

Safety, Clinical Activity, and Pharmacokinetics of Alflutinib (AST2818) in Patients With Advanced NSCLC With *EGFR* T790M Mutation

Yuankai Shi, MD,^{a,*} Shucui Zhang, MD,^b Xingsheng Hu, MS,^a Jifeng Feng, MD,^c Zhiyong Ma, BMed,^d Jianying Zhou, MSc,^e Nong Yang, MD,^f Lin Wu, MD,^g Wangjun Liao, MD,^h Dafang Zhong, PhD,ⁱ Xiaohong Han, PhD,^a Ziping Wang, MD,^j Xiaodong Zhang, BMed,^k Shukui Qin, MSc,^l Kejing Ying, MD,^m Jian Feng, MSc,ⁿ Jian Fang, MD,^o Li Liu, MD,^p Yong Jiang, MSc^q

^aDepartment of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, People's Republic of China

^bDepartment of Oncology, Beijing Chest Hospital, Capital Medical University/Beijing Tuberculosis and Thoracic Oncology Institute, Beijing, People's Republic of China

^cJiangsu Cancer Hospital & Jiangsu Institute of Cancer Research, Nanjing Medical University Affiliated Cancer Hospital, Nanjing, People's Republic of China

^dDepartment of Medical Oncology, Affiliated Cancer Hospital of Zhengzhou University/Henan Cancer Hospital, Zhengzhou, People's Republic of China

^eDepartment of Respiratory Medicine, the First Affiliated Hospital of College of Medicine, Zhejiang University, Hangzhou, People's Republic of China

^fDepartment of Medical Oncology, Lung Cancer and Gastrointestinal Unit, Hunan Cancer Hospital/the Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, People's Republic of China

^gDepartment of Gastroenterology, Hunan Cancer Hospital, Changsha, People's Republic of China

^hDepartment of Medical Oncology, Nanfang Hospital, Nanfang Medical University, Guangzhou, People's Republic of China

ⁱShanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, People's Republic of China

^jDepartment of Thoracic Oncology, Unit I, Peking University Cancer Hospital, Beijing, People's Republic of China

^kDepartment of Medical Oncology, Nantong Cancer Hospital, Nantong, People's Republic of China

^lDepartment of Medical Oncology, PLA Cancer Center of Bayi Hospital Affiliated to Nanjing University of Chinese Medicine, Nanjing, People's Republic of China

^mDepartment of Respiratory Medicine, Sir Run Shaw Hospital, Affiliated With Zhejiang University School of Medicine, Hangzhou, People's Republic of China

ⁿDepartment of Respiratory Medicine, Affiliated Hospital of Nantong University, Nantong, People's Republic of China

^oDepartment of Thoracic Oncology, Unit II, Peking University Cancer Hospital, Beijing, People's Republic of China

^pDepartment of Thoracic Oncology, Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China

^qClinical Affairs and Regulatory Department, Shanghai Allist Pharmaceuticals Co., Ltd., Shanghai, People's Republic of China

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ABSTRACT

Introduction: Alflutinib (AST2818) is a newly developed third-generation *EGFR* tyrosine kinase inhibitor selective

for *EGFR*-sensitizing and T790M-resistant mutations. We assessed the safety, efficacy, and pharmacokinetics of alflutinib in patients with advanced NSCLC with confirmed

*Corresponding author.

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Address for correspondence: Yuankai Shi, MD, Department of Medical Oncology, National Cancer Center/National Clinical Research Center

for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing 100021, People's Republic of China. E-mail: syuantkai@cicams.ac.cn

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EGFR T790M mutation, whose status progressed after the first- or second-generation EGFR tyrosine kinase inhibitor therapy.

Methods: In the dose-escalation (NCT02973763) and dose-expansion (NCT03127449) studies, patients received alflutinib orally until disease progression, unacceptable toxicity, or subject withdrawal. The primary end points were safety, tolerability, and pharmacokinetics for the dose-escalation study and the objective response rate (assessed by an independent radiological review committee) for the dose-expansion study.

