ORIGINAL ARTICLE

# Efficacy and Safety of Limertinib (ASK120067) in Patients With Locally Advanced or Metastatic *EGFR* Thr790Met-Mutated NSCLC: A Multicenter, Single-Arm, Phase 2b Study

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## ABSTRACT

**Introduction:** Limertinib (ASK120067) is a newly developed third-generation EGFR tyrosine kinase inhibitor targeting both sensitizing *EGFR* and *EGFR* Thr790Met (T790M) mutations. This study aimed to evaluate the efficacy and safety of limertinib in patients with locally advanced or metastatic *EGFR* T790M-mutated NSCLC.

**Methods:** This is a single-arm, open-label, phase 2b study conducted at 62 hospitals across the People's Republic of China. Patients with locally advanced or metastatic NSCLC with centrally confirmed *EGFR* T790M mutations in tumor tissue or blood plasma who progressed after first- or second-generation EGFR tyrosine kinase inhibitors or with primary *EGFR* T790M mutations were enrolled. Patients received limertinib 160 mg orally twice daily until disease progression or unacceptable toxicity. The primary end point was objective response rate (ORR) assessed by independent review committee per the Response Evaluation Criteria in Solid Tumors version 1.1. Secondary end points included disease control rate, progression-free survival (PFS), duration of response (DoR), overall survival, and safety. Safety was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

**Results:** From July 16, 2019, to March 10, 2021, a total of 301 patients were enrolled and started the treatment of limertinib. All patients entered the full analysis set and safety set. By the data cutoff date on September 9, 2021, 76 (25.2%) remained on treatment. The median follow-up time was 10.4 months (range: 0.3–26.3). On the basis of full analysis set, the independent review committee-assessed ORR was 68.8% (95% confidence interval [CI]: 63.2%–74.0%) and disease control rate was 92.4% (95% CI: 88.8%–95.1%). The median PFS was 11.0 months (95% CI: 9.7–12.4), median DoR was 11.1 months (95% CI: 9.6–13.8), and median OS was not reached (95% CI 19.7 months–not evaluable). Objective responses were achieved across all prespecified subgroups. For 99 patients (32.9%) with central nervous system (CNS) metastases, the ORR was 64.6% (95% CI: 54.4%–74.0%), median PFS was 9.7 months (95% CI: 5.9–11.6), and median DoR was 9.6 months (95% CI: 8.1–15.2). For 41 patients who had assessable CNS lesion, the confirmed CNS-ORR was 56.1% (95% CI: 39.7%–71.5%) and median CNS-PFS was 10.6 months (95% CI: 5.6–not evaluable). In safety set, 289 patients (96.0%) experienced at least one treatment-related adverse event (TRAE), with the most common being diarrhea (81.7%), anemia (32.6%), rash (29.9%), and anorexia (28.2%). Grade $\geq$3 TRAEs occurred in 104 patients (34.6%), with the most common including diarrhea (13.0%), hypokalemia (4.3%), anemia (4.0%), and rash (3.3%). TRAEs leading to dose interruption and dose discontinuation occurred in 24.6% and 2% of patients, respectively. No TRAE leading to death occurred.

**Conclusions:** Limertinib (ASK120067) was found to have promising efficacy and an acceptable safety profile for the treatment of patients with locally advanced or metastatic *EGFR* T790M-mutated NSCLC. Clinical Trial information: NCT03502850.



*Keywords:* Limertinib; ASK120067; *EGFR* T790M mutation; Third-generation EGFR-TKI

## Introduction

As a common oncogenic driver gene, *EGFR* mutations are found in approximately 50% of East-Asian and 20% to 25% of Western country patients with lung adenocarcinoma.[1–3] *EGFR*-sensitizing mutations (i.e., exon 19 deletions and exon 21 L858R mutations) account for approximately 90% of *EGFR* mutations[1,2] and sensitively respond to first- and second-generation EGFR tyrosine kinase inhibitors (TKIs).[4–10] However, drug resistance inevitably happens, which is mainly owing to the acquired *EGFR* Thr790Met (T790M) mutation.[11,12]

Osimertinib is the first ever marketed and wildly approved third-generation EGFR TKI for the treatment of patients with *EGFR* T790M-positive advanced NSCLC after progression on previous first- or second-generation EGFR TKI therapy.[13] Subsequently, other two third-generation EGFR TKIs almonertinib (HS-10296)[14,15] and furmonertinib (AST2818)[16,17] were marketed in the People's Republic of China with favorable efficacy against NSCLC harboring *EGFR* T790M mutation. Moreover, owing to the high proportion of patients with NSCLC harboring *EGFR* mutations and unmet clinical need, multiple novel third-generation EGFR TKIs are being developed and under investigation currently.[18]

Limertinib (ASK120067) is a novel third-generation EGFR TKI developed by Jiangsu Aosaikang Pharmaceutical Co. Ltd. (Nanjing, People's Republic of China) which selectively inhibits both *EGFR*-sensitizing and *EGFR* T790M mutations. Preclinical studies have revealed the promising selectivity and anticancer activity of limertinib and its active metabolite CCB4580030 (data unpublished). As part of an overall phases 1 and 2 study, the results of its phase 1 dose-escalation and phase 2a dose-expansion arm revealed the clinical efficacy and manageable toxicity of limertinib on patients with locally advanced or metastatic NSCLC harboring *EGFR* T790M mutation and determined its recommended phase 2 dose as 160 mg twice daily (data unpublished). Accordingly, a multicenter, single-arm, phase 2b study was conducted to further evaluate the efficacy and safety of limertinib for the treatment of patients with locally advanced or metastatic *EGFR* T790M-positive NSCLC.

