patients (10–30%) [5]. First- and second-generation TKIs, such as gefitinib, erlotinib, and afatinib, have demonstrated superiority to conventional chemotherapy for patients with previously untreated advanced or metastatic EGFR-mutated (EGFRm) NSCLC. In such patients, EGFR TKI therapy results in high response rates and extended progression-free survival, with a median PFS (mPFS) of 9–13 months reported in Phase 3 trials, compared with 4–6 months on chemotherapy [6-8]. Consequently, EGFR TKI therapy is currently recommended as a standard first-line therapy for EGFRm NSCLC in Korea and other regions. Despite response rates of 70% or more in the first-line setting, disease progression due to acquired resistance typically occurs within 10–14 months of starting EGFR TKI therapy [6-8]. In approximately 50% of cases, this is due to the EGFR Thr790Met (T790M) resistance mutation [4,9].
A lesser degree of benefit with first- or second-generation EGFR TKI therapy has been described in certain patient subgroups, notably those with pre-existing central nervous system (CNS) involvement and those with L858R-positive tumours. Among patients with pre-existing brain metastases (BM), development of further BM on EGFR TKI therapy is common, and is associated with worse outcomes than in patients without prior BM [10,11]. The limited activity of first- or second-generation EGFR TKIs against BM has been attributed to the minimal CNS penetration of these drugs [11]. In addition, clinical trial data indicate less favourable outcomes with EGFR TKI therapy in patients with the L858R mutation than those with Ex19del mutations [7, 12-14].

To overcome T790M resistance and address the need for improved first-line treatment options, third-generation EGFR TKIs have been developed that selectively target activating mutant and T790M mutant EGFR while sparing the wild-type form. These third-generation EGFR TKIs include osimertinib (approved in the United States as a first-line therapy in 2018 based on the results of the FLAURA study [14]), and lazertinib, which was approved in Korea in 2021 for the treatment of patients with T790M-positive advanced NSCLC who previously received EGFR TKI therapy [15]. Lazertinib (YH25448, JNJ-73841937) is a brain-penetrant, highly mutant-selective and irreversible third-generation EGFR TKI. Preclinical studies showed lazertinib to have high selectivity for mutant over wild-type EGFR, and excellent CNS penetration, achieving a brain-to-plasma ratio of 0.9 and intracranial tumour-to-brain ratio of 0.7 in animal models [16]. In a Phase 1/2 study of patients with EGFRm NSCLC, lazertinib was well tolerated and exhibited promising systemic antitumor activity [17,18].

The LASER301 Phase 3 global study (ClinicalTrials.gov ID: NCT04248829) was designed to assess the efficacy and safety of monotherapy with lazertinib compared with gefitinib as a first-line therapy for EGFRm NSCLC [19]. Here, we report efficacy and safety data for the Korean subset of the LASER301 study.
Materials and Methods

LASER301 is an ongoing double-blind, randomised, Phase 3 trial comparing the efficacy and safety of lazertinib with that of gefitinib in treatment-naïve patients with NSCLC harbouring activating EGFR mutations. This subset analysis assessed efficacy and safety in Korean patients enrolled at 22 sites in Korea.

1. Study oversight and ethics

The study was approved by the institutional review boards or independent ethics committees of each study site, and was conducted in accordance with the principles expressed in the Declaration of Helsinki, the International Conference on Harmonization/Good Clinical Practice guidelines, and applicable local laws and regulations. Prior to enrollment, written informed consent was obtained from all patients. In situations where consent could not be given by patients, informed consent was obtained from a legally acceptable representative.

2. Study design and treatment

Patients in the LASER301 study were randomly assigned in a 1:1 ratio to receive either lazertinib (240 mg administered orally, once daily) or gefitinib (250 mg administered orally, once daily) (S1 Fig.). Randomization was performed centrally using the permuted block technique, stratified by EGFR mutation status (Ex19del or L858R) and race (Asian or non-Asian). A treatment cycle was 21 days. Patients received their assigned treatment until investigator-assessed objective disease progression based on the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 criteria. Patients could continue to receive their assigned treatment beyond objective disease progression as long as they continued to show clinical benefit, as judged by the investigator. Patients randomised to the gefitinib arm had the
option to receive open-label lazertinib following objective disease progression provided they met all the following criteria: disease progression confirmed by blinded, independent central review (BICR); presence of the T790M mutation post-progression, confirmed locally or centrally by plasma or tissue testing prior to unblinding; no intervening anticancer therapies following gefitinib discontinuation. An archival tumour biopsy sample was required to allow central mutation analysis. Further details of the study design, treatments and assessments are provided in the Supplementary Materials.

3. Patients

Eligible patients were ≥18 years of age with locally advanced or metastatic NSCLC not amenable to curative surgery or radiotherapy. Patients were treatment-naïve (prior adjuvant and neo-adjuvant therapy for early-stage disease was permitted if completed >12 months prior to randomization). Local or central confirmation of Ex19del or L858R mutations in a tissue biopsy, either alone or in combination with other EGFR mutations, was required. Patients had to have a WHO performance status score of 0–1 and no clinically significant deterioration over the 2 weeks before randomization. Patients with asymptomatic and stable BM were eligible.

Patients were excluded if they had leptomeningeal metastases, history of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis which required steroid treatment or clinically active ILD, or severe or uncontrolled systemic diseases. Patients with cardiovascular disease (e.g., symptomatic chronic heart failure or serious cardiac arrhythmia, myocardial infarction, or unstable angina), electrocardiogram (ECG) abnormalities or factors that increase the risk of Fridericia’s corrected QT interval (QTc) prolongation or arrhythmic events were excluded. Full inclusion and exclusion criteria for the LASER301 study are provided in the Supplementary Materials.
4. Endpoints and assessments

The primary efficacy endpoint was the duration of progression-free survival (PFS), defined as the time from randomization until investigator-assessed objective disease progression (according to RECIST v1.1 criteria), or death from any cause in the absence of progression. Assessments were performed every 6 weeks from randomization for the first 18 months, then every 12 weeks until objective disease progression, after which they were followed for survival every 6 weeks.

