Supplementary Materials

1. Study design, treatments, and assessments

The LASER301 study was a randomized, 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 non–small cell lung cancer (NSCLC) and epidermal growth factor receptor (EGFR) mutations (Ex19del or L858R substitution).

During screening, a period up to 28 days prior to randomization, 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 randomized in a 1:1 ratio to either lazertinib (n=196) or gefitinib (n=197). Randomization was stratified by race (Asian vs. non-Asian) and mutation status (Ex19del vs. L858R).

Eligible patients were administered the investigational product orally once-daily with or without food. A cycle of treatment was defined as 21 days. Patients continued on their randomized treatment until RECIST ver. 1.1 (v1.1) defined progression or until a treatment discontinuation criterion was met. However, patients could continue to receive their randomized 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 randomization 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 randomized 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 randomized treatment and submit the next scan for central imaging review according to the study schedule.)
- Tumor 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 randomized 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 randomized 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 randomized 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 one of the two 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-PANAMutyper 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 randomization 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 randomization.
- Patients must have at least one 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 or magnetic resonance imaging (MRI), and which was suitable for accurate repeated measurements. If only one measurable lesion exists, it was acceptable to be used (as a target lesion) as long as it had not been previously irradiated and baseline tumor 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 had to use reliable methods of contraception (e.g., sexual abstinence; male condom plus partner use of adequate contraception) from randomization until at least 24 weeks after discontinuation 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 randomization, 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 randomization 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 randomization (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 randomization.
• Positive hepatitis B virus 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 randomization.
• Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of randomization.
• Patients currently receiving (or unable to stop use for an appropriate washout period prior to randomization) medications or herbal supplements known to be potent CYP3A4 inhibitors or inducers. Examples of potent CYP3A4 inhibitors: boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir, dasabuvir, diltiazem, elvitegravir, indinavir, ketoconazole, nelfinavir, paritaprevir, ritonavir, saquinavir, tipranavir, grapefruit juice, lopinavir, telaprevir, telithromycin, troleandomycin, atazanavir, darunavir, mibefradil, nefazodone, ombitasvir ,voriconazole, itraconazole, posaconazole. Examples of potent CYP3A4 inducers: phenytoin, rifapentine, St. John’s wort, carbamazepine, phenobarbital, rifabutin, rifampin (rifampicin).
• Patients currently receiving the unstable doses of warfarin as an anticoagulant.
• Patients who had been treated with alternative anticancer treatment within five half-lives of the treatment or within 4 weeks (whichever was longer) prior to randomization.
• Any unresolved toxicities from prior therapy, greater than CTCAE grade 1 at randomization, 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 five half-lives of the compound or within 4 weeks (whichever was longer) prior to randomization.
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 > 250 msec).
  - Mean resting QTc >470 msec obtained from three 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 < 1.5×10^9/L.
  - Platelet count < 100×10^9/L.
  - Hemoglobin < 90 g/L.
  - Alanine aminotransferase > 2.5 times the upper limit of normal (ULN) if no demonstrable liver metastases, or > 5× ULN in presence of liver metastases.
  - Aspartate aminotransferase > 2.5× ULN if no demonstrable liver metastases or > 5× ULN in the presence of liver metastases.
  - Total bilirubin > 1.5× ULN if no liver metastases or > 3× ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia) or liver metastases.
  - Serum creatinine > 1.5× 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 > 1.5× 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.