## Materials and Methods

### Patients

This study was conducted in 62 hospitals across the People's Republic of China. Patients were eligible for enrolment if they were aged ≥18 years; histologically or cytologically confirmed as having locally advanced or metastatic NSCLC that was not suitable for radical resection or radiotherapy; radiologically confirmed disease progression after first- or second-generation EGFR TKI therapy (e.g., gefitinib or erlotinib or icotinib, or afatinib); with more than one line of previous therapy; with primary *EGFR* T790M mutation; had an Eastern Cooperative Oncology Group performance status of 0 to 2; had an estimated life expectancy of at least 12 weeks; and had measurable disease according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).

Key exclusion criteria included the following: previously treated with any third-generation EGFR TKI; received a major surgery or large-scale radiotherapy or bone marrow radiotherapy for more than 30% of the area within 4 weeks before the first administration of limertinib; spinal compression or central nervous system (CNS) metastases unless patients were asymptomatic, stable, and not requiring steroids for at least 4 weeks before the first dose of limertinib; any clinical evidence indicating severe or uncontrolled systemic disease; inadequate bone marrow reserve or organ function; and past medical history of interstitial lung disease (ILD), drug-induced ILD, or radiation pneumonitis that required steroid treatment, or clinically active ILD. The detailed study protocol of the phases 1/2 study of limertinib was presented in Supplementary Material 1.

### Study Design and Treatment

The eligible patients received limertinib 160 mg orally twice daily continuously in 21-day cycle until disease progression or unacceptable toxicity. The dose could be adjusted according to the extent of adverse events (AEs) if necessary, whereas dose escalation was not allowed under any circumstances.

Tumor response was evaluated by both independent review committee (IRC) and investigators per RECIST v1.1 by means of computed tomography or magnetic resonance imaging scans performed at baseline and every two treatment cycles (6 wk). A radiological confirmation of an initial objective response (complete response [CR] or partial response [PR]) would be

conducted in 6 weeks thereafter. After the treatment period, the long-term follow-up procedure was conducted to investigate patient disease progression status and overall survival (OS). Patients who discontinued treatment for any reason would undergo a tumor assessment every 6 weeks other than those who had a disease progression or withdrew informed consent. If the patient has used other anticancer treatment, or those who discontinued treatment due to disease progression, survival follow-up by telephone would be performed every 3 months until the patient died or lost to follow-up. For patients with CNS metastases at study entry, imaging of the brain at baseline and same follow-up modality as described previously were required and extra tumor response evaluation was needed if measurable CNS lesions of patients existed.

AEs were monitored continuously from the first dose of limertinib to 28 days after the last administration or patients undergoing under other anticancer treatment or loss of follow-up or death or withdrawing informed consent.

### *End Points and Assessments*

The efficacy analysis was conducted in full analysis set (FAS) which is defined as all enrolled patients who received at least one dose of limertinib. The primary end point was the objective response rate (ORR) per RECIST v1.1 assessed by IRC in FAS, and the secondary end points were disease control rate (DCR), progression-free survival (PFS), duration of response (DoR), OS, and safety. The safety analysis was conducted in safety set (SS) with the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. SS is defined as all patients who received at least one dose of limertinib with at least one safety assessment during follow-up.

The ORR was defined as the proportion of patients who achieved confirmed CR and PR. The DCR was defined as the proportion of patients with CR, PR, or stable disease, stable disease including stable disease and unconfirmed CR and PR. The PFS was defined as the time from the date of first dose of study drug to progression of disease or death of any cause. OS was defined as the time from the date of first dose of study drug to death of any cause. DoR was defined as the time from the date of first documented response with subsequent confirmation to the date of disease progression or death.

### *Statistical Analysis*

According to the results of previous phase 1 to 2a studies (data unpublished), 55% of patients were estimated to have an objective response to limertinib. A sample size of 271 assessable patients would be required to provide an ORR of at least 45% (the lower limit of 95% confidence interval [CI], which is the lowest clinically acceptable value) by achieving a power (1-$\beta$) of 90% in a one-sided test at a significance level ($\alpha$) of 0.025. Taking 10% dropouts into account, 301 patients were planned to be enrolled in this study.

The two-sided 95% CIs for ORR and DCR were determined using Clopper-Pearson method. Prespecified subgroup analysis of ORR was conducted based on age, sex, *EGFR* mutation status, smoking history, Eastern Cooperative Oncology Group performance status score, CNS metastasis, previous lines of systemic therapy, and the samples for *EGFR* T790M test (tissue or plasma). The median values of PFS, DoR, and OS and corresponding 95% CIs were determined by Kaplan-Meier methods. All data analyses were conducted by means of R software (version 3.3.1 or above; R Foundation for Statistical Computing) and Statistical Analysis System (SAS) software (version 9.4 or above; SAS Institute Inc.).

