ORIGINAL ARTICLE

Lazertinib for Patients with NSCLC Harboring Uncommon EGFR Mutations: A Phase II Multicenter Trial

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ABSTRACT

Introduction: Uncommon *EGFR* mutations comprise 10% to 20% of all *EGFR* mutations in NSCLC and generally report reduced responsiveness to EGFR tyrosine kinase inhibitors (TKIs). Lazertinib, a third-generation EGFR-TKI, has found efficacy in common *EGFR* mutations, but its potential in uncommon mutations remains unexplored. This study investigated the efficacy and safety of lazertinib in patients with NSCLC with uncommon *EGFR* mutations.

Method: This single-arm, multicenter phase II trial enrolled patients with advanced NSCLC harboring uncommon *EGFR* mutations excluding exon 20 insertions. Patients received lazertinib 240 mg daily until disease progression or unacceptable toxicity. The primary end point was objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors version 1.1. Secondary end points included progression-free survival (PFS), overall survival (OS), duration of response (DoR), and safety.

Results: Among 36 patients enrolled, the ORR was 50.0% (95% confidence interval [CI]: 34.5%–65.5%), with 18 partial responses, meeting the primary end point. Disease control rate was 88.9% (95% CI: 74.1%–96.2%). Patients with major uncommon mutations (G719X, L861Q, S768I) reported an ORR of 54.8% (17/31). Median PFS was 10.8 months (95% CI: 4.4–19.2), and median DoR was 15.1 months. G719X mutations reported the highest response (ORR 61%, median PFS 20.3 months), followed by S768I (ORR 60%) and L861Q (ORR 58%, median PFS 9.5 months). Treatment-emergent adverse events occurred in all patients, with grade 3 or higher events in 33.3%; most common were rash (47.2%), pruritus (36.1%), and muscle spasms (33.3%).

Conclusions: Lazertinib reported promising efficacy and a manageable safety profile in patients with NSCLC with uncommon EGFR mutations, particularly for G719X, S768I, and L861Q subtypes. These results suggest lazertinib could be an effective treatment option for this heterogeneous patient population with limited therapeutic alternatives.

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Introduction

EGFR mutations are implicated in approximately 20% of NSCLC cases in Caucasian populations, with a higher prevalence of greater than 50% in Asian populations.[1] The predominant *EGFR* mutations include exon 19 deletions and exon 21 L858R mutations, collectively known as common or sensitizing *EGFR* mutations, which comprise 80% to 90% of all *EGFR* mutations. Targeted therapies using EGFR tyrosine kinase inhibitors (EGFR-TKIs) have substantially enhanced survival rates and clinical outcomes for patients with these mutations.[2] In contrast, uncommon or atypical *EGFR* mutations generally report reduced responsiveness to EGFR-TKIs compared with common mutations.[3,4]

Uncommon *EGFR* mutations, comprising approximately 10% to 20% of all *EGFR* mutations, represent a highly heterogeneous group predominantly located in exons 18 to 21.[5] The major uncommon mutations, including G719X (exon 18), S768I (exon 20), and L861Q (exon 21), are categorized as "major uncommon mutations" owing to their relatively higher prevalence, accounting for approximately 3%, 1%, and 1% of all *EGFR* mutations, respectively. In contrast to the common *EGFR* mutations, uncommon *EGFR* mutations exhibit variable sensitivities to EGFR-TKIs, with lower response rates and shorter progression-free survival than those of common mutations. Afatinib, a second-generation EGFR-TKI, is the only US Food and Drug Administration-approved treatment for uncommon *EGFR* mutations, based on its manifest efficacy in post hoc analyses of the LUX-Lung trials: LUX-Lung 2 (NCT00525148; a phase II trial of afatinib in patients with *EGFR* mutation–positive advanced NSCLC), LUX-Lung 3 (NCT00949650; a randomized phase III trial comparing afatinib to cisplatin plus pemetrexed), and LUX-Lung 6 (NCT01121393; a randomized phase III trial comparing afatinib to cisplatin plus gemcitabine in Asian patients).[6] Despite this progress, large-scale studies have found that therapeutic outcomes for uncommon *EGFR* mutations are inconsistent.[7]

Lazertinib, a third-generation EGFR-TKI, has reported significant clinical efficacy and a favorable safety profile in patients with NSCLC harboring common *EGFR* mutations, including its role as a backbone therapy for combination regimens.[8,9] Nevertheless, its therapeutic potential in uncommon *EGFR* mutations remains largely unexplored. To address this gap, we conducted a prospective phase II trial (KCSG-LU21-16) investigating the efficacy and safety of lazertinib in patients with NSCLC harboring uncommon *EGFR* mutations, excluding exon 20 insertions. This study represents a critical step toward understanding the clinical utility of lazertinib for this heterogeneous and understudied patient population.

