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Safety, tolerability, and anti-tumor activity of olmutinib in non-small cell lung cancer with T790M mutation: A single arm, open label, phase 1/2 trial*

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ABSTRACT

Objectives: The aim of this phase 1/2 study was to evaluate the safety, tolerability, pharmacokinetics and antitumor activity of olmutinib in patients with epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC) who had failed ≥ 1 previous line of EGFR-tyrosine kinase inhibitor (TKI) therapy.

Materials and methods: Phase 1 consisted of dose-escalation and four dose-expansion parts (1: olmutinib 300 mg once daily; 2A: 800 mg once daily [*EGFR* T790 M mutation-positive patients]; 2B: 500 mg twice daily [*EGFR* T790 M mutation-positive]; 3: 800 mg once daily [*EGFR* T790 M mutation-negative]). In phase 2, *EGFR* T790 M mutation-positive patients received olmutinib 800 mg once daily. Data from expansion part 2A and phase 2 were integrated (`pooled phase 2′). Each olmutinib cycle was 21 days. Outcomes included: tumor response, treatment-emergent adverse events (TEAEs), pharmacokinetic parameters.

Results: Overall, 272 patients received at least one olmutinib dose: dose-escalation (n = 66), expansion parts (n = 165), phase 2 (n = 41). In pooled phase 2, the overall objective response rate, confirmed by independent review, was 55.1% (38/69 evaluable patients; 95% CI, 42.6–67.1). All responses were partial responses; 23 patients had stable disease. Estimated median progression-free survival was 6.9 (95% CI, 5.6–9.7) months; estimated median overall survival was not reached. The most frequent treatment-related AEs were diarrhea (59.2% of patients), pruritus (42.1%), rash (40.8%), and nausea (39.5%).

Conclusion: Olmutinib showed effective clinical activity with a manageable safety profile, indicating therapeutic potential for T790M-positive NSCLC patients who have failed ≥ 1 previous line of EGFR-TKI therapy.

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1. Introduction

Activating mutations in epidermal growth factor receptor (EGFR) tyrosine kinase domains, including exon 19 deletion (del19) and exon 21 mutation (L858R), are directly associated with malignant transformation in non-small cell lung cancer (NSCLC) [1–3]. These sensitizing mutations are observed in 30–40% of Asian patients, and in about 10% of Caucasians [4]. Antitumor agents that inhibit EGFR tyrosine kinases are established as the first-line therapy for NSCLC with *EGFR*-activating mutations [5,6].

Treatment with first-generation EGFR tyrosine kinase inhibitors (TKIs), including gefitinib and erlotinib, is associated with an excellent response rate (56–74%) and median progression-free survival (PFS: 10–14 months) [5–10]. However, most patients treated with EGFR-TKIs develop acquired resistance and disease progression within 9–24 months of starting treatment [5,6,10,11]. Among these cases, approximately 40–60% are related to the T790 M mutation in exon 20 of the *EGFR* gene [4,12,13]. *EGFR* T790 M mutation increases the binding affinity of tyrosine kinase for adenosine triphosphate (ATP), which leads to a reduced tumor response due to reversible binding of EGFR-TKIs to the ATP pocket [14].

Second-generation EGFR-TKIs (e.g. afatinib, dacomitinib), which form irreversible covalent bonds with a cysteine residue in EGFR, were developed to overcome the acquired resistance to first-generation compounds. Second-generation agents, also known as pan-HER inhibitors because of their potent inhibitory activity against both EGFR and the HER family [15,16], have superior activity against tumors with a T790 M mutation. However, second-generation compounds also strongly inhibit wild-type EGFR, and are frequently associated with adverse events (AEs) such as diarrhea and skin rash [17,18]. Thus, in many situations, second-generation agents cannot be administered at the dosages needed to produce meaningful clinical outcomes in patients with a T790 M mutation [19]. As resistance to first- and second-generation EGFR-TKIs invariably develops, and is frequently due to T790 M mutations, new targeted treatment options for *EGFR*-mutation positive NSCLC patients failing first-line treatment are needed. Osimertinib has been granted full approval by the US Food and Drug Administration based on data from a randomized, phase 3 trial (AURA3) in patients with *EGFR* T790 M NSCLC who progressed on prior EGFR-TKI therapy [20]. A higher response and prolonged PFS were achieved in the osimertinib arm compared with standard of care (median PFS was 10.1 months vs 4.4 months, objective response rate [ORR] was 71% vs 31%) [20]. Currently, due to the early termination of the clinical development of other third-generation EGFR-TKIs such as rociletinib and ASP8273, osimertinib is the only EGFR-TKI approved in patients with T790M-positive NSCLC. In addition, osimertinib has recently been approved for the first-line treatment of patients with EGFR-mutated NSCLC. Although osimertinib is a new standard of care in this setting, second-line therapy for such patients in areas where osimertinib is not commercially available usually comprises platinum-based doublet chemotherapy [21–24].