Results: Between November 30, 2016, and July 24, 2018, a total of 130 patients (14 in dose escalation, 116 in dose expansion) received alflutinib treatment (20 mg, 40 mg, 80 mg, 160 mg, or 240 mg once daily). On October 30, 2018, 79 patients (61%) remained on the treatment. No dose-limiting toxicities were observed in the dose-escalation study. In the dose-expansion study (40–240 mg), the overall objective response rate was 76.7% (89 of 116), and it was 70.6% in patients with central nervous system metastases (12 of 17). A total of 79% of all patients had possibly treatment-related adverse events (AEs) (103 of 130); 8% had treatment-related grade 3 or higher AEs (11 of 130). Serious AEs were reported in 15% of patients (20 of 130), and two serious AEs were related to treatment. No clear dose-response (antitumor activity and AEs) relationships were observed. Exposures to alflutinib and its active metabolite (AST5902) were comparable at steady state.

Conclusions: Alflutinib was clinically effective with an acceptable toxicity profile in patients with advanced NSCLC (including those with central nervous system metastases) with *EGFR* T790M mutation. Further investigation is ongoing.

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

Introduction

NSCLC accounts for approximately 85% of all types of lung cancer.¹ The first- and second-generation *EGFR* tyrosine kinase inhibitors (TKIs) (e.g., gefitinib, erlotinib, icotinib, afatinib, and dacomitinib) have been recommended as the first-line therapy for patients with *EGFR* mutation-positive NSCLC.^{2–6} However, almost all patients who benefited from *EGFR*-TKIs eventually developed clinical resistance, with approximately 50% owing to acquired *EGFR* T790M mutations.^{7,8} This led to the development of third-generation *EGFR*-TKIs, including osimertinib (Tagrisso, AZD9291), nazartinib, naquotinib,

mavelertinib, avitinib, and lazertinib.^{9–11} Among them, osimertinib is the only approved therapy worldwide, which was first approved in 2015 on the basis of targeting *EGFR* T790M resistance and then received an additional approval in 2018 as first-line therapy with improvement in progression-free survival (PFS) over a standard *EGFR*-TKI (gefitinib or erlotinib).^{9,12–14} Other candidates are in various stages of clinical development. Osimertinib remains the most robust option to overcome the T790M mutation with a manageable toxicity profile.

Alflutinib mesylate (AST2818, Shanghai Allist Pharmaceuticals Co., Ltd.) is another newly developed third-generation *EGFR*-TKI. It is a trifluoroethoxypyridine-based irreversible *EGFR*-TKI selective for *EGFR*-sensitizing and resistant mutations (e.g., G719X, exon 19 deletion, L858R, L861Q, and T790M) while sparing wild-type *EGFR*. The molecular structure of alflutinib is shown in Figure 1. Alflutinib has a pharmacologically active metabolite, AST5902, which has similar antitumor activity.

Preclinical studies revealed that alflutinib has a better safety and tolerability profile than osimertinib in rats and dogs, with potent antitumor activity comparable to that of osimertinib (data unpublished). In a well-established patient-derived xenograft model in nude mice (LU1868 model, expressing *EGFR* L858R and T790M), 10 and 30 mg/kg alflutinib were compared with 10 mg/kg osimertinib, 30 mg/kg afatinib, and 100 mg/kg gefitinib (administered through gavage once daily [QD] for 28 d). The average tumor growth inhibition was achieved in the 10 and 30 mg/kg alflutinib and 10 mg/kg osimertinib groups by 87%, 100%, and 97%, respectively, whereas the remaining two groups failed to exhibit notable tumor growth inhibition. Alflutinib was also found to have extensive tissue distribution in a ¹⁴C-alflutinib mass balance study in rats (data unpublished). The concentration ratios of drug-related substances in tissues (e.g., lungs, gastrointestinal tract, and kidneys) to plasma were more than 10, and the concentration of

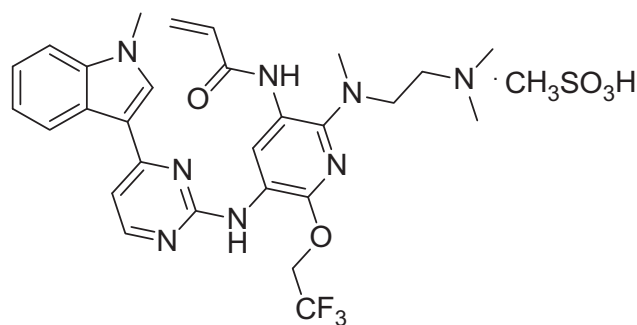


Figure 1. The molecular structure of alflutinib.

drug-related substances in the brain was slightly higher than that in plasma at 4 hours after dose administration, indicating blood–brain barrier penetration. These pre-clinical data provided a rationale for further evaluation of alflutinib in clinical programs, including in patients with central nervous system (CNS) metastases.

