ORIGINAL ARTICLE

Safety, Efficacy, and Pharmacokinetics of Rezivertinib (BPI-7711) in Patients With Advanced NSCLC With *EGFR* T790M Mutation: A Phase 1 Dose-Escalation and Dose-Expansion Study

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Received 14 June 2021; revised 11 January 2022; accepted 25 January 2022
Available online - 15 February 2022

ABSTRACT

Introduction: Rezivertinib (BPI-7711) is a novel third-generation *EGFR* tyrosine kinase inhibitor selective for *EGFR*-sensitizing and T790M mutations. This study was designed to evaluate the safety, efficacy, and pharmacokinetics of rezivertinib for patients having advanced NSCLC with *EGFR* T790M mutation.

Methods: This phase 1 study (NCT03386955) was conducted across 20 sites in the People's Republic of China. Patients received rezivertinib at six oral dose levels (30 mg, 60 mg, 120 mg, 180 mg, 240 mg, 300 mg) once daily until disease progression, unacceptable toxicity, or patient

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Disclosure: Dr. Greco is an employee of Beta Pharma and has a patent null pending. Dr. Zhang has financial activities with Beta Pharma outside of the submitted work. The remaining authors declare no conflict of interest.

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ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2022.01.015

withdrawal. The primary end points were safety for the dose-escalation phase and objective response rate by the blinded independent central review for the total study population.

Results: A total of 19 patients in dose-escalation phase using the standard 3 + 3 design principle and 153 patients in dose-expansion phase were enrolled from September 11, 2017, to August 23, 2019. The data cutoff date was on June 15, 2020. No dose-limiting toxicity occurred in the dose-escalation phase. The treatment-related adverse events were observed in 82.0% (141 of 172) of patients, and 17.4% (30 of 172) had grade greater than or equal to 3, among which decreased neutrophil count (2.9%), leukopenia (2.9%), and pneumonia (2.9%) were the most common. The overall blinded independent central review–evaluated objective response rate was 59.3% (102 of 172, 95% confidence interval: 51.6–66.7), and the median progression-free survival was 9.7 (95% confidence interval: 8.3–11.1) months.

Conclusions: Rezivertinib was found to have promising efficacy with a manageable safety profile in patients with *EGFR* T790M-mutated advanced NSCLC. Further study is warranted.

Keywords: Rezivertinib; NSCLC; *EGFR* T790M mutation; Safety; Efficacy

Introduction

Sensitizing *EGFR* mutation accounts for more than 40% of advanced lung adenocarcinoma diagnosed in Asia.[1] The first- or second-generation *EGFR* tyrosine kinase inhibitors (TKIs), including gefitinib, erlotinib, iconitinib, afatinib, and dacomitinib, have become the standard first-line treatment of NSCLC with *EGFR*-sensitizing mutations.[2–8] Most acquired resistance to the first- or second-generation *EGFR* TKIs is *EGFR* T790M mutation.[9–11] Osimertinib has been the first ever marketed third-generation *EGFR* TKI on the basis of the AURA study[12] for patients with *EGFR* T790M mutation. In addition, aumolertinib (HS-10296, formerly named as almonertinib)[13,14] and furmonertinib (AST2818, formerly named as alflutinib),[15,16] also third-generation *EGFR* TKIs, have been on the market in the People's Republic of China. Nevertheless, clinical development for multiple novel third-generation *EGFR* TKIs is ongoing owing to the high proportion of *EGFR*-mutant patients and diversified features of different third-generation *EGFR* TKIs.[17]

Rezivertinib (BPI-7711) is a third-generation *EGFR* TKI jointly developed by Beta Pharma Co., Ltd. (Shanghai, People's Republic of China) and Beta Pharma Inc. (Princeton, NJ). It can selectively target specific mutated *EGFR* and form irreversible covalent binding at the active binding site. Rezivertinib has a highly selective inhibitory effect on *EGFR* del E746-A750 and T790M as well as *EGFR* L858R and T790M double mutations, including *EGFR* single mutation, although its inhibitory effect on wild-type *EGFR* is quite weak.[18,19] Here, we present the result of phase 1 study for the safety, efficacy, and pharmacokinetics (PK) of rezivertinib in patients with advanced NSCLC with *EGFR* T790M mutation (NCT03386955).

Materials and Methods

Patients

This was a phase 1 dose-escalation and dose-expansion study conducted across 20 sites in the People's Republic of China. Patients aged 18 years or above with a histologically or cytologically confirmed locally advanced or metastatic NSCLC with *EGFR*-sensitive mutations (including exon 19 deletion [del19], L858R, G719X, L861Q, and S768I) were eligible. Besides, patients were required to have radiologically confirmed disease progression after the latest first- or second-generation *EGFR* TKI treatment and centrally confirmed *EGFR* T790M mutation according to either tumor tissues or plasma samples (the cobas *EGFR* mutation test, Version 2, Roche Diagnostics, South Branchburg, NJ). Central nervous system (CNS) metastases were acceptable if patients were asymptomatic, stable, and discontinued steroid therapy for at least 7 days before the first dose of rezivertinib. Exclusion criteria included history of interstitial lung disease, previous treatment with any third-generation *EGFR* TKI, or major surgery within 28 days or local radiotherapy within 7 days of starting study treatment. Full inclusion and exclusion criteria are presented in the protocol (Supplementary Materials 1).