Olmutinib (HM61713) is a third-generation, mutation-specific EGFR-TKI, which targets mutant-type EGFR and has minimal activity against wild-type EGFR. Olmutinib has shown excellent anticancer activity in several nonclinical studies in various lung cancer cell lines with *EGFR* mutations, including the T790 M mutation [25].

Importantly, because of its limited activity against wild-type EGFR, olmutinib has the potential to show reduced skin and gastrointestinal toxicities, and to be associated with less deterioration in quality of life, relative to first- and second-generation targeted EGFR-TKIs. The current phase 1/2 study of olmutinib in *EGFR*-mutated NSCLC was therefore designed: to evaluate olmutinib safety and tolerability by determining dose-limiting toxicities (DLTs) and the maximum tolerated dose (MTD); to characterize the pharmacokinetic profile of olmutinib; and to assess the antitumor activity of olmutinib.

2. Methods

2.1. Study design

This was a phase 1/2 study to assess the safety, tolerability, pharmacokinetics, and antitumor activity of olmutinib in NSCLC patients with *EGFR* mutation. The phase 1 component of the trial consisted of dose-escalation and dose expansion parts. In the dose escalation part, olmutinib administration was started with 50 mg twice daily, and was planned to be followed by a pre-specified dose escalation schedule. However, the starting dose was amended to 75 mg once daily because of unexpectedly high exposure to olmutinib observed in the first two cohorts. The next dose level was approximately increased/decreased after a review of the safety data at a safety review meeting followed by a pre-specified dosing schedule. If any evidence of clinical activity was observed in an escalation cohort, a dose-expansion cohort for that dose could be opened. Finally, phase 2 was added so that the antitumor effects of olmutinib observed in the expansion part could be evaluated without interruption. Each cycle of olmutinib treatment was 21 days.

2.2. Study patients

Patients were eligible for inclusion if they had locally advanced or metastatic NSCLC. Patients had to have had disease progression during previous 1st- or 2nd-generation EGFR-TKI treatment (e.g. erlotinib, gefitinib, afatinib). There was no upper limit for the number of prior EGFR-inhibitor systemic therapies. All patients required at least one *EGFR* mutation (e.g. E19del, L858R, G719X, L861Q, etc). EGFR mutation analysis was performed via local testing or central laboratory testing (PNAClamp™ which is a PCR-based assay developed independently by Panagene). For *EGFR* T790 M mutations, enrolled patients were not restricted to those with T790M-positive disease in the dose-escalation part and expansion part 1. Meanwhile, in expansion parts 2 and 3, and phase 2, patients could only be included if the tumor had documented evidence of T790 M mutation (either positive or negative), performed either at a local laboratory or centrally after disease progression during the most recent line of therapy. In expansion part 2A and phase 2, T790 M mutation was centrally confirmed using PNAClamp™, retrospectively.

Principal exclusion criteria comprised: symptomatic or uncontrolled CNS metastases, spinal cord compression or leptomeningeal carcinomatosis; history of pulmonary disease (including pulmonary fibrosis and interstitial lung disease); NYHA class III–IV congestive heart failure or left ventricular ejection fraction < 40%; and previous pancreatitis.