Materials and Methods

Study Design and Patients

This prospective, single-arm, multicenter phase II trial was conducted in the Republic of Korea (ClinicalTrials.gov identifier: NCT05277701). The study protocol was approved by the relevant institutional review boards, and all patients provided written informed consent. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonization.

Patients eligible for inclusion in this study had histologically or cytologically confirmed locally advanced or metastatic NSCLC that was ineligible for surgery or radiation therapy with curative intent. Participants were required to be aged at least 20 years, have an Eastern Cooperative Oncology Group performance status of 0 to 2, and report adequate organ function. Eligible patients harbored uncommon *EGFR* mutations, defined as point mutations or duplications in exons 18 to 21, excluding *EGFR* exon 19 deletion, L858R, T790M, and exon 20 insertions, with included mutations being G719X, S768I, L861Q, their combinations (G719X + S768I, G719X + L861Q, L861Q + S768I), L747S, S720A, E709A, and exon 18 deletions. Nevertheless, compound uncommon *EGFR* mutations combined with common mutations, such as *EGFR* del19, L858R, or T790M, and *EGFR* exon 20 insertions were excluded. For the identification of *EGFR* mutations, both cell-free DNA and tissue-based DNA testing, including both locally and centrally performed PCR and next-generation sequencing (NGS), were accepted for identifying these mutations.

Exclusion criteria included prior treatment with any EGFR-TKI and uncontrolled central nervous system (CNS) metastases or leptomeningeal carcinomatosis. Patients with uncontrolled systemic illnesses, such as hypertension, active bleeding, or active infections, were also excluded. Moreover, individuals with a history of malignancy within 5 years of study entry were excluded, unless the malignancy was basal or squamous cell skin cancer, in situ cervical cancer, well-treated thyroid cancer, early gastric cancer, or otherwise deemed curatively treated by the principal investigator.

Study Procedure

Patients received a daily dose of 240 mg of lazertinib, with each cycle comprising 21 days. Thoracic (±

abdomen, neck) radiologic assessments were conducted every 6 weeks until cycle 8 and every 12 weeks. Baseline brain magnetic resonance imaging was required for all patients, and subsequent brain imaging was conducted on the basis of baseline CNS involvement: patients with baseline CNS metastases underwent brain magnetic resonance imaging at every tumor assessment, whereas those without CNS metastases were scanned every 24 weeks. Treatment was maintained until the patients withdrew consent, were unable to continue participation, reported significant protocol violations, or experienced disease progression. Treatment beyond progression was permitted at the physician's discretion if clinical benefit was observed. If the patients experienced adverse reactions at the 240 mg dose of lazertinib, a dose reduction to 160 mg was allowed.

Study End Points

The primary objective of this study is to evaluate the antitumor efficacy of lazertinib in patients with NSCLC with uncommon *EGFR* mutations. The primary end point is the objective response rate (ORR), which is defined as the proportion of patients in whom a complete response or partial response was achieved according to the Response Evaluation Criteria in Solid Tumors version 1.1, as assessed by the investigators. The secondary end points include the disease control rate (DCR), progression-free survival (PFS), overall survival (OS), duration of response (DoR), and safety profile, which was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. PFS is defined as the duration from cycle 1, day 1 to disease progression or death. OS is defined as the duration from cycle 1, day 1 to death from any cause. Safety is assessed on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 criteria. The exploratory objective of this study is to identify the mechanisms of acquired resistance to lazertinib in patients with NSCLC with rare *EGFR* mutations. For this end, blood samples (approximately 10 mL) for blood-based (NGS) using Guardant360 (Guardant Health) were collected both before the initiation of lazertinib and after disease progression.

Statistical Analysis

The statistical design of the study was based on a one-arm binomial test with 80% power and a two-sided α of 0.1, aiming to exclude an ORR of 20% while targeting an ORR of 40%. On the basis of this design, a total of 32 patients were required, and considering a drop-out rate of 10%, 36 patients were planned for enrollment in the study.

Results

Patients and Treatment

A total of 36 patients were enrolled from five institutions across the Republic of Korea between April 2022 and May 2023. The data cut-off date was February 29, 2024. The baseline demographic and clinical characteristics of the patients are listed in Table 1. The median age was 67 years (range, 37–82), with 58.3% of patients being male (n = 21). Regarding smoking history, 16.7% were current smokers; 38.9% were ex-smokers, and 44.4% were never smokers. Most patients (88.9%) presented with metastatic disease at enrollment, whereas 11.1% had recurrent disease. All patients were diagnosed with adenocarcinoma (100%). CNS metastases were observed in 41.7% of patients (n = 15) at baseline. The most common *EGFR* mutation was G719X, identified in 18 patients (50.0%), followed by L861Q, which was observed in 12 patients (33.3%). Among the 18 patients with G719X mutations, 14 had G719X-only mutations, with the specific subtypes identified in eight cases (G719C: 1, G719A: 4, G719S: 3). Moreover, among the compound mutations, G719X + L861Q was confirmed as G719S + L861Q (n=1), whereas G719X + S768I (n = 3) included G719A + S768I (n = 1) and G719S + S768I (n = 2). Mutations in S768I were found in five patients (13.9%), whereas exon 18 deletions and exon 19 insertions were observed in four patients (11.1%) and one patient (2.8%), respectively. All exon 18 deletions were E709_T710delinsD. Among the cohort, compound mutations (e.g., G719X + S768I, G719X + L861Q) were present in four patients, comprising 11.1% of the total population.