Study Design and Treatment

Dose-escalation was designed according to the standard "3 + 3" design principle. Patients received rezivertinib orally once on the initial date of a 7-day washout period and afterward at the same dose once daily continuously in 21-day cycles. The first 28 days were defined as the dose-limiting toxicity (DLT) observation period. In dose-escalation phase, the dose of 30 mg for rezivertinib was the starting dose determined by the evidence provided from the preclinical study in nude mice (data unpublished), and the subsequent dose levels were 60 mg, 120 mg, 180 mg, 240 mg, and 300 mg. If no DLT was observed and the tumor response was determined in one dose level, this cohort was expanded to enroll more patients. Meanwhile, the dose-escalation

was continued to evaluate higher doses. In dose-expansion phase, rezivertinib was administered daily in 21-day cycles. The number of patients in dose-expansion phase was based on exploratory purpose, and determined on the basis of the efficacy and safety data, rather than formal hypothesis testing. Patients from either the dose-escalation or dose-expansion phase could discontinue the study treatment owing to disease progression, unacceptable toxicity, or withdrawal of consent. Intrapatient dose-escalation was not allowed. Nevertheless, treatment beyond progression was allowed if the investigators and the sponsor agreed that it could provide the clinical benefit.

Efficacy was evaluated at baseline and every two treatment cycles (6 wk) with enhanced computed tomography scans for chest and abdomen and enhanced magnetic resonance imaging scans for brain for all patients. Additional computed tomography or magnetic resonance imaging scans could be performed on suspected lesions determined by investigators. The images were independently evaluated by investigators and blinded independent central review (BICR). The efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1, and the efficacy for patients with CNS metastases involving at least one baseline target lesion was measured by BICR according to the Response Assessment in Neuro-Oncology Brain Metastases.[20] Plasma samples were collected at baseline and the end of 6 weeks of study drug administration to detect *EGFR* mutations, including exon del19, exon 20 insertion, S768I, L858R, G719X, L861Q, and T790M. The correlation between the clearance of *EGFR* mutations at the end of 6 weeks of study drug administration and the clinical efficacy was analyzed.

The PK blood sample collection time points for the dose-escalation phase in single administration stage were before administration and 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 12 hours, 24 hours, 48 hours, 72 hours, 120 hours, and 144 hours after administration. For continuous administration stage, the PK blood sample collection time points were days 1, 8, and 15 (before administration) of the first cycle and day 1 (before administration) of the second cycle and 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 12 hours, and 24 hours after administration (before next administration).

This study was performed in accordance with the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice Guidelines, and the applicable regulatory requirements. The protocol was approved by the institutional review board at each site. Written informed consent was obtained from each patient before initiation of the screening.

End Points and Assessments

The primary end points in dose-escalation phase were safety and tolerability. Safety referred to treatment-emergent adverse events (TEAEs). Adverse events (AEs) were evaluated by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

For the total study population, the primary end point was objective response rate (ORR) evaluated by BICR. The recommended phase 2 dose (RP2D) was determined according to data from dose-escalation and dose-expansion phases. The secondary end points included investigator-assessed ORR, disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), safety (with the exception of the dose-escalation phase), and PK parameters.

Statistical Analysis

The number of patients enrolled in dose-escalation phase depended on TEAEs and DLTs. Both dose-escalation and dose-expansion phases were put together for safety and efficacy analyses. Patients who were enrolled and received at least one dose of rezivertinib were defined as the full analysis set (FAS), and patients who received at least one postbaseline tumor response assessment were defined as the evaluable analysis set (EAS). The denominator of both ORR and DCR was the FAS. The 95% confidence interval (CI) was determined by the Clopper-Pearson exact method. The Kaplan-Meier analysis was applied to calculate DoR and PFS. CNS metastases analysis set included all patients with CNS metastases diagnosed by investigator at baseline and involving at least one CNS target lesion measured by BICR. PK analysis set included all patients with at least one evaluable PK concentration.

Results

Demographics

From September 11, 2017, to August 23, 2019, a total of 172 patients were enrolled (Fig. 1). Overall, 19 and 153 patients were enrolled in the dose-escalation phase and dose-expansion phase, respectively. At the data cutoff date on June 15, 2020, all patients received at least one dose of rezivertinib and were involved in the safety and efficacy analyses.

