Original Article

Olmutinib in T790M-Positive Non–Small Cell Lung Cancer After Failure of First-Line Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor Therapy: A Global, Phase 2 Study

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BACKGROUND: In this open-label, international phase 2 study, the authors assessed the efficacy and safety of olmutinib in patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) who had a confirmed T790M mutation and disease progression on previous epidermal growth factor receptor-tyrosine kinase inhibitor therapy. **METHODS:** Patients aged ≥20 years received once-daily oral olmutinib 800 mg continuously in 21-day cycles. The primary endpoint was the objective response rate (patients who had a confirmed best overall response of a complete or partial response), assessed by central review. Secondary endpoints included the disease control rate, the duration of objective response, progression-free survival, and overall survival. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). **RESULTS:** Overall, 162 patients (median age, 63 years; women, >60%) were enrolled from 68 sites in 9 countries. At the time of database cutoff, 23.5% of enrolled patients remained on treatment. The median treatment duration was 6.5 months (range, 0.03-21.68 months). Overall, 46.3% of patients (95% CI, 38.4%-54.3%) had a confirmed objective response (all partial responses). The best overall response (the objective response rate regardless of confirmation) was 51.9% (84 patients; 95% CI, 43.9%-59.8%). The confirmed disease control rate for all patients was 86.4% (95% CI, 80.2%-91.3%). The median duration of objective response was 12.7 months (95% CI, 8.3-15.4 months). Estimated median progression-free survival was 9.4 months (95% CI, 6.9-12.3 months), and estimated median overall survival was 19.7 months (95% CI, 15.1 months to not reached). All patients experienced treatment-emergent adverse events, and 71.6% of patients had grade ≥3 treatment-emergent adverse events. **CONCLUSIONS:** Olmutinib has meaningful clinical activity and a manageable safety profile in patients with T790M-positive non–small cell lung cancer who received previous epidermal growth factor receptor-tyrosine kinase inhibitor therapy. ***Cancer* 2021;127:1407-1416**.

KEYWORDS: epidermal growth factor receptor, non–small cell lung cancer, olmutinib, T790M, tyrosine kinase inhibitor.

INTRODUCTION

Lung cancer is the most commonly diagnosed cancer worldwide, and its incidence continues to grow.[1] Typically, approximately 85% of all lung cancers are diagnosed as non–small cell lung cancer (NSCLC).[2]

Globally, several epidermal growth factor receptor (EGFR)-targeting agents have been approved as first-line treatments for patients with *EGFR*-mutant NSCLC.[3,4] First-generation EGFR tyrosine kinase inhibitors (TKIs), such as erlotinib and gefitinib, have an excellent initial response against EGFR-activating mutations.[5,6]

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Although EGFR-TKIs represented a paradigm shift in the treatment of *EGFR*-mutant NSCLC, the emergence of tumor resistance after a median of 12 to 16 months was almost inevitable.[7-9] The most common mechanism of acquired resistance (in up to 60% of patients) involves a secondary *gatekeeper* T790M mutation.[8,10-17]

Second-generation TKIs, such as afatinib and dacomitinib, have shown promising preclinical activities against T790M-positive tumors. However, their clinical activity in T790M-positive NSCLC was poor, with dose-limiting toxicities caused by the simultaneous inhibition of wild-type EGFR.[18,19]

Third-generation EGFR-TKIs, so-called EGFR mutant-specific inhibitors (EMSIs), such as olmutinib, osimertinib, rociletinib, naquotinib, and nazartinib, were designed to address the limitations of earlier drugs. Third-generation agents irreversibly block signaling by mutant *EGFR* (including T790M as well as EGFR activation mutations) but spare wild-type *EGFR*, thus providing potential efficacy in patients with an acquired T790M mutation after failing on first-generation or second-generation EGFR-TKIs.

Olmutinib, a small-molecule EMSI, has been evaluated in the treatment of patients who had NSCLC with T790M (acquired mutation).[20,21] Preclinical studies reported that olmutinib had excellent antitumor activity in various lung cancer cell lines with EGFR mutations (including T790M mutation) while producing minimal activity against wild-type EGFR.[22] Clinical information about olmutinib is available from a phase 1 study in healthy volunteers[23] and from a phase 1/2 Korean study in patients with NSCLC who were pretreated with an EGFR-TKI.[24] Olmutinib 800 mg once daily was the maximum tolerated dose and was recommended for phase 2 evaluation. In a phase 2 trial, the objective response rate (ORR) was 55.1% (95% CI, 42.6%-67.1%), most patients had tumor shrinkage relative to baseline (maximum shrinkage ranged from 27.7% to 100%), and the estimated median progression-free survival (PFS) was 6.9 months (95% CI, 5.6-9.7 months).[24] Therefore, preclinical and clinical data indicate that olmutinib is effective in patients who have *EGFR*-mutant NSCLC with the T790M mutation. Olmutinib had a safety profile expected of an EGFR-TKI, and most adverse events (AEs) were mild to moderate.[20,21,24,25] Furthermore, specific efficacy data from the phase 1/2 study suggested that olmutinib had significant clinical activity in patients with T790M-positive NSCLC after failing initial EGFR-TKI therapy and that reduced tumor volume was positively correlated with olmutinib exposure. When the phase 1/2 study was started, no targeted therapies had been approved for T790M-positive NSCLC. Therefore, the current global trial was conducted to assess the efficacy and safety of second-line treatment (or later lines of treatment) with olmutinib in patients with locally advanced or metastatic NSCLC who had a confirmed T790M mutation and progressive disease (PD) on previous EGFR-TKI therapy.

