original reports

Osimertinib for Patients With Non–Small-Cell Lung Cancer Harboring Uncommon EGFR Mutations: A Multicenter, Open-Label, Phase II Trial (KCSG-LU15-09)

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abstract

PURPOSE Approximately 10% of patients with epidermal growth factor receptor (EGFR) mutation–positive non–small-cell lung cancer (NSCLC) harbor uncommon mutations. Here, we report the efficacy and safety of osimertinib in patients with NSCLC harboring uncommon EGFR mutations.

PATIENT AND METHODS This was a multicenter, single-arm, open-label, phase II study in Korea. Patients with histologically confirmed metastatic or recurrent NSCLC harboring EGFR mutations other than the exon 19 deletion, L858R and T790M mutations, and exon 20 insertion were eligible for the study. The primary end point of objective response rate was assessed every 6 weeks by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Secondary end points were progression-free survival, overall survival, duration of response, and safety.

RESULTS Between March 2016 and October 2017, 37 patients were enrolled. All were evaluable except one patient who withdrew consent after starting treatment. Median age was 60 years, and 22 (61%) were male. Among patients, 61% received osimertinib as first-line therapy. The mutations identified were G719X (n = 19; 53%), followed by L861Q (n = 9; 25%), S768I (n = 8; 22%), and others (n = 4; 11%). Objective response rate was 50% (18 of 36 patients; 95% CI, 33% to 67%). Median progression-free survival was 8.2 months (95% CI, 5.9 to 10.5 months), and median overall survival was not reached. Median duration of response was 11.2 months (95% CI, 7.7 to 14.7 months). Adverse events of any grade were rash (n = 11; 31%), pruritus (n = 9; 25%), decreased appetite (n = 9; 25%), diarrhea (n = 8; 22%), and dyspnea (n = 8; 22%), but all adverse events were manageable.

CONCLUSION Osimertinib demonstrated favorable activity with manageable toxicity in patients with NSCLC harboring uncommon EGFR mutations.

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INTRODUCTION

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are currently the standard first-line treatment options for patients with locally advanced or metastatic non–small-cell lung cancer (NSCLC) harboring sensitizing EGFR mutations.[1,2] A number of phase III trials demonstrated superior objective response rate (ORR) and progression-free survival (PFS) compared with platinum-based doublet chemotherapy.[3-10]

Osimertinib is an oral, third-generation, irreversible EGFR-TKI that selectively inhibits both sensitizing EGFR mutations and Thr790Met (T790M) resistance mutations.[11,12] Osimertinib is approved worldwide for the treatment of patients with metastatic NSCLC with EGFR T790M mutations that show disease progression on EGFR-TKI on the basis of results of the AURA clinical program (ClinicalTrials.gov identifiers: NCT01802632, NCT02094261, and NCT02151981).[13-15] In addition, on the basis of the positive results from the phase III FLAURA trial (ClinicalTrials.gov identifier: NCT02296125), osimertinib is also approved for first-line treatment of patients with metastatic NSCLC harboring the specific EGFR mutation exon 19 deletion or exon 21 Leu858Arg mutation (L858R).[16] Previous studies highlight promising CNS activity of osimertinib with efficacy superior to that of first-generation EGFR TKIs and platinum chemotherapy.[14,16,17]

The common EGFR mutations account for 75% to 80% of patients with NSCLC harboring EGFR mutations.[18-20] Uncommon mutations represent the

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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remainder of the EGFR mutations and are a highly heterogeneous group of molecular alterations within exons 18 to 21.[21] Several retrospective studies and case reports of first-generation EGFR-TKIs showed inconsistent responses in patients with NSCLC harboring uncommon EGFR mutations.[22-25] Recently, a post hoc analysis of prospectively collected data from the participants of the LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 trials (ClinicalTrials.gov identifiers: NCT00525148, NCT00949650, and NCT01121393) showed clinical activity of afatinib in patients with advanced NSCLC harboring uncommon EGFR mutations, especially Gly719Xaa (G719X), Leu861Gln (L861Q), and Ser768Ile (S768I), but low activity against T790M and exon 20 insertion mutations.[26] In preclinical data, osimertinib was found to be active against most uncommon EGFR mutations, apart from exon 20 insertion variants[25]; however, there are still insufficient data on the clinical efficacy of osimertinib for NSCLC with uncommon EGFR mutations. Here, we describe the first evidence of osimertinib efficacy in patients with NSCLC harboring uncommon EGFR mutations from a multicenter phase II study.