Efficacy

During the median follow-up of 9.4 months (95% CI: 4.4–11.1), 24 PFS events occurred, including 20 cases of disease progression and four deaths. The mean relative dose intensity of lazertinib was 85.1%, and the median relative dose intensity was 84.3%, indicating generally good tolerability and sustained dosing throughout the treatment period. Initial disease progression was observed at extracranial sites only in 12 patients (33.3%), at intracranial sites only in one patient (2.8%), and at both intracranial and extracranial sites in seven patients (19.4%). Among 36 enrolled patients, 34 were assessable for tumor response because two patients did not undergo posttreatment imaging owing to early death (n = 1) and adverse event (n = 1). At the data cutoff, 19 patients discontinued treatment owing to disease progression, whereas 15 patients (41.7%) remained on treatment, including three patients receiving lazertinib beyond progression (Supplementary Fig. 1). The median PFS was 10.8 months (95% CI: 4.4–19.2), and the

Table 1. Baseline Characteristics

Characteristics		N = 36
Age, median (range)		67 (37-82)
Sex, n (%)	Male	21 (58.3)
	Female	115 (41.7)
Smoking history, n (%)	Current	6 (16.7)
	Ex-smoker	14 (38.9)
	Never smoker	16 (44.4)
Current status, n (%)	Metastatic	32 (88.9)
	Recurred	4 (11.1)
Histologic diagnosis, n (%)	Adenocarcinoma	36 (100.0)
CNS metastases at baseline, n (%)		15 (41.7)
EGFR mutation status, n (%)[a]	G719X	18 (50.0)
	G719X only	14
	G719X + S768I	3
	G719X + L861Q	1
	L861Q	12 (33.3)
	L861Q only	11
	L861Q + G719X	1
	S768I	5 (13.9)
	S768I only	2
	S768I + G719X	3
	Exon 18 deletion[b]	4 (11.1)
	Exon 19 insertion (K745_E746insVPVAIK)	1 (2.8)

[a]Uncommon *EGFR* mutation categories overlap with compound mutations, so individual patients might appear in more than one category.
[b]All patients with exon 18 deletions had E709_T710delinsD.
CNS, central nervous system.

median OS was not reached (Fig. 1). The median DoR was 15.1 months (95% CI: 7.0–not available).

The ORR, the primary end point of the study, was 50.0% (95% CI: 34.5%–65.5%), with a partial response achieved in 18 patients (50.0%), thereby meeting the predefined primary end point (Table 2). Stable disease was observed in 14 patients (38.9%), and progressive disease occurred in one patient (2.8%). DCR was 88.9% (95% CI: 74.1%–96.2%).

Efficacy varied on the basis of *EGFR* mutation subtypes (Supplementary Table 1). Patients with G719X mutations reported the most favorable outcomes, achieving an ORR of 61% (11/18) and the longest median PFS of 20.3 months (95% CI: 8.3–N/A). Similarly, L861Q mutations reported an ORR of 58% (7/12) with a median PFS of 9.5 months (95% CI: 2.6–16.4). Among patients with S768I mutations, the ORR was 60% (3/5), whereas the median PFS was not reached (95% CI: 2.8–N/A). If confined to major uncommon mutations (G719X, L861Q, and S768I), the ORR was 54.8% (17/31). The response rates for solitary G719X mutations, L861Q, and S768I were 57.1% (8/14), 54.5% (6/11), and 66.7% (2/3), respectively. In contrast, an objective response was achieved in none of the patients with exon 18 deletions or exon 19 insertions. Compound mutations reported a robust response, with an ORR of 75% (3/4), indicating the potential clinical benefit of lazertinib in this subgroup. The tumor response results are graphically represented in the waterfall plot (Fig. 2), illustrating the maximum percentage change in tumor size for individual patients.

Among the 15 patients with baseline CNS metastases, the intracranial ORR was 40.0% (6/15; 95% CI, 19.8–64.3), and the intracranial DCR was 86.7% (13/15; 95% CI, 62.1–96.3). In addition, the median intracranial PFS was 10.9 months (95% CI, 8.1–27.0), and the median intracranial DoR was 9.6 months (95% CI, 3.1–N/A).

The *EGFR* mutation distribution in this subgroup included G719X (n = 7), L861Q (n = 4), S768I (n = 2), and exon 18 deletions (n = 2), with no compound mutations observed. Within individual mutation subtypes, the intracranial ORR was 57.1% for G719X (4/7), 25.0% for L861Q (1/4), 50.0% for S768I (1/2), and 0.0% for exon 18 deletion (0/2).