MATERIALS AND METHODS

Study Design

This multicenter, single-arm, open-label, global phase 2 study (ClinicalTrials.gov identifier NCT02485652) evaluated the efficacy, safety, and pharmacokinetics of olmutinib in patients with T790M-positive NSCLC after failing an EGFR-TKI (see Supporting Fig. 1).

Patients were enrolled onto the study from July 24, 2015 to July 5, 2016. All patients gave written informed consent. A tumor tissue sample taken after patients had PD during the last line of anticancer therapy (immediately before enrolment) was mandatory to confirm T790M mutation status at the central laboratory; the test kit used was *therascreen* EGFR RGQ polymerase chain reaction kit (Qiagen).

Patients received oral olmutinib 800 mg once daily, continuously in 21-day cycles, until they had radiologically confirmed PD (measured using Response Evaluation Criteria in Solid Tumors, version 1.1)[26]; patients continued to receive treatment if, in the investigator's opinion, there was evidence of clinical benefit. An olmutinib dosage reduction to 600 mg once daily was allowed according to a protocol-defined dosage-reduction scheme. For patients who benefitted from olmutinib, a dosage reduction to 400 mg once daily was permitted, after discussion with the study sponsor, in cases of olmutinib-related toxicity.

Patients were seen weekly in cycle 1 (on days 1, 8, and 15), every 3 weeks during cycles 2 through 7 (on day 1 of each cycle), and every 6 weeks thereafter (on day 1 of alternate cycles). Tumor assessments were performed at screening and every 6 weeks (±7 days), as calculated from the date of first study drug administration, until they had objective radiologic PD. All computed tomography and magnetic resonance imaging scans were sent for independent central review. All patients were evaluated at baseline using computed tomography and/or magnetic resonance imaging scans of the chest, abdomen, and pelvis. Patients who discontinued the study drug were followed for survival and poststudy anticancer treatment by telephone contact at least every 3 months until death or withdrawal of consent.

Study Patients

Patients were aged ≥20 years and had cytologically or histologically confirmed, locally advanced or metastatic

lung adenocarcinoma that was not amenable to curative surgery or radiotherapy. For inclusion, patients also had to have radiologically confirmed PD after at least 1 line of treatment with an EGFR-TKI, with or without prior chemotherapy, and a documented *EGFR* mutation (including G719X, exon 19 deletion, L858R, and L861Q) associated with susceptibility to EGFR-TKIs. All patients had an Eastern Cooperative Oncology Group performance status of 0 or 1 and a life expectancy ≥3 months, and all had centrally confirmed T790M mutation-positive tumors. All patients had to have at least 1 lesion (except in the brain) that was not previously irradiated and that could be accurately measured.

Principal exclusion criteria included: EGFR-TKI treatment (including erlotinib, gefitinib, and afatinib) within 8 days or 5-fold half-life, whichever was longer, of the first administration of study drug; previous treatment with afatinib with cetuximab or drugs targeting T790M mutant-positive *EGFR*; spinal cord compression; a history of any other malignancy (except for carcinoma in situ, nonmelanoma skin cancer, and superficial bladder tumors) in the past 5 years; psychiatric illness; and interstitial lung disease or radiation pneumonitis.

Study Endpoints

The primary endpoint was the ORR, with a confirmed best overall response (BOR) of complete response (CR) or partial response (PR), as assessed by independent central review. The BOR was the defined as the best confirmed response based on all responses from the start of treatment until PD, death, or new anticancer therapy (whichever occurred first). Tumor response was assessed every 6 weeks after the first study drug administration until PD.

Secondary endpoints included the disease control rate (DCR), the duration of objective response (DOR), overall survival (OS), the time from first study drug administration until tumor progression, tumor shrinkage (calculated as the absolute change and the percent change from baseline in the sum of tumor size at each assessment of tumor response), PFS, and safety. The DCR was defined as the proportion of patients with a documented CR, PR, or stable disease (for ≥5 weeks [6 weeks ± 7 days [visit window]). The DOR was defined as the interval between the date of the first observation of a tumor response (CR or PR, which required subsequent confirmation ≥4 weeks after initial documentation of a response) and the date of PD or death from any cause, whichever occurred first. OS was the time from first study drug administration until death from any cause. Patients who remained alive were censored at their last follow-up date. Safety analyses were conducted for all patients who had received at least 1 dose of study drug at the data cutoff according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03.

Study Conduct

The study was conducted at 68 sites in 9 countries (see Supporting Table 1) and was reported in compliance with the study protocol and its amendments, the Declaration of Helsinki, local laws, the International Council for Harmonization–Good Clinical Practice, and the clinical research organization's standard operating procedures. The Institutional Review Board for the coordinating investigator (Keunchil Park, Samsung Medical Center) approved the study on July 28, 2015. The Institutional Review Board of the coordinating investigator (Pasi A Jänne, Dana-Farber Cancer Institute) gave a favorable opinion on March 28, 2016.

