ORIGINAL ARTICLE

Efficacy and Safety of Rezivertinib (BPI-7711) in Patients With Locally Advanced or Metastatic/Recurrent *EGFR* T790M-Mutated NSCLC: A Phase 2b Study

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ABSTRACT

Introduction: Rezivertinib (BPI-7711) is a novel third-generation *EGFR* tyrosine kinase inhibitor (TKI) targeting both *EGFR*-sensitizing mutations and *EGFR* T790M mutation. This study aimed to evaluate the efficacy and safety of rezivertinib in patients with locally advanced or metastatic/recurrent *EGFR* T790M-mutated NSCLC.

Methods: Patients with locally advanced or metastatic/recurrent NSCLC with confirmed *EGFR* T790M mutation who progressed after first-/second-generation *EGFR* TKI therapy or primary *EGFR* T790M mutation were enrolled. Patients received rezivertinib at 180 mg orally once daily until disease progression, unacceptable toxicity, or withdrawal of consent. The primary end point was objective response rate (ORR) assessed by blinded independent central review per Response Evaluation Criteria in Solid Tumors version 1.1. Secondary end points included disease control rate (DCR), duration of response, progression-free survival (PFS), overall survival, and safety. This study is registered with Clinical Trials.gov (NCT03812809).

Results: A total of 226 patients were enrolled from July 5, 2019, to January 22, 2020. By the data cutoff date on January 24, 2022, the median duration of follow-up was 23.3 months (95% confidence interval [CI]: 22.8–24.0). The ORR by blinded independent central review was 64.6% (95% CI: 58.0%–70.8%), and DCR was 89.8% (95% CI: 85.1%–93.4%). The median duration of response was 12.5 months (95% CI: 10.0–13.9), and median PFS was 12.2 months (95% CI: 9.6–13.9). The median overall survival was 23.9 months (95% CI: 20.0–not calculated [NC]). Among 91 (40.3%) patients with central nervous system (CNS) metastases, the median CNS PFS was 16.6 months (95% CI: 11.1–NC). In 29 patients with more than or equal

to one brain target lesion at baseline, the CNS ORR and CNS DCR were 69.0% (95% CI: 49.2%–84.7%) and 100% (95% CI: 88.1%–100%), respectively. Time to progression of CNS was 16.5 months (95% CI: 9.7–NC). Of 226 patients, 188 (83.2%) had at least one treatment-related adverse event, whereas grade more than or equal to 3 occurred in 45 (19.9%) patients. No interstitial lung disease was reported.

Conclusions: Rezivertinib was found to have promising efficacy and favorable safety profile for patients with locally advanced or metastatic/recurrent NSCLC with *EGFR* T790M mutation.

Keywords: Rezivertinib; BPI-7711; NSCLC; *EGFR* T790M mutation; Third-generation EGFR TKI

Introduction

In patients with advanced lung adenocarcinoma, approximately 50% of east Asian and 20% of Western country patients harbored *EGFR* mutations, in which exon 19 deletion (19del) and exon 21 Leu858Arg (L858R) mutations account for approximately 90% of *EGFR* mutations.[1–4] The first- or second-generation *EGFR* tyrosine kinase inhibitors (TKIs) were developed to target *EGFR*-sensitizing mutations. Nevertheless, the emergence of the acquired *EGFR* gatekeeper T790M mutation after first- or second-generation EGFR TKIs in *EGFR*-mutated NSCLC has necessitated the development of third-generation EGFR TKIs to overcome this frequently acquired mutation. The standard treatment of advanced *EGFR* T790M-mutated NSCLC was osimertinib which was approved by the U.S. Food and Drug Administration in November 2015.[5] Subsequently, almonertinib and furmonertinib came into the market in the People's Republic of China.[5–9] In the meantime, 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.[5]

Rezivertinib (BPI-7711) is a third-generation EGFR TKI jointly developed by Beta Pharma (Shanghai) Co., Ltd., Shanghai, People's Republic of China and Beta Pharma Inc., Princeton, NJ. Phase 1 dose-escalation and dose-expansion study (NCT03386955) has revealed that rezivertinib was clinically effective with acceptable toxicity in patients with *EGFR* T790M-mutated advanced NSCLC and identified the recommended phase 2 dose as 180 mg once daily.[10] On the basis of this evidence, we designed this phase 2b study to further evaluate the efficacy and safety of rezivertinib in patients with locally advanced or metastatic/recurrent *EGFR* T790M-mutated NSCLC.