Among the 20 patients who experienced disease progression, most received further treatment. Subsequent therapies included EGFR-TKI therapy (n = 13), cytotoxic chemotherapy (n = 13), radiotherapy (n = 6), and immunotherapy (n = 3). Only two patients did not receive any additional anticancer treatment. These findings indicate that most patients with progression after lazertinib were eligible for and proceeded with further lines of therapy.

Safety

Treatment-emergent adverse events (TEAEs) were observed in all patients (100%, n = 36) (Table 3). The most common TEAEs (any grade) included rash (47.2%), pruritus (36.1%), muscle spasms (33.3%), and paresthesia (27.8%). Grade 3 or higher TEAEs occurred in 33.3% of patients (n = 12), including diarrhea (n = 1), QT prolongation (n = 1), and other individual cases. Each grade 3 or higher adverse event (AE) was reported as a single case.

Dose modifications were required in 66.7% of patients (n = 24) owing to AEs, with 47.2% (n = 17) requiring dose reductions and one patient permanently discontinuing treatment. The single case of permanent discontinuation was due to grade 2 pneumonitis. Reasons for dose reductions included muscle spasm (n = 5), peripheral neuropathy (n = 4), paresthesia (n = 3), asthenia (n = 2), mucosal inflammation (n = 1), myalgia (n = 1), paronychia (n = 1), decreased appetite (n = 1), headache (n = 1), rash (n = 1), muscle weakness (n = 1), and dermatitis (n = 1). Some patients required dose reductions owing to more than one TEAE. Interestingly, TEAEs associated with EGFR inhibition, such as paronychia, dermatitis, and mucosal inflammation, completely resolved without sequelae within 2 months. In contrast, neurologic and neuromuscular AEs, including paresthesia, peripheral sensory neuropathy, and muscle spasms, either persisted or were only partially relieved by the data cut-off time point.