In total, 68.0% (117 of 172) of patients were females and 97.1% (167 of 172) of patients had adenocarcinoma. *EGFR* mutation types included exon del19 (110 of 172), L858R (58 of 172), and other (4 of 172). CNS metastases were found in 79 patients, among whom 22 patients had at least one CNS target lesion at baseline. For *EGFR* T790M test, the tissue sample was positive in 52.9%

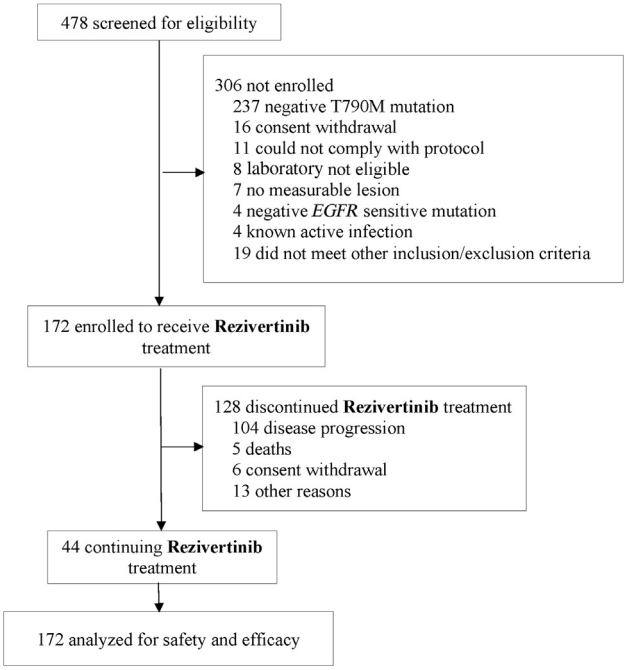

Figure 1. Trial profile (on the data cutoff date of June 15, 2020).

(91 of 172) of patients, whereas the plasma sample was positive in 64.5% (111 of 172) of patients (Table 1).

Safety

In the dose-escalation phase, no DLT occurred. Therefore, maximum tolerated dose was not reached. The incidence of TEAEs or treatment-related AEs (TRAEs) in more than or equal to 10% of patients was summarized in Table 2. Overall, 95.3% of patients reported at least one TEAE, of which most were lower than grade 3 (Supplementary Table 1). Only 31.4% of patients had grade 3 or higher TEAEs. The most common TEAEs were decreased white blood cell count (29.1%), decreased neutrophil count (27.3%), anemia (20.9%), and decreased platelet count (20.3%) (Table 2). The TRAEs were observed in 82.0% of the patients and 17.4% of the patients had grade 3 or higher (Supplementary Table 1), among which the most common involved decreased neutrophil count (2.9%), leukopenia (2.9%), and pneumonia (2.9%) (Supplementary Table 2). Serious TEAEs occurred in 13.4% of the patients; however, serious TRAEs determined by investigators occurred in 2.9% of the patients (Supplementary Table 1).

No patient experienced interstitial pneumonitis. Prolonged QT was observed in eight patients (one patient each for 30 mg and 240 mg, six patients for 180 mg). In addition, seven were grade 1 or grade 2 and one was above grade 3. Furthermore, seven of the eight prolonged QT were evaluated as possibly related to treatment. Thus, 4.1% (7 of 172) of patients had prolonged QT that could be related to treatment. Only three events (all grades 1–2) led to dose adjustment (one dose interruption and two dose reductions), and prolonged QT in the remaining patients was resolved without intervention.

TEAEs leading to dose adjustment were observed in 19.8% (34 of 172) of the patients, with those leading to dose discontinuation observed in 2.3% (4 of 172) of the patients. Overall, 15.1% (26 of 172) and 1.7% (3 of 172) of the patients experienced TRAEs that led to dose adjustment and dose discontinuation, respectively. At the data cutoff date, 46 deaths (26.7%) occurred, of which 12 (7.0%) occurred within the treatment period. Only four deaths (2.3%) were attributed to TEAEs, including pulmonary embolism ($n = 1$), sudden death ($n = 1$), and unknown cause of death ($n = 2$), none of which was possibly related to treatment evaluated by the investigators (Supplementary Table 1).

Efficacy

There were 172 patients in FAS and 161 patients in EAS. In the FAS, 102 (59.3%) patients had a partial response (PR), 55 (32.0%) had a stable disease, and seven (4.1%) had a disease progression. The BICR-evaluated ORR was 59.3% (95% CI: 51.6–66.7). DCR was 91.3% (95% CI: 86.0–95.0). Robust clinical efficacy was observed from 120 mg upward, whereas the dose-response relationship was deemed nonlinear (Table 3).

At the data cutoff date, in the 102 patients with PR, 47 had disease progression but no patient had died. The duration of treatment and response is illustrated in Supplementary Figure 1. The median DoR evaluated by BICR was 9.8 (95% CI: 8.3–15.6) months. The median PFS by BICR was 9.7 (95% CI: 8.3–11.1) months. The PFS of patients in each dose level was presented in Figure 2. In addition, tumor shrinkage was observed in most patients (Fig. 3). The best change in the target lesion measurement from baseline was minus 31% (95% CI: −95 to 45).

The subgroup analyses through both mutation type (deletion 19 versus L858R) and baseline sample source (tissue versus plasma) were observed as well. Of the 110 patients with deletion 19, on the basis of BICR, the ORR, DCR, and median PFS were 63.6% (95% CI: 53.9–72.6), 90.9% (95% CI: 83.9–95.6), and 9.7 (95% CI: 8.3–11.1) months, respectively. For the 58 L858R-mutated patients, the ORR, DCR, and median PFS were 51.7% (95% CI: 38.2–65.1), 91.4% (95% CI: 81.0–97.1), and 11.1 (95% CI: 8.3–15.2) months, respectively.