Materials and Methods

Study Design and Patients

This was a phase 2b, multicenter, single-arm, open-label study of rezivertinib conducted across the People's Republic of China. Patients with eligibility were aged at least 18 years with an Eastern Cooperative Oncology Group performance status score of 0 to 1 with no deterioration in the previous 2 weeks and at least a 12-week life expectancy. All patients were required histologic or cytologic confirmation of locally advanced or metastatic NSCLC not suitable for operation or radiotherapy and harbored *EGFR* T790M mutation and *EGFR*-sensitizing mutations (including G719X, exon 19 deletion, L858R, and L861Q) who progressed after first-/second-generation EGFR TKI therapy or primary *EGFR* T790M mutation as detected through tissue or plasma biopsies by central laboratory testing (the cobas *EGFR* Mutation Test, Version 2, Roche Diagnostics, South Branchburg, NJ), with measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. 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. Adequate organ function was required as defined by platelet count 100×10^9/L or higher, absolute neutrophil count 1.5×10^9/L or higher, hemoglobin 90 g/L or higher, total bilirubin less than 1.5 times the upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) less than three times ULN (total bilirubin $\leq 3 \times$ ULN, ALT $\leq 5 \times$ ULN, and AST $\leq 5 \times$ ULN were allowed if liver metastases existed), serum creatinine less than 1.5 times ULN, or creatinine clearance 50 mL/min or higher according to the Cockcroft-Gault equation, QTcF (QT interval corrected for heart rate) prolongation less than or equal to 470 msec at rest, and international normalized ratio and activated partial thromboplastin time less than 1.5 times ULN without taking anticoagulant. Before first dose of rezivertinib, all drug-related toxic effects (except for hair loss and peripheral nerve toxic reaction) had to be at grade 1 or less according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Key exclusion criteria included patients harboring *EGFR* 20 exon insertion mutation confirmed at any time; previous treatment with any other third-generation EGFR TKI; treatment with any first-/second-generation EGFR TKI within 5 half-lives before first dose of rezivertinib; treatment with cytotoxic chemotherapy, investigational agent, strong inhibitors, or inducers of

cytochrome P450 isoenzyme 3A4 within 14 days of the first dose of rezivertinib; any clinically meaningful electrocardiogram abnormality (such as QT interval corrected for heart rate prolongation >470 msec at rest and complete left bundle branch block), any factor that increased the risk of QTc prolongation (such as New York Heart Association II–IV, hypokalemia, and long QT syndrome); any condition that possibly affects drug absorption (such as severe or uncontrolled inflammatory gastrointestinal disease, abdominal colostomy, gastrointestinal perforation within 6 mo, extensive bowel resection, or patients on tube feeding); medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis that required steroid treatment, acute or progressive lung disease that could lead to interstitial lung disease; active infection disease (such as hepatitis B, hepatitis C, and human immunodeficiency virus), but inactive hepatitis B was acceptable; major surgery within 4 weeks, minor operation within 2 weeks; radiotherapy with a wide field within 4 weeks or radiotherapy within a limited field within 1 week before the first dose of rezivertinib; patients with any other concomitant cancer or recurrent cancer within 5 years, except radical operation of carcinoma in situ of cervix, nonmelanoma skin cancer, noninvasive superficial bladder cancer, or radical operation of carcinoma in situ with no recurrence within 3 years; patients with spinal cord compression or meningeal metastases, symptomatic brain metastases, except asymptomatic brain metastases not requiring steroids or local therapy before the first dose of rezivertinib, asymptomatic brain metastases after local therapy (such as radiotherapy), and steroids or antiepileptic therapy at least 7 days before the first dose of rezivertinib.

All patients provided written informed consent before enrollment in the study. The study was done in accordance with the Declaration of Helsinki and approved by the institutional review board or independent ethics committee associated with each participating center.

Procedures

Patients received rezivertinib at 180 mg orally (1 h before or 2 h after meal) once daily until disease progression, unacceptable toxicity, or withdrawal of consent. Dose interruption was implemented if a patient had a grade 3 or higher adverse events or intolerable toxicity caused by rezivertinib in the judgement of investigators; if the grade 3 adverse event resolved or turned to grade 1 or normal within 2 weeks, rezivertinib could be resumed at a lower dose of 120 mg or 60 mg daily no more than twice. Treatment after disease progression was permitted if clinical benefits could be obtained in the judgement of the investigators.

Tumor response was assessed by blinded independent central review (BICR) and by investigators according to RECIST version 1.1 using computed tomography or magnetic resonance imaging scans at baseline and every 2 treatment cycles (6 wk) from treatment initiation. In the period between the time when the informed consent was signed and 30 days after the last dose of rezivertinib, adverse events (graded according to Common Terminology Criteria for Adverse Events version 4.03) were monitored continuously. During the treatment period, physical examination results, vital signs, Eastern Cooperative Oncology Group performance status scores, and results of hematology, serum chemistry, urinalysis, 12-lead electrocardiograms, and echocardiography were documented and assessed at protocol-specified time points.

End Points and Assessments

The primary end point was objective response rate (ORR), defined as the proportion of patients with a best overall response (BOR) of complete response (CR) or partial response (PR) before progression, as per RECIST version 1.1. Secondary end points included disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. DCR was defined as the proportion of patients with a BOR of CR, PR, or stable disease. DoR was defined as the time lasting from first CR or PR to progression or death. PFS was defined as the time lasting from first dose date of rezivertinib to progression or death, whichever occurred first. OS was defined as the time lasting from first dose date of rezivertinib to death by any cause. Adverse events related to or not related to rezivertinib were judged by investigators. For patients confirmed with CNS metastases at baseline assessed by investigators, CNS ORR, CNS DCR, CNS DoR, CNS time to progression, and CNS PFS were evaluated on the basis of the response assessment in neuro-oncology brain metastases criteria.

Statistical Analysis

On the basis of the null hypothesis (H0: ORR $\leq$ 45%, treatment with no response) and the alternative hypothesis (H1: ORR $\geq$ 55%, treatment with response), this study would require a sample size of 201 patients. Taking 5% dropouts into account, approximately 212 patients were planned to be enrolled in this study.