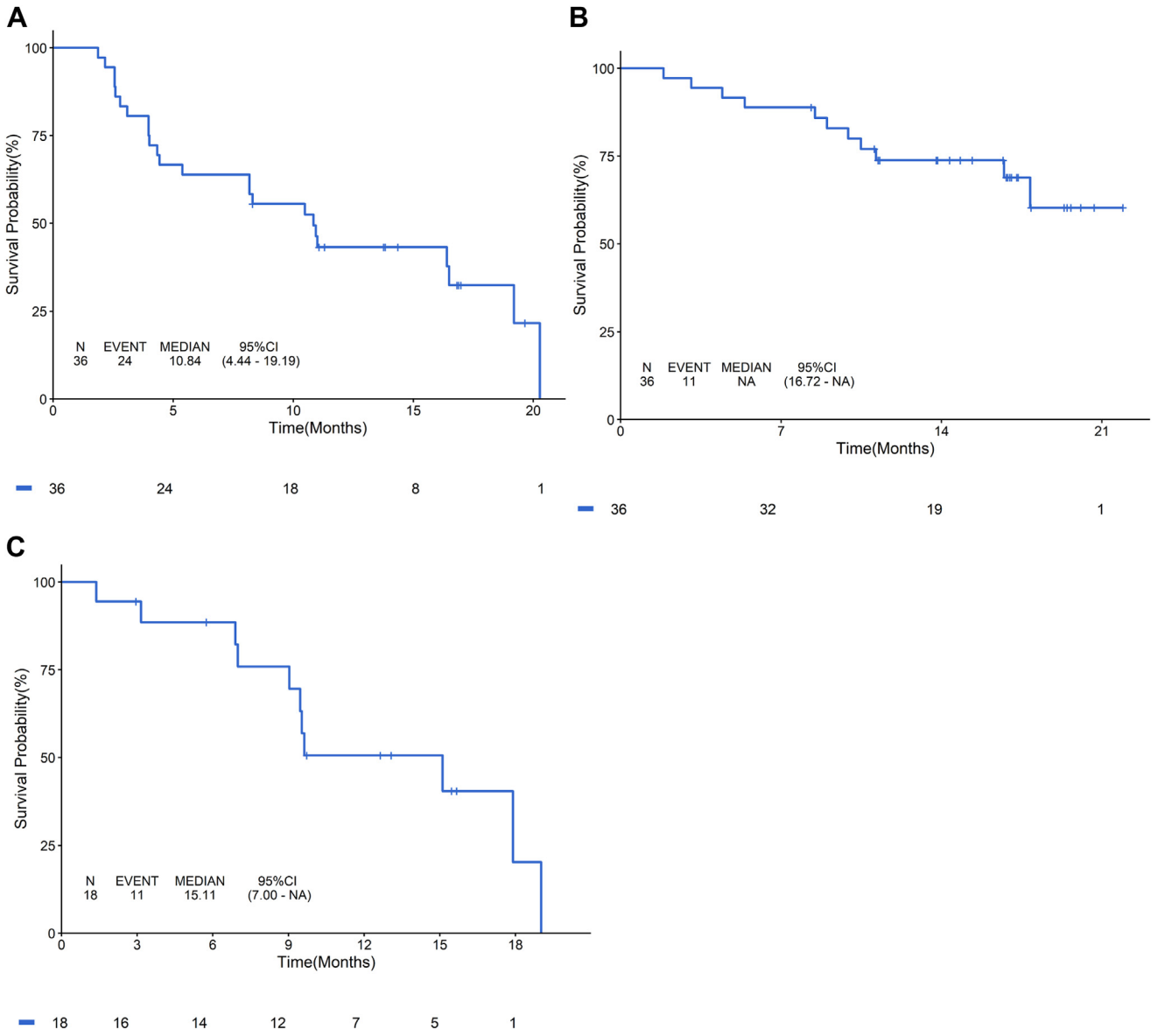

Figure 1. Kaplan-Meier curves of *(A)* PFS, *(B)* overall survival (OS), and *(C)* duration of response (DoR). Vertical lines indicate censored events. CI, confidence interval; DoR, duration of response; NA, not available; OS, overall survival; PFS, progression-free survival.

Overall, the safety profile was manageable, with most AEs being grade 1 or 2. Only a few grade 3 or higher events were observed, and dose modifications effectively managed toxicity in most patients.

Exploratory Analysis

In this study, both tissue-based and liquid biopsy (Guardant360) testing were used to assess uncommon *EGFR* mutations at different time points. At baseline, results from liquid biopsy were compared with those obtained from tissue-based molecular profiling conducted at screening. All 36 enrolled patients underwent baseline liquid biopsy, among whom 15 patients (41.7%) had nonshedding tumors (no mutations detected in liquid biopsy). The concordance rate was 41.7% (15/36) between tissue and liquid biopsy in NSCLC (Supplementary Table 2). Moreover, baseline liquid biopsy identified several cases (five patients, 13.9%) with additional *EGFR* mutations not detected in tissue biopsy. These included EGFR G724S, E709K, V774M, V592I, E1137D, L833V, and E685E. Post-progression liquid biopsy was also conducted in 14 patients to explore potential resistance mechanisms after disease progression (Fig. 3). Among these, five patients (35.7%, 5/14) retained their baseline *EGFR* mutations without acquiring additional genomic

Table 2. Tumor Response

Response Category	N = 36
Best overall response	
Complete response, n (%)	0 (0)
Partial response, n (%)	18 (50.0)
Stable disease, n (%)	14 (38.9%)
Progressive disease, n (%)	1 (2.8)
Not applicable, n (%)	2 (5.6)
Objective response rate (95% CI)	50.0% (34.5-65.5)
Disease control rate (95% CI)	88.9% (74.1-96.2)

CI, confidence interval.

alterations at disease progression. New mutations appearing postprogression included APC C1249*, TP53 R175H, TP53 V31I, RET P766L, and additional alterations in ERBB2 D1144H. In addition, one patient reported reemergence of the EGFR L861Q mutation in postprogression liquid biopsy. These findings suggest heterogeneous resistance mechanisms, underscoring the importance of individualized genomic profiling to guide subsequent therapeutic decisions after progression on lazertinib.

Discussion

Lazertinib has previously reported significant clinical activity and a favorable safety profile in patients with NSCLC harboring common *EGFR* mutations, establishing its role as a backbone therapy for advanced *EGFR*-mutated lung cancer.[8,9] To our knowledge, this study represents the