For patients with positive tissue sample at baseline ($n = 91$), the ORR, DCR, and median PFS were 61.5%

Table 1. Patient Baseline Demographic and Disease Characteristics

Characteristics	Dose-Escalation, n (%) (n = 19)	Overall, n (%) (N = 172)
Age, y		
<65	18 (94.7)	128 (74.4)
≥65	1 (5.3)	44 (25.6)
Sex		
Male	7 (36.8)	55 (32.0)
Female	12 (63.2)	117 (68.0)
ECOG PS		
0	14 (73.7)	56 (32.6)
1	5 (26.3)	116 (67.4)
Histology		
Adenocarcinoma	18 (94.7)	167 (97.1)
Adenosquamous carcinoma	0	2 (1.2)
Squamous cell carcinoma	0	1 (0.6)
Other	1 (5.3)	2 (1.2)
EGFR-sensitive mutation type		
Exon 19 deletion	14 (73.7)	110 (64.0)
L858R	5 (26.3)	58 (33.7)
Other	0	4 (2.3)
CNS metastases		
Yes	9 (47.4)	79 (45.9)
No	10 (52.6)	93 (54.1)
EGFR T790M-positive sample[a]		
Tissue	16 (84.2)	91 (52.9)
Plasma	13 (68.4)	111 (64.5)
Dose level		
30 mg	4 (21.1)	11 (6.4)
60 mg	3 (15.8)	6 (3.5)
120 mg	3 (15.8)	26 (15.1)
180 mg	3 (15.8)	86 (50.0)
240 mg	3 (15.8)	33 (19.2)
300 mg	3 (15.8)	10 (5.8)

[a]For a total of 172 enrolled patients, 91 patients were tested positive for tissue sample (including 30 plasma positive, 58 plasma negative, and three with no plasma test result) and 111 were tested positive for plasma sample.
CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

(95% CI: 50.8–71.6), 90.1% (95% CI: 82.1–95.4), and 9.7 (95% CI: 8.3–15.2) months, respectively. Comparatively, for patients with positive plasma sample at baseline (n = 111), the ORR, DCR, and median PFS were 55.9% (95% CI: 46.1–65.3), 89.2% (95% CI: 81.9–94.3), and 9.7 (95% CI: 8.3–11.1) months, respectively. For patients with both tissue and plasma samples positive for *EGFR* T790M at baseline (n = 30), the ORR and PFS were 53.3% (95% CI: 34.3–71.7) and 8.2 (95% CI: 4.1–9.7) months, and for patients with tissue positive but plasma negative for *EGFR* T790M (n = 58), the ORR and PFS were 65.5% (95% CI: 51.9–77.5) and 13.8 (95% CI: 9.7–17.9) months, respectively. The hazard ratio for PFS of patients with both tissue and plasma samples positive for *EGFR* T790M compared with patients with tissue positive but plasma negative for *EGFR* T790M was 0.507 (95% CI: 0.278–0.924) (Supplementary Fig. 2).

Of the 22 patients with CNS metastases, evaluated by BICR, 11 patients (50.0%) had an intracranial PR, nine patients (40.9%) had an intracranial stable disease, and the rest two were not evaluated for intracranial response. Consequently, the BICR-evaluated intracranial ORR and DCR were 50.0% (95% CI: 28.2–71.8) and 90.9% (95% CI: 70.8–98.9), respectively. The median intracranial DoR was 11.2 (95% CI: 2.8–12.4) months, and the median intracranial time to progression was 13.9 (95% CI: 6.9–not reached) months.

Pharmacokinetics

The median time to reach peak concentration (T_{max}) after multiple-day dose was between 3.9 hours and 8.1 hours. The T_{max} for 180 mg daily dose was 6.0 hours (95% CI: 4.0–8.0). On the basis of a single dose, the average half-time period ($t_{1/2}$) was 52.6 to 59.5 hours, and the $t_{1/2}$ of 180 mg dose was 59.5 plus or minus 7.4 hours (Supplementary Fig. 3*A* and *B*). Rezivertinib dose proportion increased from 30 mg to 180 mg. By linear regression analysis, there was linearity in dose exposure with the β_1 of 0.97 (90% CI: 0.75–1.31). Dose absorption limit was observed from 180 mg to 300 mg, and the absorption in the 240 mg was close to the 180 mg after multiple-day dose.

The Determination of RP2D

According to the safety and efficacy data, also referring to the PK data, the dose of 180 mg once daily was chosen as the RP2D for rezivertinib.