Here, we report the results from the first-in-human phase I dose-escalation study (NCT02973763) and a subsequent phase I-II dose-expansion study (NCT03127449), which assessed the safety, tolerability, antitumor activity, and pharmacokinetics (PK) of alflutinib in patients with advanced NSCLC with *EGFR* T790M mutation, whose status progressed after the first- or second-generation *EGFR*-TKI therapy.

Materials and Methods

Study Design

Both dose-escalation (study 1) and dose-expansion (study 2) studies were open-label, single-arm, multicenter studies. Study 1 was designed to determine the maximum tolerated dose (MTD) and the dose-limiting toxicity (DLT). On the basis of the results of study 1, appropriate doses were to be selected for further evaluation in study 2 to select a recommended dosing regimen for subsequent phase IIb and III studies.

Study 1 and study 2 were conducted at three and 14 centers in People's Republic of China, respectively, in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol, amendments, and patients' informed consent were approved by the independent ethics committee at each participating site. Written informed consent was obtained from all patients before enrolment in each study.

Study Population

Both studies had similar inclusion and exclusion criteria. Eligible patients (≥ 18 years old) had histologically or cytologically confirmed locally advanced or metastatic NSCLC not suitable for operation or radiotherapy. Patients had measurable disease as defined by the Response Evaluation Criteria in Solid Tumors version 1.1 guidelines¹⁵ and radiological documentation of disease progression after previous first- or second-generation *EGFR*-TKI therapy, with additional lines of treatment allowed. All patients were required to be *EGFR* T790M-positive. It was also allowed to enroll patients with primary T790M mutation (study 2 only) or patients with asymptomatic, stable CNS metastases not requiring steroids for at least 4 weeks before the first dose of alflutinib. Full inclusion and exclusion criteria are included in the [Supplementary Materials](#).

Procedures

Study 1 (dose escalation) assessed the following doses in five cohorts: 20 mg, 40 mg, 80 mg, 160 mg, and 240 mg. The dose increment was no more than 100% of the current dose. The starting dose of 20 mg was selected on the basis of the data from toxicology study in dogs and preclinical patient-derived xenograft models predicting that this would be an effective dose (data unpublished), according to the International Council for Harmonization (ICH) S9 guidelines.¹⁶

Each cohort consisted of a single-dose period (7 d) followed by a multiple-dose period, in which the patients received the same oral dose QD until unacceptable toxicity, documented disease progression, or patient withdrawal (21 d per cycle). The DLT observation period was the first 28 days. DLTs were defined as any possibly treatment-related grade 4 or higher hematological toxicities, grade 3 or higher nonhematological toxicities (except for alopecia and those without clinical significance), symptomatic cardiac dysfunction (including QTc ≥ 500 msec or 60 msec change from baseline), interstitial lung disease (ILD), and dose interruption for more than 7 days owing to unresolved toxicities.

Study 1 followed the traditional 3+3 escalation principle,¹⁷ in which at least three and up to six patients were needed at each dose level. Specifically, if there was no occurrence of DLT in three patients at a dose level, it could be escalated to the next dose level; however, if DLT occurred in one of the three patients, three additional patients needed to be enrolled. Once another DLT occurred (i.e., the total number of patients with DLT reached two), the previous dose immediately below this dose would be determined as the MTD. A safety review was required to be conducted to evaluate available safety and PK data to determine the next dose or dosing frequency before patients could be enrolled to the next cohort. Of note, there was one exception for the starting dose cohort, in which two patients could be enrolled to minimize the number of patients exposed to potential subtherapeutic dose; however, if a treatment-related grade 3 or higher adverse event (AE) was observed during the DLT period, the standard 3+3 escalation rule would also be followed in this cohort.

In study 2 (dose expansion), the following four doses were selected for further evaluation: 40 mg, 80 mg, 160 mg, and 240 mg. Study 2 had the same dosing schedule as study 1, except that there were no single-dose period and DLT observation period. The patients received the daily dose from the first day of dosing. The procedures were very similar in both studies.