2.3. Study assessments

Tumor evaluation was performed every 2 cycles by the site investigator and independent central review according to RECIST version 1.1, and was used as a basis for treatment determination, and for supplementary analysis of ORR. Tumor response had to be confirmed by repeat radiologic imaging ≥4 weeks after initial documentation. To qualify for stable disease (SD), the condition had to be maintained for ≥5 weeks. Survival follow-up was done every 3 months, from 28 (+7) days after the last treatment, only in patients who gave consent.

Treatment-emergent AEs (TEAEs) were summarized by study part using System Organ Class (SOC) and Preferred Term (PT) of Medical Dictionary for Regulatory Activities (MedDRA) version 14.0, and

severity was graded according to National Cancer Institute-Common Terminology Criteria for AEs (NCI-CTCAE), version 4.03.

Blood samples were collected for all subjects to assess the pharmacokinetic profile (e.g. C_{max}, T_{max}, AUC) of olmutinib and its metabolites (M1, M2), according to a pre-specified schedule.

2.4. Study conduct

The protocol, informed consent form, and their amendments were reviewed and approved before study start by the Korean Ministry of Food and Drug Safety, and the Institutional Review Board of each study institution. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice. Each patient provided written informed consent to participate.

2.5. Statistical analysis

Demographic and safety analyses included all patients who received at least one dose of study drug. Efficacy analyses included all patients who received at least one dose of study drug and who had at least one post-baseline tumor assessment (full analysis set; FAS). Tumor response analyses were conducted based on investigator assessment for phase 1, and independent-reviewer assessment for pooled phase 2 (expansion part 2A and phase 2). For pooled phase 2, sensitivity analysis was conducted based on investigator assessment.

Olmutinib efficacy was also explored according to brain lesion status at baseline. For ORR (complete response [CR] + partial response [PR]) and disease control rate (DCR; CR + PR + SD for ≥5 weeks), the numbers and proportions of patients who achieved an objective response and disease control were presented with 95% confidence intervals (CIs). Maximum percentage tumor shrinkage was calculated using sum of the longest diameter in target lesions. Event-driven variables, including overall survival (OS), PFS, time to tumor progression (TTP), and duration of overall response (DOR) were analyzed using Kaplan-Meier methods; median values were presented with 95% CIs. For patients with no relevant event until the end of the study, each variable was censored at the time of the last evaluable assessment.

3. Results

3.1. Patient disposition

Between March 2012 and May 2016, a total of 272 patients received at least one dose of olmutinib across 16 sites in Korea: 66 in the dose-escalation part, 165 across four expansion parts and 41 in phase 2. Four expansion parts were opened: expansion part 1 (300 mg once daily), part 2A (800 mg once daily in *EGFR* T790 M mutation-positive patients), part 2B (500 mg twice daily in *EGFR* T790 M mutation-positive patients), and expansion part 3 (800 mg once daily in *EGFR* T790 M mutation-negative patients). The results obtained from expansion part 2A and phase 2 (800 mg once daily in *EGFR* T790 M mutation-positive patients) were integrated for analysis since the study population, inclusion/exclusion criteria, and study objectives/endpoints were the same (this part is depicted as pooled phase 2; N = 76). With the exception of those in the dose-escalation and expansion part 1, patients were enrolled based on either positive or negative T790 M results, assessed by local testing. In pooled phase 2, all patients were T790M-positive with local testing at screening, but 3 patients were T790M-negative with retrospective central testing. All dose cohorts in this study are described in Fig. 1.

Baseline characteristics of the study population are shown in Table 1. Median age was 61.0 (range 32–85) years, and most patients were female (64.7%), never smokers (73.5%). ECOG performance status was 0 or 1 in 89.0% of patients, and 31.6% of patients had brain metastases. Baseline characteristics of patients enrolled in pooled phase 2 were similar to those enrolled in the overall study.