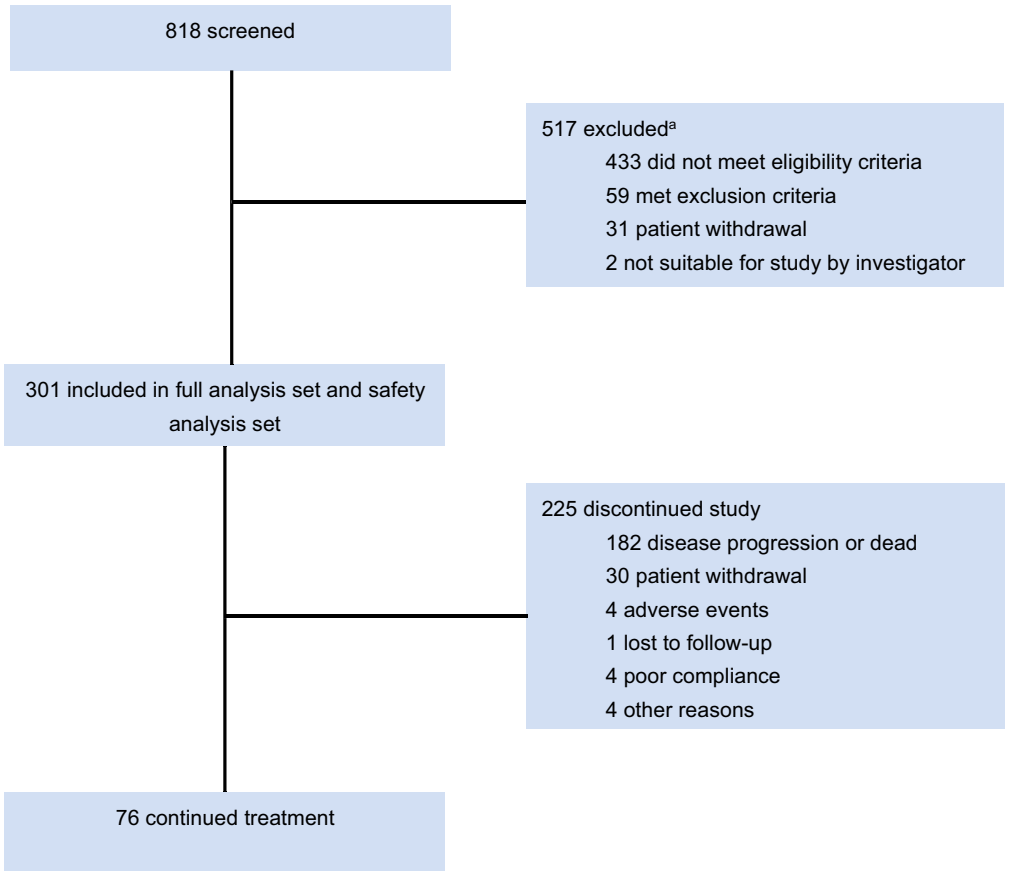
The study was conducted in accordance with the ethical standards of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice Guidelines, the applicable regulatory requirements, and the policy. The protocol was approved by Institutional Research Ethics Board at each participating site. Written informed consent was obtained from each patient before the initiation of the study procedures. This study was registered with Clinical Trials.gov: NCT03502850.

## Results

### *Patients*

From July 16, 2019, to March 10, 2021, a total of 301 patients were enrolled in this study and started the treatment of limertinib (Fig. 1). At the data cutoff date on September 9, 2021, all 301 patients received at least one dose of limertinib and were involved in the efficacy analysis in FAS and safety analysis in SS.

Patient baseline demographic and characteristics were presented in Table 1. Overall, 62.1% (187 of 301) of patients were female and 98.3% (296 of 301) of patients had lung adenocarcinoma. Furthermore, 77.4% (233 of 301) of the patients received one line of therapy before participating in this study. *EGFR* mutation types included exon 19 deletion (61.1%), L858R (33.2%), and other (3.3%). All patients were positive for *EGFR* T790M test, among which 210 patients (69.8%) underwent the test based on tissue sample, whereas 90 patients (29.9%) were based on plasma sample, and one patient was based on cytology result of pleural effusion. CNS metastases were found in 32.9% (99 of 301) of the patients.




[a] : If a patient was excluded for more than one reason, each reason was counted as one.

**Figure 1.** Patient disposition.

## *Efficacy*

The median follow-up time was 10.4 months (range: 0.3–26.3). On the basis of FAS, 207 patients (68.8%) had confirmed PR, 71 patients (23.6%) had stable disease (including 19 patients with unconfirmed CR or PR), and seven patients (2.3%) had disease progression (PD). The IRC-assessed ORR was 68.8% (95% CI: 63.2%–74.0%), and the lower limit of ORR was 63.2% which is higher than the lowest clinically acceptable value of 45%. The objective responses across various prespecified subgroups were presented in Figure 2. The ORR of patients with *EGFR* T790M mutation based on the test of tissue sample was 75.6% (95% CI: 65.8%–78.3%), whereas that of plasma sample was 60.7% (95% CI: 49.1%–70.2%). The IRC-assessed DCR was 92.4% (95% CI: 88.8%–95.1%).

Of the 207 patients deemed to have an objective response, 83 (40.1%) had subsequently progressed or died by the time of data cutoff, whereas data of 124 patients (59.9%) were censored. The median DoR was 11.1 months (95% CI: 9.6–13.8). The DoR rates at 3 months, 6 months, and 12 months were 96.1% (95% CI: 92.0%–98.1%), 82.5% (95% CI: 75.6%–87.6%), and 46.3% (95% CI: 36.9%–55.3%), respectively. The median PFS was 11.0 months (95% CI: 9.7–12.4) (Fig. 3*A*), and median OS was not reached (95% CI: 19.7 months–not evaluable). The PFS rates at 3 months, 6 months, and 12 months were 89.7% (95% CI: 85.4%–92.7%), 77.4% (95% CI: 71.6%–82.2%), and 47.1% (95% CI: 39.4%–54.5%), respectively. The OS rates at 3 months, 6 months, and 12 months were 95.8% (95% CI: 92.7%–97.6%), 90.1% (95% CI: 85.9%–93.1%), and 72.9% (95% CI: 66.3%–78.5%), respectively (Table 2). Tumor shrinkage was found in 276 (91.7%) of 301 patients (Fig. 3*B*). The efficacy in FAS evaluated by the investigators were summarized in Supplementary Table 1.