Secondary efficacy endpoints reported in this subset analysis include the objective response rate (ORR), duration of response (DoR), disease control rate (DCR), overall survival (OS), and pharmacokinetics of lazertinib. Overall survival (OS) was defined as the time from randomization until death due to any cause; patients alive at the time of analysis were censored at the last recorded date they were known to be alive. All patients were followed for survival, disease progression (per local standard practice) and any post-study anticancer treatment until loss to follow up, withdrawal of consent, or death (whichever was earlier). Patients who had not progressed or died at the time of analysis (data cut-off) were censored at the time of their last evaluable assessment.

5. Safety

Patient safety was monitored through adverse events (AEs), clinical laboratory parameters, vital signs, ECG parameters and physical examination. Serious AEs and AEs with at least a possibly causal relationship to the study treatment were described for each treatment group and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.
6. Statistical methods

The first Korean patient was dosed on 13 February 2020, and the data cut-off date was 29 July 2022. The full analysis set (FAS) used for efficacy analyses included all randomised patients. The safety set (SS) consisted of patients who received at least one dose of study treatment.

The primary endpoint, PFS, was compared in the 2 groups using a log-rank test stratified by mutation subtype (Ex19del or L858R) and race (Asian or non-Asian), with the Breslow approach used for handling ties. In the overall LASER301 trial population, to provide 90% power at a two-sided 5% significance level, it was estimated that approximately 207 progression events would be required to detect a hazard ratio (HR) of 0.64, based on an estimated median PFS of 16.5 months for the lazertinib group and 10.5 months for the gefitinib group. Median PFS and 95% confidence intervals (CIs) were estimated using the Kaplan-Meier method, and HRs were estimated using Cox regression models stratified by mutation type and race. The numbers of events and proportions of patients without an event at 6, 12, 18, and 24 months were also summarised for each treatment group.

For the secondary endpoints, ORR and DCR were analysed using logistic regression models stratified by mutation subtype and race. Similar to PFS, the median time to event and 95% CIs were estimated for DoR and OS using the Kaplan-Meier method. Plasma concentrations of lazertinib were summarised by nominal sampling time. AEs were summarised by treatment group. For this Korean subset analysis, only mutation subtype was used for the stratified analysis. All analyses were performed using SAS version 9.4 (SAS Institute, Inc, Cary, NC).
Results

1. Patients

The LASER301 study randomised patients to treatment between February 2020 and September 2021. The Korean subset comprised 172 patients (lazertinib: 87 patients; gefitinib: 85 patients) randomised (Fig. 1). Patients’ baseline demographics and disease characteristics appeared representative of the intended target patient population and were balanced between the treatment groups (Table 1). Almost all patients had metastatic disease. A higher proportion of patients had Ex19del mutations (lazertinib: 57.5%; gefitinib: 56.5%) than L858R mutations (lazertinib: 42.5%; gefitinib: 43.5%). One-third of patients had CNS metastases at study entry: 31 (35.6%) and 25 (29.4%) patients in the lazertinib and gefitinib groups, respectively.

All randomised patients received at least one dose of the assigned study treatment. The median durations of study treatment for the lazertinib and gefitinib groups were 84.1 weeks (range: 0.9–126.0) and 46.0 weeks (range: 0.3–120.3), respectively. In total, 44 (50.6%) patients who received lazertinib and 72 (84.7%) patients who received gefitinib discontinued their assigned treatment in the main study period. The main reasons for treatment discontinuation were progressive disease [24 (27.6%) in the lazertinib group and 58 (68.2%) patients in the gefitinib group] and AEs [lazertinib: 11 (12.6%) patients; gefitinib: 11 (12.9%)]. Twenty-six (30.6%) patients in the gefitinib group who discontinued the assigned study treatment crossed over to receive open-label lazertinib after centrally confirmed disease progression, as permitted by the protocol. At data cut-off, 43 (49.4%) patients were still receiving lazertinib and 13 (15.3%) were receiving gefitinib.
2. Efficacy

The full analysis set (FAS) for efficacy analyses included all randomised patients. At data cut-off, disease progression or death events had occurred in 45 (51.7%) patients in the lazertinib group and 68 (80.0%) patients in the gefitinib group. The median follow-up for PFS was 23.3 (interquartile range [IQR]: 20.6–26.0) months for the lazertinib group, and 26.1 (IQR: 23.3–26.1) months for the gefitinib group. The HR for disease progression or death favoured lazertinib, 0.41 (95% CI: 0.28–0.60). Median PFS was significantly longer in the lazertinib group (20.8, 95% CI: 16.7–26.1 months) than in the gefitinib group (9.6, 95% CI: 8.2–12.3 months) (p<0.001, stratified log-rank test).

PFS rates consistently favoured lazertinib at all timepoints analysed (6, 12, 18 and 24 months). At 24 months, 45.0% of patients on lazertinib and 12.9% of patients on gefitinib remained progression-free (Table 2). The separation of Kaplan-Meier PFS curves in favour of lazertinib occurred within the first 3 months, and was largely maintained over the follow-up period (Fig. 2). The results of investigator-assessed PFS were supported by the sensitivity analysis of PFS based on BICR (S2 Fig.). In almost all pre-defined sub-groups, the HR for disease progression or death consistently and strongly favoured lazertinib (Fig. 3). This included patients with BM at baseline (HR 0.28, 95% CI: 0.15–0.53, p<0.001) (Fig. 4), and patients with L858R-positive tumours (HR 0.36, 95% CI: 0.20–0.63, p<0.001) (Fig. 5).

Table 2 summarises the results for the secondary efficacy endpoints. The ORR (lazertinib: 80.5%; gefitinib: 80.0%) and DCR (lazertinib: 97.7%; gefitinib: 94.1%) were similar in the 2 treatment groups (Table 2). However, the median DoR in the lazertinib group (19.6 months) was twice as long as that in the gefitinib group (9.0 months). Although the best overall response profile was similar in the 2 treatment groups, the percentage of patients remaining in response was consistently higher at all timepoints in the lazertinib group than the
gefitinib group.

At data cut-off, 49 deaths had occurred (28% data maturity), with 24 deaths (27.6%) in the lazertinib group and 25 deaths (29.4%) in the gefitinib group. Since OS data were immature, median OS was not reached in either treatment group (S3 Fig.). The HR for death was 0.91 (95% CI: 0.52–1.60, p=0.754). A total of 36 (42%) patients in the gefitinib group received lazertinib post-progression: 26 received it as the per-protocol cross-over treatment, and 10 patients received lazertinib outside of the study as second-line or later line therapy.

