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ORIGINAL RESEARCH

Safety, pharmacokinetics, and efficacy of BPI-15086 in patients with *EGFR* T790M-mutated advanced non-small-cell lung cancer: results from a phase I, single-arm, multicenter study

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Background: Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) resistance frequently occurs in patients with non-small-cell lung cancer (NSCLC). *EGFR* Thr790Met mutation (T790M+) is seen in ∼50% of patients. We assessed the safety, tolerability, and pharmacokinetics (PK) of BPI-15086, a novel, ATP-competitive, irreversible, third-generation, mutation-selective EGFR-TKI in patients with *EGFR* T790M-mutated NSCLC.

Patients and methods: This two-center, phase I, dose-escalation study included patients who were 18-65 years old, with an Eastern Cooperative Oncology Group performance status of 0-2, with histologically or cytologically confirmed locally advanced or metastatic T790M+ NSCLC who were not surgical or radiotherapy candidates, and had imaging-identified disease progression after prior EGFR-TKIs. This dose-escalation study enrolled patients using a 3 + 3 study design. Patients received 25, 50, 100, 200, and 300 mg/day orally in 21-day cycles. The primary endpoints were safety, tolerability, and PK. Secondary endpoints were objective response rate (ORR) and disease control rate (DCR). The dose-expansion study was not conducted.

Results: We enrolled 17 patients from 29 December 2016 to 16 May 2018, in the safety and full analysis sets. All patients completed a single dosing trial, and no adverse events (AEs) causing drug discontinuation were seen. Grade 1-2 nausea, hypoalbuminemia, and decreased appetite were the most common treatment-related AEs. Grade 3 hyperglycemia was seen in one patient dosed at 300 mg/day. The ORR and DCR were 17.7% [95% confidence interval (CI) 3.8% to 43.4%] and 47.1% (95% CI 23.0% to 72.2%), respectively.

Conclusion: BPI-15086 is a safe and tolerable third-generation EGFR-TKI with a rationale for further clinical studies.

Key words: epidermal growth factor receptor, NSCLC, tyrosine kinase inhibitor, third generation

INTRODUCTION

Lung cancer is an exceptionally deadly disease accounting for ∼10 million deaths worldwide in 2020.[1] Non-small-cell lung cancer (NSCLC) represents ∼80% of those cases.[2] After the discovery of epidermal growth factor receptor (EGFR) in NSCLC,[3] specific EGFR-tyrosine kinase inhibitors (TKIs) were introduced in 2000.[4] The first-generation EGFR-TKIs, gefitinib and erlotinib, were molecularly targeted drugs to treat *EGFR*-mutated NSCLC with a median progression-free survival (PFS) of 9.7-10.8 months and a median overall survival (OS) of 19.3-30.5 months.[5-8] Icotinib, also a first-generation EGFR-TKI, was approved in China with a median PFS of 11.2 months and a median OS of 30.5 months.[9] Second-generation EGFR-TKIs were introduced, including afatinib and dacomitinib, which were irreversible inhibitors that covalently bound to *EGFR*.[10-12]

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The *EGFR* Thr790Met (T790M) mutation is the most common mechanism of acquired resistance to first- or second-generation EGFR-TKIs. Approximately 50% of patients develop resistance because of a secondary *EGFR* T790M mutation.[13-15] Alternative strategies of inhibiting *EGFR* T790M could be therapeutically efficacious, prompting preclinical and clinical development of third-generation EGFR-TKIs. Osimertinib is the first third-generation EGFR-TKI to be approved worldwide in patients with *EGFR* T790M-mutated metastatic NSCLC who progressed on first- or second-generation EGRF-TKIs. Osimertinib is an irreversible EGFR-TKI that inhibits sensitizing *EGFR* mutations and *EGFR* T790M resistance mutations, with lower activity against wild-type *EGFR*. Randomized controlled trials of osimertinib reported longer PFS and OS than first-generation TKIs in untreated *EGFR*-mutated patients, and favorable efficacy for *EGFR* T790M-mutated patients who had disease progression on prior EGFR-TKIs.[16-18] More recently, aumolertinib (formerly named as almonertinib), furmonertinib (formerly named as aflutinib), and lazertinib, all third-generation EGFR-TKIs, with different structural groups from osimertinib, were approved in patients with *EGFR* mutation-positive NSCLC for use in China and Korea.[19-23]

BPI-15086 is an ATP-competitive, irreversible *EGFR* T790M-mutant selective kinase inhibitor developed by Betta Pharmaceuticals Co., Ltd (Hangzhou, China). Preclinical studies have suggested that BPI-15086 showed selective inhibition for both *EGFR* and *EGFR* T790M mutations. At kinase level, the half-maximal inhibitory concentration (IC_{50}) of BPI-15086 against *EGFR* T790M was 15.7 nM, which was ∼30-fold that of wild-type *EGFR* (503 nM), exhibiting favorable selectivity and sensitivity (unpublished data). This finding provides evidence that BPI-15086 may function as a potential new third-generation EGFR-TKI. BPI-15086 was also demonstrated to be well tolerated in animals in preclinical studies (unpublished data). In this two-center, open-label, phase I trial, we aimed to evaluate the safety, tolerability, pharmacokinetics (PK), and efficacy of BPI-15086 in patients with *EGFR* T790M-mutated NSCLC.