PATIENTS AND METHODS

Study Design and Participants

This was a multicenter, open-label, single-arm, phase II study in Korea (KCSG-LU15-09, ClinicalTrials.gov identifier: NCT03424759). Eligible patients were age 19 years or older, with a histologically confirmed diagnosis of metastatic or recurrent NSCLC harboring EGFR mutations other than exon 19 deletion, L858R, T790M, or exon 20 insertion; Eastern Cooperative Oncology Group performance status of 2 or less; and adequate organ and bone marrow function. Exclusion criteria were previous treatment with any other EGFR-TKI, radiation therapy, or chemotherapy within 2 weeks of the first osimertinib dose; documented history of interstitial lung disease; active infection requiring systemic therapy; or uncontrolled symptomatic brain metastasis.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The study protocol and all amendments were approved by all associated institutional review boards. All patients provided written informed consent.

Procedures

Eligible patients received osimertinib 80 mg orally once per day and continued treatment until RECIST version 1.1–defined progression, development of unacceptable toxicity, or withdrawal of consent. Baseline assessments consisted of patient history, physical examination, computed tomography scan or magnetic resonance imaging, and laboratory tests (hematology, coagulation, blood chemistry, and pregnancy test, if indicated). Physical examinations, laboratory tests, and chest X-rays were performed every 3 weeks, and tumor assessment by computed tomography scan was performed every 6 weeks (every two cycles of osimertinib) according to RECIST 1.1. EGFR mutations were identified using one of the following local test methods for each type of uncommon mutation: peptide nucleic acid–mediated polymerase chain reaction clamping, direct sequencing, and/or next-generation sequencing.

Adverse events (AEs) were recorded by an investigator at baseline and at each visit, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Osimertinib was withheld if patients experienced prespecified treatment-related grade 3 or greater AEs. Rechallenge or dose reduction of osimertinib was allowed once AEs were resolved at the physicians' discretion.

Outcomes

The primary end point was ORR, which was defined as the proportion of patients achieving a complete response or partial response (PR) by investigator assessment. Secondary end points were PFS, overall survival (OS), duration of response (DoR), and safety profile. PFS was defined as the time from the date of first dose to first documented disease progression, per RECIST 1.1, or death from any cause, whichever occurred first. OS was defined as the time from the date of first dose to death as a result of any cause. DoR was defined as the time from the date of first documented objective response until disease progression or death by any cause.

Statistical Analysis

We conducted efficacy and safety analyses in 36 patients who received at least one dose of the study treatment. Given the rarity of uncommon mutations, this study was planned to include patients in a single cohort. The statistical design of the study was based on Simon's two-stage phase II optimal design (power of 90% and one-sided α of .05) to rule out a 10% objective response and to target a 30% objective response.[27] Considering a 10% dropout rate, a total of 37 patients were enrolled.

PFS, OS, and DoR were analyzed using the Kaplan-Meier method and are expressed as median value and corresponding 95% CI. All statistical analyses were two sided, and $P < .05$ was considered statistically significant. We used the Statistical Package for the Social Sciences (SPSS) for Windows version 24 (SPSS, Chicago, IL) for all statistical analyses.

RESULTS

Demographics

Between March 2016 and October 2017, a total of 37 patients were enrolled from 7 institutes in Korea. Excluding one patient who withdrew consent, 36 patients were included in the efficacy and safety analyses (Fig 1). The data cutoff date was October 31, 2018.