The pharmacokinetic (PK) analysis set included patients receiving lazertinib who had at least 1 measurable concentration collected post-dose. The lazertinib plasma concentration-time profile (geometric mean plasma concentrations at pre-dose, 1–3 hours and 4–6 hours post-dose on each Day 1 of Cycle 1, 2, 5, 9 and 13) is shown in S4 Fig. The geometric mean of the trough plasma concentrations of lazertinib ranged from 195.0–211.4 ng/mL and remained similar from Cycles 2 to 13.

3. Safety

The safety analysis set consisted of patients who received at least one dose of study treatment. One or more AEs due to any cause were reported in 87 (100%) of patients on lazertinib and 84 (98.8%) of patients on gefitinib (Table 3). AEs of Grade 3 or higher occurred in 34 (39.1%) patients in the lazertinib group and 43 (50.6%) patients in the gefitinib group. Serious AEs occurred in 29 (33.3%) patients in the lazertinib group and 24 (28.2%) patients in the gefitinib group. Eleven patients in each group (lazertinib 12.6%; gefitinib 12.9%) reported AEs leading to permanent treatment discontinuation.

Table 4 summarises treatment-emergent AEs (any cause) that occurred in ≥15% of patients in either treatment group. The most commonly reported AEs were paraesthesia in the
lazertinib group (52.9% of patients; 8.2% in the gefitinib group), rash (46.0% and 50.6% of patients, respectively), pruritus (43.7% and 35.3% of patients, respectively), and diarrhoea (28.7% and 48.2% of patients, respectively) in both groups. ILD was reported in 2 (2.3%) patients in the lazertinib group and 2 (2.4%) patients in the gefitinib group, leading to treatment withdrawal in these 4 patients. No severe (Grade ≥3) QTc prolongation events were reported for patients in the lazertinib group, compared with 2 (2.4%) patients in the gefitinib group.

Discussion

Analyses for the overall LASER301 study demonstrated the superior efficacy of lazertinib as first-line treatment compared with gefitinib, a standard-of-care EGFR TKI for EGFRm NSCLC, with a HR for progression or death of 0.45 (95% CI: 0.34–0.58) [19]. Within the Korean subset, the 59% reduction in the risk of disease progression or death with lazertinib was consistent with that in the overall study population, and translated to significantly longer PFS for patients receiving lazertinib (mPFS of 20.8 versus 9.6 months for the gefitinib group). The Kaplan-Meier PFS curves showed early and clear separation favouring lazertinib over the study period. The analysis of investigator-assessed PFS was supported by the results of BICR assessment. Importantly, PFS benefit with lazertinib was consistently observed across the pre-defined subgroups, notably for patients with BM, and those with the L858R mutation. Response rates were high, approximately 80% in both treatment arms, though mainly consisting of partial responses. However, the lazertinib group showed a much more durable response, with a median DoR 10 months longer than the gefitinib group.

The results of this subset analysis in Korean patients were consistent with those of the overall study, and with available clinical data for lazertinib in EGFRm NSCLC. The mPFS on lazertinib for the Korean subset (20.8 months) was similar to that reported in the Asian
subgroup analysis in the overall LASER301 population (20.6 months) [19]. This is among the longest reported for EGFR TKIs in Phase 3 global studies to date, and is consistent with the long mPFS (24.6 months) observed for patients who received lazertinib as the first-line treatment in the Phase 1/2 LASER201 study [20]. The mPFS in the gefitinib comparator group was within the range of 9–13 months previously reported in trials involving Asian patients with untreated \textit{EGFR}m NSCLC [6, 21, 22]. As previously reported for osimertinib, another EGFR mutant-selective third-generation TKI [14], lazertinib therapy significantly improved PFS compared with standard first-line therapy (gefitinib) in the Korean subset, with durable responses. Subgroup analyses for osimertinib in Asian cohorts showed significantly longer mPFS (16.5–19.1 months) with first-line osimertinib than with standard-of-care TKIs [21, 22]. The corresponding HRs for osimertinib versus comparator TKIs ranged from 0.54 (95% CI: 0.41–0.72) [22] to 0.61 (95% CI: 0.38–0.99) [21].

Standard first-line EGFR TKIs, such as gefitinib and erlotinib, show poor penetration of the blood-brain barrier and limited CNS efficacy [11, 23]. It has been estimated that nearly 25% of patients with \textit{EGFR}m NSCLC have BM at initial diagnosis, with an additional 2-year CNS progression risk of up to 20% [11, 24]. In Korea, a higher baseline BM incidence has been reported (38.9% of \textit{EGFR}m patients with BM at diagnosis [25]), which could be related to the routine use of brain MRI during lung cancer diagnostic workup. The same study estimated that a further 10% of patients with \textit{EGFR}m NSCLC could be expected to develop BM by the time of progression on first-line EGFR TKI therapy. Considering the impact of BM on quality of life, health resource utilisation and survival, availability of therapies that can improve control of CNS disease is important, especially in the first-line setting. Patients with stable or asymptomatic BM were able to enrol in LASER301. At study entry, around one-third of patients in the Korean subset had BM, which is associated with increased risk of further BM
development and poorer outcomes [10]. In these patients, there was a significant reduction in risk of progression or death with lazertinib (HR 0.28, 95% CI: 0.15–0.53), as in patients without baseline BM (HR 0.46, 95% CI: 0.29–0.74). These findings are consistent with preclinical and clinical data for lazertinib [16-18]. The LASER201 Phase 1/2 study reported promising intracranial responses to lazertinib in patients with measurable baseline CNS disease [18]. Unlike osimertinib, lazertinib is not a substrate of breast cancer resistance protein (BCRP) and only a weak substrate of multidrug resistance-1 (MDR1/P-glycoprotein), and thus may be minimally affected by these efflux transporters, which reduce CNS penetration of drugs [16]. The BM subgroup results also compare favourably with similar subgroup data for osimertinib, which indicated significant PFS benefit in Asian patients with BMs [22]. CNS-specific progression was not assessed in this Korean subset analysis, but will be addressed in a separate analysis of intracranial disease outcomes in patients with available data.