PATIENTS AND METHODS

Study design and participants

This was a single-arm, open-label, multicenter, phase I study (NCT02914990) of BPI-15086 which was carried out in two centers around China. The study was planned as two parts: part 1 was a dose-escalation study with a 3 + 3 design to determine the dose-limiting toxicity (DLT), maximum tolerated dose (MTD), and recommended dose for part 2 based on safety, tolerability, and PK; part 2 was to be a dose-expansion study planned to further evaluate the safety, tolerability, and efficacy of BPI-15086 at the recommended dose. On 18 July 2019, the study was terminated, and there were no active patients on study when the study was terminated. Part 2 of the study was not conducted.

Patients with histologically or cytologically confirmed locally advanced or metastatic NSCLC who were not candidates for surgery or radiotherapy were included in this study. Other inclusion criteria were (i) imaging-identified disease progression after prior EGFR-TKI (e.g. gefitinib, erlotinib, icotinib, afatinib, and dacomitinib) therapy with one of the following criteria: *EGFR*-sensitive mutations (exon 19 deletion, exon 21 L858R or L861R mutation, G719X mutations); (ii) a clinical benefit from EGFR-TKI therapy according to the Jackman criteria; previous tertiary care or a *EGFR* T790M mutation after disease progression on EGFR-TKIs (dose-escalation study); (iii) available tumor tissues to confirm *EGFR* T790M mutations confirmed by a central laboratory after disease progression with EGFR-TKI therapy (dose-expansion study); (iv) male or female patients aged 18-65 years (18-75 years for the dose-expansion study); (v) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2; and (vi) an expected survival ≥12 weeks.

The main exclusion criteria were (i) a time from previous therapy that did not exceed 8 or 14 days or 5 half-lives (whichever is longer) with reversible first-generation EGFR-TKIs (erlotinib, gefitinib, and icotinib) or irreversible second-generation EGFR-TKIs (afatinib and dacomitinib), respectively; (ii) use of experimental or other anticancer drugs within 14 days of the first BPI-15086 dose; previous treatments with other third-generation EGFR-TKIs, including osimertinib, rociletinib, nazartinib (EGF816), olmutinib, ASP8273, and abivertinib (AC0010); (iii) patients with brain/meningeal metastases [except those with asymptomatic brain metastases, stable disease (SD) without the need for steroid therapy 4 weeks before the start of study drug]; (iv) previous interstitial lung disease, drug-induced interstitial disease, radiation pneumonia requiring hormone therapy, or any clinical evidence of active interstitial lung disease with imaging findings of idiopathic pulmonary fibrosis at baseline; and (v) uncontrolled massive pleural or pericardial effusion.

This study was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines, and the study protocols were approved by the ethics committees of Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, and Shanghai Chest Hospital. Written informed consent was obtained from all patients before enrollment.

Molecular analysis

All mutation analyses were carried out at the laboratory of Medical Oncology Department in Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College. DNA from tissue was extracted using the DNA FFPE Tissue Kit (Qiagen, Hilden, Germany). *EGFR* T790M mutation was detected by an amplification refractory mutation system (AmoyDx Co. Ltd., Xiamen, China).

Procedures

For the dose-escalation study, we used a 3 + 3 design (Figure 1). BPI-15086 was administered as an oral tablet on an empty stomach and was dosed once (qd) or twice (b.i.d.) daily. Patients received a single dose of the study drug on day 1. Safety and PK evaluations were carried out during this period (cycle 0). After 7 days, a 21-day continuous daily