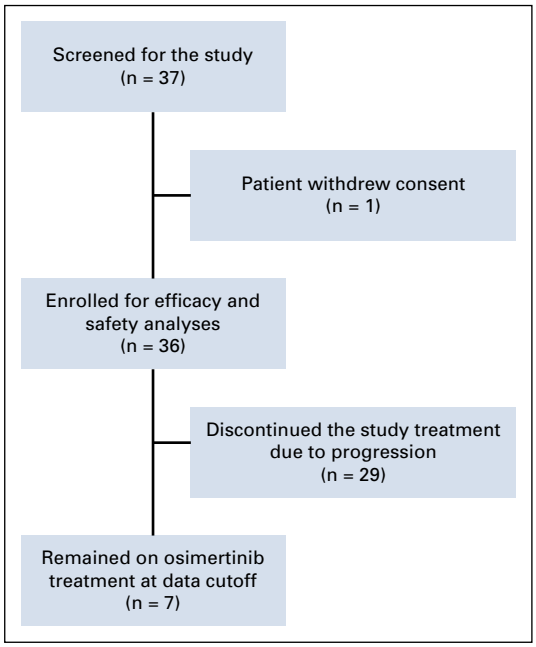

FIG 1. Trial profile.

Patient characteristics are listed in Table 1. Median age was 60 years (range, 27 to 81 years), and 22 (61%) of 36 patients were male. Sixteen patients (44%) were never-smokers and 35 (97%) had adenocarcinoma. The most common uncommon EGFR mutation was G719X (53%), followed by L861Q (25%) and S768I (22%). Of 36 patients, 22 (61%) received osimertinib treatment as first-line therapy, 11 (31%) as second-line therapy, and three (8%) as third-line therapy. No patient had a history of exposure to EGFR-TKI. Twenty-three patients (64%) were initially diagnosed with metastatic NSCLC, and 13 patients (36%) had recurrent disease.

Efficacy

At the time of data cutoff, median follow-up duration was 20.6 months (range, 12.2 to 31.3 months). Thirty-six patients were evaluable for response. A total of 29 patients are still alive, of whom seven continue to receive osimertinib. Twenty-nine (81%) of 36 patients discontinued osimertinib because of disease progression. A total of 18 patients (50%) showed a PR, 14 (39%) had stable disease, and four (11%) had progressive disease (Appendix Table A1, online only). The ORR was 50% (18 of 36 patients; 95% CI, 33% to 67%), and the disease control rate was 89% (32 of 36 patients; 95% CI, 78% to 100%).

Overall, 15 (83%) of 18 responders had a documented initial response at their first scheduled tumor assessment by computed tomography scan at 6 weeks (two cycles of osimertinib) according to RECIST 1.1. The median DoR was 11.2 months (95% CI, 7.7 to 14.7 months). Tumor shrinkage was observed in 28 patients (78%; Fig 2). The

TABLE 1. Baseline Characteristics of Participants

Characteristic	Patients (N = 36)
Median age, years (range)	60 (27-81)
Sex	
Men	22 (61)
Women	14 (39)
ECOG performance status	
0	2 (6)
1	34 (94)
Smoking status	
Never smoked	16 (44)
Ex-smoker	18 (50)
Current smoker	2 (6)
Histology	
Adenocarcinoma	35 (97)
Squamous cell carcinoma	1 (3)
Uncommon EGFR mutation*	
G719X	19 (53)
G719X	15
G719X + L861Q	2
G719X + S768I	2
L861Q	9 (25)
L861Q	7
L861Q + G719X	2
S768I	8 (22)
S768I	6
S768I + G719X	2
L747S	1 (3)
S720A	1 (3)
Exon 18 deletion	1 (3)
Exon 20 insertion H773_V774insH	1 (3)
Line of therapy	
First line	22 (61)
Second line	11 (31)
Third line	3 (8)
Site of metastasis	
Adrenal gland	3 (8)
Bone	10 (28)
CNS (brain/spinal cord/ophthalmic)	9 (25)
Liver	3 (8)
Local/regional lymph nodes	9 (25)
Distant lymph nodes	6 (17)
Lung	17 (47)
Peritoneum	0 (0)
Pleura	16 (44)

(continued on following page)

TABLE 1. Baseline Characteristics of Participants (continued)

Characteristic	Patients (N = 36)
Median No. of metastasis sites (range)	2 (1-4)
Overall disease classification	
Metastatic	23 (64)
Recurrent	13 (36)

NOTE. Data are presented as No. (%) unless otherwise indicated.

Abbreviation: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

*Uncommon mutation categories overlap those with compound mutations, so individual patients might appear in more than one category.

median best percentage change in target lesion size from baseline was −35% (range, −79% to 44%).