As reported for the overall LASER301 study population, Korean patients with either of the common activating mutation subtypes showed comparable PFS benefit with lazertinib, with a HR of 0.36 (95% CI: 0.20–0.63) in the L858R subgroup, similar to the Ex19del group (HR 0.43, 95% CI: 0.26–0.72). This contrasts with trial data for other EGFR TKIs including gefitinib, erlotinib and osimertinib, that consistently documented shorter PFS in patients with L858R mutations compared with Ex19del mutations [7, 12-14]. Differences in total time on treatment, PFS and OS outcomes by EGFR mutation subtype have also been noted in real-world settings: patients with L858R had poorer outcomes than those with Ex19del mutations [25-27]. The possible mechanisms underlying the greater efficacy of EGFR TKIs in patients with Ex19del versus L858R mutations are not fully understood and may be complex. In-vitro studies indicate that the L858R mutant is less sensitive than Ex19del mutants to EGFR TKIs such as gefitinib and erlotinib [28, 29]. Ex19del mutations strongly stabilise EGFR in its active
conformation and increase inhibitor binding, whereas the structure-destabilising L858R mutation is thought to reduce binding affinity and therefore sensitivity to EGFR TKI inhibition. Lazertinib, on the other hand, shows potent in-vitro activity against both L858R and Ex19del (>90% inhibition relative to vehicle), and against T790M and L858R/T790M mutant kinases [16]. It has been suggested that the less favourable outcomes in patients with the L858R mutation in earlier studies could be due to higher frequencies of co-occurring pre-treatment T790M or other less TKI-sensitive uncommon EGFR mutations. Finally, studies using L858R and Ex19del mutant cell lines indicated mutation-specific patterns of EGFR phosphorylation and downstream signalling; this represents yet another possible explanation for the observed differences in outcomes such as duration of response to TKI therapy [27]. With the indications of PFS benefit regardless of mutation subtype, lazertinib monotherapy may be an option for patients with L858R-positive tumours, as an alternative to the concept of EGFR TKI and anti-angiogenic combination therapy that was explored in the RELAY study [12].

Pharmacokinetic analyses showed that the lazertinib plasma concentration-time profile was similar to that previously reported for the 240 mg dose level, with steady state of lazertinib achieved within 22 days of dosing, by Day 1 of Cycle 2 [17].

The observed safety profile of lazertinib was largely consistent with expectations from earlier clinical studies [17, 18]. The frequency of AEs reported in the Korean subset was somewhat higher than in the overall LASER301 population, but the relative frequencies of these AEs were similar to that in the overall population. Since PK exposure in the Korean subset did not differ from that in the overall population, we consider it unlikely that the higher frequency of AEs was due to higher lazertinib exposure. Paraesthesia, rash, and pruritus were the most common treatment-emergent AEs with lazertinib, and were mostly mild or moderate in severity, consistent with the EGFR wild-type-sparing activity of lazertinib. The incidence of
any-cause Grade ≥3 AEs and treatment-related Grade ≥3 AEs was lower in the lazertinib group than the gefitinib group, mainly due to a higher incidence of liver enzyme (ALT, AST) elevation in the latter. Treatment-related discontinuation rates were similar in the 2 groups, and there were no treatment-related deaths. ILD was reported in 2 patients in each treatment group. Consistent with safety assessments in previous studies [17, 18, 30], which showed that lazertinib had no clinically relevant effects on QT interval, no severe QTc prolongation was observed in patients receiving lazertinib. Off-target inhibition of HER2 has been suggested as a possible underlying mechanism for EGFR TKI-associated cardiotoxicity. In in-vitro studies, lazertinib showed high selectivity for mutant EGFR and negligible inhibition of HER2, which may translate to lower potential for HER2-related cardiotoxicity compared with osimertinib or other EGFR TKIs [30].

1. Limitations

Only one standard-of-care EGFR TKI, gefitinib, was included as a comparator in this study. However, the results of a network meta-analysis indicate that gefitinib, erlotinib, and afatinib have similar efficacy in the first-line setting [31]. The mPFS in patients treated with lazertinib is significantly longer than that reported for these first- or second-generation EGFR TKIs. At data cut-off, OS data were not mature for the overall study population (28% maturity) or for the Korean subset. It is thus premature to make formal conclusions about whether or not there is a clear survival difference between the two study arms. The interim analysis of OS in the Korean subset indicated a slight numerical improvement favouring lazertinib, consistent with the result for the overall population [19]. The final analysis of OS will be performed after approximately 45 months of survival follow-up from the first patient randomised. The results are expected to confirm whether the PFS advantage with first-line lazertinib treatment could
potentially translate to longer survival. Post-progression treatment is a well-known confounding factor influencing overall survival. Of note, 46% of the patients in the gefitinib group received lazertinib after disease progression, either by post-progression cross-over as permitted by the protocol (26 patients), or as subsequent therapy outside of the trial (10 patients). We acknowledge the possibility that OS differences attributable specifically to the assigned first-line treatment (gefitinib or lazertinib) could be masked due to the high cross-over rate from gefitinib to open-label lazertinib after disease progression.

This subset analysis did not address questions relating to post-progression outcomes, CNS-specific progression, or acquired resistance mechanisms. However, the significant PFS benefit observed in patients with and without pre-existing BM is consistent with published clinical data on the intracranial efficacy of lazertinib [18]. As part of the study procedures, brain scans and samples for cell-free DNA testing are being collected at regular intervals. Analyses of these additional data for the overall LASER301 population are planned to address CNS efficacy and mechanisms of acquired resistance to first-line lazertinib therapy.

Besides PFS and OS, we expect that clinicians’ benefit/risk evaluation will also consider a range of factors such as the underlying EGFR mutation profile, CNS disease, tolerability and quality of life when selecting a first-line treatment.

In conclusion, this analysis of the Korean subset of the LASER301 study showed clinically meaningful PFS benefit and durable responses with lazertinib treatment, compared with standard-of-care gefitinib. This clinical benefit was consistently documented across patient subgroups, regardless of baseline BM status or EGFR mutation subtype (L858R or Ex19del), as reported for the overall study population. These results support lazertinib as a new potential treatment option for patients with untreated locally advanced or metastatic EGFRm NSCLC in the Korean population.
Ethical Statement

The LASER301 study was performed in accordance with the principles expressed in the Declaration of Helsinki and International Council for Harmonisation Guidelines on Good Clinical Practice. The study was approved by the relevant Institutional Review Board/Ethics Committee for each study site. IRB approval details for study sites in Korea are provided in the Supplementary Information file. All patients provided written informed consent for study participation.