EGFR Mutation Clearance

The clearance of *EGFR* mutations, including exon del19, L858R, L861Q, and S768I, at the end of 6 weeks of study treatment was significantly correlated with tumor responses ($p = 0.0045$) (Supplementary Table 3). Moreover, PFS of patients with complete clearance of *EGFR* mutation at the end of 6 weeks of study treatment was longer than those still harboring plasma *EGFR* mutation (11.1 [95% CI: 9.7–16.9] mo versus 5.6 [95% CI: 4.2–8.3] mo, $p < 0.0001$) (Supplementary Fig. 4). Besides, PFS of patients with negative plasma *EGFR* mutation at the end of 6 weeks of treatment was also longer than those with positive result (11.2 [95% CI: 11.0–16.9] mo versus 5.6 [95% CI: 4.2–8.3] mo, $p = 0.0002$) (Supplementary Fig. 5). In contrast, among the 111 patients with positive *EGFR* T790M mutation in plasma at baseline, six patients did not provide plasma samples at the end of 6 weeks of study treatment. Among the 105 patients with plasma samples at the end of 6 weeks of

Table 2. Incidence of TEAEs or TRAEs in More Than or Equal to 10% of Patients (N = 172)

	TEAEs, n (%)		TRAEs, n (%)	
Adverse Events	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Decreased white blood cell count	50 (29.1)	0	49 (28.5)	0
Decreased neutrophil count	47 (27.3)	5 (2.9)	47 (27.3)	5 (2.9)
Anemia	36 (20.9)	1 (0.6)	29 (16.9)	1 (0.6)
Decreased platelet count	35 (20.3)	3 (1.7)	34 (19.8)	2 (1.2)
Leukopenia	34 (19.8)	5 (2.9)	31 (18.0)	5 (2.9)
Upper respiratory tract infection	30 (17.4)	1 (0.6)	0	0
Increased alanine aminotransferase	23 (13.4)	0	20 (11.6)	0
Decreased weight	23 (13.4)	1 (0.6)	0	0
Decreased lymphocyte count	22 (12.8)	4 (2.3)	20 (11.6)	4 (2.3)
Decreased appetite	22 (12.8)	0	12 (7.0)	0
Increased aspartate aminotransferase	19 (11.0)	0	17 (9.9)	0
Vomiting	18 (10.5)	0	10 (5.8)	0
Cough	18 (10.5)	0	2 (1.2)	0
Diarrhea	18 (10.5)	0	10 (5.8)	0
Hypertriglyceridemia	18 (10.5)	0	7 (4.1)	0

TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

study treatment, 100.0% of patients (105 of 105) were undetected for *EGFR* T790M mutation.

Discussion

In this phase 1 study, rezivertinib was found to have a manageable safety profile and promising efficacy. Up to 300 mg was still well tolerated by the patients without DLT. According to the AURA study evaluating osimertinib,[12] the most common TEAEs were gastrointestinal disorders, including diarrhea (47%), nausea (22%), and decreased appetite (21%), and skin disorders, including rash (40%). In comparison, hematological TEAEs, including decreased white blood cell count (29.1%), decreased neutrophil count (27.3%), decreased platelet count (20.3%), and anemia (20.9%), were the most frequently reported with rezivertinib in our study. The safety profile was different from other *EGFR* T790M-specific TKIs, and the hematological toxicity was more common with rezivertinib in our study, which was not identified in preclinical studies. Nevertheless, the reason for hematopoiesis inhibition in our study is still unclear,

Table 3. Clinical Efficacy of Rezivertinib by Dose Level in FAS (N = 172)

Dose Level	30 mg, n (%)	60 mg, n (%)	120 mg, n (%)	180 mg. n (%)	240 mg, n (%)	300 mg, n (%)	Total, n (%)
No. of patients	11	6	26	86	33	10	172
BOR							
CR	0	0	0	0	0	0	0
PR	4 (36.4)	1 (16.7)	19 (73.1)	52 (60.5)	20 (60.6)	6 (60.0)	102 (59.3)
SD	4 (36.4)	4 (66.7)	6 (23.1)	27 (31.4)	11 (33.3)	3 (30.0)	55 (32.0)
PD	2 (18.2)	1 (16.7)	1 (3.8)	2 (2.3)	1 (3.0)	0	7 (4.1)
NE	1 (9.1)	0	0	5 (5.8)	1 (3.0)	1 (10.0)	8 (4.7)
ORR	4 (36.4)	1 (16.7)	19 (73.1)	52 (60.5)	20 (60.6)	6 (60.0)	102 (59.3)
95% CI	(10.9-69.2)	(0.42-64.1)	(52.2-88.4)	(49.3-70.9)	(42.1-77.1)	(26.2-87.8)	(51.6-66.7)
DCR	8 (72.7)	5 (83.3)	25 (96.2)	79 (91.9)	31 (93.9)	9 (90.0)	157 (91.3)
95% CI	(39.0-94.0)	(35.9-99.6)	(80.4-99.9)	(84.0-96.7)	(79.8-99.3)	(55.5-99.8)	(86.0-95.0)
PFS							
No. of events	9 (81.8)	4 (66.7)	18 (69.2)	40 (46.5)	14 (42.4)	2 (20.0)	87 (50.6)
Median	2.8	5.6	9.7	9.7	11.1	NC	9.7
95% CI	(0.8-18.0)	(1.4-NC)	(6.9-15.2)	(8.3-13.8)	(8.3-NC)	(4.2-NC)	(8.3-11.1)
DoR							
Median	10.5	NC	9.9	9.8	9.7	NC	9.8
95% CI	(4.2-16.6)	(NC-NC)	(6.9-15.6)	(8.3-NC)	(6.9-NC)	(6.9-NC)	(8.3-15.6)

Note: Efficacy was evaluated by BICR.