3.2. Observed dose-limiting toxicities and phase 2 dose selection

Olmutinib dose was started at 75 mg daily and increased up to 1200 mg daily in the dose escalation part. Overall, 9 cases of DLTs from 5 patients were reported across dose cohorts: amylase or lipase elevation, liver enzyme elevation, gastrointestinal disorders and idiosyncratic drug reaction. Two cases of DLTs (grade 3 abdominal pain and grade 3 diarrhea) occurred in the 1200 mg once daily cohort (Supplemental Table 1). Therefore, 800 mg once daily dose was declared as the MTD and selected as the recommended phase 2 dose

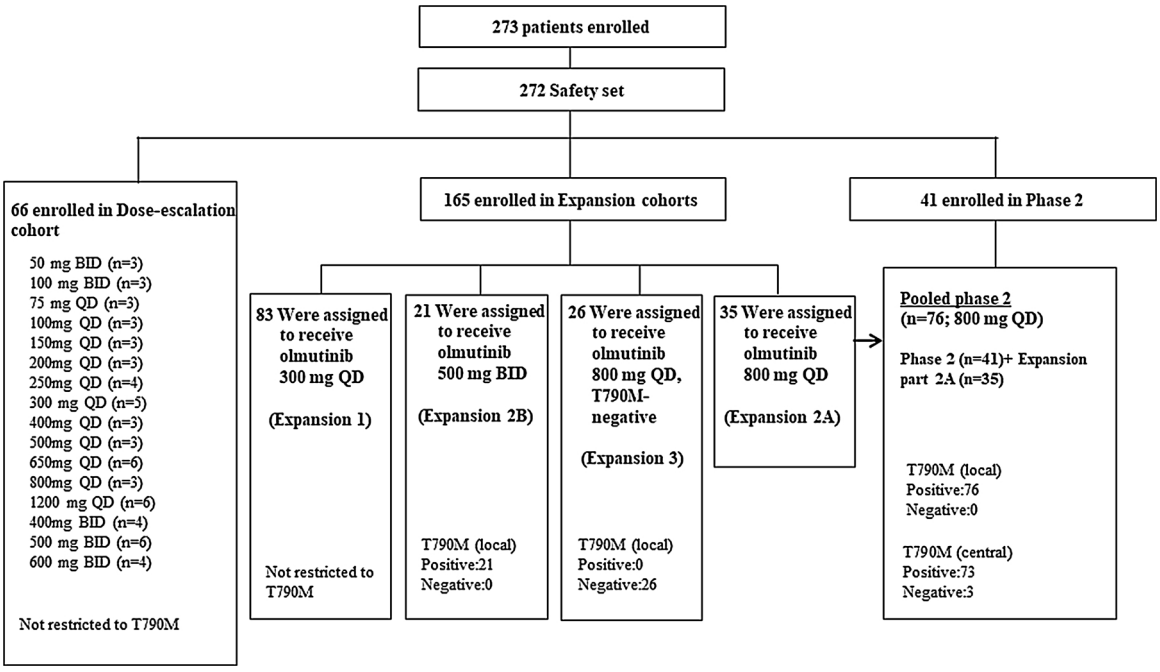

Fig. 1. Study disposition. BID, twice daily; QD, once daily.

Table 1
Baseline characteristics (pooled phase 2 safety and overall study populations).

Variable	Pooled phase 2 (N = 76)	Overall (N = 272)
Age, years; median (range)	59.5 (32, 85)	61.0 (32, 85)
Male, n (%)	32 (42.1)	96 (35.3)
Female, n (%)	44 (57.9)	176 (64.7)
Smoking habit, n (%):		
Never	53 (69.7)	200 (73.5)
Former	21 (27.6)	69 (25.4)
Current	2 (2.6)	3 (1.1)
ECOG performance status, n (%)		
0 or 1	61 (80.3)	242 (89.0)
2	15 (19.7)	30 (11.0)
Patients with brain metastases, n (%)		
Yes	24 (31.6)	86 (31.6)
No	52 (68.4)	186 (68.4)
T790M mutation at screening, n (%) pts*		
Yes	73 (96.1)	138 (50.7)
No	3 (3.9)	69 (25.4)
Not tested	–	65 (23.9)
Number of previous lines of EGFR-TKI treatment, n (%) pts		
One	58 (76.3)	223 (82.0)
Two	14 (18.4)	42 (15.4)
≥Three	4 (5.3)	7 (2.6)

ECOG, Eastern Cooperative Oncology Group; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; NA, not available; pts, patients; SD, standard deviation.