This study was approved by the Institutional Review of Severance Hospital, Yonsei University, (No. 4-2019-1222), Samsung Medical Center (No. SMC 2019-11-036-005), Asan Medical Center (No. 2019-1707), Chungbuk National University (No. CBNUH 2019-11-005-103), National Cancer Center (No. NCC2020-0026), Seoul National University Hospital (No. NCC2020-0026), Seoul National University Bundang Hospital (No. B-2002-597-404), Gachon University Gil Medical Center (No. GCIRB2020-027), Gyeongsang National University Hospital (No. GNUH 2019-11-037-023), SMG-SNU Boramae Medical Center (No. 10-2020-13), St. Vincent's Hospital (No. VC19MDGT0260), Ulsan University Hospital (No. UUH 2019-11-024-063), CHA Bundang Medical Center (No. CHAMC 2019-11-015-043), Haeundae Paik Hospital (No. HPIRB 2019-12-004-077), Korea University Anam Hospital (No. 2020AN0008), Kangbuk Samsung Hospital (No. KBSMC 2019-11-023-060), Bucheon St. Mary’s Hospital (No. HC19MDGT0116), Dongsan Hospital (No. DSMC 2019-12-001-032), Ajou University Hospital (No. AJIRB-MED-CT3-19-484), Yeungnam University Hospital (No. YUMC 2019-11-057-040), Eunpyeong St. Mary's Hospital (No. PC19MDGT0135), and Seoul St. Mary's Hospital (KC20MDGT0011).
Author Contributions

Conceived and designed the analysis: Cho BC, Ahn MJ, Kim DW, Kang JH.


Performed the analysis: Choi SY.


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Conflicts of Interest

Ki Hyeong Lee reports participation in advisory boards and honoraria from BMS, MSD, AstraZeneca, Pfizer, Eli Lilly, Yuhan Corporation, and research funding from Merck outside the submitted work.

Byoung Chul Cho has received research funding from MOGAM Institute, LG Chem, Oscotec, Interpark Bio Convergence Corp, GIInnovation, GI-Cell, Abion, Abbvie, AstraZeneca, Bayer, Blueprint Medicines, Boehringer Ingelheim, Champions Oncology, CJ bioscience, CJ Blossom Park, Cyrus, Dizal Pharma, Genexine, Janssen, Lilly, MSD, Novartis, Nuvalent, Onceternal, Ono, Regeneron, Dong-A ST, Bridgebio Therapeutics, Yuhan Corporation, ImmuneOncia, Illumina, Kanaph therapeutics, Therapex, JINTSbio, Hanmi and CHA Bundang Medical Center. He has received consulting fees from Abion, BeiGene, Novartis, AstraZeneca, Boehringer-Ingelheim, Roche, BMS, CI, CureLogen, Cyrus Therapeutics, Ono Pharmaceutical, Onegene Biotechnology, Yuhan Corporation, Pfizer, Eli Lilly, GI-Cell,

Myung-Ju Ahn reports research funding from AstraZeneca, Lilly, MSD, Merck, Ono Pharmaceutical, Takeda, Yuhan Corporation, Amgen, Pfizer, Novartis, Roche, Alpha-Pharmaceuticals and honoraria from AstraZeneca, Lilly, MSD, Merck, Ono, Takeda, Yuhan Corporation, Amgen, Pfizer, Novartis and Roche.

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Jin Hyoung Kang reports research funding from AstraZeneca, Ono Pharma Korea, Daiichi Sankyo/UCB Japan, Yuhan Corporation and received honoraria from AstraZeneca, Ono Pharmaceutical, Lilly and Boehringer Ingelheim. He is a consultant for MSD Oncology, AstraZeneca, Ono Pharmaceutical, Boehringer Ingelheim, Yuhan Corporation, Genexine and
was invited speaker for Boehringer Ingelheim, Pfizer and Roche. Jangyoung Wang and SeokYoung Choi are employees of Yuhan Corporation. All other authors have no relevant relationships to disclose. The study was sponsored by Yuhan Corporation. The study sponsor funded medical writing and editorial support for the publication.

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References


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Table 1. Patient demographics and clinical characteristics at baseline

<table>
<thead>
<tr>
<th></th>
<th>Lazertinib (n=87)</th>
<th>Gefitinib (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>65.6 (11.5)</td>
<td>65.7 (11.2)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>67 (34–86)</td>
<td>66 (43–85)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36 (41.4)</td>
<td>42 (49.4)</td>
</tr>
<tr>
<td>Female</td>
<td>51 (58.6)</td>
<td>43 (50.6)</td>
</tr>
<tr>
<td><strong>Smoking history, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>55 (63.2)</td>
<td>59 (69.4)</td>
</tr>
<tr>
<td>Ever</td>
<td>32 (36.8)</td>
<td>26 (30.6)</td>
</tr>
<tr>
<td><strong>WHO performance status, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>18 (20.7)</td>
<td>20 (23.5)</td>
</tr>
<tr>
<td>1</td>
<td>69 (79.3)</td>
<td>65 (76.5)</td>
</tr>
<tr>
<td><strong>CNS metastases at study entry</strong></td>
<td>31 (35.6)</td>
<td>25 (29.4)</td>
</tr>
<tr>
<td><strong>Overall disease classification, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>85 (97.7)</td>
<td>84 (98.8)</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>2 (2.3)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td><strong>Histology, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>87 (100)</td>
<td>85 (100)</td>
</tr>
<tr>
<td>Others b)</td>
<td>1 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td><strong>EGFR mutation subtype c), n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex19del</td>
<td>50 (57.5)</td>
<td>48 (56.5)</td>
</tr>
<tr>
<td>L858R</td>
<td>37 (42.5)</td>
<td>37 (43.5)</td>
</tr>
</tbody>
</table>

a)Baseline CNS metastasis status was determined from NSCLC history in medical records; no baseline imaging was performed. b)Squamous cell carcinoma was also confirmed in one patient, in whom the predominant histology was adenocarcinoma. c)Mutation status at randomisation as confirmed by local or central laboratory testing. CNS, central nervous system; EGFR, epidermal growth factor receptor gene; SD, standard deviation; WHO, World Health Organisation.
### Table 2. Secondary efficacy endpoints