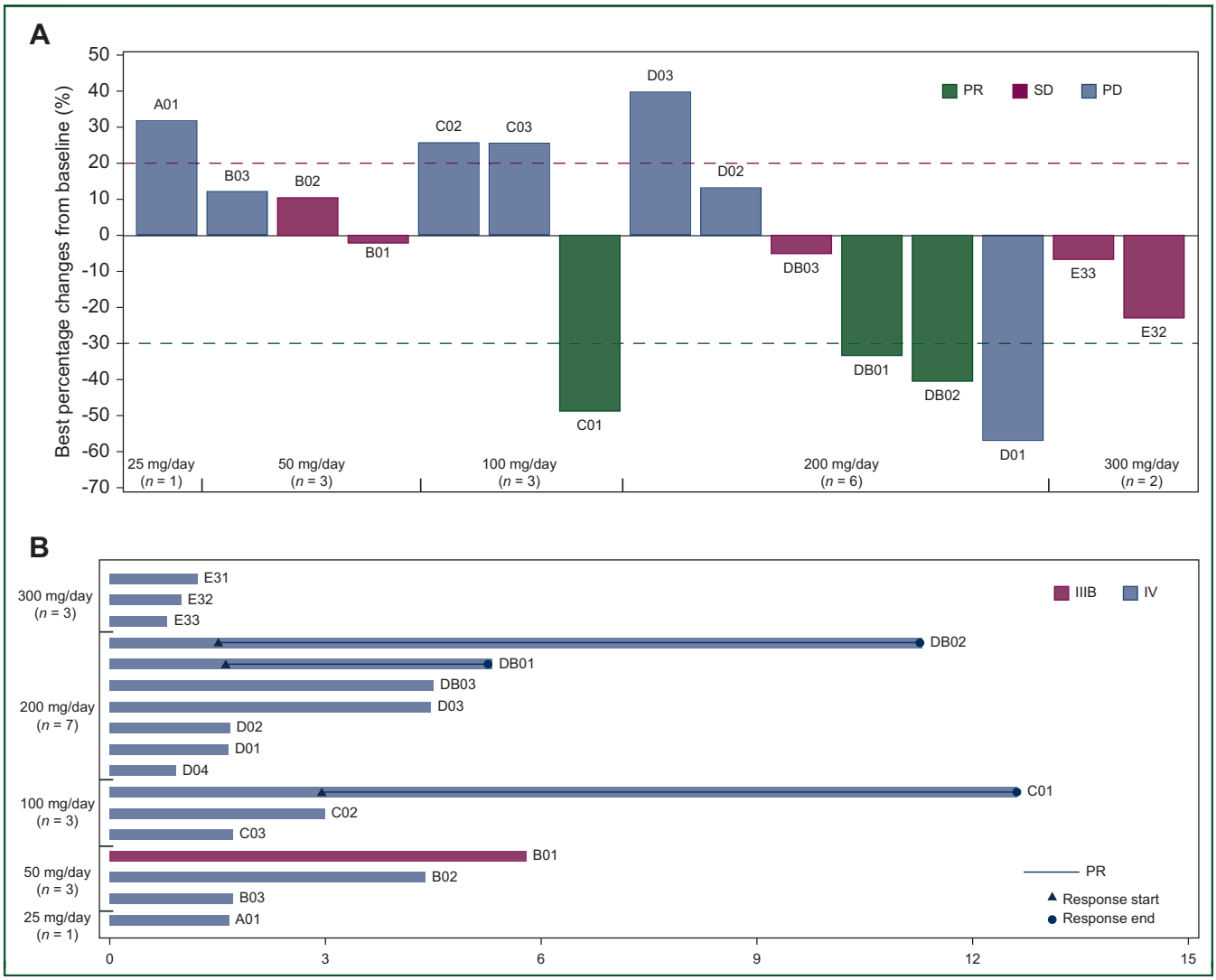

Figure 1. Graphical tumor response presentations after different patients were given various doses of BPI-15086.
The waterfall (A) shows the best change in the target lesions from baseline in 15/17 patients given different doses of the study drug. Two patients were excluded because lesions were not evaluated at baseline. The colors represent partial response (PR), stable disease (SD), and progressive disease (PD). The dashed lines at 20% and −30% represent the boundaries for PD (red) and PR (green). One patient in the 100-mg/day dosing group (C01) and two patients in the 200-mg/day dosing group (DB01 and DB02) showed a PR. One patient (D01) in the 200-mg/day group achieved PR for target lesion; however, this patient was finally evaluated as PD due to the new lesions. The swimmer plot (B) shows a graphical presentation of all 17 patients (full analysis set) divided by dosing group. The three patients with PR are shown with darker blue bars. The response start (triangle) and response end (circle) times are also shown. The blue color indicates stage IV, and the red color indicates the one patient with a stage IIIB tumor.

dosing schedule was initiated. Dose escalation was terminated if MTD was reached. The MTD was defined as the dose level immediately below that at which 33% of patients experienced a DLT from the first dose of study treatment (day 1, cycle 0) to the last dose of study treatment in cycle 1 (day 21).

The initial dose was daily dosing of 25 mg. The following dose cohorts received a 100% dose increase (50 mg, 100 mg, 200 mg), except for the last dose that reached 300 mg. If MTD or PK saturation was encountered, the study was moved to the expanded enrollment part, and patients received the determined dose for 21-day continuous dosing cycles.

Patients continued BPI-15086 treatment until disease progression as per the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). If a patient was experiencing a clinical benefit from the drug treatments, as assessed by RECIST v1.1 and PK evaluations in the high-dose group, high-dose treatments could be continued as long as there was agreement between the investigator, sponsor, and patient.

Endpoints and assessments

Primary endpoints were DLTs, MTDs, and PK. Secondary endpoints included clinical response by measuring the objective response rate (ORR), disease control rate (DCR), and evaluation of the relationship between BPI-15086 exposure and safety as well as efficacy parameters.

Safety and tolerability were assessed by the presence of adverse events (AEs) according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03). Efficacy evaluations were

carried out at baseline and cycles 2, 4, and 6, and then every 2 cycles until disease progression or intolerable toxicities occurred. Computed tomography (CT) or magnetic resonance imaging of the brain, CT of the neck, chest, and abdomen, and bone scans (carried out every eight cycles) were carried out for efficacy evaluation. Electrograms were assessed before and 1, 2, 4, 6, 10, and 24 h after the first dose in the dose-escalation study.