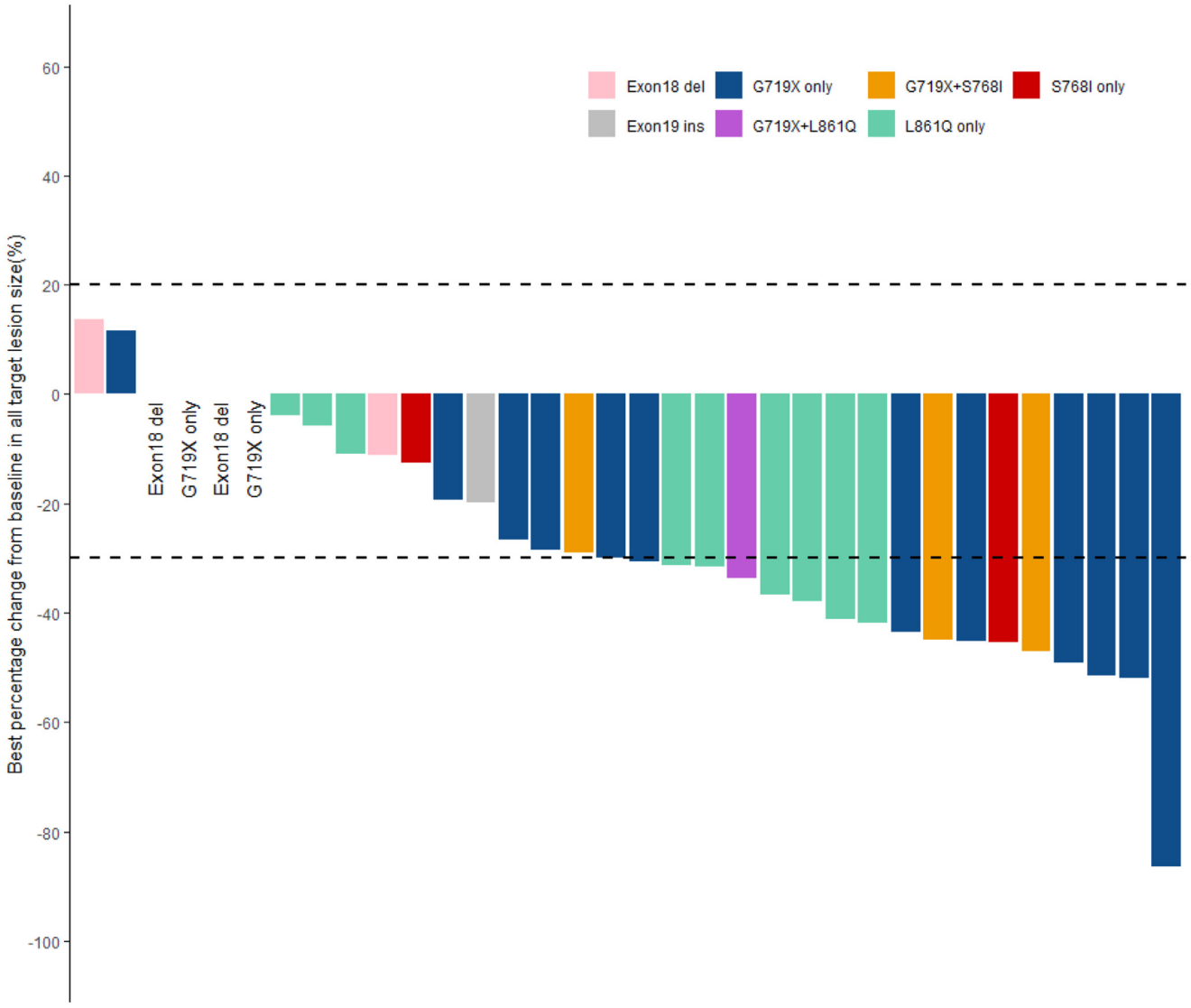

Figure 2. Best percentage change in target lesion size from baseline as assessed by investigator in the assessable-for response (n = 34). Tumor shrinkage relative to baseline was observed in 28 of 34 patients (82.4%). The upper dashed line represents the threshold for progressive disease (20% increase in the sum of the longest diameter of the target lesions), and the lower dashed line at −30% represents the boundary for the determination of partial response.

Table 3. Treatment-Emergent Adverse Events, n (%)

Event	Any Grade	Grade 3 or Higher
Any event	36 (100)	12 (33.3)
Rash	17 (47.2)	-
Pruritus	13 (36.1)	-
Muscle spasms	12 (33.3)	-
Paresthesia	10 (27.8)	-
Decreased appetite	7 (19.4)	-
Dermatitis	5 (13.9)	-
Neuropathy peripheral	5 (13.9)	-
Peripheral sensory neuropathy	5 (13.9)	-
Headache	4 (11.1)	-
Asthenia	3 (8.3)	-
Diarrhea	3 (8.3)	1 (2.8)
Dry skin	3 (8.3)	-
Nail disorder	3 (8.3)	-
Paronychia	3 (8.3)	-
Abdominal discomfort	2 (5.6)	-
AST elevation	2 (5.6)	-
Dyspepsia	2 (5.6)	-
Electrocardiogram QT prolonged	2 (5.6)	1 (2.8)

AST, aspartate transaminase.

first prospective trial evaluating the therapeutic efficacy of the third-generation EGFR-TKI, lazertinib, in patients with NSCLC harboring uncommon *EGFR* mutations, excluding exon 20 insertions. Among 36 patients enrolled, the study observed an ORR of 50% and a median PFS of 10.8 months. These findings are particularly noteworthy given the heterogeneity of uncommon *EGFR* mutations, highlighting the potential of lazertinib to provide meaningful clinical benefit in this challenging patient population.

Previous studies evaluating afatinib and osimertinib in patients with uncommon *EGFR* mutations have been conducted, reporting their clinical activity in this population. In a post hoc analysis of the LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 trials, afatinib reported an ORR of 56% to 77% and a median PFS of 8.2 to 10.8 months, depending on the specific mutation subtype.[10] Similarly, the KCSG-LU15-09 study, a multicenter phase II trial of osimertinib in uncommon *EGFR* mutations, reported an ORR of 50% and a median PFS of 8.2 months.[11] More recently, the UNICORN trial, which evaluated first-line osimertinib in patients who were treatment naïve with uncommon *EGFR* mutations, found an ORR of 55% and a median PFS of 9.4 months.[6] These findings align closely with our study results, and given these comparable efficacy outcomes, lazertinib may offer an effective treatment option for patients with uncommon *EGFR* mutations, particularly those harboring G719X, L861Q, and S768I mutations.