Statistical Analyses

A Simon 2-stage design[27] was used to test the null hypothesis that the ORR was ≤30% versus the alternative that the response was ≥45%.[28] In the first stage, 49 patients were accrued: if there were ≤16 responses, then possible study discontinuation because of futility would be recommended by the independent data monitoring committee. The primary efficacy analysis was planned when the first 81 treated patients had had an assessment of the primary endpoint or had been prematurely withdrawn: the null hypothesis would be rejected if ≥33 responses were observed. This design was expected to yield a 1-sided type I error rate of 2.5%, with a power of 80%, when the true response rate was 45%. To provide further safety data as well as a supportive efficacy evaluation, recruitment was planned to continue until 150 patients had entered the study.

The ORR, DCR, and BOR were reported with category counts (percentages and 95% CIs). All time-to-event endpoints (ie, PFS, OS, DOR) were evaluated using Kaplan-Meier estimates, and curves were generated based on these estimates. For tumor shrinkage, percent changes from baseline in sums of tumor size at each assessment were calculated. ORR, DCR, DOR, PFS, and OS also were summarized according to the number of previous lines of anticancer therapy, background *EGFR* mutation type, and the presence of baseline brain metastases.

Safety data were analyzed using descriptive statistics. Treatment-emergent AEs (TEAEs) were defined as those starting or worsening in severity any time between the

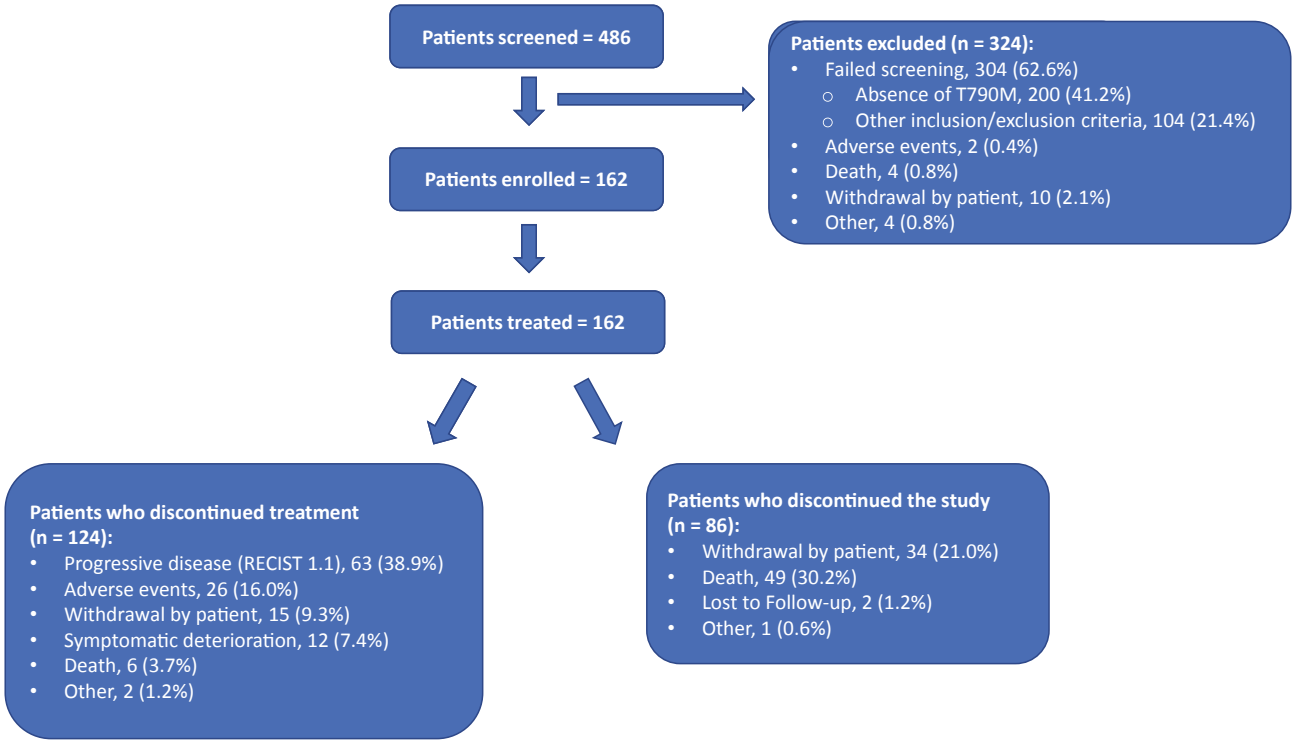

Figure 1. Patient disposition in the current study is illustrated. RECIST 1.1 indicates Response Evaluation Criteria in Solid Tumors, version 1.1.

date of first study drug administration and 28 days after the last study drug administration.

Circulating Cell-Free DNA Analysis

Plasma samples were collected (optional consent) from enrolled patients at every tumor assessment and limited as pairs (screening and after treatment). Circulating cell-free DNA (cfDNA) was analyzed using a targeted next-generation sequencing (NGS) assay (Axen Cancer Panel 1; Macrogene) at a Clinical Laboratory Improvement Amendments (CLIA)-certified, College of American Pathologists-accredited laboratory (Macrogene). Briefly, cfDNA (minimum, 20 ng) was isolated and enriched using targeted hybridization capture for library preparation, followed by sequencing on the Illumina HiSeq platform, with genetic alterations annotated by the Genome Analysis Toolkit, version 3 (GATK3) (Broad Institute).