For the PK analysis, blood was obtained on cycle 0, at pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, and 144 h post-dose. During continuous dosing, blood was obtained on cycle 1 day 8, day 15 (both at pre-dose), and day 21 (at pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 h post-dose). During b.i.d. multiple doses, blood was collected at cycle 1 day 21 until 12 h post-dose. All blood samples were centrifuged to obtain plasma samples, and then were stored at -80°C before analysis. The PK parameters included the peak concentration (C_{max}), time to peak (T_{max}), terminal half-life ($T_{1/2}$), area under the plasma concentration—time curve ($AUC_{0\text{-}t}$), apparent clearance (CL/F), and apparent volume of distribution (Vz/F). Standard PK parameters were calculated by a noncompartmental method with WinNonlin v8.1 (Certara Inc., St. Louis, MO).

The ORR was defined as the number of patients who had a complete response (CR) or partial response (PR) confirmed with an imaging every 6 weeks. The DCR was defined as the number of patients with a best overall response of patients with CR, PR, or SD confirmed with an imaging every 6 weeks. The exploratory assessments were PFS, OS, and duration of response (DOR). PFS was defined as the time from the first drug administration to the onset of disease progression or death, whichever occurs first. OS was defined as the time from the first drug administration to all-cause death. DOR was defined as the time from the first CR or PR assessment to the first progressive disease (PD) assessment or death from any cause.

Statistical analysis

For the dose-escalation arm of the study, using the 3 + 3 design, cohorts of 3-6 patients were required at each dose level.

All analyses were carried out by dose group based on observed data, and no data filling (no outliers) was carried out. All patients who had received at least one dose of BPI-15086 were included in the safety set (SS) for safety assessment. All patients who had received at least one dose of BPI-15086 and who did not significantly violate the enrollment criteria were enrolled for efficacy analysis (full analysis set, FAS). All patients who had received at least one dose of BPI-15086 and who had PK data carried out on plasma were included in the PK set. Finally, all patients with good study adherence, defined as $\geq$ 70% in the FAS, and who had all major efficacy indicators available with no major protocol deviations, were included in the per-protocol set (PPS).

Descriptive statistics were used for analyses, and all analyses were based on observed data. For quantitative data, the means $\pm$ standard deviations were used for normally distributed data, and the median and quartiles were used for non-normally distributed data. Minimum and maximal values with 95% confidence intervals (CIs) were also determined. All statistical analyses were carried out with SAS software, v. 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Patient baseline characteristics

Between 29 December 2016 and 16 May 2018, 36 patients were screened; 19 failed screening, and 17 were successfully screened and enrolled in the phase I dose-escalation study. Each patient was administered at least one dose of BPI-15086.

Patient baseline characteristics are shown in Table 1. In the FAS population, all had previous EGFR-TKI treatment and *EGFR* T790M mutation. The median age was 56 years (range, 47-64 years), with 6 males (35.3%) and 11 females (64.7%). Twelve (70.6%) had an ECOG PS of 0, and five (29.4%) had an ECOG PS of 1. Sixteen (94.1%) had adenocarcinoma, and one (5.9%) had squamous cell carcinoma.

Safety

All 17 patients were enrolled in the SS and completed a single dosing trial, and all recorded at least one treatment-related adverse event (TRAE) (Table 2). No DLTs were observed during the 28-day evaluation period (7 days after administration of a single dose and 21 days of daily dosing) at any dose level, and thus the MTD was not reached. No AEs

Table 1. Patient baseline characteristics in FAS

	All patients (n = 17)
Age, years, median	56 (47-64)
Sex	
Male	6 (35.3)
Female	11 (64.7)
ECOG PS	
0	12 (70.6)
1	5 (29.4)
Staging	
IIIB	1 (5.9)
IV	16 (94.1)
Metastatic lesions	
Intrapulmonary	10 (58.8)
Liver	4 (23.5)
Brain	9 (52.9)
Bone	7 (41.2)
Lymph node	14 (82.4)
Adrenal	1 (5.9)
Other	4 (23.5)
Histologic type	
Adenocarcinoma	16 (94.1)
Squamous cell carcinoma	1 (5.9)
Previous treatment	
Chemotherapy	10 (58.8)
EGFR-TKIs	17 (100.0)
Radiotherapy	4 (23.5)
Other	2 (11.8)

Data are presented as median (range) or n (%), unless otherwise stated.
ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; FAS, full analysis set; PS, performance status; TKI, tyrosine kinase inhibitor.