Moreover, 82 patients experienced dose reduction due to AEs, most of whom limertinib were reduced to 80 mg twice daily from 160 mg twice daily. The IRC-assessed ORRs of patients with and without dose adjustment were 76.8% (95% CI: 66.2%–85.4%) and 65.8% (95% CI: 59.1%–72.0%), respectively. The median PFS of patients with and without dose adjustment were 15.2 months (95% CI: 11.0–19.3) and 11.0 months (95% CI: 8.9–12.4), respectively. The results revealed stable and favorable efficacy of limertinib under reduced dose.

**Table 1.** Patient Baseline Characteristics

| Parameters | All Patients (N = 301) | |
|---|---|---|
| Age, y | | |
| | Mean ± SD | 59.7 ± 10.1 |
| | Median (range) | 60.0 (33-83) |
| Sex, n (%) | | |
| | Male | 114 (37.9) |
| | Female | 187 (62.1) |
| Smoking status, n (%) | | |
| | Never | 232 (77.3) |
| | Ever | 68 (22.7) |
| ECOG PS, n (%) | | |
| | 0 | 40 (13.3) |
| | 1 | 244 (81.1) |
| | 2 | 17 (5.6) |
| Histology, n (%) | | |
| | Adenosquamous carcinoma | 1 (0.3) |
| | Adenocarcinoma | 296 (98.3) |
| | Squamous cell carcinoma | 1 (0.3) |
| | Other | 3 (1.0) |
| Stage, n (%) | | |
| | III B | 7 (2.3) |
| | III C | 2 (0.7) |
| | IV A | 104 (34.6) |
| | IV B | 188 (62.5) |
| *EGFR* mutation, n (%) | | |
| | L858R | 100 (33.2) |
| | DEL19 | 184 (61.1) |
| | L858R + L861Q | 1 (0.3) |
| | S768I | 2 (0.7) |
| | DEL19 + L858R | 2 (0.7) |
| | DEL19 + S768I | 1 (0.3) |
| | G719X | 3 (1.0) |
| | G719X + DEL19 | 1 (0.3) |
| | Not detected | 7 (2.3) |
| CNS metastases at entry, n (%) | | |
| | Yes | 99 (32.9) |
| | No | 202 (67.1) |
| Sample for *EGFR* T790M mutation test, n (%) | | |
| | Plasma | 210 (69.8) |
| | Tissue | 90 (29.9) |
| | Pleural effusion cytology | 1 (0.3) |
| Treatment cohort, n (%) | | |
| | First-line | 2 (0.7) |
| | Second-line | 233 (77.4) |
| | Third-line | 46 (15.3) |
| | Fourth-line and above | 20 (6.6) |

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; PS, performance status; SD, standard deviation; T790M, Thr790Met.

### *Intracranial Responses*

For 99 patients (32.9%) with CNS metastases, the ORR was 64.6% (95% CI: 54.4%–74.0%), median PFS was 9.7 months (95% CI: 5.9–11.6), and median DoR was 9.6 months (95% CI: 8.1–15.2). For 41 patients who had assessable CNS lesion, the confirmed CNS-ORR was 56.1% (95% CI: 39.7%–71.5%), CNS-DCR was 100%, and median CNS-PFS was 10.6 months (95% CI 5.6–not evaluable). The intracranial responses of 41 patients with assessable CNS lesion were summarized in Supplementary Table 2.

### *Safety*

The incidence of treatment-emergent adverse events (TEAEs) or treatment-related adverse events (TRAEs) of any grade (>10%) and grade ≥3 was summarized in Table 3. On the basis of the analysis on SS, the TEAEs were observed in 299 patients (99.3%) and 150 patients

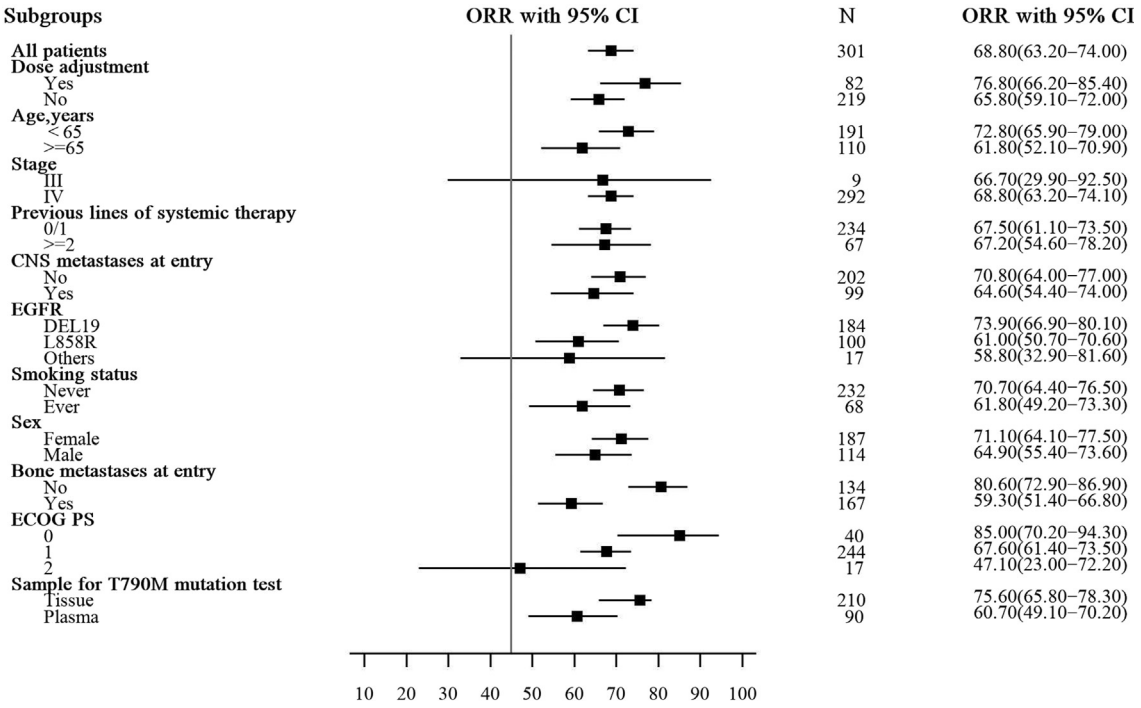



**Figure 2.** Forest plot of subgroups of patients showing objective responses in the full analysis set. CI, confidence interval; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; PS, performance status; ORR, objective response rate; T790M, Thr790Met.