RESULTS

In total, 486 patients were screened (Fig. 1), of whom 162 were enrolled in the study (the *full-analysis set*) (see Supporting Table 1). Approximately 40% of patients failed screening because of the absence of T790M. Of the 162 patients enrolled, 38 (23.5%) remained on treatment at the time of database cutoff. The principal reasons for treatment discontinuation were PD (38.9% of patients), AEs (16%), and patient withdrawal (9.3%). The median study duration, including the follow-up period, at database cutoff was 12.7 months (range, 0.03-21.7 months).

Baseline characteristics for the safety set are listed in Table 1. The median patient age was 63 years, >60% of patients were women, and all patients had an Eastern Cooperative Oncology Group performance status ≤1. Approximately one-third of patients were former smokers, slightly more than one-half of all patients had stable brain metastases, >60% had the exon 19 del *EGFR* mutation, and all had the T790M mutation. Approximately 80% of patients had received 1 or 2 previous lines of systemic therapy, including EGFR-TKIs.

Overall, the median treatment duration was 6.5 months (range, 0.03-21.68 months). Fifty-four patients (33.3%) had an olmutinib dosage reduction (until they developed PD) to 600 mg daily, and 12 (7.4%) had a reduction to 400 mg daily.

Seventy-five patients in the safety set (46.3%; 95% CI, 38.4%-54.3%) had a confirmed objective response

TABLE 1. Baseline Characteristics for the Safety Set, n = 162

Characteristic	No. of Patients (%)
Age: Median [range], y	63 [36-85]
Women	99 (61.1)
ECOG performance status	
0	45 (27.8)
1	117 (72.2)
Smoking history	
Current	4 (2.5)
Former	50 (30.9)
Never	108 (66.7)
Patients with brain metastases at baseline	
Yes	83 (51.2)
No	79 (48.8)
EGFR mutation	
Exon 19 del	100 (61.7)
L858R	52 (32.1)
Other	4 (2.5)
Unclassified[a]	6 (3.7)
T790M mutation at baseline[b]	
Positive	162 (100.0)
Negative	0 (0.0)
Previous lines of systemic therapy[c]	
1	92 (56.8)
2	37 (22.8)
3	12 (7.4)
≥4	21 (13.0)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.
[a]Patients categorized as unclassified were enrolled based on documented EGFR mutation status, but there was no information about specific mutation subtypes.
[b]Central confirmation was performed using the Therascreen EGFR RGQ polymerase chain reaction kit (QIAGEN).
[c]Systemic therapy included EGFR tyrosine kinase inhibitors. Adjuvant and neoadjuvant chemotherapy were not counted.

TABLE 2. Overall Response by Independent Central Review for the Safety Set, n = 162

Parameter	Response Rate, No. (%)	95% CI
Overall response rate (regardless of being confirmed)	84 (51.9)	43.9-59.8
Overall response rate (confirmed)	75 (46.3)	38.4-54.3
Partial response	75 (46.3)	
Stable disease	65 (40.1)	
Disease control rate (confirmed)	140 (86.4)	80.2-91.3
Progressive disease (PD)	8 (4.9)	
Non-CR/Non-PD	2 (1.2)	
Not evaluable	12 (7.4)	

Abbreviation: CR, complete response.

(all PRs), as assessed by independent central review. Sixty-five patients had stable disease (40.1%), 8 had PD (4.9%), and the confirmed DCR was 86.4% (95% CI, 80.2%-91.3%) (Table 2). The best response (ORR regardless of confirmation) was 51.9% (84 patients; 95% CI, 43.9%-59.8%).

A waterfall plot of the maximum percentage tumor shrinkage, assessed by independent review, is shown in Figure 2. Most patients had tumor shrinkage, and the median DOR was 12.7 months (95% CI, 8.3-15.4 months).

In the safety set, 83 patients (51.2%) had a PFS event, and the estimated median PFS was 9.4 months (95% CI, 6.9-12.3 months). In total, 54 patients (33.3%) had an OS event, and the estimated median OS was 19.7 months (95% CI, 15.1 months to not reached) (Fig. 3).

In patients who had baseline brain metastases (n = 83), the confirmed ORR was 49.4% (95% CI, 38.2%-60.6%) and the DCR was 86.8% (95% CI, 77.5%-93.2%); corresponding values in patients without brain metastases at baseline (n = 79) were 43.0% (95% CI, 31.9%-54.7%) and 86.1% (95% CI, 76.5%-92.8%), respectively. The median PFS for patients who had baseline brain metastases was 8.1 months (95% CI, 5.6-10.8 months) compared with 11.2 months (95% CI, 7.2-15.2 months) for patients without baseline brain metastases ($P = .076$; log-rank test) (see Supporting Table 2).

In the dosage-reduction subgroups, the median treatment duration until the first dose reduction (from olmutinib 800 mg daily to 600 mg daily) was 1.4 months (95% CI, 0.3-15.2 months) and the second dose reduction (from olmutinib 600 mg daily to 400 mg daily) was 3.8 months (95% CI, 0.4-12.3 months). No significant differences were noted between the 3 groups regarding confirmed ORRs and confirmed DCRs (see Supporting Table 3). Regarding other subgroup analyses, no major between-group differences in efficacy results were noted between patients who had received 1 or ≥2 previous lines of chemotherapy (see Supporting Table 4).