<table>
<thead>
<tr>
<th></th>
<th>Lazertinib (n=87)</th>
<th>Gefitinib (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS rate, % (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6 months</td>
<td>91.7 (83.4, 96.0)</td>
<td>77.2 (66.5, 84.8)</td>
</tr>
<tr>
<td>At 12 months</td>
<td>77.1 (66.5, 84.8)</td>
<td>40.9 (30.1, 51.3)</td>
</tr>
<tr>
<td>At 18 months</td>
<td>57.4 (46.0, 67.3)</td>
<td>25.5 (16.6, 35.5)</td>
</tr>
<tr>
<td>At 24 months</td>
<td>45.0 (32.9, 56.3)</td>
<td>12.9 (6.2, 22.1)</td>
</tr>
<tr>
<td><strong>Objective response rate (ORR)(^a)</strong>, number of patients</td>
<td>n=70</td>
<td>n=68</td>
</tr>
<tr>
<td>ORR, % of patients (95% CI)(^b)</td>
<td>80.5 (70.6, 88.2)</td>
<td>80.0 (69.9, 87.9)</td>
</tr>
<tr>
<td>Odds ratio (95% CI), p-value(^c)</td>
<td>1.02 (0.48, 2.18), p=0.959</td>
<td></td>
</tr>
<tr>
<td><strong>Disease control rate (DCR)(^d)</strong>, number of patients</td>
<td>n = 85</td>
<td>n = 80</td>
</tr>
<tr>
<td>DCR, % of patients (95% CI)(^b)</td>
<td>97.7 (91.9, 99.7)</td>
<td>94.1 (86.8, 98.1)</td>
</tr>
<tr>
<td>Odds ratio (95% CI), p-value(^c)</td>
<td>2.70 (0.49, 14.75), p=0.252</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of response (DoR) (median, 95% CI), months(^e)</strong></td>
<td>19.6 (16.6, NR)</td>
<td>9.0 (6.9, 13.8)</td>
</tr>
<tr>
<td><strong>Best overall response, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Response (CR)</td>
<td>1 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>69 (79.3)</td>
<td>68 (80.0)</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>15 (17.2)</td>
<td>12 (14.1)</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>1 (1.1)</td>
<td>3 (3.5)</td>
</tr>
<tr>
<td>Not Evaluable</td>
<td>1 (1.1)</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td><strong>Percentage of patients remaining in response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6 months</td>
<td>92.7</td>
<td>68.0</td>
</tr>
<tr>
<td>At 12 months</td>
<td>77.9</td>
<td>40.2</td>
</tr>
<tr>
<td>At 18 months</td>
<td>59.5</td>
<td>24.7</td>
</tr>
<tr>
<td>At 24 months</td>
<td>46.8</td>
<td>14.5</td>
</tr>
</tbody>
</table>

\(^a\) ORR was defined as the percentage of patients with measurable disease with at least one recorded status of complete response (CR) or partial response (PR). \(^b\) 95% exact confidence intervals (CI) were computed using the Clopper-Pearson method. \(^c\) ORR and DCR were analysed using logistic regression models stratified by mutation type. \(^d\) DCR was defined as the percentage of patients who had a best overall response of CR or PR or stable disease (SD for ≥6 weeks, prior to any progression event). \(^e\) Median duration and 95% CI were calculated from Kaplan-Meier estimates. NR=not reached.
Table 3. Overall summary of adverse events

<table>
<thead>
<tr>
<th>Adverse events, n (% of patients)</th>
<th>Lazertinib (n=87)</th>
<th>Gefitinib (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs, any cause</td>
<td>87 (100)</td>
<td>84 (98.8)</td>
</tr>
<tr>
<td>Any Grade ≥3 AE</td>
<td>34 (39.1)</td>
<td>43 (50.6)</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>29 (33.3)</td>
<td>24 (28.2)</td>
</tr>
<tr>
<td>Any AE leading to death</td>
<td>4 (4.6)</td>
<td>3 (3.5)</td>
</tr>
<tr>
<td>Any AE leading to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporary drug interruption</td>
<td>26 (29.9)</td>
<td>29 (34.1)</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>18 (20.7)</td>
<td>10 (11.8)</td>
</tr>
<tr>
<td>Permanent discontinuation</td>
<td>11 (12.6)</td>
<td>11 (12.9)</td>
</tr>
<tr>
<td>AEs, possibly causally related</td>
<td>82 (94.3)</td>
<td>77 (90.6)</td>
</tr>
<tr>
<td>Any related Grade ≥3 AE</td>
<td>15 (17.2)</td>
<td>23 (27.1)</td>
</tr>
<tr>
<td>Any related serious AE</td>
<td>5 (5.7)</td>
<td>4 (4.7)</td>
</tr>
<tr>
<td>Any related AE leading to death</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 4. Summary of adverse events reported in ≥15% of patients in either treatment group

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Lazertinib (n=87)</th>
<th>Gefitinib (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade, n (%)</td>
<td>Grade ≥3, n (%)</td>
</tr>
<tr>
<td>Rash</td>
<td>40 (46.0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>38 (43.7)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>25 (28.7)</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>46 (52.9)</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>23 (26.4)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>11 (12.6)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>25 (28.7)</td>
<td>0</td>
</tr>
<tr>
<td>Paronychia</td>
<td>15 (17.2)</td>
<td>0</td>
</tr>
<tr>
<td>AST increased</td>
<td>9 (10.3)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>17 (19.5)</td>
<td>0</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>15 (17.2)</td>
<td>0</td>
</tr>
<tr>
<td>Productive cough</td>
<td>4 (4.6)</td>
<td>0</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Fig. 1. Patient disposition. DCO, data cut-off.
Fig. 2. Kaplan-Meier estimates of investigator-assessed progression-free survival (PFS) by treatment group.
Fig. 3. Hazard ratios for progression or death in predefined patient sub-groups. Subgroup categories with less than 20 events were excluded from the analysis.
**Fig. 4.** Kaplan-Meier estimates of investigator-assessed progression-free survival (PFS) for A. Patients with brain metastases at study entry. B. Patients without brain metastases at study entry. NR, not reached.
Fig. 5. Kaplan-Meier estimates of investigator-assessed progression-free survival for A. Patients with Ex19del mutation; B. Patients with L858R mutation. NR, not reached.
Supplementary materials

1. Study design, treatments, and assessments

The LASER301 study was a randomised, double-blind, multinational phase III study to assess the efficacy and safety of lazertinib 240 mg administered once daily orally compared with gefitinib 250 mg administered once daily orally in treatment-naïve patients with locally advanced or metastatic NSCLC and EGFR mutations (Ex19del or L858R substitution).