(49.8%) had grade ≥3 TEAEs. Meanwhile, 289 patients (96.0%) experienced at least one TRAE, with the most common being diarrhea (81.7%), anemia (32.6%), rash (29.9%), and anorexia (28.2%). Grade ≥3 TRAEs occurred in 104 patients (34.6%), and the most common included diarrhea (13.0%), hypokalemia (4.3%), anemia (4.0%), and rash (3.3%). TRAEs leading to dose interruption and dose discontinuation occurred in 74 (24.6%) and six patients (2%), respectively. Until the data cutoff date, most TRAEs have recovered. The safety overview of AEs was summarized in Supplementary Table 3.

ILD was reported in one patient which belonged to grade 2 TRAE. Prolonged electrocardiogram QT as another important AE was observed in 16 patients (5.3%), among which three patients had grade 3 and others had grades 1 to 2. In three patients with grade 3 prolonged electrocardiogram QT, one patient recovered without taking any change or treatment and other two patients recovered after discontinuation of limertinib or taking symptomatic treatment.

Serious TEAEs occurred in 75 patients (24.9%), among which 28 (9.3%) were considered as treatment-related serious adverse events (SAEs), including hypokalemia, diarrhea, anorexia (four [1.3%] each), decreased platelet count (three [1%]), vomiting (two [0.7%]), elevated serum creatine kinase, acute renal injury, hyponatremia, malnutrition, epigastric pain, gastritis, gastrointestinal diseases, urinary tract infection, skin infection, impetigo, chronic renal disease, headache, rash, and liver function (one each).

In 82 patients who experienced dose reduction, patients who underwent TRAEs decreased from 82 patients (100.0%) to 71 patients (86.6%) after dose adjustment; those with grade ≥3 TRAEs decreased from 50 patients (61.0%) to 12 patients (14.6%); the incidence of grade ≥3 diarrhea decreased from 30.5% to 4.9%; and the incidence of SAEs decreased from 10 patients (12.2%) to two patients (2.4%).

At the data cutoff date, 12 deaths (4%) occurred, which were all attributed to TEAEs, including acute respiratory failure (n = 1), pulmonary embolism (n = 1), craniocerebral injury (n = 1), infectious pneumonia (n = 1), gastrointestinal bleeding (n = 1), and unknown cause of death (n = 7), none of which was related to the study drug assessed by the investigators.

## Discussion

In this phase 2b study, a novel third-generation EGFR TKI, limertinib (ASK120067), was found to have promising efficacy and manageable safety profile in patients with locally advanced or metastatic *EGFR* T790M-mutated NSCLC. Limertinib achieved the primary end point of this study with a confirmed IRC-