All patients experienced TEAEs, and 71.6% had grade ≥3 TEAEs. Drug-related TEAEs were reported in 152 patients (93.8%) and the most frequently reported were diarrhea (38.3%), nausea (27.2%), hyperkeratosis (26.5%), and rash (26.5%). Grade ≥3 drug-related TEAEs were reported in 78 patients (48.2%), and the most frequently reported were palmar-plantar erythrodysesthesia syndrome (4.3%), rash (4.3%), diarrhea (3.1%), increased alanine aminotransferase (3.1%), and hyperkeratosis (2.5%). One case of grade 5 toxic epidermal necrolysis (TEN) and 2 cases of grade 3 interstitial lung disease were reported (Table 3; see also Supporting Table 5). Overall, 61 patients (37.7%) had AEs that led to olmutinib dosage reductions (from 800 to 600 mg, 51 patients; from 600 to 400 mg, 10 patients), and 28 patients (17.3%) had AEs that led to treatment discontinuation; in 14 patients (8.6%), TEAEs that led to treatment discontinuation were considered drug-related, which most

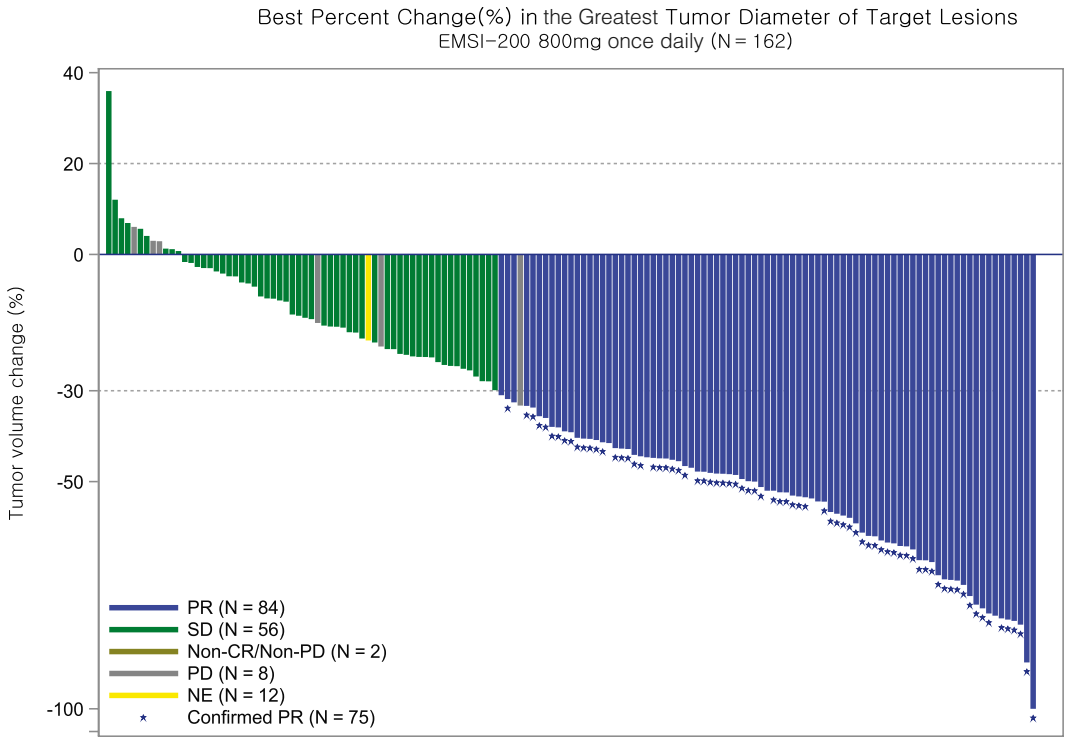

Figure 2. This is a waterfall plot of the maximum percentage of tumor shrinkage (determined by independent review). CR indicates complete response, NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease. *Fifteen of 162 patients who had no tumor shrinkage results after treatment are not presented in the figure; their best overall responses were non-CR/non-PD (2 patients), PD (2 patients), and not evaluable (11 patients).

frequently comprised palmar-plantar erythrodysesthesia syndrome (2.5%), rash (1.2%), and pneumonia (1.2%). In total, 79 patients (48.8%) had serious AEs and, in 30 patients (18.5%), these AEs were classified as drug-related (the most frequent were diarrhea [2.5%] and pyrexia [2.5%]). Twelve patients had fatal AEs, but most of these events were not drug-related, except 1 case of TEN. Subgroup analysis of TEAEs revealed decreased incidences of any TEAE, drug-related grade ≥3 AEs, TEAEs leading to discontinuation, and serious AEs in the 600-mg and 400-mg dose-reduced groups after the last dose reduction of each patient (see Supporting Table 6).

To investigate the mechanism(s) of resistance after olmutinib treatment, plasma samples from 27 patients were selected for retrospective NGS analysis. After cfDNA extraction and sequencing, results for 15 patients were evaluable for data analysis (see Supporting Fig. 2). Six patients showed loss of T790M mutation, whereas the actionable EGFR mutations were retained at PD (40%). Acquired EGFR mutations after treatment were observed in 3 patients: C797S (13.3%; n = 2) and L718Q (6.7%; n = 1). The allele frequency of baseline EGFR mutations changed during treatment, and the C797S mutation was only detected at PD (see Supporting Fig. 3).