The full analysis set included all patients who have received at least one dose of rezivertinib. The full analysis set would be used to analyze the efficacy and safety data. The 95% confidence interval (CI) for ORR and DCR was determined by the Clopper-Pearson method. The 95% CI for median values of PFS, DoR, and OS was

calculated by the Kaplan-Meier method. This study was registered with ClinicalTrials.gov (NCT03812809).

Results

Demographics

Between July 5, 2019, and January 22, 2020, 636 patients were screened in 50 hospitals across the People's Republic of China, of whom 226 were enrolled and started on rezivertinib treatment, including 91 (40.3%) patients with brain metastases. The baseline demographic and characteristics of the patients are presented in Table 1.

By the data cutoff date on January 24, 2022, all patients were terminated from the study treatment, of which 128 (56.6%) had progressed, 39 (17.3%) terminated by sponsor, 30 (13.3%) withdrew of consent, 12 (5.3%) owing to adverse events, 10 (4.4%) owing to investigator decision, and seven (3.1%) died (Fig. 1). The median follow-up duration was 23.3 months (95% CI: 22.8–23.9).

Efficacy

ORR. The ORR by BICR was 64.6% (146 of 226, 95% CI: 58.0%–70.8%), and the DCR was 89.8% (203 of 226, 95% CI: 85.1%–93.4%) (Table 2). The median time to response was 1.6 months (95% CI: 1.5–2.8). The percentage change in sum by BICR is shown in Figure 2*A*. The ORR of tissue sample T790M positive was 70% (95% CI: 61.0%–78.0%), and plasma sample T790M positive was 56.9% (95% CI: 47.4%–66.1%). The ORR of *EGFR* exon 19 deletion and L858R mutations was 72.4% (95% CI: 64.4%–79.5%) and 51.9% (95% CI: 40.4%–63.3%), respectively (Fig. 2*B*). Of 226 patients, 91 had CNS metastases, and the ORR and DCR were 57.1% (52 of 91, 95% CI: 46.3%–67.5%) and 83.5% (76 of 91, 95% CI: 74.3%–90.5%), respectively. Among 91 patients with CNS metastases, 29 patients who had more than or equal to one brain target lesion at baseline had the CNS ORR and CNS DCR of 69.0% (95% CI: 49.2%–84.7%) and 100% (95% CI: 88.1%–100%), respectively (Supplementary Table 1). The ORRs of the other subgroups are found in Figure 2*B*.

DoR. The median DoR was 12.5 months (95% CI: 10.0–13.9) (Fig. 3*A*). The median DoR of patients with brain metastases was 11.1 months (95% CI: 7.0–13.8) and 13.3 months (95% CI: 9.7–15.2) for patients without brain metastases (hazard ratio [HR] 0.91 [95% CI: 0.59–1.43], $p = 0.6993$) (Supplementary Fig. 1). Among 91 patients

Table 1. Patient Baseline Characteristics in FAS

Characteristics	All Patients (n = 226)	With Brain Metastases (n = 91)	Without Brain Metastases (n = 135)
Age, y			
Mean	59.1	57.4	60.3
Median	59.5 (30-81)	57.0 (30-81)	61.0 (38-76)
Sex, n (%)			
Male	70 (31.0)	27 (29.7)	43 (31.9)
Female	156 (69.0)	64 (70.3)	92 (68.1)
ECOG PS n (%)			
0	67 (29.6)	28 (30.8)	39 (28.9)
1	159 (70.4)	63 (69.2)	96 (71.1)
Disease status at study entry, n (%)			
Locally advanced	3 (1.3)	0	3 (2.2)
Metastases	223 (98.7)	91 (100.0)	132 (97.8)
Clinical staging at the diagnosis, n (%)			
II	4 (1.8)	1 (1.1)	3 (2.2)
III	14 (6.2)	6 (6.6)	8 (5.9)
IV	178 (78.8)	74 (81.3)	104 (77.0)
Unknown	30 (13.3)	10 (11.0)	20 (14.8)
EGFR mutation subtype, n (%)			
Exon 19 deletion	145 (64.2)	57 (62.6)	88 (65.2)
L858R	79 (35.0)	32 (35.2)	47 (34.8)
Others	2 (0.9)	2 (2.2)	0
Tissue sample T790M positive, n (%)	120 (53.1)	38 (41.8)	82 (60.7)
Plasma sample T790M positive, n (%)	116 (51.3)	56 (61.5)	60 (44.4)
Previous anticancer treatment, n (%)			
Chemotherapy	34 (15.0)	12 (13.2)	22 (16.3)
EGFR TKI treatment	161 (71.2)	64 (70.3)	97 (71.9)
Others	31 (13.7)	14 (15.4)	17 (12.6)

ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; PS, performance status; TKI, tyrosine kinase inhibitor.