During screening, a period up to 28 days prior to randomisation, patients were assessed for eligibility. Patients were enrolled based on either a locally available EGFR mutation result, performed in an accredited local laboratory based on the Qiagen-Therascreen® EGFR Mutation Detection Kit RGQ (Scorpions ARMS), the Amoy Diagnostics-the AmoyDx® EGFR Mutation Test Kit, the PANAGENE-PANAMutyper™ or the Roche Diagnostics-Cobas® EGFR Mutation Test v2, or at a designated central laboratory. All patients who were enrolled based on locally available EGFR mutation results, were required to provide biopsy tissue and blood for central testing of the two most common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del and L858R).

A total of 393 patients were randomised in a 1:1 ratio to either lazertinib (n=196) or gefitinib (n=197). Randomisation was stratified by race (Asian vs. non-Asian) and mutation status (Ex19del vs. L858R).

Eligible patients were administered the investigational product (IP) orally once daily with or without food. A cycle of treatment was defined as 21 days. Patients continued on their randomised treatment until RECIST version 1.1 (v1.1) defined progression or until a treatment discontinuation criterion was met. However, patients could continue to receive their randomised treatment beyond RECIST v1.1 defined progression as long as they continued to show clinical benefit, as judged by the investigator.

Efficacy assessments according to RECIST v1.1 were performed every 6 weeks for the first 18 months and then every 12 weeks relative to date of randomisation using the RECIST v1.1 until objective progression. Patients were followed for survival every 6 weeks following objective disease progression.

Adverse events (AEs) were graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.
For patients who could not tolerate the protocol-specified dosing schedule due to drug related toxicities, dose interruptions and/or reductions were recommended in order to allow patients to continue the treatment. Where a patient required a dose interruption of > 21 days from the intended day of the next scheduled dose due to study treatment related toxicity, the patient was discontinued from the study treatment.

1) Cross-over treatment (gefitinib arm)

Patients who were randomised to the gefitinib arm had the option to receive open-label lazertinib following objective disease progression according to RECIST v1.1, as per investigator assessment, provided ALL the following criteria were met, and the patient wished to do so:

- Disease progression confirmed by blinded independent central review (BICR) which had to be established prior to a patient being unblinded. (Note: if disease progression was not centrally confirmed, the patient was not eligible to be considered for cross-over. Should it be in the patient’s best interests, they could continue to receive randomised treatment and submit the next scan for central imaging review according to the study schedule.)
- Tumour confirmed as T790M mutation positive by means of plasma or tissue testing (local or central) following disease progression had to be established prior to a patient being unblinded.
- The patient could not cross-over if they received intervening therapy following discontinuation of randomised treatment.
- Any unresolved toxicities from prior therapy had to be controlled, and be no greater than CTCAE grade 1 (with the exception of alopecia) at the time of starting open-label lazertinib treatment.

Provided all of the above criteria were met, and the patient was randomised to the gefitinib arm, the patient was permitted to commence open-label lazertinib. If the patient was unblinded and found not eligible for cross-over or chose not to cross-over, the patient was not permitted to recommence or continue on the randomised treatment. After the Independent Data Monitoring Committed (IDMC) in consultation with sponsor and regulators determined that the primary endpoint of PFS was achieved, all patients determined to have objective disease progression according to RECIST v1.1 as per Investigator’s assessment and T790M mutation
positive were given the opportunity to begin treatment with open-label Lazertinib. Central blinded confirmation of disease progression was not required if the patient was eligible under the criteria described above.

2. Inclusion and exclusion criteria

Patients were eligible to be included in the study only if all of the following criteria applied:

1) Age and Sex
   - Male or female patients had to be ≥ 18 years of age and satisfy the legal age of consent in the jurisdiction in which the study was being conducted.

2) Type of Patient and Disease Characteristics
   - Patients with pathologically confirmed adenocarcinoma of the lung (e.g., as systemic recurrence after prior surgery for early stage disease or Patients newly diagnosed with Stage IIIB/C or IV disease). Patients with mixed histology were eligible if adenocarcinoma was the predominant histology.
   - Patients with locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy.
   - Patients with at least 1 of the 2 common EGFR mutations known to be associated with EGFR TKI sensitivity (Ex19del or L858R), either alone or in combination with other EGFR mutations, assessed in tissue biopsy by an accredited local laboratory based on the Qiagen-Therascreen® EGFR Mutation Detection Kit RGQ (Scorpions ARMS), the Amoy Diagnostics-the AmoyDx® EGFR Mutation Test Kit, the PANAGENE-PANAMutyperTM or the Roche Diagnostics-Cobas® EGFR Mutation Test v2 or by central testing in a designated laboratory.
   - Mandatory provision of an unstained, archived tumor tissue sample in a quantity sufficient to allow for central analysis of EGFR mutation status for patients.
   - Patients had to be treatment-naïve for locally advanced or metastatic NSCLC. (Note: Prior adjuvant and neo-adjuvant therapy (e.g., chemotherapy, radiotherapy, investigational products) for early stage disease was permitted if completed > 12 months prior to randomisation provided all other entry criteria were satisfied)
Patients must have a WHO performance status score of 0 to 1 with no clinically significant deterioration over the previous 2 weeks before randomisation.

Patients must have at least 1 measurable lesion, not previously irradiated and not chosen for biopsy during the study Screening period, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have a short axis of ≥15 mm) with computerised tomography (CT) or magnetic resonance imaging (MRI), and which was suitable for accurate repeated measurements. If only 1 measurable lesion exists, it was acceptable to be used (as a target lesion) as long as it had not been previously irradiated and baseline tumour assessment scans were done at least 2 weeks after the screening biopsy was performed.

3) Male Patients

A male patient who had not undergone a vasectomy must agree to follow the contraceptive guidance in Appendix 3 of this protocol during the study treatment period and for at least 24 weeks after the last dose of study treatment and refrain from donating sperm during this period.

