






## STUDY PROTOCOL

# A phase II, multicenter study of lazertinib as consolidation therapy in patients with locally advanced, unresectable, *EGFR* mutation-positive non-small cell lung cancer (stage III) who have not progressed following definitive, platinum-based, chemoradiation therapy (PLATINUM trial)

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## Abstract

**Introduction:** The PACIFIC study demonstrated that durvalumab consolidation therapy significantly improved progression-free survival (PFS) and overall survival (OS) in patients with unresectable stage III non-small cell lung cancer (NSCLC) after concurrent chemoradiotherapy (CCRT). However, there was no clinical benefit in both PFS and OS in epidermal growth factor receptor (EGFR) mutation-positive patient groups in a post hoc exploratory analysis. Moreover, the clinical effects of immune checkpoint inhibitors (ICIs) in *EGFR* mutation-positive stage IV NSCLC were demonstrated to be poor. Personalized treatment according to the mutation status is also required in stage III NSCLC. Lazertinib, a third-generation *EGFR* tyrosine kinase inhibitor (TKI), is newly developed and approved for use in Korea.

**Methods:** This prospective, open, single-arm, multicenter, phase II clinical trial aims to evaluate the efficacy and safety of lazertinib as a consolidative therapy after CCRT treatment in unresectable, *EGFR* mutation-positive NSCLC stage III patients. The primary endpoint of this study is PFS, and the secondary endpoints are OS, objective

Clinical Trial Registration: This study is registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (<https://clinicaltrials.gov>, registration number NCT05338619).

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response rate (ORR), duration of response (DoR), time to death or distant metastasis (TTDM), and safety profiles.

**Discussion:** Our study may extend the indications for third-generation EGFR-TKIs to treat patients with stage III NSCLC. Moreover, using this drug to treat stage III NSCLC would emphasize the value of mutation analysis and personalized medicine.

#### KEYWORDS

chemoradiotherapy, consolidation therapy, EGFR, lazertinib

## INTRODUCTION

With the development of target therapy and immune checkpoint inhibitors (ICIs), the treatment landscape of non-small cell lung cancer (NSCLC) is constantly evolving.<sup>1</sup> However, the 24-month survival rate of patients with stage III NSCLC is still low, ranging from 27.0% to 45.3%.<sup>2</sup> Stage III NSCLC has various treatment options including concurrent chemoradiotherapy (CCRT). Consolidation therapy after CCRT is also being studied.<sup>3</sup> The PACIFIC study demonstrated that durvalumab consolidation therapy significantly improved progression-free survival (PFS) and overall survival (OS) in patients with unresectable stage III NSCLC.<sup>4</sup> In the PACIFIC study, patients were allowed to participate regardless of their mutation status. Out of a total of 713 participants, only 35 (4.9%) patients were epidermal growth factor receptor (EGFR) mutation-positive. Of these patients 24 (68.6%) received durvalumab and 11 (31.4%) received a placebo. There was no clinical benefit in terms of PFS and OS for these *EGFR* mutation-positive patient groups (hazard ratio [H<sup>1</sup>R] = 0.91, HR = 1.02, respectively).<sup>5</sup> A recent post hoc subgroup analysis also showed that PFS and OS outcomes with durvalumab were similar to those with placebo in the *EGFR* mutant population.<sup>5</sup> The benefit of ICI consolidation therapy in this population remains unclear.

The prevalence of *EGFR* mutation has previously been reported to be approximately 30%–50% in an Asian population with lung adenocarcinoma, and in this study it was determined that there was no relationship with cancer stage.<sup>6</sup> *EGFR* mutation is common in women, nonsmokers, and Asians, and in a report analyzing 85 clinical studies, it was confirmed to be 33.8% (29.8% to 37.8%) in stage III NSCLC.<sup>7</sup> Although there may be differences depending on the *EGFR* type, the effect of ICIs in *EGFR* mutation-positive stage IV NSCLC is poor.<sup>8</sup> Just as “personalized treatment” for each patient is performed according to the mutation status and programmed death-ligand 1 (PD-L1) expression in advanced NSCLC stage IV, the consolidation therapy of unresectable stage III NSCLC requires an individual optimized treatment. Recently, a prospective study using concurrent thoracic radiotherapy with a first-generation *EGFR* TKI instead of cytotoxic chemotherapy demonstrated the tolerability and possible efficacy in *EGFR* mutation-positive NSCLC.<sup>9</sup> In a multi-institutional retrospective analysis of patients with unresectable stage III *EGFR*-mutation-positive NSCLC who underwent CCRT, it was reported that

durvalumab consolidation therapy showed no benefit in PFS ( $p = 0.993$ ).<sup>10</sup> Furthermore, it was reported that there was a statistically significant improvement in PFS when third-generation *EGFR* tyrosine kinase inhibitor (TKI) was administered after CCRT ( $p = 0.023$ ) in a retrospective study.<sup>10</sup>