DISCUSSION

This phase 2 study of olmutinib clearly demonstrated a tumor response (46.3%) in patients with T790M-positive NSCLC who had progressed after previous EGFR-TKIs with or without prior chemotherapy. Efficacy was unaffected by the presence of brain metastases at baseline, by a dosage reduction from 800 to 600 mg daily, or by the number of previous lines of chemotherapy. Overall, the olmutinib ORR (regardless of confirmation) was 51.9%, the median DOR was 12.7 months, and the median PFS was 9.4 months, which compare favorably with those of earlier EGFR-TKIs[29-34] but fall short of the outcomes obtained with osimertinib in AURA3 (ClinicalTrials.gov number NCT02151981).[35]

Although almost 40% of patients required AE-related dose reductions, the safety and tolerability of olmutinib were generally predictable and manageable during the study, with gastrointestinal, skin, and subcutaneous tissue disorders the most common TEAEs. The

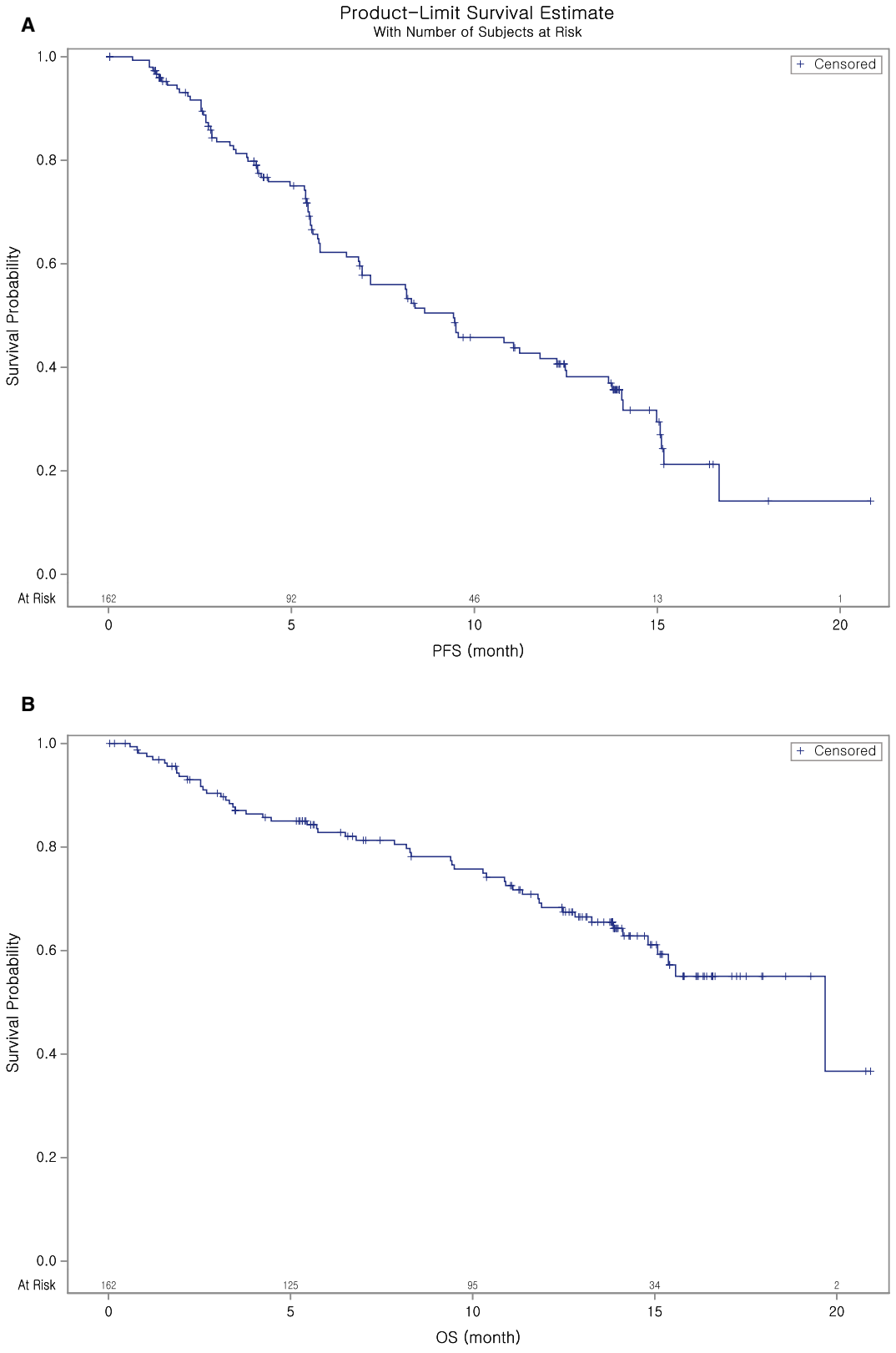

Figure 3. Kaplan-Meier curves illustrate (A) progression-free survival (PFS) and (B) overall survival (OS) determined by independent review.