Dose interruption could occur if a patient had a grade 3 or higher AE, QTc prolongation (≥ 500 msec), new symptoms of acute or progressive lung disease, severe

skin reactions, or other unacceptable toxicity. If the AE resolved or returned to grade 2 or less within 21 days, alflutinib treatment may be resumed at the same dose or a lower dose level (not applicable for the DLT observation period in study 1). Otherwise, the patient should be discontinued from the study, and the AE should be followed until resolution, stabilization, or return to baseline.

Patients underwent imaging evaluation with either computed tomography or magnetic resonance imaging scans of the chest, abdomen, pelvis, and any other suspected areas at baseline, every two cycles (6 w) from cycle 1 to cycle 16, and every four cycles (12 w) after cycle 17. In addition, contrast-enhanced computed tomography or magnetic resonance imaging of the brain was performed at baseline; subsequent brain imaging was required when clinically indicated and in patients with confirmed CNS metastases. The tumor response was assessed on the basis of the Response Evaluation Criteria in Solid Tumors version 1.1.¹⁵ Of note, in study 1 (dose escalation), only investigator assessment was performed on tumor response for the purpose of fast decision making because the focus was on the safety and tolerability of alflutinib, whereas the tumor response was assessed by both investigators and an independent radiological review committee (IRRC) in study 2 (dose expansion).

AEs were monitored throughout the study and graded on the basis of the Common Terminology Criteria for Adverse Events 4.03. Physical examinations, vital signs, 12-lead electrocardiograms, and laboratory tests were evaluated at baseline and protocol-specified time points.

Serial plasma samples for PK analysis of alflutinib and its active metabolite (AST5902) were collected after a single oral dose and at a steady state in all patients in study 1 and a subset of patients in study 2 (see the [Supplementary Materials](#) for details).

End Points and Assessments

In study 1 (dose escalation), the primary end points were the safety, tolerability, PK parameters of alflutinib and AST5902, and the key secondary end points were the investigator-assessed objective response rate (ORR) and disease control rate (DCR).

In study 2 (dose expansion), the primary end point was the IRRC-assessed ORR, and the key secondary end points were the IRRC-assessed DCR, duration of response (DOR), PFS, safety, tolerability, and PK parameters of alflutinib and AST5902.

An objective response was defined as confirmed complete response or partial response. The DCR was defined as the percentage of patients who had best overall response, including complete response, partial

response, or stable disease with a duration of at least 12 weeks. The DOR was defined as the time from the date of first documented objective response (subsequently confirmed) until the date of documented disease progression or all-cause death before disease progression. The PFS was defined as the time from the date of first dose until the date of documented disease progression or all-cause death before disease progression.

PK parameters included area under the concentration-time curve over a 24-hour dosing interval (AUC_{0-24}), peak concentration (C_{max}), time to reach C_{max} (T_{max}), trough concentration (C_{min}), and steady-state accumulation ratios of AUC_{0-24} and C_{max} . PK analysis was performed with Phoenix 64 Win-Nonlin version 7.0 using a standard noncompartmental analysis method.

Statistical Analysis

No formal hypothesis testing was conducted for both studies. All statistical analyses for efficacy, safety, and PK parameters were descriptive.

On the basis of the PK and efficacy results from preclinical studies and study 1 (dose escalation), the optimal dose was suggested to be between 80 mg and 160 mg. Thus, in study 2 (dose expansion), 80 mg and 160 mg dose groups were considered to explore the efficacy of the treatment. The sample size for 80 mg and 160 mg groups was determined on the basis of Simon two-stage design.¹⁸ Because this study was for efficacy exploration to determine whether a further phase II study would be conducted, only the sample size for the first stage of the two-stage design was considered. This two-stage design was based on the power of 80% and alpha of 0.05 (two-sided). The sample size calculation was based on the following assumptions: the two-stage design to test the null hypothesis that p is less than or equal to 0.45 versus the alternative that p is greater than or equal to 0.59. This study required a sample size of approximately 30 patients for each dose group for the first-stage test. If more than 15 responders in the 30 response evaluable patients were observed for 80 mg or 160 mg dose groups, a formal phase II study would be planned to further confirm the efficacy of alflutinib in a selected dose group. In addition, for the exploratory purpose, it was planned that six and 15 patients would be enrolled for the 40 mg and 240 mg dose groups, respectively. The final sample size of 116 patients (six at 40 mg, 45 at 80 mg, 50 at 160 mg, and 15 at 240 mg) enrolled in study 2 was to fulfill P. R. China's regulatory New Drug Application submission requirement not only for efficacy but also for the safety data.