Table 2. Treatment-related adverse events in the dose escalation

	25 mg/day (n = 1)	50 mg/day (n = 3)	100 mg/day (n = 3)	200 mg/day (n = 7)	300 mg/day (n = 3)	All (n = 17)
All grades	1 (100.0)	2 (66.7)	3 (100.0)	7 (100.0)	3 (100.0)	16 (94.1)
Nausea	0	1 (33.3)	1 (33.3)	1 (14.3)	3 (100.0)	6 (35.3)
Decreased appetite	1 (100.0)	0	0	1 (14.3)	3 (100.0)	5 (29.4)
Hypoalbuminemia	0	0	0	5 (71.4)	0	5 (29.4)
Elevated serum creatinine	0	1 (33.3)	1 (33.3)	2 (28.6)	0	4 (23.5)
Elevated blood uric acid	0	0	1 (33.3)	3 (42.9)	0	4 (23.5)
Vomiting	0	0	1 (33.3)	1 (14.3)	2 (66.7)	4 (23.5)
Proteinuria	0	0	0	3 (42.9)	0	3 (17.6)
Elevated blood glucose	0	1 (33.3)	0	2 (28.6)	0	3 (17.6)
Decreased total protein	0	0	1 (33.3)	2 (28.6)	0	3 (17.6)
Diarrhea	0	0	0	2 (28.6)	1 (33.3)	3 (17.6)
Hyperglycemia	0	0	0	0	3 (100.0)	3 (17.6)
Anemia	0	0	0	3 (42.9)	0	3 (17.6)
Elevated γ-glutamyltransferase	0	0	0	2 (28.6)	0	2 (11.8)
Elevated ALT	0	0	0	1 (14.3)	1 (33.3)	2 (11.8)
Elevated conjugated bilirubin	0	0	0	2 (28.6)	0	2 (11.8)
Elevated blood triglycerides	0	0	0	2 (28.6)	0	2 (11.8)
Grade 3 and 4	0	0	0	0	1 (33.3)	1 (5.9)
Hyperglycemia	0	0	0	0	1 (33.3)	1 (5.9)

Data are presented as n (%). Treatment-related adverse events (all grades) occurred in 10% or more of patients, and all grade 3 and 4 events are presented.
ALT, alanine aminotransferase.

leading to drug discontinuation were observed. The most common TRAEs were nausea (35.3%, 6/17), hypoalbuminemia (29.4%, 5/17), decreased appetite (29.4%, 5/17), vomiting (23.5%, 4/17), elevated serum creatinine (23.5%, 4/17), elevated blood uric acid (23.5%, 4/17), diarrhea (17.6%, 3/17), proteinuria (17.6%, 3/17), elevated blood glucose (17.6%, 3/17), decreased total protein (17.6%, 3/17), hyperglycemia (17.6%, 3/17), anemia (17.6%, 3/17), elevated γ-glutamyltransferase (11.8%, 2/17), elevated alanine aminotransferase (11.8%, 2/17), elevated conjugated bilirubin (11.8%, 2/17), and elevated blood triglycerides (11.8%, 2/17). All TRAEs were grades 1-2, except for one patient in the 300-mg dose group who had grade 3 hyperglycemia. Serious AEs were observed in two patients (11.8%), while one (hyperglycemia) was considered to be treatment-related in the 300-mg/day group.

Pharmacokinetics

The C_{max} and $AUC_{0\text{-}t}$ of BPI-15086 increased in a dose-dependent manner across the range from 25 to 300 mg after single dose and multiple doses (Table 3). Median T_{max} was 1.97-4.02 h post-dose across the lowest to highest doses and the mean apparent terminal elimination half-life ($t_{1/2}$) was 9.91-14.1 h. BPI-15086 reached a steady state in plasma after 21 days of multiple doses with a $T_{max,ss}$ of 2.02-3.00 h and a $C_{max,ss}$ of 24.6-924 ng/ml. These values were not significantly changed in the multiple doses compared with the single dose, except for C_{max} in the 300-mg qd dose. For 300-mg qd dose, the C_{max} was 924 ng/ml after multiple doses and 354 ng/ml after single dose, suggesting that there displayed some accumulation. At steady state, the mean apparent oral clearance (CL_{ss}/F) was 49.3-166 l/h, the mean $t_{1/2}$ was 4.78-9.84 h, and the mean Vz/F was

Table 3. Pharmacokinetic parameters of BPI-15086 after single administration and multiple dosing for 21 days