At the time of data cutoff, 29 (81%) of 36 patients had experienced disease progression or had died. The median PFS was 8.2 months (95% CI, 5.9 to 10.5 months; Fig 3A). The proportion of patients who were progression free at 6 and 12 months was 64% (95% CI, 47% to 80%) and 39% (95% CI, 22% to 56%), respectively. Seven patients (19%) had died at the time of data cutoff, but the median OS was not reached (Fig 3B). The 12-month survival rate was 86% (95% CI, 74% to 98%), and the 18-month survival rate was 56% (95% CI, 39% to 73%).

Of the seven patients who did not experience progression, five continued to show a response at 11, 18, 19, 24, and 31 months, respectively, after the start of osimertinib at data cutoff. The remaining two patients continued to show stable disease according to RECIST 1.1 at 11 and 16 months, respectively, after the initiation of osimertinib. Twenty-nine patients (81%) experienced disease progression events, new lesions developed in six patients (17%), and disease progression in preexisting target or nontarget lesions was observed in 23 patients (64%).

We performed a subset analysis of ORR and PFS according to uncommon EGFR mutation type, including the G719X, L861Q, and S768I mutations, which are the three most frequently detected types of uncommon EGFR mutations (Table 2). Objective responses were noted in 78% of patients with the L861Q mutation, followed by 53% with G719X and 38% for S768I (Table 2). Accordingly, PFS of patients with L861Q, G719X, or S768I mutations was 15.2 months (95% CI, 1.3 to 29.1 months), 8.2 months (95% CI, 6.2 to 10.2 months), and 12.3 months (95% CI, 0 to 28.8 months), respectively. Four patients harbored compound uncommon EGFR mutations: two patients with G719X and L861Q and two patients with G719X and S768I (Table 1).

Nine patients had CNS metastasis at the time of enrollment in the study. The median PFS was shorter in patients with CNS metastasis than in those without (median, 5.4 months [95% CI, 2.8 to 8.0 months] *v* 9.8 months [95% CI, 0.8 to 18.8 months]). Four patients were excluded from the analysis of CNS response to osimertinib because they underwent gamma knife surgery or whole-brain radiotherapy along with osimertinib in this study. Among the five evaluable patients, intracranial ORR was 40% (2 of 5 patients). One patient harboring G719X achieved complete response in brain metastasis, where multiple enhancing lesions disappeared after 6 months of osimertinib treatment. CNS DoR and CNS PFS of this patient were 2.8 months and 8.9 months, respectively. Another patient with G719X showed PR, and CNS DoR and CNS PFS were 7.0 months and 8.2 months, respectively.

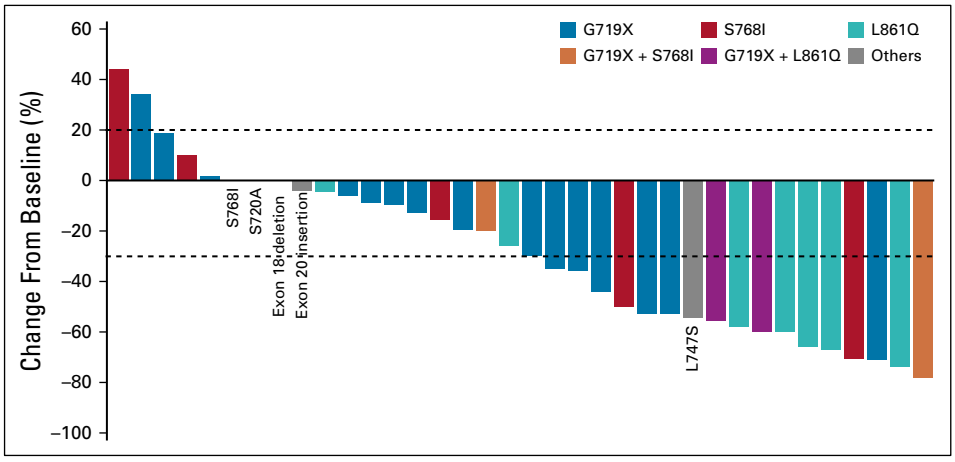

FIG 2. Best percentage change in target lesion size from baseline by independent review in the evaluable-for-response set. Tumor shrinkage relative to baseline was observed in 28 patients (78%). The upper dashed line represents the threshold for progressive disease (20% increase in the sum of the longest diameter of the target lesions), and the lower dashed line at −30% represents the boundary for the determination of partial response.