There have been studies analyzing the usefulness of first- or second-generation *EGFR* TKIs after surgery in stage II–IIIA NSCLC patients.<sup>11–13</sup> However, first- or second-generation *EGFR* TKIs did not demonstrate improvement in OS in patients with operable NSCLC. On the other hand, the ADAURA study showed that osimertinib as adjuvant therapy after surgery significantly prolonged disease-free survival in *EGFR* mutation-positive patients.<sup>14</sup> Based on multi-institutional retrospective analysis and the ADAURA study performed in the adjuvant setting, third-generation *EGFR*-TKIs can be a feasible option as consolidation treatment after CCRT in *EGFR*-mutant NSCLC.

Lazertinib, approved for use in Korea in 2021, is a third-generation *EGFR*-TKI similar to osimertinib and has shown excellent anticancer effects in preclinical studies and in early clinical settings.<sup>15,16</sup> It is a novel, highly potent, blood–brain barrier (BBB)-penetrating, irreversible *EGFR*-TKI, which selectively blocks *EGFR* sensitizing and T790M mutations. It showed an excellent antitumor effect and good BBB permeability in an *EGFR*-mutant brain metastasis model.<sup>14</sup> Lazertinib also demonstrated clinically significant efficacy and safety in patients with advanced *EGFR* T790M-positive NSCLC after previous *EGFR* TKIs through a phase I/II study (median PFS was 11.1 months and the ORR was 55.3%).<sup>16</sup> Regarding recurrence patterns, there were more distant metastases in *EGFR* mutation NSCLC than in wild-type (76% vs. 40%,  $p = 0.001$ ).<sup>17</sup> In particular, brain recurrence was 35% in *EGFR*-mutant NSCLC and 15% in wild-type.<sup>17</sup> Since lazertinib has good BBB permeability, it can effectively inhibit brain metastasis and be a good option for consolidation therapy after CCRT in *EGFR* mutation-positive stage III NSCLC.

The aim of this study was to confirm the efficacy and safety of lazertinib consolidation therapy in patients with unresectable, *EGFR* mutation-positive stage III NSCLC. The positive results of this study may extend the indications for third-generation *EGFR*-TKIs to inoperable *EGFR* mutation-positive stage III NSCLC patients, thereby also drawing attention to mutation analysis and personalized medicine in stage III NSCLC treatment.

## METHODS

### Study design

The PLATINUM trial is a prospective, open, single-arm, multicenter, phase II clinical trial (Figure 1). This trial aims to evaluate the efficacy and safety of lazertinib as a consolidative therapy after CCRT treatment in unresectable, *EGFR* mutation-positive NSCLC stage III patients. The target number of enrolled patients is 77, and nine university hospitals will undertake competitive enrollment. Aiming for the statistically adequate number of cases to be 70, the number was set at 77, considering the 10% dropout rate. The patient registration period is from June 2022 to May 2023, and patient registration ends when all the target patient groups are registered. We plan to follow up for 3 years from the time of the last participant registration, when the final analysis would be carried out. Interim analysis is performed when more than 39 (50% of 77) patients have enrolled (at least 24 months after the start of the study). Regarding median progression-free survival (mPFS), we speculate with reference to previous studies involving osimertinib in untreated, *EGFR*-mutated advanced NSCLC and durvalumab in the PACIFIC trial. We estimate that the mPFS of this study should show the efficacy of at least 18.9 months of the FLAURA trial, and that it should have a threshold higher than PFS of 16.8 months (durvalumab group) of the PACIFIC trial.

The Data and Safety Monitoring Board comprises two medical experts and one statistician. This protocol was approved by the Institutional Review Board of all participating institutes. This study will follow the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including the study of identifiable human substances and data.