* Central confirmation (analyzed using PNAClamp™, an assay developed independently by Panagene).

considering tolerability, pharmacokinetics and antitumor activity. Additional twice-daily cohorts (400 mg, 500 mg and 600 mg) were opened in order to explore the feasibility of a twice-daily regimen in the dose escalation part; based on favorable safety, 500 mg twice daily was evaluated in expansion part 2B.

3.3. Pharmacokinetics

The pharmacokinetics of olmutinib after single (day 1) or multiple oral doses (steady-state; day 24) of 50–100 mg twice daily and 75–1200 mg once daily were investigated in this study (Supplemental Fig. 1 and Supplemental Table 2). As mentioned above, observed olmutinib exposure was higher than expected in early twice-daily dose cohorts, leading to a change to once-daily dosing. Pharmacokinetic analyses showed that olmutinib exposure generally increased with increasing dose. Single and repeated dosing resulted in similar pharmacokinetics. No, or very limited, accumulation was observed after repeated-dose administration in most dose groups, except in the 200 mg once daily group.

3.4. Efficacy

3.4.1. Phase 1

In the dose-escalation part, 62 patients were evaluable for response. Objective responses were observed starting from the 100 mg once daily cohort. Seventeen patients (27.4%) had a confirmed PR and 32 (51.6%) had SD (Supplemental Table 3). In expansion part 1, 83 patients received olmutinib 300 mg once daily and 15 (18.1%) had a confirmed PR. Median PFS was 2.8 (95% CI, 2.6 to 5.4) months, and median DOR was 11.2 (95% CI, 5.6 to 13.6) months (Supplemental Table 4).

In expansion part 2B, 21 patients received olmutinib 500 mg twice daily and 19 were evaluable for response. The confirmed ORR was 26.3% (5/19 patients) and median PFS was 5.3 (95% CI, 2.0–11.0) months. In expansion part 3, 26 evaluable patients were all negative for *EGFR* T790 M mutation at baseline and received olmutinib 800 mg once daily. The confirmed ORR was 7.7% (2/26 patients). Details of efficacy outcomes in the expansion parts are summarized in Supplemental Table 4.

Table 2
Primary and secondary study outcomes[a] in pooled phase 2 (N = 69).

Confirmed ORR; n (%) [95% CI]	38 (55.1) [42.6, 67.1]
Confirmed best overall response; n (%)	
CR	0 (0.0)
PR	38 (55.1)
SD	23 (33.3)
PD	4 (5.8)
NE	4 (5.8)
Maximum percent tumor shrinkage; %	27.7–−100.0[b]
Median PFS; months [95% CI]	6.9 [5.6, 9.7]
Median TTP; months [95% CI]	6.8 [5.4, 8.8]
Median DOR; months	8.4 [5.7, 14.2]
Disease control rate; n (%) [95% CI]	61 (88.4) [78.4, 94.9]
Median Overall Survival, months [95% CI]	Not reached [24.0, not reached]

CI, confidence interval; CR, complete response; DOR, duration of overall response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTP, time to tumor progression.

[a] By independent reviewer assessment.

[b] See waterfall plot (Fig. 2).

3.4.2. Pooled phase 2

Overall, 38 of the 69 FAS patients had an objective response confirmed by independent review (ORR 55.1%; 95% CI, 42.6–67.1). All 38 responses were PRs, and 23 patients had SD (Table 2). A waterfall plot of maximum percentage tumor shrinkage is shown in Fig. 2. Most patients had tumor shrinkage relative to baseline values, and the median maximum percentage tumor shrinkage was −43.6% (range −100 to 27.7). Estimated median PFS was 6.9 (95% CI, 5.6–9.7) months (Fig. 3). Estimated median OS was not reached. Median TTP was 6.8 (95% CI, 5.4–8.8) months (Table 2), and estimated median DOR was 8.4 (95% CI, 5.7–14.2) months.