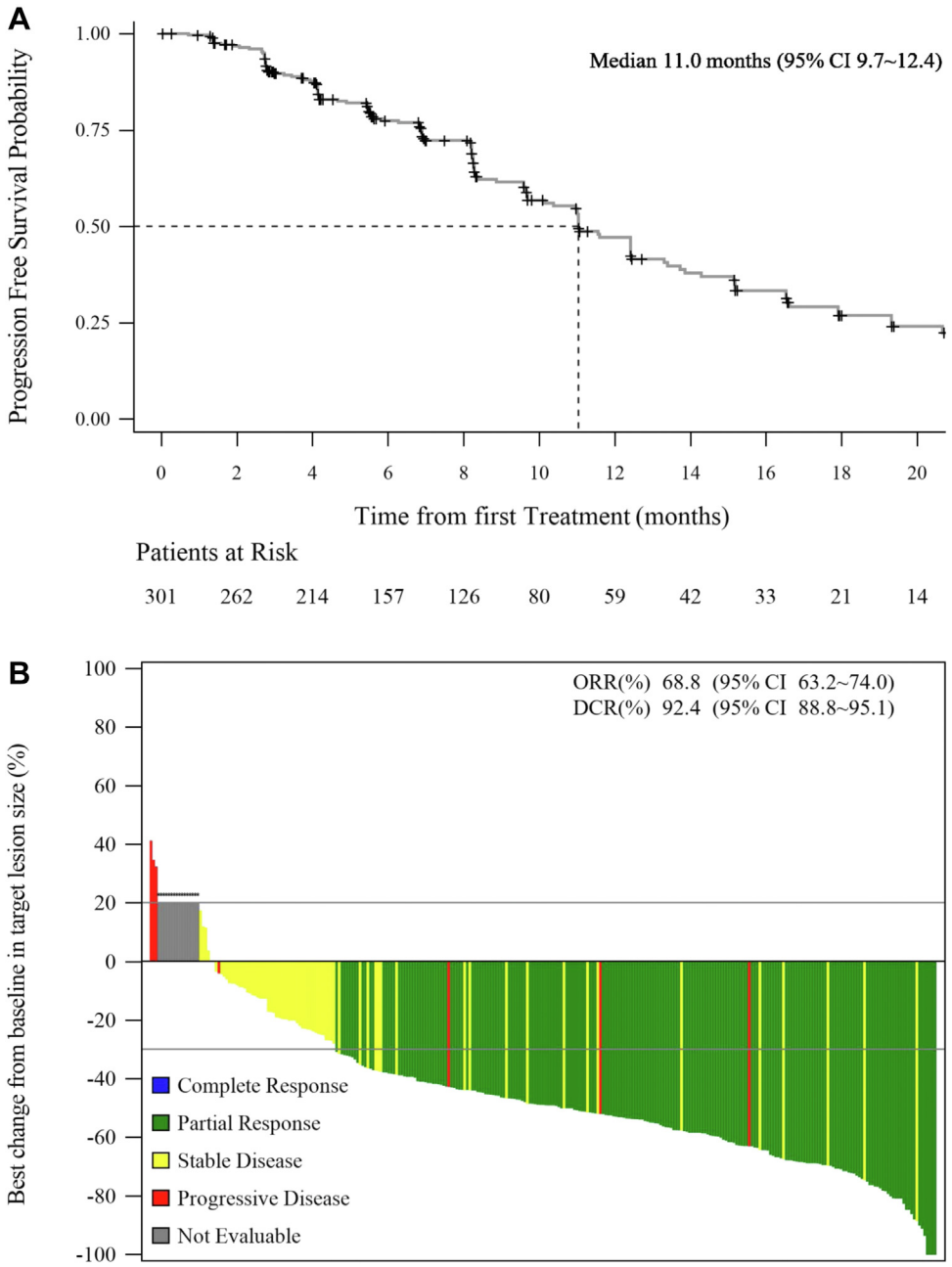



**Figure 3.** Response of limertinib. (*A*) K-M curve of progression-free survival. (*B*) Waterfall plot for best percentage change from baseline in target lesion size by IRC in FAS. CI, confidence interval; DCR, disease control rate; FAS, full analysis set.; IRC, independent review committee; K-M, Kaplan Meier; ORR, objective response rate.

assessed ORR of 68.8% (95% CI: 63.2%–74.0%), whose lower limit of the 95% CI was above the null hypothesis of 45%. In addition, a DCR of 92.4%, a DoR of 11.1 months, and a PFS of 11.0 months were observed in the whole population.

The efficacy of limertinib was consistent with those of former third-generation EGFR TKIs. In a pooled analysis of AURA extension study and AURA2 study, osimertinib achieved an ORR of 66% and a DCR of 91%, respectively, in patients with pretreated *EGFR* T790M-positive advanced NSCLC.[19–21] The efficacy of osimertinib was also investigated exclusively in pretreated *EGFR* T790M-positive advanced NSCLC in Asian population, with an ORR of 62%, a DCR of 88%, a median DoR of 9.9 months, a median PFS of 9.7 months, and a median OS of 23.2 months, respectively.[22] The third-generation EGFR TKI aumolertinib was approved in the People's Republic of China for patients with *EGFR* T790M-positive NSCLC with an ORR of 68.9% and a DCR of 93.4%; the median DoR and PFS of aumolertinib were 15.1 months and 12.4

**Table 2.** Efficacy in FAS by IRC

| Efficacy | All Patients (N = 301) |
|---|---|
| PR, n (%) | 207 (68.8) |
| Stable disease, n (%) | 71 (23.6)[a] |
| PD, n (%) | 7 (2.3) |
| NE, n (%) | 16 (5.3) |
| ORR, % (95% CI) | 68.8 (63.2-74.0) |
| DCR, % (95% CI) | 92.4 (88.8-95.1) |
| DoR | |
| Events, n (%) | 83 (40.1) |
| Median, mo, (95% CI) | 11.1 (9.6-13.8) |
| 3-mo DoR rate, % (95% CI) | 96.1 (92.0-98.1) |
| 6-mo DoR rate, % (95% CI) | 82.5 (75.6-87.6) |
| 12-mo DoR rate, % (95% CI) | 46.3 (36.9-55.3) |
| PFS | |
| Events, n (%) | 130 (43.2) |
| Median, mo, (95% CI) | 11.0 (9.7-12.4) |
| 3-mo PFS rate, % (95% CI) | 89.7 (85.4-92.7) |
| 6-mo PFS rate, % (95% CI) | 77.4 (71.6-82.2) |
| 12-mo PFS rate, % (95% CI) | 47.1 (39.4-54.5) |
| OS | |
| Events, n (%) | 84 (27.9) |
| Median, mo, (95% CI) | NE (19.7-NE) |
| 3-mo OS rate, % (95% CI) | 95.8 (92.7-97.6) |
| 6-mo OS rate, % (95% CI) | 90.1 (85.9-93.1) |
| 12-mo OS rate, % (95% CI) | 72.9 (66.3-78.5) |

[a]71 patients had stable disease which including 19 patients with unconfirmed CR or PR.
CI, confidence interval; DCR, disease control rate; DoR, duration of response; FAS, full analysis set; IRC, independent review committee; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response.

months, respectively. Furmonertinib is another third-generation EGFR TKI approved in the People's Republic of China, whose ORR, DCR, and PFS were 74%, 94%, and 9.6 months, respectively.[17]

Moreover, limertinib was found to have encouraging efficacy in 99 patients with CNS metastases with an ORR of 64.6% and a DoR of 9.6 months, whereas for those who had assessable CNS lesion (n = 41), a confirmed CNS-ORR of 56.1% and a CNS-DCR of 100% were achieved. In a pooled analysis of osimertinib, the confirmed CNS-ORR and CNS-DCR were 54% and 92%, respectively, in 50 patients who had assessable CNS lesion.[23] In phase 2 study of aumolertinib, an ORR of 60.9% and a DCR of 91.3% were observed in 23 patients with assessable CNS metastases.[15] In a phase 2b study of furmonertinib, the CNS-ORR and CNS-DCR were 66% and 100% in 19 patients with assessable CNS metastases, respectively; whereas a CNS-ORR of 34% and a CNS-DCR of 98% were achieved in 87 patients with CNS metastases.[17] Limertinib was found to have similar favorable blood-brain penetration and good CNS activities with other third-generation EGFR TKIs.