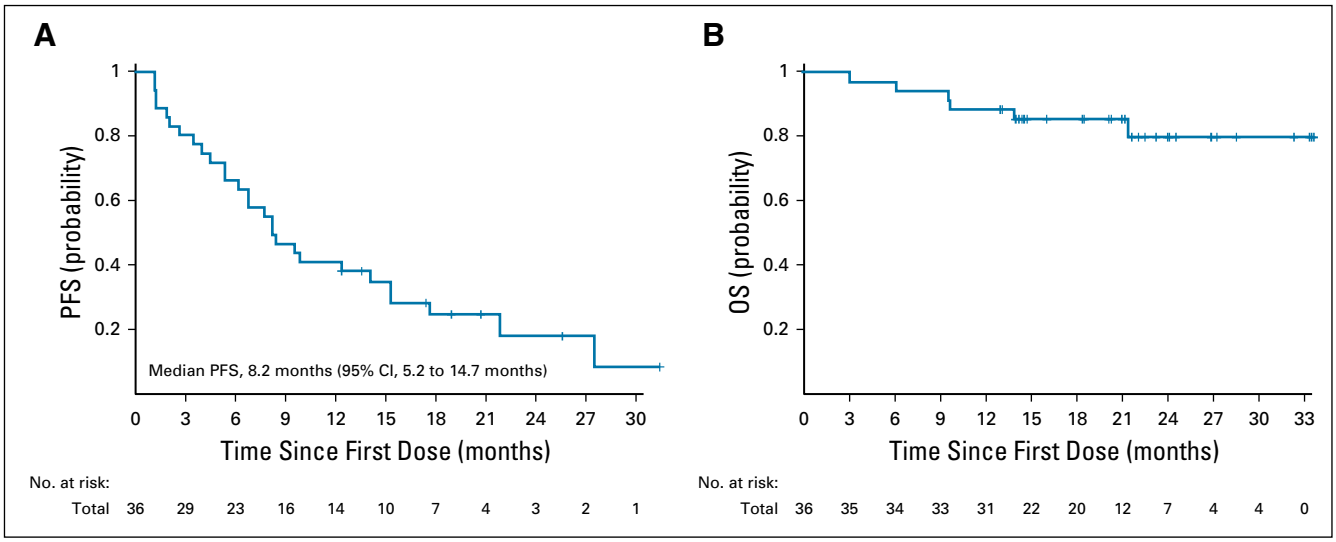

FIG 3. Kaplan-Meier curves of (A) progression-free survival (PFS) and (B) overall survival (OS). Vertical lines show censored events.

Safety

Table 3 provides a summary of AEs. Nearly all patients experienced at least one AE (34 [94%] of 36 patients) during the study treatment. The most frequently observed AEs of any grade, regardless of their relationship with osimertinib (by investigator assessment), were rash (n = 11; 31%), pruritus (n = 9; 25%), anorexia (n = 9; 25%), diarrhea (n = 8; 22%), and dyspnea (n = 8; 22%), which is consistent with previous reports. The majority of AEs were mild (grade 1 or 2 in severity). Grade 3 or 4 AEs were only observed in two patients (6%). One patient experienced grade 3 dyspnea, and another had grade 3 headache. No patients suffered from interstitial pneumonitis or QT prolongation.

The median number of cycles of osimertinib treatment was 13 (range, 2 to 42 cycles). Of 36 patients, treatment cycle delay was observed in six (17%). Reasons for treatment delay were AEs (n = 3; 8%), schedule conflict (n = 2; 6%), and disease evaluation (n = 1; 3%). Only one patient required a dose reduction of osimertinib (3%). None of the patients discontinued treatment due to AEs.