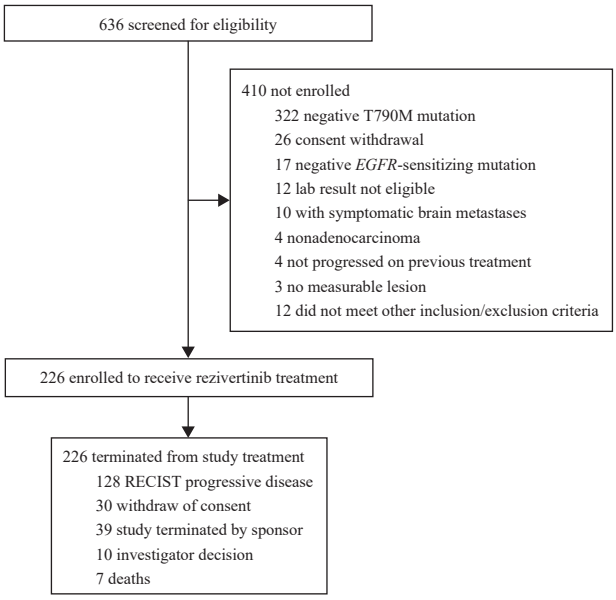

Figure 1. Patient disposition. Lab, laboratory; RECIST, Response Evaluation Criteria in Solid Tumors.

with CNS metastases, the median CNS DoR was 15.2 months (95% CI: 8.3–not calculated [NC]) (Supplementary Table 1). For patients aged 65 years or more, the median DoR was 13.9 months (95% CI: 9.7–22.0), and for those aged under 65 years, the median DoR was 12.2 months (95% CI: 9.6–13.8).

PFS. The median PFS for all 226 patients was 12.2 months (95% CI: 9.6–13.9) (Fig. 3*B*). The median PFS for patients with brain metastases and without brain metastases was 10.3 months (95% CI: 7.0–12.5) and 12.4 months (95% CI: 9.7–15.2), respectively (HR = 0.75 [95% CI: 0.54–1.06], $p = 0.1033$) (Supplementary Fig. 2). The median PFS for patients with *EGFR* exon 19 deletion and L858R mutations was 12.4 months (95% CI: 8.8–15.1) and 10.3 months (95% CI: 8.3–13.9), respectively (HR = 1.21 [95% CI: 0.87–1.73], $p = 0.2564$) (Supplementary Fig. 3). The median PFS for patients with tissue sample T790M positive and plasma sample T790M positive was 13.9 months (95% CI: 11.3–17.9) and 9.6 months (95% CI: 7.0–11.0), respectively (HR = 0.53 [95% CI: 0.39–0.74], $p = 0.0002$) (Supplementary Fig. 4). Among 91 patients with CNS metastases, the median CNS PFS was 16.6 months (95% CI: 11.1–NC) (Supplementary Table 1). Of the 91 patients, 29 who had more than or equal to one CNS measurable lesion at baseline had the median CNS time to progression of 16.5 months (95% CI: 9.7–NC).

OS

By the data cutoff date on January 24, 2022, the median follow-up duration was 23.3 months (95% CI: 22.8–23.9) and the median OS was 23.9 months (95% CI: 20.0–NC) (Fig. 3*C*). The median OS for patients with brain metastases and without brain metastases was 17.5 months (95% CI: 12.9–20.2) and NC (95% CI: 24.1–NC), respectively (HR = 0.48 [95% CI: 0.33–0.69], $p < 0.0001$) (Supplementary Fig. 5).

Safety

Treatment-emergent adverse events (TEAEs) occurred in 223 patients (98.7%), and treatment-related adverse events (TRAEs) occurred in 188 patients

Table 2. Efficacy Assessed by BICR in FAS

Parameters	All Patients (n = 226)	Subgroup		p Value
		With Brain Metastases (n = 91)	Without Brain Metastases (n = 135)	
Best overall response, n (%)				
Complete response	0	0	0	
Partial response	146 (64.6)	52 (57.1)	94 (69.6)	
Stable disease	57 (25.2)	24 (26.4)	33 (24.4)	
Progression disease	9 (4.0)	5 (5.5)	4 (3.0)	
Not evaluable	14 (6.2)	10 (11.0)	4 (3.0)	
ORR, n (%)	146 (64.6)	52 (57.1)	94 (69.6)	0.0542
95% CI, %	58.0-70.8	46.3-67.5	61.1-77.2	
DCR, n (%)	203 (89.8)	76 (83.5)	127 (94.1)	0.0100
95% CI, %	85.1-93.4	74.3-90.5	88.7-97.4	
DoR, mo Median (95% CI)	12.5 (10.0-14.0)	11.1 (7.0-13.8)	13.3 (9.7-15.2)	0.6993
PFS, mo Median (95% CI)	12.2 (9.6-13.9)	10.3 (7.0-12.5)	12.4 (9.7-15.2)	0.1033
OS, mo Median (95% CI)	23.9 (20.0-NC)	17.5 (12.9-20.2)	NC (24.1-NC)	<0.0001

BICR, blinded independent central review; CI, confidence interval; DCR, disease control rate; DoR, duration of response; FAS, full analysis set; NC, not calculated; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