TABLE 3. The Most Common Drug-Related Treatment-Emergent Adverse Event for the Safety Set, Incidence ≥20%[a]

Preferred Term	No. of Patients (%)	
	All Patients	Patients With Grade ≥3 Events
All drug-related TEAEs	152 (93.8)	78 (48.2)
Diarrhea	62 (38.3)	5 (3.1)
Nausea	44 (27.2)	1 (0.6)
Hyperkeratosis	43 (26.5)	4 (2.5)
Rash	43 (26.5)	7 (4.3)
Skin exfoliation	38 (23.5)	1 (0.6)
Vomiting	37 (22.8)	3 (1.9)
Palmar-plantar erythrodysesthesia syndrome	35 (21.6)	7 (4.3)
Increased alanine aminotransferase	33 (20.4)	5 (3.1)

Abbreviation: TEAEs, treatment-emergent adverse events.
[a]One case of fatal toxic epidermal necrolysis was reported, and 2 cases of grade 3 interstitial lung disease (ILD) were reported. (ILD/pneumonitis, ILD-like events).

most frequent drug-related AEs (occurring in ≥20% of patients) were rash, palmar-plantar erythrodysesthesia syndrome, diarrhea, increased alanine aminotransferase, hyperkeratosis, and vomiting. Thirty patients had drug-related serious AEs, which most frequently comprised diarrhea and pyrexia. Twelve patients had TEAEs that led to death but, with the exception of 1 case of TEN, none were considered to be drug-related. Although hyperkeratosis and palmar-plantar erythrodysesthesia syndrome tended to occur more frequently with olmutinib compared with other EGFR-TKIs (see Supporting Fig. 4),[36] these events were generally tolerable and manageable.

Cases of severe skin reactions (ie, Stevens-Johnson syndrome and TEN) have been observed in 3 patients treated with olmutinib, including 1 fatal case of TEN associated with olmutinib 35 days after the last dose in the study, in which the patient then developed septic shock and renal failure, resulting in death. All 3 cases were treated with olmutinib 800 mg daily. The mechanism underlying drug-induced Stevens-Johnson syndrome/TEN is considered to be a delayed-type hypersensitivity reaction. However, previous studies have reported a potential association between specific human leukocyte antigen (HLA) genotype and drug-induced hypersensitivity reactions for abacavir-HLA-B*5701 and carbamazepine-HLA-B*1502.[37]

It is noteworthy that most (approximately 90%) enrolled patients were Asian, reflecting the natural history of NSCLC, all of whom had the T790M mutation. Moreover, in our study, an olmutinib dosage reduction from 800 to 600 mg daily did not appear to compromise efficacy but was associated with a reduced incidence of TEAEs. The efficacy and safety of olmutinib 600 mg daily in T790M-positive NSCLC was planned to be further investigated in a phase 1b trial to determine the optimal dose; however, as discussed below, the planned trial has not been conducted.

In our exploratory cfDNA NGS analysis, known EGFR mutations, such as loss of T790M, acquired C797S, and atypical L718Q, that also affect the activity of other third-generation EGFR TKIs[38-40] were observed in olmutinib-treated samples. The variants and incidence of these EGFR mutations are similar to those in osimertinib-treated patients.[41] Other uncommon EGFR mutations or amplification of driver genes (eg, MET, EGFR) were not detected in this analysis. This may reflect the small evaluable data set (samples were limited to cases in which optional patient consent had been obtained) and the limitations of cfDNA NGS to identify copy number alterations and, as such, limit the ability to draw clear conclusions. In the case of patients who lost the T790M mutation after treatment, several commutations of off-target genes were observed in an intrinsic or acquired manner. However, these mutations were mostly benign or were unknown functional variants (data not shown).

On the basis of the results from an earlier phase 1/2 study in Korean patients,[24] olmutinib was granted breakthrough therapy designation for NSCLC by the US Food and Drug Administration in December 2015. At that time, the initial profile of olmutinib, including target selectivity, was comparable to that of third-generation EMSIs (eg, rocelitinib, naquotinib, and nazartinib), which were terminated early. However, based on outcomes obtained in the current global trial, it appears that olmutinib was less selective than originally anticipated compared with osimertinib based on in vitro kinase selectivity (EGFR wild-type/T790M); and, eventually, olmutinib was also terminated because this current global trial reported inferior results in terms of safety and efficacy profiles compared with the outcomes obtained with osimertinib in the AURA3 trial.[35]

In summary, to our knowledge, this global phase 2 study is the largest prospective study of olmutinib in patients with locally advanced or metastatic NSCLC who had PD with T790M mutations after at least 1 line of EGFR-TKI therapy. Efficacy and safety data from this analysis highlight that olmutinib 600 to 800 mg once daily has meaningful clinical activity with a largely predictable safety profile in patients with T790M-positive NSCLC who had received previous EGFR-TKI therapy. However, based on

an assessment of the competitive landscape of evolving EMSI treatment options, the development of olmutinib to treat patients with NSCLC has since been discontinued. While recognizing that large, multicenter studies with long-term follow-up are required for new drug development, early outcomes from the olmutinib studies are quite promising; in recent times, safety and risk/benefit concerns have resulted in the discontinued clinical development of several other third-generation EGFR-TKIs, such as rociletinib, naquotinib, nazartinib, and canertinib.[42]

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CONFLICT OF INTEREST DISCLOSURES