In this study, limertinib presented a manageable safety profile. Grade ≥3 TRAEs occurred in 34.6% of patients with the most common being diarrhea (13.0%), hypokalemia (4.3%), anemia (4.0%), and rash (3.3%). Furthermore, 82 patients experienced dose reduction due to AEs; the incidence of all-grade TRAEs, grade ≥3 TRAEs, and SAEs decreased after the dose reduction, with most patients adjusted from 160 mg twice daily to 80 mg twice daily, suggesting after dose reduction, the tolerance of patients was greatly improved and the anticancer activity was not affected.

Compared with other third-generation EGFR TKIs, the most common grade ≥3 TRAEs of osimertinib were rash (1%), decreased platelet count (1%), and diarrhea (<1%).[21] In phase 2 study of aumolertinib, the most common grade ≥3 TRAEs of aumolertinib occurred in 16.4% of the patients, with the most common being increased blood creatine phosphokinase level (7%) and increased alanine aminotransferase (ALT) (1.2%).[15] In phase 2b study of furmonertinib, grade ≥3 TRAEs occurred in 11% of patients with the most common being increased aspartate aminotransferase (AST) (1%), increased ALT (1%), and increased γ-glutamyltransferase (GGT) (1%).[17] The tolerance of the patients under limertinib treatment was significantly improved under dose reduction and the efficacy of limertinib was not impaired. Moreover, limertinib was found to have mild adverse impact on liver function with increased ALT (1%), increased AST (<1%), and increased GGT (<1%) of grade 3 or higher.

In other AEs, ILD was reported in one patient which belonged to grade 2 TRAE. Though six patients (5.3%) were observed to have prolonged electrocardiogram QT, grade 3 of which was only reported in three patients, and they all recovered with or without intervention. All-grade prolonged electrocardiogram QT was reported in 21 patients (5%) in osimertinib,[21] 15 patients (6.1%) in aumolertinib,[15] and 34 patients (15%) in furmonertinib.[17] Grade ≥3 prolonged electrocardiogram QT was reported in five patients in osimertinib[21], none of the patients in aumolertinib[15] and furmonertinib.[17] There is no evidence of a higher risk of prolonged electrocardiogram QT of limertinib compared with other third-generation EGFR TKIs at this moment. Generally, patients were well tolerant to AEs brought by limertinib. The overall safety of limertinib was similar to those of other third-generation EGFR TKIs, and no new safety signals were found.

Several limitations existed in this study. First, it is a single-arm study, and caution should be taken when comparing the efficacy and safety of limertinib with other third-generation EGFR TKIs as well as interpreting the results of subgroup analysis. In addition, this study only enrolled Chinese patients, and its utility in other ethnicities needs to be investigated in further studies.

**Table 3.** TEAEs and TRAEs of Any Grade (>10%) and Grade ≥3 in SS

| | TEAEs | | TRAEs | |
|---|---|---|---|---|
| AEs | All Grade, n (%) | Grade ≥ 3, n (%) | All Grade, n (%) | Grade ≥ 3, n (%) |
| Diarrhea | 255 (84.7) | 45 (15.0) | 246 (81.7) | 39 (13.0) |
| Anemia | 134 (44.5) | 16 (5.3) | 98 (32.6) | 12 (4.0) |
| Hypokalemia | 103 (34.2) | 20 (6.6) | 61 (20.3) | 13 (4.3) |
| Anorexia | 102 (33.9) | 2 (0.7) | 85 (28.2) | 2 (0.7) |
| Rash | 95 (31.6) | 10 (3.3) | 90 (29.9) | 10 (3.3) |
| Nausea | 94 (31.2) | 1 (0.3) | 83 (27.6) | 0 |
| Vomiting | 91 (30.2) | 4 (1.3) | 69 (22.9) | 2 (0.7) |
| Weight loss | 92 (30.6) | 4 (1.3) | 45 (15.0) | 2 (0.7) |
| Malaise | 52 (17.3) | 3 (1.0) | 35 (11.6) | 2 (0.7) |
| Fecal occult blood positive | 51 (16.9) | 0 | 37 (12.3) | 0 |
| Increased serum creatinine | 51 (16.9) | 2 (0.7) | 45 (15.0) | 2 (0.7) |
| Upper respiratory tract infection | 51 (16.9) | 1 (0.3) | 4 (1.3) | 0 |
| Hypoalbuminemia | 50 (16.6) | 0 | 27 (9.0) | 0 |
| Decreased platelet count | 48 (15.9) | 3 (1.0) | 47 (15.6) | 3 (1.0) |
| Urinary tract infection | 42 (14.0) | 3 (1.0) | 18 (6.0) | 1 (0.3) |
| Decreased white blood cell count | 40 (13.3) | 0 | 36 (12.0) | 0 |
| Hyperuricemia | 39 (13.0) | 2 (0.7) | 26 (8.6) | 1 (0.3) |
| Headache | 38 (12.6) | 3 (1.0) | 20 (6.6) | 3 (1.0) |
| Proteinuria | 37 (12.3) | 0 | 35 (11.6) | 0 |
| Hypertriglyceridemia | 36 (12.0) | 0 | 19 (6.3) | 0 |
| Cough | 33 (11.0) | 0 | 5 (1.7) | 0 |
| Increased aspartate aminotransferase | 32 (10.6) | 1 (0.3) | 28 (9.3) | 1 (0.3) |

AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; SS, safety set.