TABLE 2. Activity of Osimertinib in Specific Uncommon Mutations

Mutation	Objective Response		Median Progression-Free Survival, Months (95% CI)
	No. (%)	95% CI	
G719X (n = 19)	10 (53)	28 to 77	8.2 (6.2 to 10.2)
G719X (n = 15)			
G719X + S768I (n = 2)			
G719X + L861Q (n = 2)			
L861Q (n = 9)	7 (78)	44 to 100	15.2 (1.3 to 29.1)
L861Q (n = 7)			
L861Q + G719X (n = 2)			
S768I (n = 8)	3 (38)	0 to 81	12.3 (0 to 28.8)
S768I (n = 6)			
S768I + G719X (n = 2)			

NOTE. Uncommon mutation categories overlap those with compound mutations, so each patient might belong to more than one group.

DISCUSSION

This is the first prospective study demonstrating the efficacy of the third-generation EGFR TKI osimertinib in NSCLC from a multicenter phase II study in patients with uncommon EGFR mutations, excluding the exon 20 insertion. The ORR was 50% and the median PFS was 8.2 months among a total of 36 patients. This high response rate and long PFS are clinically meaningful given that uncommon EGFR mutations constitute a heterogeneous group of genetic alterations.

Data are still insufficient on the clinical efficacy of EGFR TKIs for NSCLC with uncommon EGFR mutations because of the high molecular heterogeneity and low prevalence. Response rates to EGFR TKIs in patients with NSCLC with sensitizing EGFR mutations (exon 19 deletions or L858R) are approximately 60% to 80%,[3,5] whereas available data regarding the efficacy of first- or second-generation TKIs in patients with NSCLC with uncommon EGFR mutations are inconsistent as a result of retrospective or post hoc analyses. In the NEJ002 trial, the response rate and PFS with gefitinib were significantly lower in patients with uncommon EGFR mutations (G719X or L861Q) compared with those with common EGFR mutations (20% *v* 76%; 2.2 months *v* 11.4 months).[24] In contrast, Wu et al[25] reported that objective responses to gefitinib or erlotinib were observed in 57.1% of patients with Gly719 or Leu861 mutations, with a PFS of 6.0 months. Recently, Yang et al[26] reported a post hoc analysis of afatinib data from the LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 trial populations. With afatinib

TABLE 3. All Adverse Events Regardless of Relationship With Osimertinib

Adverse Event*	All Grade	Grade 1	Grade 2	Grade 3	Grade 4
Rash	11 (31)	9 (25)	2 (6)		
Pruritus	9 (25)	8 (22)	1 (3)		
Anorexia	9 (25)	4 (11)	5 (14)		
Diarrhea	8 (22)	7 (19)	1 (3)		
Dyspnea	8 (22)	3 (8)	4 (11)	1 (3)	
Constipation	4 (11)	2 (6)	2 (6)		
Mucosal inflammation	4 (11)	3 (8)	1 (3)		
Headache	4 (11)	1 (3)	2 (6)	1 (3)	
Dry skin	4 (11)	3 (8)	1 (3)		

NOTE. Data are presented as No. (%).

*That occurred in ≥ 10% of patients overall (as assessed by the investigator; N = 36).

treatment among patients with uncommon EGFR mutations, ORR was 71% and PFS was 11 months, except for those with the T790M or exon 20 insertion mutations, for whom ORR was 9% to 14% and PFS was less than 3 months. Based on these results, the indication for afatinib was expanded by the US Food and Drug Administration to include the first-line treatment of patients with metastatic NSCLC whose tumors have nonresistant EGFR mutations, including L861Q, G719X, and S768I. That study originally focused on patients with both EGFR-sensitizing mutations and uncommon mutations. In contrast, our study focused only on uncommon mutations. We performed a subset analysis by uncommon mutation type. The exon 18 G719X mutation was most frequent among the rare mutations. This is generally recognized as a sensitizing mutation, with ORR and disease control rate comparable to those with common EGFR mutations. Wu et al[25] documented an ORR of 53.3% and a PFS of 8.1 months in patients with G719X mutation who were treated with gefitinib or erlotinib. In contrast, with afatinib, an ORR of 77.8% and a PFS of 13.8 months were reported.[26] In the current study, ORR and PFS were 53% and 8.2 months, respectively. Although cross-trial comparisons should be performed with caution, osimertinib demonstrated a response rate comparable to those of other EGFR TKIs in patients with G719X mutations. Exon 21 L861Q is the second most common rare EGFR mutation and is considered a sensitizing mutation. In preclinical studies, the L861Q mutation is resistant to first-generation TKIs, whereas it might be sensitive to afatinib or osimertinib.[28-31] Chiu et al[32] reported the largest cohort of patients with NSCLC harboring L861Q mutations. Among 54 patients, ORR was 40% and PFS was 8.1 months with the first-generation TKI erlotinib or gefitinib. In a post hoc analysis by Yang et al,[26] ORR to afatinib was 56%, with a PFS of 8.2 months. In contrast, our results demonstrated an ORR of 78% and a PFS of 15.2 months, which are better clinical outcomes than with other uncommon mutations. We suggest that osimertinib can be another treatment option for this mutation. The third most common rare mutation is exon 20 S768I mutation. Clinical data with this mutation are inconsistent among studies. Chiu et al[32] reported an ORR of only 33.3% with first-generation EGFR TKI in patients with only the S768I mutation. In contrast, with afatinib, ORR was 100% (8 of 8) and median PFS was 14.7 months. Considering that two patients with L858R were included in this cohort, caution should be emphasized in interpreting the results. Our study demonstrated an ORR of 38% with a PFS of 12.3 months in patients with just the S768I mutation.