BICR, blinded independent central review; BOR, best objective response; CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; FAS, full analysis set; NC, not calculable; NE, not evaluable; No., number; ORR, objective response rate; PD, disease progression; PFS, progression-free survival; PR, partial response; SD, stable disease.

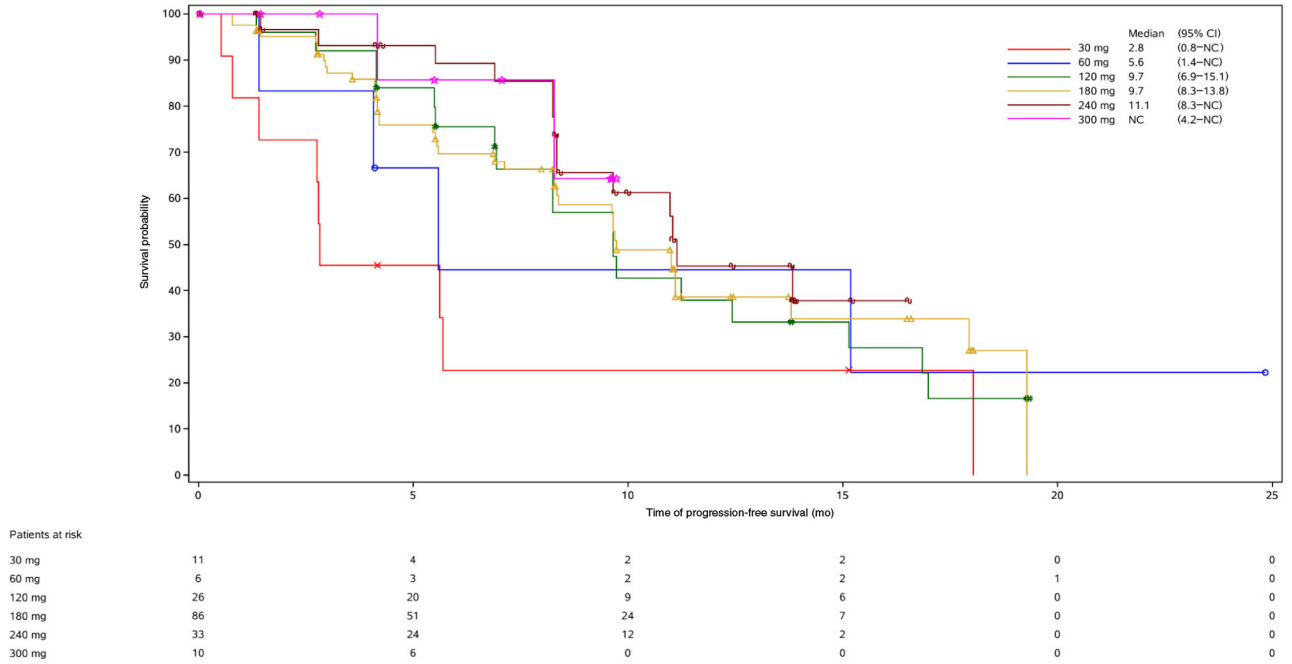

Figure 2. BICR-evaluated progression-free survival in patients at dose levels of 30 mg, 60 mg, 120 mg, 180 mg, 240 mg, and 300 mg in FAS (N = 172). BICR, blinded independent central review; CI, confidence interval; FAS, full analysis set; NC, not calculable.

and more investigation is needed. In addition, the grade 3 or higher TEAEs occurred merely in 2.9% of the patients (5 of 172). Notably, no patient experienced interstitial lung disease in our study. Taken together, rezivertinib had a favorable safety profile.

Unlike the study design of the AURA study, *EGFR* T790M-negative patients were excluded for enrollment in our study. The EAS-based ORR of osimertinib for the *EGFR* T790M-mutated patients was 61% (78 of 127), and median PFS was 9.6 months.[12] In comparison, the