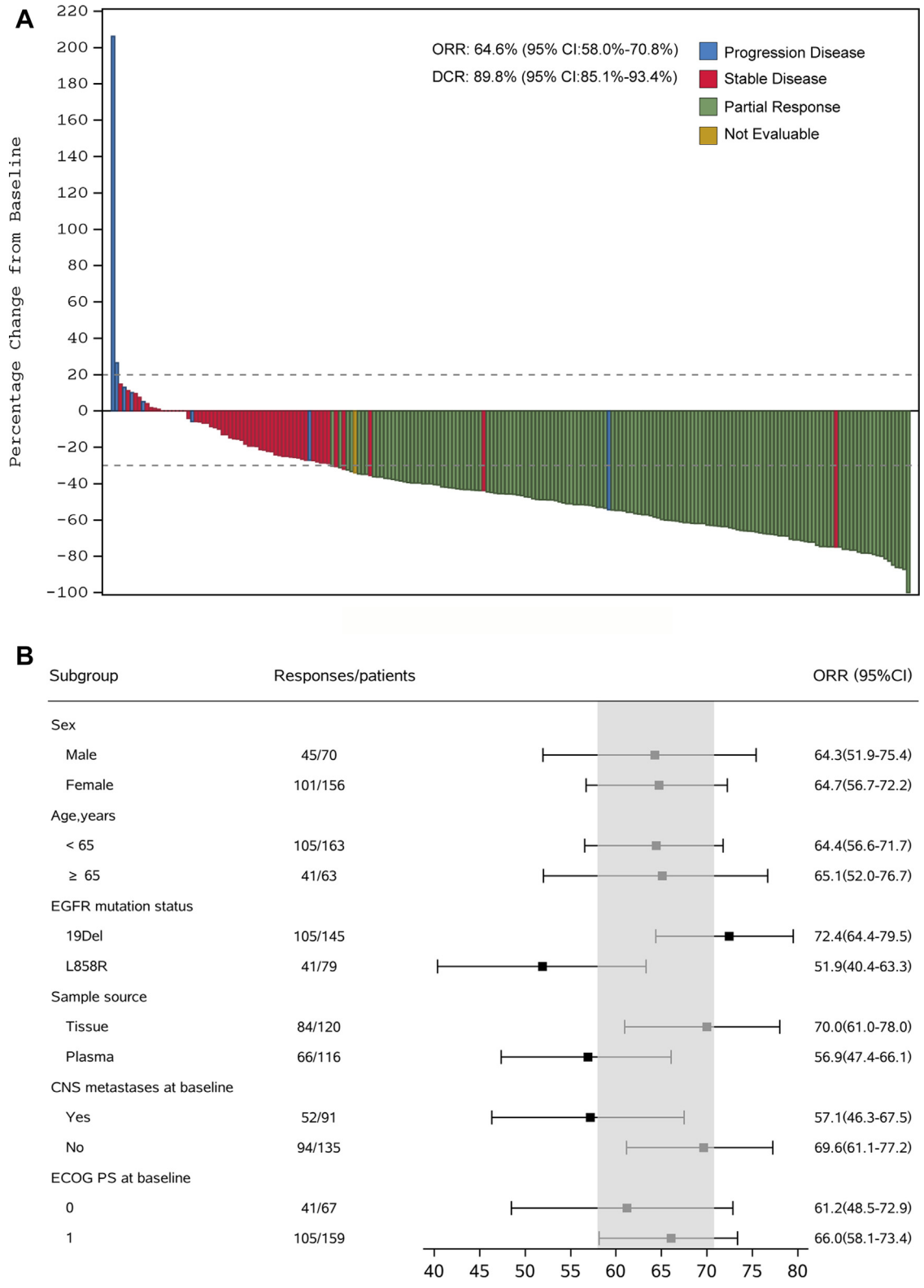

Figure 2. (*A*) Waterfall plot of percentage change in sum of tumor size by BICR in FAS. (*B*) Forest plot of subgroups of patients having objective responses in FAS. Note: The dashed line at 20% represents the boundary for determination of progressive disease, and the dashed line at -30% represents the boundary for determination of partial response. BICR, blinded independent center review; CI, confidence interval; CNS, central nervous system; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; ORR, objective response rate; PS, performance status.