G719X is the most common among the uncommon *EGFR* mutations.[7] G719X mutations include G719A, G719C, and G719S, but data on individual subtypes are limited owing to their low prevalence. In contrast to previous Korean studies, which did not separately report response rates for solitary G719X mutations, the UNICORN trial found an ORR of only 30% in this subgroup.[6,11] Given this finding, our observed ORR of 57.1% (8/14) for solitary G719X mutations seems relatively higher, suggesting that lazertinib may provide improved efficacy in this subset compared with osimertinib. Furthermore, the median PFS (mPFS) for overall G719X mutations in our study was 20.3 months, which is notably longer than the mPFS reported in the UNICORN trial (5.1 months) and in the study by Cho et al.[11] (8.2 months).[6] These findings further suggest that lazertinib may offer a clinical advantage in patients with G719X mutations. Nevertheless, differences in patient selection and baseline characteristics across studies should be considered when interpreting these results.

E709_T710delinsD is extremely rare, and clinical data on this mutation are very limited.[12] Most reports are at the case report level, describing heterogeneous treatment outcomes.[13] In addition, the present study did not identify any responders in this subgroup. Given the lack of efficacy observed, further preclinical investigations are warranted to better understand the biological characteristics of this mutation before advancing to clinical trials.

Overall, the UNICORN trial allowed patients with compound mutations comprising both common and uncommon *EGFR* mutations, some of which are known to have higher sensitivity to EGFR-TKIs than solitary uncommon *EGFR* mutations, potentially influencing the overall efficacy outcomes, and in the actual study population, compound mutations accounted for 45% of cases.[6,14] In contrast, our study excluded compound mutations comprising both common and uncommon *EGFR* mutations, and only four patients had compound uncommon mutations, indicating that our study population comprised a more challenging-to-treat group with inherently lower EGFR-TKI sensitivity than in the UNICORN trial.

The safety profile of lazertinib in patients with uncommon *EGFR* mutations was consistent with previous studies with sensitizing *EGFR* mutations, with most AEs being mild to moderate and manageable.[8] Although grade 3 or higher TEAEs occurred in some patients, the overall incidence was comparable to prior reports, and dose modifications effectively mitigated toxicity in most cases. Importantly, treatment discontinuation due to AEs was rare, indicating that lazertinib was generally well tolerated in this patient population. These findings support the