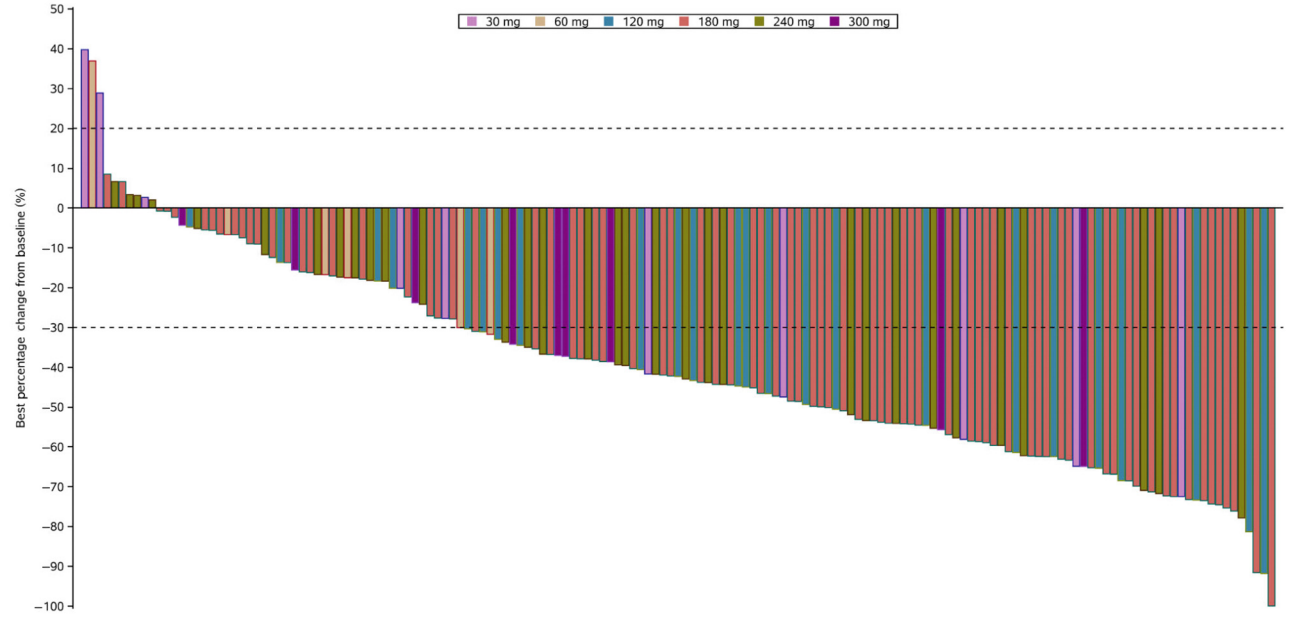

Figure 3. Best percentage change in target lesion size by dose for patients with measurable lesions evaluated by BICR in EAS (N = 159). Note: Of 161 patients in EAS, one patient was without BICR-evaluated efficacy data at the data cutoff date and one patient was without evaluable lesion evaluated by BICR. BICR, blinded independent central review; EAS, evaluable analysis set.

EAS-based ORR and the median PFS for rezivertinib in our study were 60.9% (98 of 161) and 9.7 (95% CI: 8.3–11.1) months, respectively. The most critical efficacy data between osimertinib and rezivertinib are similar despite the different sample sources of *EGFR* T790M detection test.

There was a relatively high proportion of patients with CNS metastases (46%) in our study. Comparatively, the proportion was 35% in the aumolertinib (HS-10296, formerly named as almonertinib) phase 1 study[13] and 36% in the aumolertinib (HS-10296, formerly named as almonertinib) phase 2 study,[14] 48% in the furmonertinib (AST2818) phase 2b study,[16] 33% in AURA3,[21] 37% in AURA17,[22] and 39% in the AURA pooled analysis.[23] Despite the small sample size (12.8%, 22 of 172), rezivertinib was found to have promising clinical activity in patients with *EGFR* T790M-mutant NSCLC and CNS metastases diagnosed by investigator at baseline and involving at least one CNS target lesion measured by BICR. The intracranial ORR of 50.0% and the intracranial DCR of 90.9% are quite close to the ORR (59.3%) and DCR (91.3%) derived from the overall study population, which reveals that rezivertinib could penetrate the blood-brain barrier exactly.

On the basis of the efficacy results, both ORR and median PFS in 120 mg, 180 mg, and 240 mg of rezivertinib were comparable with those of osimertinib in the AURA study.[12] Nevertheless, all top three TRAEs (decreased white blood cell count, decreased neutrophil count, and decreased platelet count) observed in the subgroup of 180 mg were less than those in the subgroup of either 120 mg or 240 mg (Supplementary Table 4). Besides, PK analysis revealed that the exposure of 240 mg was lower than that of the 180 mg and the exposure increase from 180 mg or 240 mg to 300 mg was not linear. Therefore, considering the antitumor activity would not be improved but the incidence rate of AEs increased in dose levels more than 180 mg, 180 mg once daily was chosen to be the RP2D.

The high diagnostic accuracy of circulating tumor DNA (ctDNA) has been reported,[24] and ctDNA is a specific and sensitive biomarker for identification of tumor-associated genetic and molecular alterations,[25] including *EGFR* mutation status. Guidelines of both the United States[26] and the People's Republic of China[27] suggest ctDNA be used to identify *EGFR* mutations if tissue sample is limited or insufficient for *EGFR* mutation test. Therefore, either sample source could be provided for the central *EGFR* mutation testing in our study.

In our study, 100% of patients (105 of 105) achieved complete clearance of *EGFR* T790M mutation at the end of 6 weeks of study treatment, indicating the clearance of *EGFR* T790M mutation was not a reliable predictor for efficacy of rezivertinib. Comparatively, the change percentage of *EGFR* mutations including exon del19, L858R, L861Q, and S768I (no patient had exon 20 insertion and G719X mutations at baseline) at the end of 6 weeks of study treatment was 62.8% (Supplementary Table 3) and the corresponding chi-square test revealed the high positive correlation between the clearance of *EGFR* mutations and the response of advanced NSCLC treated with rezivertinib. Moreover, markedly positive association was observed between the clearance of *EGFR* mutations at the end of 6 weeks of study treatment and prolonged PFS of patients treated with rezivertinib.