	25 mg qd	50 mg qd	100 mg qd	100 mg b.i.d.	200 mg qd	300 mg qd
Single dose	n = 1	n = 3	n = 3	—	n = 7	n = 3
$AUC_{0\text{-}24\ h}$, h × ng/ml	285 (NA)	324 (47.7)	580 (37.3)	—	2630 (91.2)	3860 (41.3)
C_{max}, ng/ml	31.6 (NA)	31.3 (40.1)	46.1 (34.7)	—	273 (97.8)	354 (29.5)
T_{max}, h	1.97 (1.97-1.97)	2.93 (2.02-4.05)	3.00 (2.03-4.00)	—	4.02 (2.02-5.13)	4.00 (3.98-5.00)
$t_{1/2}$, h	12.2 (NA)	13.4 (35.2)	11.3 (23.3)	—	9.91 (15.5)	14.1 (58.6)
Multiple doses	n = 1	n = 3	n = 3	n = 3	n = 3	n = 1
AUC_{ss}, h × ng/ml	297 (NA)	462 (54.3)	911 (58.2)	1830 (49.1)	2460 (70.2)	6090 (NA)
$C_{max,ss}$, ng/ml	24.6 (NA)	48.5 (64.3)	84.6 (65.6)	240 (37.9)	209 (71.1)	924 (NA)
$T_{max,ss}$, h	2.88 (2.88-2.88)	2.08 (2.02-4.00)	3.00 (2.00-3.95)	2.98 (2.03-3.00)	2.02 (1.98-3.00)	2.02 (2.02-2.02)
MR_{ss}	0.045 (NA)	0.063 (12.7)	0.051 (10.5)	0.043 (25.5)	0.103 (25.4)	0.046 (NA)
R_{ac}	1.04 (NA)	1.38 (11.4)	1.47 (38.4)	1.28 (65.3)	1.23 (26.5)	1.60 (NA)
CL_{ss}/F, l/h	84.1 (NA)	150 (77)	166 (87.2)	70 (67.5)	108 (53.8)	49.3 (NA)
$t_{1/2}$, h	ND	8.94 (NA)	ND	4.78 (NA)	9.09 (1.51)	9.84 (NA)
V_z/F, l	1540 (NA)	2820 (33.2)	3830 (102)	556 (46.9)	1910 (64.4)	700 (NA)

Data represent the arithmetic mean (percentage coefficient of variation) except for T_{max} and $T_{max,ss}$, which are the median (range).
AUC, area under the plasma concentration—time curve; $C_{max,}$ maximum plasma concentration; CL_{ss}/F, apparent oral clearance; MRss, metabolic ratio (M7-1/BPI-15086) based on AUC at steady state; NA, not applicable; ND, not determined; R_{ac}, accumulation ratio based on AUC_{ss}; T_{max}, time to reach C_{max}; $T_{max,ss}$, time to reach C_{max} at steady state; $t_{1/2}$, apparent terminal elimination half-life; V_z/F, apparent volume of distribution.

556-3830 l. The mean $t_{1/2}$ of the multiple qd dosing group was not significantly different from that of the single dosing group. The accumulation ratios (Rac) of AUC0-24 h were 1.04-1.60. M7-1 was the major metabolite, with AUC_{ss} values that were 4.3%-10.3% of the BPI-15086.

Efficacy

All 17 patients were included in the FAS for efficacy analysis. At data cut-off date on 7 March 2019, three (17.6%) had a confirmed PR, five (29.4%) had SD, seven (41.2%) had PD, and two (11.8%) could not be assessed for response (Table 4 and Figure 1). The ORR was 17.6% (95% CI 3.8% to 43.4%) and the DCR was 47.1% (95% CI 23.0% to 72.2%). For the one patient of the 25-mg/day dose group, no response was observed. The DCRs of the 50-mg/day, 100-mg/day, 200-mg/day, and 300-mg/day groups were 66.7% (95% CI 9.4% to 99.2%) in 2/3 patients, 33.3% (95% CI 0.8% to 90.6%) in 1/3 patients, 42.9% (95% CI 9.9% to 81.6%) in 3/7 patients, and 66.7% (95% CI 9.4% to 99.2%) in 2/3 patients, respectively. PR was seen in one (33.3%) and two (28.6%) patients of the 100-mg/day and 200-mg/day groups, respectively. No patients showed CR and none of the patients in the 25-mg/day, 50-mg/day, and 300-mg/day groups experienced PR. SD was noted in two (66.7%), one (14.3%), and two (66.7%) patients of the 50-mg/day, 200-mg/day, and 300-mg/day groups, respectively. PD was seen in one (100%), one (33.3%), two (66.7%), and three (42.9%) patients of the 25-mg/day, 50-mg/day, 100-mg/day, and 200-mg/day groups, respectively. None of the three patients in the 300-mg/day group showed PD.

The median DOR was 9.7 months (95% CI 3.7-9.8 months) (Table 4 and Supplementary Figure S1A, available at https://doi.org/10.1016/j.esmoop.2022.100473). The median PFS and OS for all patients were 1.6 months (95% CI 1.6-5.3 months) and 15.0 months (95% CI 8.34-16.1 months), respectively (Table 4 and Supplementary Figure S1B and C, available at https://doi.org/10.1016/j.esmoop.2022.100473). The median DOR for the 100-mg/day and 200-mg/day groups was 9.7 months [95% CI not estimable (NE)-NE] and 6.7 months (95% CI 3.7-9.8 months), respectively. The median PFS for the 25-mg/day, 50-mg/day, 100-mg/day, and 200-mg/day dose groups was 1.5 months (95% CI could not be estimated), 4.3 months (95% CI 1.6-5.8 months), 1.6 months (95% CI 1.5-12.6 months), and 3.0 months (95% CI 1.6-11.3 months), respectively. The median PFS for the 300-mg/day group could not be estimated.