4) Female Patients

A female patient was eligible to participate if she was not pregnant, not breastfeeding, and at least one of the following conditions applies:

- Not a woman of childbearing potential (WOCBP) OR
- A WOCBP who agreed to follow the contraceptive guidance from the time of screening until 24 weeks after the last dose of study treatment.
- A WOCBP must have a negative serum pregnancy test (beta human chorionic gonadotropin) at screening.

Patients were excluded from the study if any of the following criteria applied:

5) Medical Conditions

Symptomatic and unstable brain metastases. Patients with asymptomatic and stable brain metastases may participate in this study. If treatment was required, these Patients must have completed any planned radiation therapy and/or surgery, were not on steroids, for >2 weeks prior to randomisation, and remain asymptomatic. Patients had to be neurologically stable,
having no new neurologic deficits on clinical examination, and no new findings on central nervous system (CNS) imaging.

- Leptomeningeal metastases
- Symptomatic spinal cord compression. If steroid treatment was not required within at least 2 weeks prior to randomisation then the patient may be enrolled.
- History of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD.
- Any medical conditions requiring chronic continuous oxygen therapy.
- History of any malignancy other than the disease under study within 3 years before randomisation (exceptions were squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with concurrence with the medical monitor, was considered cured, or with minimal risk of recurrence within a year from screening).
- Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the Investigator’s opinion made it undesirable for the patient to participate in the study, or which would jeopardise compliance with the protocol.
- Any cardiovascular disease as follows:
  - History of symptomatic chronic heart failure or serious cardiac arrhythmia requiring active treatment.
  - History of myocardial infarction or unstable angina within 24 weeks of randomisation.
- Positive hepatitis B (HBV) surface antigen (HBsAg), Positive hepatitis C antibody (anti-HCV), other clinically active infectious liver disease or confirmed positive human immunodeficiency virus test results. (Note: Patients with a prior history of HCV, who have completed antiviral treatment and have subsequently documented HCV RNA below the lower limit of quantification per local testing were eligible.)
- Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of study treatment.
- History of hypersensitivity to active or inactive excipients of investigational product(s), or drugs with a similar chemical structure or class to investigational product(s).
Any history of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption
Clinically significant chronic infection or significant medical or psychiatric illness.
Undergone a bone marrow or solid organ transplant.
Any condition which would prevent patient compliance with study procedures, restrictions, and requirements, as determined by the Investigators.

6) Prior/Concomitant Therapy
Prior treatment with any systemic antineoplastic therapy for locally advanced or metastatic NSCLC (Stage IIIB/C or Stage IV) including chemotherapy, biological therapy, immunotherapy, or any investigational drug.
Any prior treatment with an epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI).
Major surgery (excluding placement of vascular access) within 4 weeks of randomisation.
Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of randomisation.
Patients currently receiving (or unable to stop use for an appropriate washout period prior to randomisation) medications or herbal supplements known to be potent CYP3A4 inhibitors or inducers (Appendix 6).
Patients currently receiving the unstable doses of warfarin as an anticoagulant.
Patients who had been treated with alternative anti-cancer treatment within 5 half-lives of the treatment or within 4 weeks (whichever was longer) prior to randomisation.
Any unresolved toxicities from prior therapy, greater than CTCAE grade 1 at randomisation, with the exception of alopecia and grade 2, prior chemotherapy-induced neuropathy.

7) Prior/Concurrent Clinical Study Experience
Patients who had been treated with an investigational drug within 5 half-lives of the compound or within 4 weeks (whichever was longer) prior to randomisation.

8) Diagnostic Assessments
Patients had any of following cardiac criteria:
• Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block, second degree heart block, PR interval >250msec).
• Mean resting QTc >470 msec obtained from 3 electrocardiograms (ECGs), using the screening ECG machine derived QTc value.
• Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first degree relatives or any concomitant medications known to prolong QT interval or induce Torsades de Pointes.
• Left ventricular ejection fraction <50%

• Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:
  • Absolute neutrophil count <1.5 x 10^9/L.
  • Platelet count <100 x 10^9/L.
  • Hemoglobin <90 g/L.
  • Alanine aminotransferase >2.5 times the upper limit of normal (ULN) if no demonstrable liver metastases, or >5x ULN in presence of liver metastases.
  • Aspartate aminotransferase >2.5x ULN if no demonstrable liver metastases or >5x ULN in the presence of liver metastases.
  • Total bilirubin >1.5x ULN if no liver metastases or >3x ULN in the presence of documented Gilbert’s syndrome (unconjugated hyperbilirubinemia) or liver metastases.
  • Serum creatinine >1.5x ULN concurrent with creatinine clearance <50 ml/min measured by the study site’s standard method (e.g., Cockcroft and Gault equation). Confirmation of creatinine clearance was only required when creatinine was >1.5x ULN.

3. Sample size considerations

The Korean subset was a subgroup of the overall LASER301 study population for which no formal sample size estimation or power calculations were performed. The statistical
comparison for the treatment effect on the primary efficacy endpoint of PFS by investigator assessment was not powered for the Korean subset.
**S1 Fig.** Study design.

- **Eligibility assessments**
  - N=380 (1:1)

- **Stratification Factor**
  - Mutation type (Ex19del or L858R)
  - Asian vs. Non-Asian

- **Screening period**
  - All patients to have RECIST v1.1 assessments every 6 weeks for the first 18 months and then every 12 weeks

- **Treatment period**
  - Lazertinib 240 mg orally once daily (N=190)
  - Gefitinib 250 mg orally once daily (N=190) *For optional cross-over to open label lazertinib

- **Post-treatment follow-up**
  - All patients to be followed for PFS2 and OS every 6 weeks

*If disease progression assessed by the investigator according to RECIST v1.1 is confirmed by blinded independent central review (BICR), and T790M mutation positive, it will be given the opportunity of open-label lazertinib treatment to patients who were randomized to the gefitinib.*
S2 Fig. Kaplan-Meier estimates of progression-free survival (PFS) by blinded independent central review.
S3 Fig. Interim analysis of overall survival (OS).
S4 Fig. Trough plasma concentration-time profile of lazertinib after 240 mg once-daily administration. Data shown are the geometric mean ± 95% confidence intervals of the plasma concentration of lazertinib (pre-dose, 1–3 hours, and 4–6 hours) on each Day 1 of Cycle 1, 2, 5, 9 and 13 after lazertinib 240 mg once-daily administration.