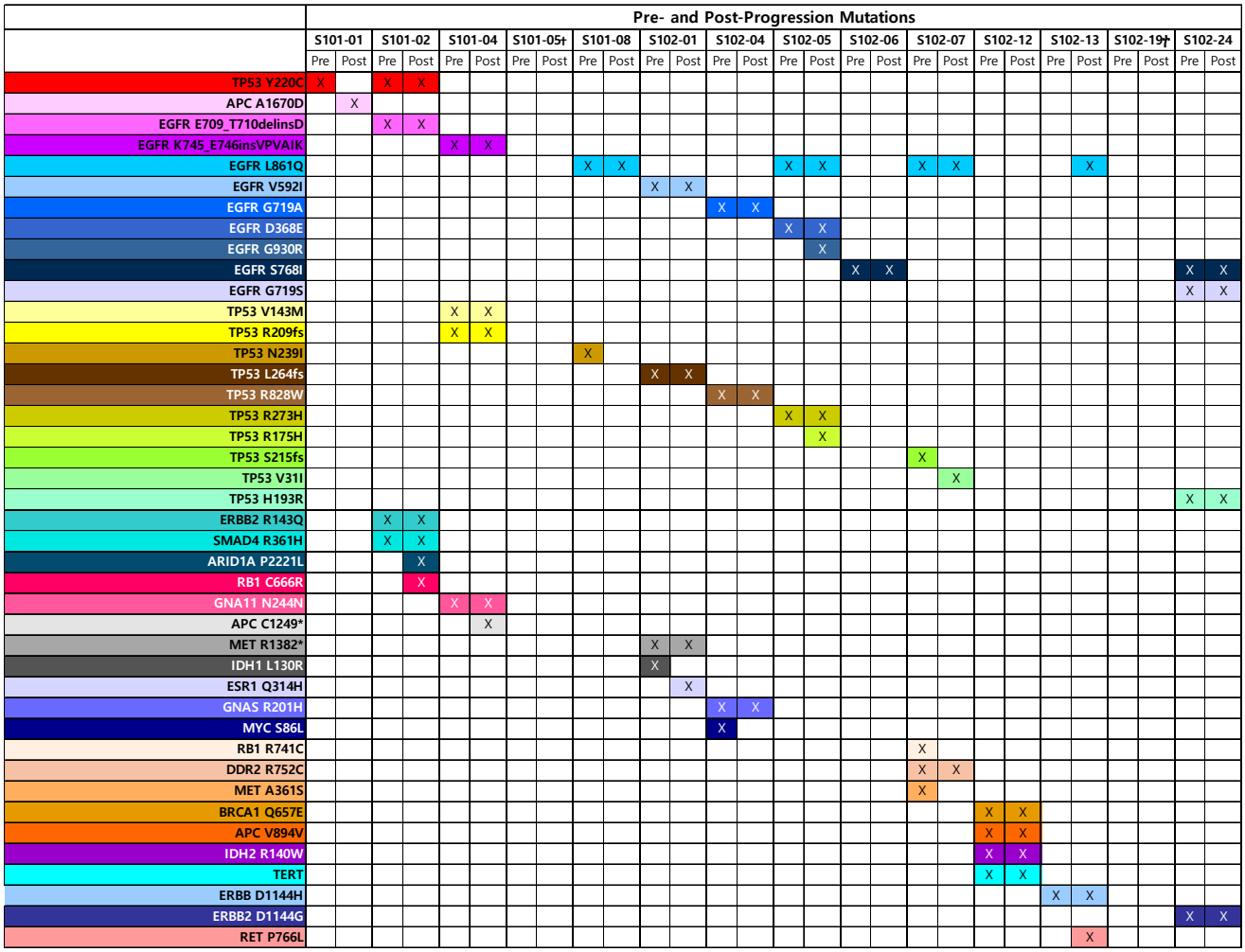

Figure 3. Comparison of pre- and postprogression liquid biopsy (Guardant360) results in patients treated with lazertinib (n = 14). S101-05, S102-19: No significant mutation detected.

feasibility of lazertinib as a treatment option for uncommon *EGFR* mutations, with an acceptable safety profile.

A recent study evaluating the combination of amivantamab and lazertinib in 49 patients who were treatment naïve with uncommon *EGFR* mutations found a remarkably long mPFS of 19.5 months.[15] This finding highlights the potential benefit of dual EGFR and MET inhibition, given preclinical studies have found that the lazertinib-amivantamab combination enhances antitumor activity through multiple mechanisms, including cell-cycle arrest, apoptosis, and improved antibody-dependent cellular cytotoxicity, suggesting that combination strategies may further improve outcomes compared with EGFR-TKI monotherapy.[16] Nevertheless, patients with G719X mutations reported substantial efficacy with lazertinib monotherapy, suggesting that whereas combination therapy may offer additional benefits, patient selection will be crucial in determining whether a combination approach is necessary or whether lazertinib monotherapy is sufficient for optimal treatment outcomes.

This study has several limitations. First, as a single-arm study, it lacks a direct comparator, making it difficult to assess the relative efficacy of lazertinib against other EGFR-TKIs such as afatinib or osimertinib. Second, the small sample size, particularly the limited number of patients in each uncommon mutation subtype, restricts the generalizability of our findings and limits robust subgroup analyses. Third, the follow-up duration was not sufficient to evaluate OS and long-term outcomes, necessitating extended observation to determine the durability of responses. Future randomized controlled trials with larger cohorts and longer follow-up are warranted to validate these findings.

Despite these limitations, we believe our study represents the first prospective evaluation of a third-generation EGFR-TKI in patients who are treatment naïve with uncommon *EGFR* mutations, incorporating

postprogression blood NGS to investigate resistance mechanisms, and provides valuable insights into the efficacy and safety of lazertinib by successfully meeting its primary end point. Further research, including larger randomized trials and biomarker-driven patient selection strategies, will be essential to refine treatment approaches and optimize outcomes for this heterogeneous patient population.

CRediT Authorship Contribution Statement

Sehhoon Park: Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing, Funding acquisition.

Hee Kyung Ahn: Data curation, Investigation, Writing - review & editing.

Seoyoung Lee: Formal analysis, Visualization, Writing - review & editing.

Young Joo Min: Investigation, Data curation, Writing - review & editing.

Hyun Ae Jung: Investigation, Data curation.

Jong-Mu Sun: Investigation, Supervision, Writing - review & editing.

Se-Hoon Lee: Investigation, Supervision, Writing - review & editing.

Jin Seok Ahn: Investigation, Supervision, Writing - review & editing.

Myung-Ju Ahn: Investigation, Supervision, Writing - review & editing.

Jii Bum Lee: Investigation, Supervision.

Sun Min Lim: Investigation, Supervision.

Hye Ryun Kim: Investigation, Supervision.

Byoung Chul Cho: Conceptualization, Supervision.

Min Hee Hong: Conceptualization, Methodology, Investigation, Data curation, Writing - original draft, Writing - review & editing, Project administration, Funding acquisition.

Disclosure

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2025.05.006.

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