In the PPS, 13 patients in the FAS were response-assessable. The ORR was 23.1% (95% CI 5.0% to 53.8%) and the DCR was 46.2% (95% CI 19.2% to 74.8%) in the escalation cohort. The median DOR was 9.7 months (95% CI 3.7-9.8 months). The median PFS and OS were 1.6 months (95% CI 1.6-5.3 months) and 15.0 months (95% CI 8.4-16.1 months), respectively (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100473).

DISCUSSION

This study examined the safety, PK, and efficacy of BPI-15086 in patients with *EGFR* T790M-mutated advanced NSCLC after previous EGFR-TKI therapy. The results of this study showed that BPI-15086 was safe, with good tolerability and preliminary efficacy.

Since EGFRs are normally present in gastrointestinal and skin tissues, cutaneous and gastrointestinal toxicities are often seen with EGFR-TKIs.[24] In our study, the most common TRAEs were nausea, decreased appetite, and hypoalbuminemia. Hypoalbuminemia was seen in 29% of patients in our study, compared with 75% of patients having this AE in a phase II osimertinib trial.[25] One grade 4 treatment-related interstitial lung disease with almonertinib was reported.[19] Of other third-generation EGFR-TKIs, rash/pruritis (lazertinib) and rash/diarrhea [nazartinib and abivertinib (AC0010)] were reported to be the most common TRAEs.[26-28] Notably, we only observed 3/17 patients with diarrhea and no patient with rash/pruritis, which suggests a different safety profile for BPI-15086 compared with other third-generation EGFR-TKIs.

In our study, BPI-15086 showed preliminary efficacy in treating patients with *EGFR* T790M-mutated NSCLC, who had progressed on first-generation EGFR-TKIs. The ORR in the FAS

Table 4. Summary of efficacy in FAS (n = 17)

	25 mg/day (n = 1)	50 mg/day (n = 3)	100 mg/day (n = 3)	200 mg/day (n = 7)	300 mg/day (n = 3)	All (n = 17)
Best overall response						
Complete response	0	0	0	0	0	0
Partial response	0	0	1 (33.3)	2 (28.6)	0	3 (17.6)
Stable disease	0	2 (66.7)	0	1 (14.3)	2 (66.7)	5 (29.4)
Progressive disease	1 (100.0)	1 (33.3)	2 (66.7)	3 (42.9)	0	7 (41.2)
Not evaluable	0	0	0	1 (14.3)	1 (33.3)	2 (11.8)
ORR, n (%) [95% CI]	0 (0.0) [0.0-97.5]	0 (0.0) [0.0-70.8]	1 (33.3) [0.8-90.6]	2 (28.6) [3.7-71.0]	0 (0.0) [0.0-70.8]	3 (17.6) [3.8-43.4]
DCR, n (%) [95% CI]	0 (0.0) [0.0-97.5]	2 (66.7) [9.4-99.2]	1 (33.3) [0.8-90.6]	3 (42.9) [9.9-81.6]	2 (66.7) [9.4-99.2]	8 (47.1) [23.0-72.2]
PFS (months), median (95% CI)	1.5 (NE-NE)	4.3 (1.6-5.8)	1.6 (1.5-12.6)	3.0 (1.6-11.3)	NE (NE-NE)	1.6 (1.6-5.3)
OS (months), median (95% CI)	NE (NE-NE)	15.0 (8.4-15.0)	16.1 (NE-NE)	NE (NE-NE)	9.2 (NE-NE)	15.0 (8.4-16.1)
DOR (months), median (95% CI)	—	—	9.7 (NE-NE)	6.7 (3.7-9.8)	—	9.7 (3.7-9.8)

Data are presented as n (%) or n (% [95% CI]) for all assessable patients, defined as those who were ongoing with study treatment and had at least one post-baseline response assessment at the time of data cut-off, or who had discontinued study treatment.

—, not applicable; CI, confidence interval; DCR, disease control rate; DOR, duration of response; FAS, full analysis set; NE, not estimable; ORR, objective remission rate; OS, overall survival; PFS, progression-free survival.

was 17.6%, with PR observed in the 100-mg/day (one patient) and 200-mg/day groups (two patients). The DCR was 47.1%. Osimertinib is effective for patients with metastatic *EGFR* T790M+ NSCLC that progressed during or after first-line EGFR-TKI therapy, with an ORR of 61%-71% and a median PFS of 9.6-15.2 months.[18,29-31] Furthermore, osimertinib has showed superior central nervous system activity to first- and second-generation EGFR-TKIs, with an intracranial ORR of 54% and an intracranial DCR of 92%.[32] Almonertinib had an ORR of 50%, a DCR of 89%, and a PFS of 9.6 months in a phase I trial,[19] and was approved by the National Medical Products Administration (NMPA) of China as second-line treatment for patients with *EGFR* T790M-mutated NSCLC on 17 March 2020. Besides, the updated ORR was 68.9% and intracranial ORR was 60.9% in *EGFR* T790M+ advanced NSCLC after progression on prior EGFR-TKI therapy.[33] Recently, furmonertinib (formerly named as flumertinib) was approved by the NMPA of China as second-line treatment for patients with *EGFR* T790M-mutated NSCLC on 3 March 2021. The ORR and median PFS were 74% and 9.6 months, respectively.[22] BPI-15086 also showed preliminary efficacy, with favorable tolerability profile. Further studies are warranted to confirm the efficacy and safety of BPI-15086.