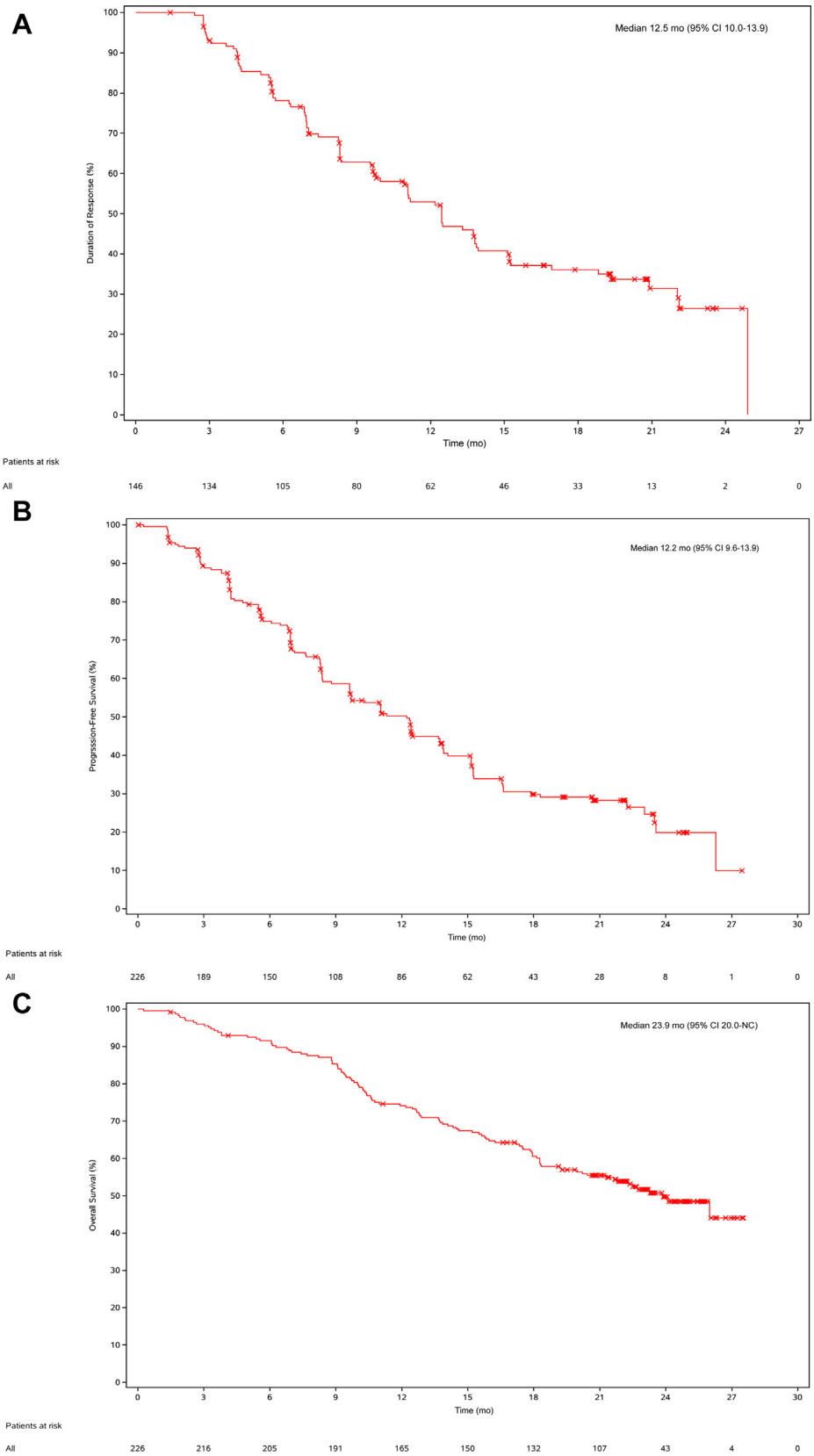

Figure 3. Kaplan-Meier curve of BICR-assessed (*A*) DoR in FAS; (*B*) PFS in FAS; and (*C*) OS in FAS. BICR, blinded independent center review; CI, confidence interval; DoR, duration of response; FAS, full analysis set; NC, not calculated; OS, overall survival; PFS, progression-free survival.

Table 3. Summary of Most Common TRAEs of Rezivertinib in FAS

TRAEs	Any Grade (%)	Grade ≥ 3 (%)
Decreased white blood cell count	63 (27.9)	2 (0.9)
Decreased platelet count	52 (23.0)	7 (3.1)
Anemia	51 (22.6)	4 (1.8)
Decreased neutrophil count	42 (18.6)	1 (0.4)
Increased aspartate aminotransferase	37 (16.4)	2 (0.9)
Increased alanine aminotransferase	27 (11.9)	2 (0.9)
Vomiting	24 (10.6)	2 (0.9)
Decreased appetite	23 (10.2)	0
Pruritus	20 (8.8)	0
Rash	20 (8.8)	0
Decreased lymphocyte count	19 (8.4)	5 (2.2)
Increased blood creatine phosphokinase	19 (8.4)	2 (0.9)
Diarrhea	17 (7.5)	0
Decreased weight	16 (7.1)	1 (0.4)
Increased blood creatinine	16 (7.1)	0
Leukopenia	16 (7.1)	1 (0.4)
Thrombocytopenia	15 (6.6)	1 (0.4)
Electrocardiogram QT prolonged	12 (5.3)	4 (1.8)
Increased amylase	12 (5.3)	0
Increased blood alkaline phosphatase	12 (5.3)	0
Hypertriglyceridemia	12 (5.3)	0
Decreased ejection fraction	10 (4.4)	4 (1.8)
Lymphopenia	10 (4.4)	5 (2.2)
Increased gamma-glutamyltransferase	9 (4.0)	4 (1.8)

Note: FAS would be used to analyze the safety data. TRAEs were graded by CTCAE version 4.03, and coded by MedDRA version 24.1. Data are indicated as n (%). Any-grade TRAE of 5% or higher and grades 3 to 5 TRAE of 1% or higher are reported.
CTCAE, Common Terminology Criteria for Adverse Events; FAS, full analysis set; TRAE, treatment-related adverse event.

(83.2%) (Supplementary Table 2). The most common TRAEs (any-grade TRAE of ≥5% and grade ≥3 TRAE of ≥1%) were decreased white blood cell count (63 of 226, 27.9%), decreased platelet count (52 of 226, 23.0%), anemia (51 of 226, 22.6%), decreased neutrophil count (42 of 226, 16.8%), increased AST (37 of 226, 16.4%), increased ALT (27 of 226, 11.9%), vomiting (24 of 226, 10.6%), and decreased appetite (23 of 226, 10.2%) (Table 3). No interstitial lung disease was reported.