In patients without baseline brain lesions (N = 47), the confirmed ORR was 59.6% (95% CI, 44.3–73.6), DCR was 89.4% (95% CI, 76.9–96.5) and median PFS was 7.6 (95% CI, 5.4–11.1) months. In patients with brain metastases at baseline (N = 22), ORR was 45.5% (95% CI, 24.4–67.8), DCR was 86.4% (95% CI, 65.1–97.1) and median PFS was 6.2 (95% CI, 2.8–9.5) months (Supplemental Table 5).

3.5. Safety

3.5.1. Overall study population (N = 272)

In the overall population, 248 patients (91.2%) had treatment-related AEs, 73 patients (26.8%) had grade ≥ 3 events. The most frequent treatment-related AEs were diarrhea (37.1%), rash (35.3%), and nausea (28.3%) [Table 3]; the most common treatment-related AEs of grade ≥ 3 severity were rash (3.7%) and liver enzyme elevation (ALT and AST elevation, 2.9% and 2.2%, respectively). Eighteen patients (6.6%) discontinued study treatment due to AEs. A total of 29 patients (10.7%) had treatment-related serious AEs (SAE). There were 14 fatal adverse events, only one of which (pneumonia) was considered treatment-related due to being 'unassessable' (Supplemental Table 6). Of note, there was a case of non-fatal toxic epidermal necrolysis (TEN); the patient discontinued olmutinib, and the event resolved with supportive care.

3.5.2. Pooled phase 2 (N = 76)

All patients had at least one TEAE; in 74 patients (97.4%), AEs were considered treatment-related. The most frequent treatment-related AEs were diarrhea (59.2% of patients), pruritus (42.1%), rash (40.8%), nausea (39.5%), palmar-plantar erythrodysesthesia syndrome (31.6%), decreased appetite (31.6%), dry skin (27.6%), skin exfoliation (26.3%) [Table 3]. Overall, 23 patients (30.3%) had at least one treatment-related grade ≥3 AE, the most frequent of which were rash (5.3% of

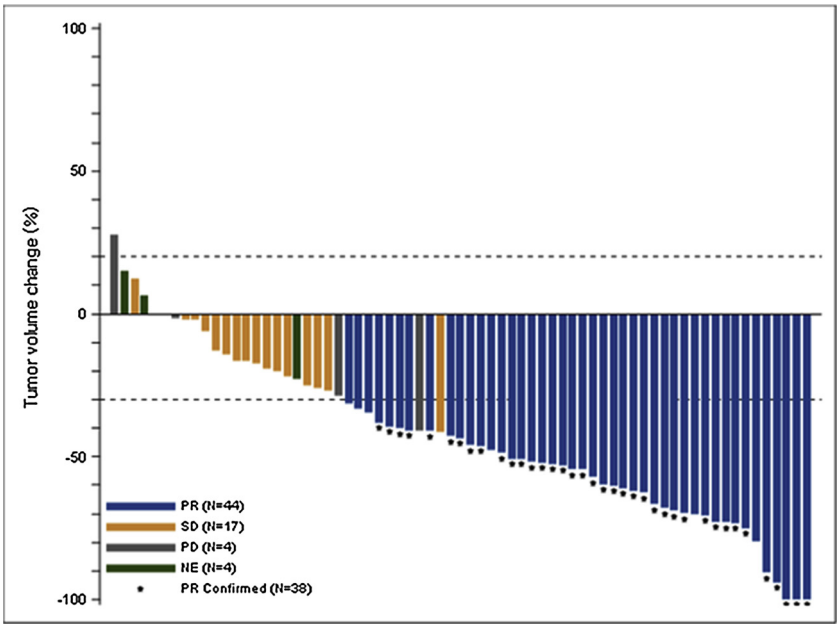

Fig. 2. Waterfall plot of maximum percent tumor shrinkage in pooled phase 2 (by independent review; N = 69).

patients), palmar-plantar erythrodysesthesia syndrome (3.9%), neutrophil count decreased (3.9%), and vomiting, ALT increased, AST increased, electrocardiogram QT prolonged, blood amylase increased (each 2.6%). Eleven patients (14.5%) had one or more treatment-related SAE, which most frequently comprised pyrexia (n = 5) or abdominal pain (n = 3). AEs leading to treatment discontinuation occurred in 12 patients (15.8%). There were 5 fatal AEs, none of which were reported as being treatment related.