There are several limitations to this study that should be mentioned. The sample size is relatively small, and only dose-escalation study was conducted. Future studies with larger sample size and dose expansion are warranted.

In conclusion, the third-generation irreversible EGFR-TKI BPI-15086 is safe and tolerable, with preliminary efficacy for patients with *EGFR* T790M-mutated locally advanced or metastatic NSCLC who progressed on previous first- or second-generation EGFR-TKIs. A further study (NCT03452150) is ongoing in the hope of finding a better candidate to treat patients with NSCLC.

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DISCLOSURE

LD, YW, LC, HL, LL, and XC are employees of Betta Pharmaceuticals Co., Ltd. All other authors have declared no conflicts of interest.

DATA SHARING

Data are available upon reasonable request.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
2. Chan BA, Hughes BG. Targeted therapy for non-small cell lung cancer: current standards and the promise of the future. *Transl Lung Cancer Res*. 2015;4(1):36-54.
3. Cerny T, Barnes DM, Hasleton P, et al. Expression of epidermal growth factor receptor (EGF-R) in human lung tumours. *Br J Cancer*. 1986;54(2):265-269.
4. Kris MG, Herbst R, Rischin D, et al. Objective regressions in non-small cell lung cancer patients treated in phase I trials of oral ZD1839 (IressaTM), a selective tyrosine kinase inhibitor that blocks the epidermal growth factor receptor (EGFR). *Lung Cancer*. 2000;29(suppl 1):72.
5. Kris MG, Natale RB, Herbst RS, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. *JAMA*. 2003;290(16):2149-2158.
6. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*. 2005;353(2):123-132.
7. 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(25):2380-2388.
8. 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(3):239-246.
9. 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(10):2443-2450.
10. Park K, Tan EH, O'Byrne K, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. *Lancet Oncol*. 2016;17(5):577-589.
11. Mok TS, Cheng Y, Zhou X, et al. Updated overall survival in a randomized study comparing dacomitinib with gefitinib as first-line treatment in patients with advanced non-small-cell lung cancer and EGFR-activating mutations. *Drugs*. 2021;81(2):257-266.
12. 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(11):1454-1466.
13. Suda K, Onozato R, Yatabe Y, Mitsudomi T. EGFR T790M mutation: a double role in lung cancer cell survival? *J Thorac Oncol*. 2009;4(1):1-4.
14. Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. *PLoS Med*. 2005;2(3):e73.
15. 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(8):786-792.
16. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, *EGFR*-mutated advanced NSCLC. *N Engl J Med*. 2020;382(1):41-50.
17. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378(2):113-125.
18. Jänne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med*. 2015;372(18):1689-1699.
19. 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(12):1907-1918.
20. Lu S, Wang Q, Zhang G, et al. Abstract CT190: A multicenter, open-label, single-arm, phase II study: the third generation EGFR tyrosine kinase inhibitor almonertinib for pretreated EGFR T790M-positive locally advanced or metastatic non-small cell lung cancer (APOLLO). *Cancer Res*. 2020;80(16_supplement):CT190.
21. 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(6):1015-1026.
22. 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(8):829-839.
23. 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(5):740-763.
24. Hirsh V. Managing treatment-related adverse events associated with egfr tyrosine kinase inhibitors in advanced non-small-cell lung cancer. *Curr Oncol*. 2011;18(3):126-138.
25. Nakao A, Hiranuma O, Uchino J, et al. Final results from a phase II trial of osimertinib for elderly patients with epidermal growth factor receptor t790m-positive non-small cell lung cancer that progressed during previous treatment. *J Clin Med*. 2020;9(6):1762.
26. Tan DS, Leighl NB, Riely GJ, et al. Safety and efficacy of nazartinib (EGF816) in adults with EGFR-mutant non-small-cell lung carcinoma: a multicentre, open-label, phase 1 study. *Lancet Respir Med*. 2020;8(6):561-572.
27. Ahn MJ, Han JY, Lee KH, et al. Lazertinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: results from the dose escalation and dose expansion parts of a first-in-human, open-label, multicentre, phase 1-2 study. *Lancet Oncol*. 2019;20(12):1681-1690.
28. Ma Y, Zheng X, Zhao H, et al. First-in-human phase I study of AC0010, a mutant-selective EGFR inhibitor in non-small cell lung cancer: safety, efficacy, and potential mechanism of resistance. *J Thorac Oncol*. 2018;13(7):968-977.
29. 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(12):1643-1652.
30. Yang JC, 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(12):1288-1296.
31. Mok TS, Wu Y-L, Ahn M-J, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med*. 2017;376(7):629-640.
32. 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. *Ann Oncol*. 2018;29(3):687-693.
33. 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(3):411-422.