All patients who received at least one dose of alflutinib with measurable disease at baseline were included

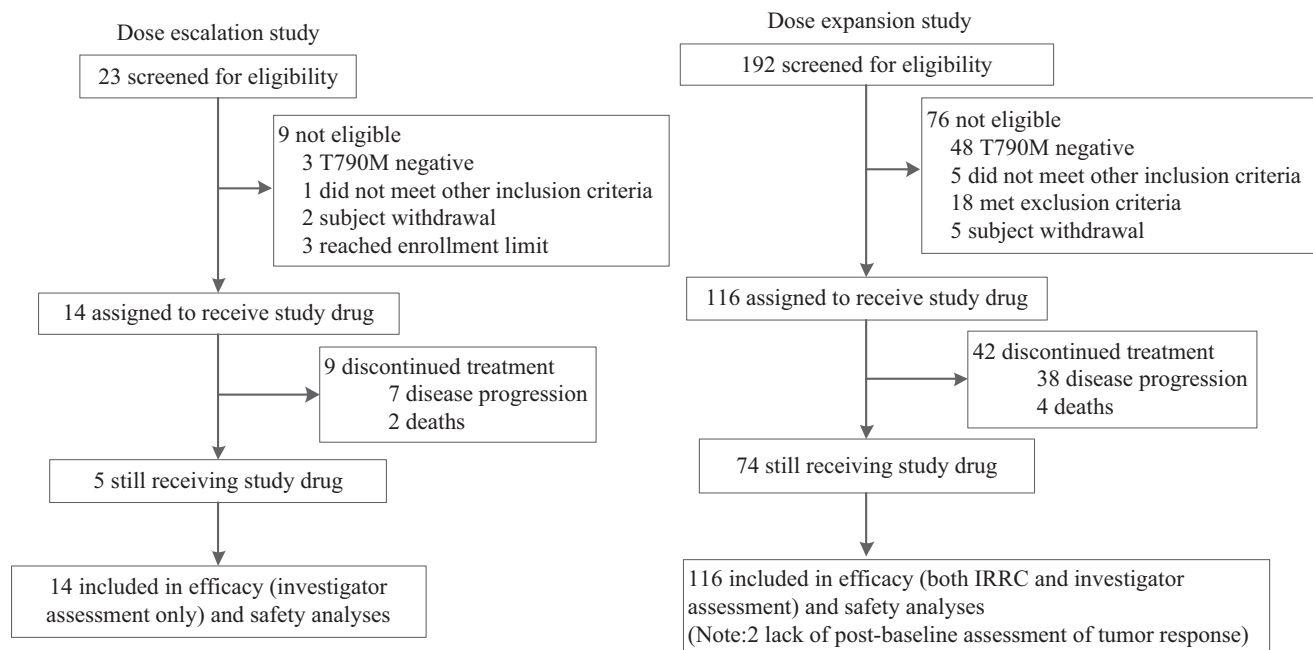


Figure 2. Trial profile (at analysis cutoff date of October 30, 2018).

for efficacy and safety analyses. The ORR and DCR were calculated on the basis of the confirmed best overall response of tumors during the study, and the corresponding 95% confidence intervals (CIs) were determined by Clopper-Pearson exact method. Subgroup analyses of the objective response based on baseline characteristics were performed using the same method as for the overall population. In addition, we used the Kaplan-Meier method to evaluate the median DOR, PFS, and 95% CIs. The SAS system version 9.4 was used for all the efficacy and safety analyses.

Results

Between November 30, 2016, and July 24, 2018, a total of 215 patients were screened, of whom 130 patients (14 in dose-escalation study, 116 in dose-expansion study) received alflutinib treatment (20 mg, 40 mg, 80 mg, 160 mg, or 240 mg, QD, in tablet form). The data cutoff was October 30, 2018. On this date, 79 patients (61%) remained on the treatment (Fig 2). The median duration of exposure to alflutinib was 7.4 months (range: 0.1–16.9). The overall population characteristics are presented in Table 1.

Safety ($n = 130$)

Alflutinib was well tolerated at daily doses up to 240 mg. No DLT was observed; thus, MTD was not reached in the dose-escalation study.