Dose interruptions owing to any TEAEs were reported in 25 patients (11.1%), 21 (9.3%) of whom interrupted owing to TRAEs. Furthermore, 15 patients (6.6%) required dose reduction owing to any TEAEs, of whom 13 (5.8%) were owing to TRAEs. There were 14 patients (6.2%) who discontinued treatment owing to TEAEs, 11 (4.9%) of which were related to rezivertinib (Supplementary Table 2).

Discussion

In this phase 2b study, rezivertinib was found to have promising efficacy in *EGFR* T790M-mutated NSCLC patients and those patients with CNS metastases. The lower limit of the 95% CI for ORR was 58.0%, which was above the null hypothesis of 45%. Safety of rezivertinib was also favorable and manageable.

Until now, osimertinib remains the only worldwide-approved third-generation EGFR TKI and the standard of care for patients with *EGFR* T790M-mutated NSCLC. In the People's Republic of China, almonertinib and furmonertinib have also been approved by the National Medical Products Administration for the treatment of *EGFR* T790M-mutated NSCLC.[5–9] The greatest utility of third-generation EGFR TKIs in development will also be in the frontline setting.[11,12] Encouragingly, the patient enrollment of a phase 3 trial "REZOR" comparing rezivertinib to gefitinib in the first-line setting has been completed (NCT03866499).

The design of this study is similar to that of the osimertinib phase 2 study (AURA2).[13] The most critical efficacy data between osimertinib and rezivertinib are similar despite the different sample sources of the *EGFR* T790M detection test. In this study, 120 of 226 (53.1%) patients were identified as tumor tissue *EGFR* T790M positive and 116 of 226 (51.3%) were plasma *EGFR* T790M positive. The PFS in patients with tumor tissue *EGFR* T790M positive were significantly longer than those with plasma *EGFR* T790M positive (13.9 mo [95% CI: 11.3–17.9] versus 9.6 mo [95% CI: 7.0–11.0]; HR 0.53 [95% CI: 0.39–0.74], $p = 0.0002$). Patients with plasma *EGFR* T790M positive usually have shorter PFS compared with those negative ones.[10,14,15] In the AURA2 study, patients only with tissue *EGFR* T790M positive were enrolled, and the ORR of osimertinib was 70% (95% CI: 64%–77%), and the median PFS was 9.9 months (95% CI: 8.5–12.3).[13] In comparison, the ORR and the median PFS for rezivertinib in this study were 64.6% (95% CI: 58.0%–70.8%) and 12.2 months (95% CI: 9.6–13.9), respectively. The ORR of rezivertinib was slightly lower than that of osimertinib. One possible reason may be that the AURA2 study enrolled patients with tissue *EGFR* T790M positive only, whereas 51.3% of patients in this study were identified as plasma *EGFR* T790M positive. In the almonertinib, furmonertinib, befotertinib, and oritinib similar phase 2 study, only tissue or pleural effusion cells were required to confirm the *EGFR* T790M mutation in the inclusion criteria whereas tissue and plasma samples were allowed in limertinib phase 2 study, and the ORRs of almonertinib, furmonertinib, befotertinib, limertinib, and oritinib were 68.9% (95% CI: 62.6%–74.6%), 74% (95% CI: 68%–80%), 67.6% (95% CI: 61.9%–72.9%), 68.8% (95% CI:

63.2%–74.0%), and 60.4% (95% CI: 53.7%–66.8%), respectively. The median PFS was 12.4 months (95% CI: 9.7–15.0), 9.6 months (95% CI: 8.2–9.7), 12.5 months (95% CI: 11.1–13.8), 11.0 months (95% CI: 9.7–12.4), and 12.6 months (95% CI: 9.7–15.3), respectively.[6,7,16–18] In addition, patients with CNS metastases usually have worse efficacy compared with those without that.[6–13] The proportion of patients with CNS metastases was 41% in AURA2,[13] 37% in the almonertinib phase 2 study,[6] 48% in the furmonertinib phase 2b study,[7] 29% in the befotertinib phase 2 study,[16] 32.9% in the limertinib phase 2b study,[17] and 35.2% in the oritinib phase 2 study.[18] Despite a higher proportion (40%, 91 of 226) of patients with CNS metastases in this study, rezivertinib still had an encouraging overall ORR, DCR, and median PFS compared with other third-generation EGFR TKIs in similar phase 2 study.

