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
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 EGFR-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 aflumertinib), and lazerinib, 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 (IC50) 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) with one of the following criteria: EGFR-sensitive mutations (exon 19 deletion, exon 21 L858R or L858R 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
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 (Cmax), time to peak (Tmax), terminal half-life (T1/2), area under the plasma concentration–time curve (AUC0-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 ≥ 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 ± 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.
leading to drug discontinuation were observed. The most common TRAEs were nausea (35.3%, 6/17), hypoproteinemia (29.4%, 5/17), decreased appetite (29.4%, 5/17), vomiting (23.5%, 4/17), elevated alanine transaminase (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.

### Pharmacokinetics

The C\text{max} and AUC\text{0-12 h} 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\text{max} was 1.97-4.02 h post-dose across the lowest to highest doses and the mean apparent terminal elimination half-life (T\text{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\text{max,ss} of 2.02-3.00 h and a C\text{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\text{max} in the 300-mg qd dose. For 300-mg qd dose, the C\text{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 (C\text{L(F)} was 49.3-166 l/h, the mean T\text{1/2} was 4.78-9.84 h, and the mean V\text{z(F) was }

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

| Dose     | All (n = 17) | Nausea (n = 17) | Decreased appetite (n = 17) | Hypoalbuminemia (n = 17) | Elevated serum creatinine (n = 17) | Elevated blood uric acid (n = 17) | Vomiting (n = 17) | Proteinuria (n = 17) | Elevated blood glucose (n = 17) | Decreased total protein (n = 17) | Diarrhea (n = 17) | Hyperglycemia (n = 17) | Anemia (n = 17) | Elevated \( \gamma \)-glutamyltransferase (n = 17) | Elevated ALT (n = 17) | Elevated conjugated bilirubin (n = 17) | Elevated blood triglycerides (n = 17) | Grade 3 and 4 (n = 17) | Hyperglycemia (n = 17) |
|----------|--------------|-----------------|-----------------------------|--------------------------|-----------------------------------|----------------------------------|-------------------|----------------------|-------------------------------|-----------------------------|------------------|------------------------|----------------|---------------------------------|------------------|---------------------------------|-------------------------------|-----------------------|----------------------|
| 25 mg/day| All (n = 17) | 1 (100.0)       | 0 (0.0)                     | 0 (0.0)                  | 0 (0.0)                           | 0 (0.0)                          | 0 (0.0)           | 0 (0.0)              | 0 (0.0)                       | 0 (0.0)                     | 0 (0.0)          | 0 (0.0)                 | 0 (0.0) | 0 (0.0)                           | 0 (0.0)          | 0 (0.0)                           | 0 (0.0)                     | 0 (0.0)             | 0 (0.0)              |
| 50 mg/day| All (n = 17) | 2 (66.7)        | 1 (33.3)                    | 1 (33.3)                 | 0 (0.0)                           | 2 (66.7)                         | 0 (0.0)           | 2 (66.7)             | 2 (66.7)                      | 1 (33.3)                    | 0 (0.0)          | 1 (33.3)                | 0 (0.0) | 1 (33.3)                           | 0 (0.0)          | 1 (33.3)                           | 0 (0.0)                     | 1 (33.3)            | 1 (33.3)          |
| 100 mg/day| All (n = 17) | 3 (100.0)       | 3 (100.0)                   | 3 (100.0)                | 3 (100.0)                         | 3 (100.0)                        | 3 (100.0)        | 3 (100.0)            | 3 (100.0)                     | 3 (100.0)                   | 3 (100.0)       | 3 (100.0)               | 3 (100.0) | 3 (100.0)                          | 3 (100.0)       | 3 (100.0)                          | 3 (100.0)                     | 3 (100.0)          | 3 (100.0)          |
| 200 mg/day| All (n = 17) | 7 (100.0)       | 7 (100.0)                   | 7 (100.0)                | 7 (100.0)                         | 7 (100.0)                        | 7 (100.0)        | 7 (100.0)            | 7 (100.0)                     | 7 (100.0)                   | 7 (100.0)       | 7 (100.0)               | 7 (100.0) | 7 (100.0)                          | 7 (100.0)       | 7 (100.0)                          | 7 (100.0)                     | 7 (100.0)        | 7 (100.0)          |
| 300 mg/day| All (n = 17) | 3 (100.0)       | 3 (100.0)                   | 3 (100.0)                | 3 (100.0)                         | 3 (100.0)                        | 3 (100.0)        | 3 (100.0)            | 3 (100.0)                     | 3 (100.0)                   | 3 (100.0)       | 3 (100.0)               | 3 (100.0) | 3 (100.0)                          | 3 (100.0)       | 3 (100.0)                          | 3 (100.0)                     | 3 (100.0)        | 3 (100.0)          |

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.
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 three (25-mg/day, 50-mg/day, and 300-mg/day groups) patients of the 100-mg/day and 200-mg/day groups, respectively. PR was seen in 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 for the 300-mg/day group could not be estimated. 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), 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. In our study, the most common TRAEs were nausea, decreased appetite, and hyypoalbuminemia. Hyypoalbuminemia was seen in 29% of patients in our study, compared with 75% of patients having this AE in a phase II osimertinib trial. One grade 4 treatment-related interstitial lung disease with almonertinib was reported. Of other third-generation EGFR-TKIs, rash/pruritis (lazertinib) and rash/diarrhea [nazartinib and abivertinib (AC0010)] were reported to be the most common TRAEs. 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 | 1 (33.3) | 2 (28.6) | 0 | 3 (17.6) |
| Partial response | 0 | 0 | 1 (33.3) | 2 (28.6) | 0 | 3 (17.6) |
| Stable disease | 0 | 0 | 1 (33.3) | 2 (28.6) | 0 | 3 (17.6) |
| Progressive disease | 1 (100.0) | 1 (33.3) | 2 (66.7) | 3 (42.9) | 0 | 7 (41.2) |
| Not evaluable | 0 | 0 | 1 (33.3) | 2 (66.7) | 0 | 3 (17.6) |
| ORR, n (%) (95% CI) 0.0-0.975.95% CI | 0 (0.0) | 0.0-0.708 | 1 (33.3) | 0.8-90.6 | 2 (28.6) | 0.0-70.8 | 0.0 (0.0) | 1 (33.3) | 0.8-90.6 | 2 (28.6) | 0.0-70.8 | 3 (17.6) | 3.8-43.4 |
| DCR, n (%) (95% CI) | 0.0-0.975 | 2 (66.7) | 9-199.2 | 1 (33.3) | 0.8-90.6 | 3 (42.9) | 9-98.2 | 2 (66.7) | 9-99.2 | 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) | 11.1 (NE-NE) | 9.2 (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) | — | 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. 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%. Almonertinib had an ORR of 50%, a DCR of 89%, and a PFS of 9.6 months in a phase I trial, 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. 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. 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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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.

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