To the best of our knowledge, the number of patients in our study is the largest among any other phase 1 studies for the third-generation *EGFR* TKIs in Chinese patients with the acquired *EGFR* T790M mutation.[13,15] Nevertheless, this study was conducted in Chinese patients only and caution should be taken when extrapolating the safety and efficacy data to other races. Besides, the subgroup analyses should be interpreted with caution, owing to the potential imbalances between groups. The PK analysis was only performed in three patients in each dose level, and further PK studies will be needed in future.

In summary, this study revealed that rezivertinib had a manageable safety and promising efficacy profile for Chinese patients with advanced NSCLC with *EGFR* T790M mutation. On the basis of the results of this study, a registration phase 2b clinical trial (NCT03812809) of rezivertinib in *EGFR* T790M-positive NSCLC has completed accrual. A phase 3 clinical trial (REZOR, NCT03866499) of rezivertinib with comparison to gefitinib as the first-line treatment of locally advanced or recurrent/metastatic *EGFR*-mutated NSCLC is ongoing.

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.

Yanqiu Zhao, Sheng Yang, Jianying Zhou, Liangming Zhang, Gongyan Chen, Jian Fang, Bo Zhu, Xingya Li, Yongqian Shu, Jianhua Shi, Rongsheng Zheng, Donglin Wang, Huiqing Yu, Jianan Huang, Zhixiang Zhuang, Gang Wu, Longzhen Zhang, Zhongliang Guo: Investigation, Resources, Data curation, Writing - review and editing.

Michael Greco: Conceptualization, Methodology, Investigation, Resources, Data curation, Writing - review and editing.

Xiao Li: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources,

Data curation, Writing - review and editing, Visualization, Supervision, Project administration.

Yu Zhang: Software, Investigation, Validation, Formal analysis, Resources, Data curation, Writing - original draft, Writing - review and editing, Visualization.

Acknowledgments

This study (NCT03386955) was funded by Beta Pharma Co., Ltd. (Shanghai, People's Republic of China) and supported in part by the China National Major Project for New Drug Innovation (2017ZX09304015) and the New National Natural Science Foundation of China (81972805). The authors thank all the participating patients, their families, and the participating study teams. Special thanks to Bo Li and Xiaodong Shi for their assistance with figure and table preparation. The authors thank Dr. Haizhu Chen and Dr. Yu Zhou (National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, People's Republic of China) for providing medical editing assistance with this article.

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.2022.01.015.

References

1. Shi Y, Au JS, 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. 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.
3. 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.
4. 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.
5. Sequist LV, Yang JC, 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.
6. 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.
7. 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.
8. 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.
9. 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.
10. 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.
11. Mok TSK, Kim SW, Wu YL, et al. Gefitinib plus chemotherapy versus chemotherapy in epidermal growth factor receptor mutation-positive non-small-cell lung cancer resistant to first-line gefitinib (IMPRESS): overall survival and biomarker analyses. *J Clin Oncol*. 2017;35:4027–4034.
12. Jänne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med*. 2015;372:1689–1699.
13. Yang JC, 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.
14. 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.
15. 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.
16. 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.
17. 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.
18. Wilde VL, Greco MN, Costanzo MJ, et al. Preclinical evidence of BPI-7711 activity in EGFR-mutant non-small cell lung cancer (NSCLC) in orthotopically implanted human tumor xenografts in the lung and brain. Paper presented at: The Asia Pacific Lung Cancer Conference (APLCC). Chiang Mai: Thailand; May 13–16. 2016.

19. Wilde VL, Peng J, Greco MN, et al. BPI-7711, a covalent selective EGFR inhibitor, inhibits the growth of NSCLC cell lines with EGFR activating and T790M resistance mutations. Beta Pharma. http://betapharma.com/wp-content/uploads/2019/10/BPI7711Poster1.pdf. Accessed June 7, 2020.
20. Lin NU, Lee EQ, Aoyama H, et al. Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol*. 2015;16:e270–e278.
21. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med*. 2017;376:629–640.
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(suppl 9):ix150–ix169.
23. 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.
24. Uchida J, Kato K, Kukita Y, et al. Diagnostic accuracy of noninvasive genotyping of EGFR in lung cancer patients by deep sequencing of plasma cell-free DNA. *Clin Chem*. 2015;61:1191–1196.
25. Schwarzenbach H, Hoon DS, Pantel K. Cell-free nucleic acids as biomarkers in cancer patients. *Nat Rev Cancer*. 2011;11:426–437.
26. Lindeman NI, Cagle PT, Aisner DL, et al. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: guideline from the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. *Arch Pathol Lab Med*. 2018;142:321–346.
27. Chinese Association for Clinical O, Medical Oncology Branch of Chinese International Exchange. Promotion Association for Medical and Healthcare [Clinical practice guideline for stage IV primary lung cancer in China (2021 version)]. *Zhonghua Zhong Liu Za Zhi*. 2021;43:39–59.