4. Discussion

In this exploratory, single-arm, open-label phase 1/2 study, various olmutinib doses were evaluated for safety and efficacy. Four expansion cohorts were opened according to potentially efficacious doses of olmutinib and *EGFR* T790 M mutation status, and the 800 mg once daily dose was selected to further assess the efficacy of olmutinib in *EGFR* T790 M mutation-positive patients.

In the pooled phase 2 part of the study, a confirmed ORR of 55.1% was achieved in patients who had progressed after previous anticancer therapy, including EGFR-TKIs. At the time of analysis, the efficacy profile of olmutinib was comparable to those reported for third-generation EGFR-TKIs such as CO-1686, ASP8273 [26,27]. The lower limit (42.6%) of the 95% CI of confirmed ORR was higher than the prespecified threshold (33.1%) required for further drug development in phase 3. Kaplan-Meier analysis showed that the 20-month PFS rate was approximately 20% (Fig. 3), indicating that olmutinib treatment may have shown long-term benefit. In addition, *post hoc* analysis of ORRs suggested that olmutinib efficacy was unaffected by the presence of brain lesions at baseline; however, this analysis should be interpreted with caution because of the relatively small sample size.

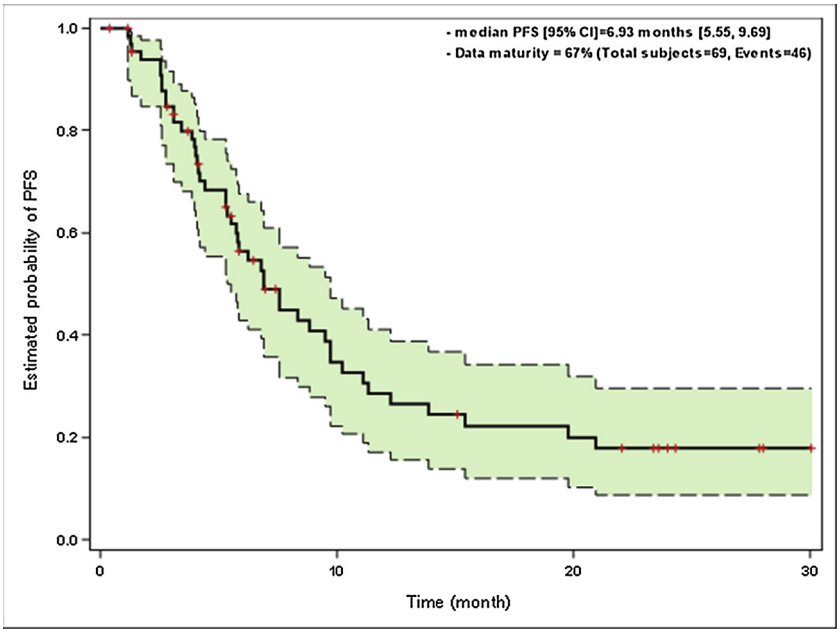

Fig. 3. Kaplan-Meier curve of progression-free survival in pooled phase 2 (PFS; by independent review). CI, confidence interval.

Table 3
Treatment-related adverse events[a] occurring in ≥ 10% of patients (according to MedDRA preferred term).