The primary endpoint of this study is PFS, defined as the time from the study registration to the disease progression or death in the case of death without disease progression. The secondary endpoints are OS, ORR, duration of response (DoR), and time to death or distant metastasis (TTDM). OS is defined as the time from the trial registration date to death due to any reason. If the subject's mortality is unknown by the time of analysis, statistical follow-up analysis is performed by the last known surviving date. ORR is the ratio (%) of patients with at least one complete or partial response based on response evaluation criteria in solid tumor (RECIST) version 1.1. DoR is the time from the date of the first documented response until the first date of documented progression (or death in the absence of disease progression). TTDM is defined as the time from the enrollment date until the first date of distant metastasis or death without distant metastasis. Safety profiles evaluate adverse events, adverse drug reactions, serious adverse events, and permanent discontinuation due to adverse events, based on common terminology criteria for adverse events (CTCAE) version 5.0.

- Unresectable Stage III NSCLC without progression after definitive CCRT
- *EGFR* mutation positive (Ex19del or L858R)
- 18 years or older
- ECOG PS score 0, 1

Lazertinib 240mg daily QD (N=77)  
28-day / cycle

Treatment until RECIST v1.1-defined PD, until intolerable toxicity

#### Primary end point

- PFS

#### Secondary end points

- OS, ORR, DoR, TTDM, safety profile

**FIGURE 1** Study flowchart. PD, progressive disease; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; DoR, duration of response; TTDM, time to death or distant metastasis

## Eligibility criteria

The inclusion criteria are as follows: (a) Age > 18 years; (b) histologically confirmed as having locally advanced, unresectable, stage III NSCLC (staging according to the International Association for the Study of Lung Cancer [IASLC] staging manual version 8 in thoracic oncology); (c) tissue is positive for *EGFR* mutation (exon 19del or L858R); (d) Eastern Cooperative Oncology group (ECOG) performance status 0 or 1; (e) life-expectancy of 6 months or more at the time of registration; (f) patients who received two or more cycles of platinum-based CCRT for curative purposes and within 1–42 days after the end of the last radiation therapy; (g) patients without disease progression after CCRT; (h) patients with a total radiation dose of 60 Gy  $\pm$  10% (54–66 Gy); and (i) voluntary agreement in writing by the patient or his/her legal representative to participate in this clinical trial. Patients with a history of interstitial lung disease, symptomatic pneumonitis following CCRT, other primary malignancies, or previous *EGFR*-TKI treatment will be excluded from the study.

## Data collection

As baseline characteristics, information on sex, age, and history of smoking, related lung diseases, cardiovascular disease, previous cancer, and other comorbidities will be collected. Information related to CCRT, including the cytotoxic chemotherapy regimen, dose reduction, total radiation dose, and the best response, will be collected. For lung cancer, information on pathology type, stage, mutation analysis, and PD-L1 status will be collected. Mutation analysis and PD-L1 status are based on biopsy at the time of diagnosis prior to CCRT. In the case of the *EGFR* test, it will be performed on cancer tissue during enrollment, and on tissue or liquid sample when it progresses.

Each cycle is based on every 4 weeks  $\pm$  3 days (28 days  $\pm$  3 days) unless there is a delay in administration due to toxicity. Regardless of the delay in administering the test drug, one visit every 8 weeks  $\pm$  1 week is required to conduct follow-up imaging tests and evaluations. Safety profiles and concomitant medications will be evaluated at every cycle.

## Treatment plan

Following the approval of lazertinib for use in Korea (approval date January 18, 2021), the recommended dose of lazertinib in this clinical trial is 240 mg (80 mg, three tablets), taken orally at a fixed time once every day, regardless of the meals. Lazertinib is administered from the study enrollment date (cycle 1, first day of CID1) to disease progression or unacceptable toxicity. Patients will receive lazertinib for at least 3 years. At the end of 3 years, additional use of lazertinib is possible at the judgment of the

investigator. If a dose reduction is necessary according to safety and tolerability, the dosage can be reduced to 160 mg (80 mg, 2 tablets) once a day.

## Statistical analysis

All statistical analyses are two-sided, and the confidence interval (CI) is set to 95%. The analysis tool will use the statistical program SAS version 9.4 (SAS Institute Inc.). The mean, standard deviation, median, minimum, quartile, maximum, and 95% CI will be presented for continuous data, whereas frequency and percentage (%) will be presented for categorical data. The Kaplan–Meier method and log-rank test will analyze PFS, OS, DoR, and TTDM. For subjects who will have not experienced an event by the time of analysis, the last date of evaluation or the last date the subject is known to be alive, will be considered. ORR and safety evaluation will analyze the frequency and proportion of subjects.

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## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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