Improved activity against CNS metastases is one of the advantages of osimertinib over first- and second-generation EGFR TKIs.[19–22] In a pooled analysis of AURA extension and AURA2 studies, CNS ORR and CNS DCR of osimertinib for 50 patients with more than or equal to one measurable CNS lesion were 54% (95% CI: 39%–68%) and 92% (95% CI: 81%–98%), respectively.[23] In the almonertinib phase 2 study, among 23 patients with assessable CNS metastases, the CNS ORR and CNS DCR were 60.9% (95% CI: 38.5%–80.3%) and 91.3% (95% CI: 72.0%–98.9%), respectively. The CNS PFS was 11.8 months (95% CI: 5.5–15.3).[6] In the phase IIb study of furmonertinib, 29 patients had more than or equal to one CNS lesion, the CNS ORR and CNS DCR were 66% (95% CI: 46.0%–82.0%) and 100%, the CNS PFS was 11.6 months (95% CI: 8.3–13.8).[7] In the befotertinib phase 2 study, among 21 patients with more than or equal to one measurable brain target lesion, CNS ORR and CNS DCR were 57.1% (95% CI: 34.0%–78.2%) and 100.0% (95% CI: 83.9%–100.0%), respectively.[16] In the limertinib phase 2b study, among 41 patients who had assessable CNS lesion, the CNS ORR and CNS DCR were 56.1% (95% CI: 39.7%–71.5%) and 100%, respectively. The CNS PFS was 10.6 months (95% CI: 5.6–not evaluable).[17] For the oritinib phase 2 study, among the 31 assessable patients who had measurable CNS lesions, the CNS ORR and CNS DCR were 35.5% (95% CI: 19.2%–54.6%) and 93.5% (95% CI: 78.6%–99.2%), respectively. The CNS PFS was only 4.3 months (95% CI: 4.1–6.9).[18] Compared with these third-generation EGFR TKIs, rezivertinib had a promising CNS efficacy in this phase 2b study; among 91 (40%) patients with CNS metastases, the median CNS PFS was 16.6 months (95% CI: 11.1–NC). Moreover, in the 29 patients who had more than or equal to one measurable CNS lesion, the CNS ORR and CNS DCR were 69.0% (95% CI: 49.2%–84.7%) and 100% (95% CI: 88.1%–100.0%), respectively.

In terms of safety, rezivertinib was associated with less treatment-related rash (8.8% for any grade) and diarrhea (7.5% for any grade) but more myelosuppression: decreased white blood cell count (27.9%), decreased platelet count (23.0%), anemia (22.6%), decreased neutrophil count (18.6%) for any grade when compared with results of osimertinib in the AURA2.[13] The incidence of TRAEs of more than or equal to three was 19.9% for rezivertinib in this study, compared with that 12% for osimertinib, 16.4% for almonertinib, 11% for furmonertinib, 29.3% for befotertinib, 34.6% for limertinib, and 15.4% for oritinib.[6,7,13,16–18] In addition, the occurrence rate of dose interruption owing to TEAE is 11.1% in this study compared with that of 21% in the AURA2.[13] Interstitial lung disease was found in 1% and 4% of patients in the AURA17 and AURA3 studies of osimertinib.[24,25] Grade more than or equal to three interstitial lung disease was observed in one patient in the phase 2b study of furmonertinib, two patients had interstitial lung disease of grade 3 after befotertinib treatment in phase 2 study, whereas interstitial lung disease was reported in one patient which belonged to grade 2 TRAE in the limertinib phase 2b study.[7,16,17] In this current study and the previous phase 1 study of rezivertinib, no interstitial lung disease was reported.[10]

It should be noted that, in the AURA2 study of osimertinib, the date of the last patient enrolled was October 27, 2014, and the date of data cutoff was November 1, 2015, whereas the article has only reported the safety data within approximately 12 months after the last patient was enrolled.[13] In this study, the date of the last patient enrolled was January 22, 2020, and the date of data cutoff was January 24, 2022. We reported the safety data of approximately 24 months after the last patient was enrolled. Even so, the safety data of rezivertinib are similar to those of osimertinib. Nevertheless, the time range of the safety data in this study is much longer than that of osimertinib in the AURA2 study. Yet, this is a single-arm study, and the subgroup analysis is not prespecified which was conducted on Chinese patients only. So, there might be a potential bias when compared with other ethnic patients.

In summary, this study revealed that rezivertinib, a third-generation EGFR TKI, had promising antitumor activity with an acceptable and manageable safety profile for patients with NSCLC with *EGFR* T790M mutation. Rezivertinib will potentially serve as a new option for the treatment of this patient population.

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.

Shiman Wu, Ke Wang, Shundong Cang, Wenxiu Yao, Yun Fan, Lin Wu, Meijuan Huang, Xingya Li, Yueyin Pan, Zhixiong Yang, Bo Zhu, Gongyan Chen, Jianhua Shi, Meili Sun, Jian Fang, Lijun Wang, Zhaohong Chen, Chunling Liu, Jingzhang Li, Jiwei Liu, Shenghua Sun, Yanqiu Zhao, Yanzhen Guo, Zili Meng, Zhefeng Liu, Zhigang Han, Hong Lu, Rui Ma, Sheng Hu, Guofang Zhao, Zheng Liu, Congying Xie, Diansheng Zhong, Hui Zhao, Huiqing Yu, Longzhen Zhang, Minghong Bi, Shanyong Yi, Shuliang Guo, Tienan Yi, Wen Li, Yingcheng Lin, Yongqian Shu, Zhendong Chen, Zhongliang Guo: Investigation, Resources, Data curation, Writing—review and editing.

Michael Greco: Conceptualization, Methodology, Resources, Data curation, Writing—review and editing, Supervision, Project administration.

Tingting Wang, Haijiao Shen: Conceptualization, Methodology, Validation, Formal analysis, Resources, Data curation, Writing—review and editing, Visualization, Supervision, Project administration.

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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.2022.08.015.

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