In conclusion, limertinib (ASK120067) was found to have promising clinical anticancer activity and manageable safety profile in patients with *EGFR* T790M-mutated NSCLC in this study. Limertinib is expected to become a new treatment option for Chinese patients with locally advanced or metastatic *EGFR* T790M-mutated NSCLC. A phase 3 trial of limertinib compared with gefitinib as the first-line treatment for patients with locally advanced or metastatic *EGFR*-mutated NSCLC is ongoing (NCT04143607).

## CRediT Authorship Contribution Statement

**Yuankai Shi:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing—original draft, Writing—review and editing, Visualization, Supervision, Project administration, Funding acquisition.

**Baolan Li, Lin Wu, Yueyin Pan, Zhijie Pan, Yunpeng Liu, Yun Fan, Yinghua Ji, Jian Fang, Qin Shi, Jianhua Shi, Hongjun Gao, Yanping Hu, Xiang Wang, Zhiyong He, Rui Ma, Yu Zhang, Da Jiang, Yuansong Bai, Yi Zhang, Linian Huang, Tong Zhou, Hailong Liu, Daqing Wang, Qinglian Wen, Gongyan Chen, Aimin Zang, Xiuwen Wang, Xinri Zhang, Jianbing Hu, Runxiang Yang, Guojun Zhang, Kangsheng Gu, Lin Wang, Qiming Wang, Zonghui Wei, Li Zeng, Hongda Lu, Helong Zhang:** Investigation, Resources, Data curation, Writing—review and editing.

**Hongyu Chen, Tingting Song**: Methodology, Software, Validation, Formal analysis, Resources, Data curation, Writing—review and editing, Visualization.

## 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.2022.05.011.

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## References


1. Shi Y, Au JSK, Thongprasert S, et al. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). *J Thorac Oncol*. 2014;9:154–162.
2. Shi Y, Li J, Zhang S, et al. Molecular epidemiology of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology - Mainland China subset analysis of the PIONEER study. *PLoS One*. 2015;10:e0143515.
3. D'angelo SP, Pietanza MC, Johnson ML, et al. Incidence of EGFR exon 19 deletions and L858R in tumor specimens from men and cigarette smokers with lung adenocarcinomas. *J Clin Oncol*. 2011;29:2066–2070.
4. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol*. 2010;11:121–128.
5. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med*. 2010;362:2380–2388.
6. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012;13:239–246.
7. Shi Y, Zhang L, Liu X, et al. Icotinib versus gefitinib in previously treated advanced non-small-cell lung cancer (ICOGEN): a randomised, double-blind phase 3 non-inferiority trial. *Lancet Oncol*. 2013;14:953–961.
8. Shi YK, Wang L, Han BH, et al. First-line icotinib versus cisplatin/pemetrexed plus pemetrexed maintenance therapy for patients with advanced EGFR mutation-positive lung adenocarcinoma (CONVINCE): a phase 3, open-label, randomized study. *Ann Oncol*. 2017;28:2443–2450.
9. Sequist LV, Yang JCH, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol*. 2013;31:3327–3334.
10. Wu YL, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18:1454–1466.
11. Kobayashi S, Boggon TJ, Dayaram T, et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2005;352:786–792.
12. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res*. 2013;19:2240–2247.
13. Jänne PA, Yang JCH, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med*. 2015;372:1689–1699.
14. Yang JCH, Camidge DR, Yang CT, et al. Safety, efficacy, and pharmacokinetics of almonertinib (HS-10296) in pretreated patients with EGFR-mutated advanced NSCLC: a multicenter, open-label, phase 1 trial. *J Thorac Oncol*. 2020;15:1907–1918.
15. Lu S, Wang Q, Zhang G, et al. Efficacy of aumolertinib (HS-10296) in patients with advanced EGFR T790M+ NSCLC: updated post-national medical products administration approval results from the Apollo registrational trial. *J Thorac Oncol*. 2022;17:411–422.
16. Shi Y, Zhang S, Hu X, et al. Safety, clinical activity, and pharmacokinetics of alflutinib (AST2818) in patients with advanced NSCLC with EGFR T790M mutation. *J Thorac Oncol*. 2020;15:1015–1026.
17. Shi Y, Hu X, Zhang S, et al. Efficacy, safety, and genetic analysis of furmonertinib (AST2818) in patients with EGFR T790M mutated non-small-cell lung cancer: a phase 2b, multicentre, single-arm, open-label study. *Lancet Respir Med*. 2021;9:829–839.
18. Nagasaka M, Zhu VW, Lim SM, Greco M, Wu F, Ou SI. Beyond osimertinib: the development of third-generation EGFR tyrosine kinase inhibitors for advanced EGFR+ NSCLC. *J Thorac Oncol*. 2021;16:740–763.
19. Yang JCH, Ahn MJ, Kim DW, et al. Osimertinib in pretreated T790M-positive advanced non-small-cell lung cancer: AURA study phase II extension component. *J Clin Oncol*. 2017;35:1288–1296.
20. Goss G, Tsai CM, Shepherd FA, et al. Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2): a multicentre, open-label, single-arm, phase 2 study. *Lancet Oncol*. 2016;17:1643–1652.
21. Ahn MJ, Tsai CM, Shepherd FA, et al. Osimertinib in patients with T790M mutation-positive, advanced non-small cell lung cancer: long-term follow-up from a pooled analysis of 2 phase 2 studies. *Cancer*. 2019;125:892–901.
22. Zhou C, Wang M, Cheng Y, et al. AURA17 study of osimertinib in Asia-Pacific patients (pts) with EGFR T790M-positive advanced non-small cell lung cancer (NSCLC): updated phase II results including overall survival (OS). *Ann Oncol*. 2018;29:ix157.
23. Goss G, Tsai CM, Shepherd FA, et al. CNS response to osimertinib in patients with T790M-positive advanced NSCLC: pooled data from two phase II trials[J]. *Ann Oncol*. 2018;29:687–693.