Although both afatinib and osimertinib showed relatively high efficacy in uncommon EGFR mutations, we should take several issues into account for the choice of drug, such as CNS activity, toxicities, and EGFR mutation type. Given the limited number and heterogeneity of patients and the retrospective study design, the clinical efficacy of EGFR TKIs in patients with this rare mutation should be further investigated.[33]

Osimertinib has a higher CNS ORR and a longer CNS PFS than gefitinib and erlotinib in the treatment of CNS metastases in patients with EGFR-mutated NSCLC, as shown by the results from the phase III FLAURA trial. The enhanced blood–brain barrier penetrance of osimertinib may explain the higher CNS responses observed in patients with NSCLC. In two phase II studies of patients with T790M-positive NSCLC and CNS metastasis, osimertinib demonstrated a CNS ORR of 54% and a CNS disease control rate of 92%.[17] In the AURA3 phase III trial, osimertinib demonstrated significantly higher efficacy than platinum-based chemotherapy in patients with T790M-positive NSCLC.[14] Of interest, the current study also showed an encouraging CNS response (40%; 2 of 5 patients).

The safety profile of osimertinib in this study was quite acceptable and mostly confined to grade 1 to 2 AEs, which is consistent with previous reports. Osimertinib was associated with a low incidence of discontinuation and dose modification due to AEs.

There are some limitations of this study. First, we used local testing to detect EGFR mutations. The applied polymerase chain reaction–based or direct sequencing methods might have had limitations for the detection of compound EGFR mutations because of low sensitivity compared with next-generation sequencing. Second, since both first-line treatment and additional lines of therapy were included, additional study with homogeneous group should be investigated. Third, given the limited number for each subtype of uncommon EGFR mutation, we appreciate that additional studies with large number of patients are warranted.

In conclusion, to our knowledge, this study is the first prospective investigation of osimertinib in patients with NSCLC with uncommon EGFR mutations. Osimertinib was associated with a high response rate, an encouraging PFS,

and a long DoR with manageable toxicity in patients with NSCLC harboring uncommon EGFR mutations. Although a small number of patients were assessed, osimertinib can be considered as a treatment option for patients with NSCLC with uncommon EGFR mutations on the basis of this study.

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PRIOR PRESENTATION

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.00931.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

TABLE A1. Treatment Efficacy

Outcome	All Patients (N = 36)
Complete response	0
Partial response	18 (50)
Stable disease	14 (39)
Progressive disease	4 (11)
Objective response, No. (%)*	18 (50)
95% CI	33 to 67
Disease control rate, No. (%)†	32 (89)
95% CI	78 to 100
Median progression-free survival, months	8.2
95% CI	5.9 to 10.5
Median overall survival, months	NR
95% CI	
Duration of response, months	11.2
95% CI	7.7 to 14.7
Median No. of cycles (range)	13. (2-42)

NOTE. Data are presented as No. (%) unless otherwise indicated.

Abbreviation: NR, not reached.

*Confirmed complete and partial responses according to independent review and RECIST version 1.1.

†Complete response, partial response, and stable disease.