Keunchil Park reports personal fees from Hanmi Pharmaceutical Company, Ltd, during the conduct of the study; grants from MSD Pharmaceuticals, outside the submitted work; and personal fees from AbbVie, Amgen, AstraZeneca, BluePrint Medicines, Bristol-Myers Squibb, Boehringer-Ingelheim, Daiichi Sankyo, Eisai, Eli Lilly, JNJ, Merck KGaA, MSD Pharmaceuticals, Puma Biotechnology, and Takeda, outside the submitted work. Pasi A. Jänne reports other support from Hanmi Pharmaceutical Company, Ltd, during the conduct of the study; grants from Boehringer-Ingelheim, Eli Lilly, Daiichi Sankyo, Takeda Oncology, outside the submitted work; personal fees from AstraZeneca, Boehringer-Ingelheim, Pfizer, Roche/Genentech, Chugai Pharmaceuticals, Ignyta, Loxo Oncology, Eli Lilly, SFJ Pharmaceuticals, Voronoi, Daiichi Sankyo, Biocartis, Novartis, Sanofi Oncology, Takeda Oncology, Mirati Therapeutics, Transcenta, Silicon Therapeutics, Syndax, Astellas, PUMA, and Revolution Medicines, outside the submitted work; and postmarketing royalties from a Dana-Farber Cancer Center–owned patent (EGFR Mutations) licensed to Lab Corp. Dong-Wan Kim reports grants and nonfinancial support from Hanmi Pharmaceutical Company, Ltd, during the conduct of the study; institutional grants from Alpha Biopharm, Amgen, AstraZeneca/Medimmune, Boehringer-Ingelheim, Daiichi-Sankyo, Janssen, Meurs, Mirati Therapeutics, MSD Pharmaceuticals, Novartis, Ono Pharmaceutical, Pfizer, Roche/Genentech, Takeda, TP Therapeutics, Xcovery, and Yuhan, outside the submitted work; and nonfinancial support from Amgen and Daiichi-Sankyo, outside the submitted work. Ji-Youn Han reports research funding from Ono Pharmaceutical, Pfizer, Roche, and Takeda, outside the submitted work; and personal fees from AstraZeneca, Bristol-Myers Squibb, MSD Pharmaceuticals, Roche, Eli Lilly, MSD Oncology, Novartis, Pfizer, and Takeda, outside the submitted work. Dae Ho Lee reports personal fees from AbbVie, AstraZeneca, Boehringer-Ingelheim, Takeda, Bristol-Myers Squibb, ChongKunDang, CJ Healthcare, Eli Lilly, Janssen, Merck, MSD Pharmaceuticals, Mundipharma, Novartis, Ono Pharmaceutical, Pfizer, Roche, Samyang Biopharm, ST Cube, GreenCross, and Genexine, outside the submitted work. Byoung Chul Cho reports research funding from Novartis, Bayer, AstraZeneca, MOGAM Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, Ono Pharmaceutical, Dizal Pharma, MSD Pharmaceuticals, AbbVie, Medpacto, GI Innovation, Eli Lilly, Blueprint Medicines, and Interpark Bio Convergence Corporation, outside the submitted work; personal fees from Novartis, AstraZeneca, Boehringer-Ingelheim, Roche, Bristol-Myers Squibb, Ono Pharmaceutical, Yuhan, Pfizer, Eli Lilly, Janssen, Takeda, MSD Pharmaceuticals, Medpacto, Blueprint Medicines, TheraCanVac Inc, Gencurix Inc, Bridgebio Therapeutics, Cyrus Therapeutics, Interpark Bio Convergence Corp, KANAPH Therapeutic Inc, and Guardant Health, outside the submitted work; stock ownership in TheraCanVac Inc, Gencurix Inc, Bridgebio Therapeutics, and KANAPH Therapeutic Inc; is the founder of DAAN Biotherapeutics; receives royalties from Champions Oncology; and is a member the boards of Gencurix Inc and Interpark Bio Convergence Corporation, outside the submitted work. Yong Kek Pang reports other support from Hanmi Pharmaceutical Company, during the course of the study. Enriqueta Felip reports personal fees from AbbVie, Amgen, AstraZeneca, Bayer, Blueprint Medicines, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Glaxo-Smith-Kline, Janssen, Medscape, Merck KGaA, MSD Pharmaceuticals, Novartis, Roche, Peervoice, Pfizer, Prime Oncology, Puma Biotechnology, Roche, Sanofi Genzyme, Springer, Takeda, and Touchime, outside the submitted work; grants from Grant for Oncology Innovation (GOI) and Fundacion Merck Salud, outside the submitted work; and is an independent member of the board of Grifols. Hyunjin Kim, Eunhye Baek, and Young Su Noh are employees of Hanmi Pharmaceutical Company, Ltd. Ming-Fang Wu, Jong-Seok Lee, and Chong-Jen Yu made no disclosures.

AUTHOR CONTRIBUTIONS

Keunchil Park: Study design, data acquisition, statistical analysis, article preparation, writing, and approval. **Pasi A. Jänne**, **Dong-Wan Kim**, **Ji-Youn Han**, **Ming-Fang Wu**, **Jong-Seok Lee**, **Jin-Hyoung Kang**, **Dae Ho Lee**, **Byoung Chul Cho**, **Chong-Jen Yu**, **Yong Kek Pang**, **Enriqueta Felip:** Patient enrolment. **Hyunjin Kim:** Biomarker data analysis and writing. **Eunhye Baek:** Data acquisition and statistical analysis. **Young Su Noh:** Article preparation and writing.

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