Adverse event (preferred term)	Pooled phase 2 (N = 76)		Overall study population (N = 272)	
	Any treatment-related AE	Grade ≥ 3 treatment-related AE	Any treatment-related AE	Grade ≥ 3 treatment-related AE
Any event	74 (97.4)	23 (30.3)	248 (91.2)	73 (26.8)
Diarrhea	45 (59.2)	0 (0.0)	101 (37.1)	4 (1.5)
Pruritus	32 (42.1)	1 (1.3)	75 (27.6)	1 (0.4)
Rash	31 (40.8)	4 (5.3)	96 (35.3)	10 (3.7)
Nausea	30 (39.5)	1 (1.3)	77 (28.3)	3 (1.1)
Decreased appetite	24 (31.6)	0 (0.0)	67 (24.6)	1 (0.4)
Palmar-plantar erythrodysesthesia syndrome	24 (31.6)	3 (4.0)	61 (22.4)	5 (1.8)
Dry skin	21 (27.6)	1 (1.3)	46 (16.9)	1 (0.4)
Skin exfoliation	20 (26.3)	1 (1.3)	71 (26.1)	4 (1.5)
Constipation	13 (17.1)	0 (0.0)	26 (9.6)	0 (0.0)
Vomiting	13 (17.1)	2 (2.6)	38 (14.0)	3 (1.1)
Abdominal pain	12 (15.8)	0 (0.0)	25 (9.2)	3 (1.1)
Upper abdominal pain	12 (15.8)	0 (0.0)	32 (11.8)	1 (0.4)
ALT increased	12 (15.8)	2 (2.6)	40 (14.7)	8 (2.9)
Hyperkeratosis	12 (15.8)	0 (0.0)	32 (11.8)	1 (0.4)
AST increased	10 (13.2)	2 (2.6)	35 (12.9)	6 (2.2)
Fatigue	10 (13.2)	1 (1.3)	27 (9.9)	3 (1.1)
Skin hyperpigmentation	10 (13.2)	0 (0.0)	19 (7.0)	0 (0.0)
Dyspepsia	9 (11.8)	0 (0.0)	24 (8.8)	0 (0.0)
Nail disorder	9 (11.8)	0 (0.0)	17 (6.3)	0 (0.0)
Platelet count decreased	9 (11.8)	0 (0.0)	24 (8.8)	1 (0.4)
Pyrexia	9 (11.8)	0 (0.0)	16 (5.9)	0 (0.0)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities.
[a] Incidence; n (%) of patients.

Olmutinib had generally manageable safety and tolerability profiles in our study, and most AEs were manageable with supportive care or dosage modifications where necessary. Gastrointestinal disorders and skin and subcutaneous disorders were the most common AEs (by SOC), and the most frequent treatment-related AEs (occurring in > 20% of patients) were diarrhea, rash, nausea, pruritus, skin exfoliation, decreased appetite, and palmar-plantar erythrodysesthesia syndrome. Treatment-related SAEs most frequently reported were pyrexia or abdominal pain. Abdominal pain was reported in the 800 mg once daily or higher dose cohorts and was considered to be related to the HCl salt form of olmutinib. The high dose of olmutinib (500 mg twice daily) administered in expansion part 2B was not tolerable, supported by a high proportion of severe adverse events (52.4%) and treatment discontinuations (19.05%).

The current study was an exploratory, single-arm, open-label phase 1/2 study. In the absence of direct, head-to-head clinical trials of the oral third-generation EGFR-TKIs olmutinib and osimertinib, extreme caution is required when attempting to compare efficacy and safety data. In the phase III AURA3 clinical trial of patients with T790M-positive advanced NSCLC pretreated with EGFR TKIs, osimertinib significantly prolonged median PFS (10.1 months vs 4.4 months) and improved ORR (71% vs 31%) compared to pemetrexed plus platinum-based combination chemotherapy [20]. In AURA3, the proportion of patients with treatment-related AEs of grade ≥3 was lower with osimertinib (6%) than with pemetrexed/platinum therapy (34%). In the current study, estimated median PFS was 6.9 months, ORR was 55.1% and 30% of patients had at least one treatment-related grade ≥3 AE.

In conclusion, olmutinib showed effective clinical activity with a manageable safety profile in patients with *EGFR* T790M-positive NSCLC, indicating therapeutic potential for the treatment of T790M-positive patients with NSCLC who have failed ≥1 previous line of EGFR-TKI therapy. Olmutinib was being developed with the aim of confirming its efficacy and tolerability in larger studies. However, in April 2018, based on consideration of the competitive landscape of evolving *EGFR*-mutant NSCLC treatment options, the company decided to terminate the study programs with the conclusion of not pursuing further olmutinib development.

5. Disclaimers

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Appendix A. Supplementary data

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