In the overall population, all-cause AEs occurred in 97% of the patients (126 of 130), most of which were grade 1 or 2, and 19% of the patients (25 of 130) had

grade 3 or higher AEs. Serious AEs were reported in 15% of the patients (20 of 130). The most common all-cause AEs (in $\geq 10\%$ of patients, Table 2) were decreased white blood cell count (28%), diarrhea (19%), cough (19%), increased alanine aminotransferase (19%), decreased neutrophil count (18%), anemia (17%), proteinuria (16%), increased serum creatinine (15%), upper respiratory tract infection (15%), increased aspartate aminotransferase (AST) (12%), and rash and urinary tract infection (10% each).

According to the investigator's assessment, 79% of the patients (103 of 130) had at least one possibly treatment-related AE; 8% (11 of 130) had treatment-related grade 3 or higher AEs, with the most common being decreased neutrophil count ($n = 3$, 2%), decreased platelet count, and anemia ($n = 2$ each, 2%); all other grade 3 or grade 4 AEs were reported in one patient each (Table 2). Only two serious AEs were assessed as possibly related to treatment (liver injury at 40 mg and hyperuricemia at 240 mg).

QT prolongation was reported in 6% of patients (eight of 130) (in 20 mg, 40 mg, 80 mg, and 160 mg groups; $n = 2$ each). All were grade 1 or grade 2 and assessed as possibly related to treatment. Two events (grade 2 at 80 mg, grade 2 at 160 mg) led to dose interruption before resolution. QT prolongation in the remaining patients was resolved without intervention, except for one event (grade 1) reported as worsening.

Dose reductions and interruptions owing to treatment-related AEs occurred in 3% (four of 130) and 8% (11 of 130) of the patients, respectively. Reasons for dose reduction included decreased neutrophil count (grade 2,

Table 1. Patient Baseline Demographics and Disease Characteristics (n = 130)

Characteristic	Study 1 (Dose Escalation) (n = 14)	Study 2 (Dose Expansion) (n = 116)
Weight, kg, median (range)	69 (48-80)	64 (38-111)
Age, y, median (range)	58 (45-64)	55 (27-74)
<65	14 (100%)	89 (77%)
≥65	0	27 (23%)
Sex		
Male	6 (43%)	42 (36%)
Female	8 (57%)	74 (64%)
ECOG PS		
0	7 (50%)	32 (28%)
1	5 (36%)	79 (68%)
2	2 (14%)	5 (4%)
Tumor histology		
Adenocarcinoma	14 (100%)	109 (94%)
Squamous cell carcinoma	-	1 (1%)
Other	-	6 (5%)
EGFR-TKI sensitizing mutation status ^a		
Exon 19 deletion	8 (57%)	71 (61%)
L858R	6 (43%)	45 (39%)
CNS metastases at study entry		
CNS metastases	5 (36%)	17 (15%)
No CNS metastases	9 (64%)	99 (85%)
Previous lines of systemic therapy	1 (1-3)	1 (1-6)
Previous chemotherapy ^b	5 (36%)	43 (37%)
Previous EGFR-TKI therapy ^c	14 (100%)	112 (97%) ^d
Icotinib	7 (50%)	58 (50%)
Gefitinib	5 (36%)	46 (40%)
Erlotinib	3 (21%)	13 (11%)
Simotinib	-	2 (2%)
Duration of most recent previous EGFR-TKI therapy		
None	-	4 (3%) ^d
<6 mo	1 (7%)	12 (10%)
≥6 mo	13 (93%)	100 (86%)
Patients enrolled in each cohort		
20 mg	2 (14%)	-
40 mg	3 (21%)	6 (5%)
80 mg	3 (21%)	45 (39%)
160 mg	3 (21%)	50 (43%)
240 mg	3 (21%)	15 (13%)

Data are number of patients (%).

^aBased on the central laboratory testing results.

^bMost patients received pemetrexed, paclitaxel, docetaxel, or gemcitabine alone or in combination with platinum.

^cA few patients received more than one previous EGFR-TKI therapies.

^dFour patients were diagnosed with primary T790M mutation and did not receive any EGFR-TKI therapy before study entry.

ECOG PS, Eastern Cooperative Oncology Group performance status; TKI, tyrosine kinase inhibitor.

80 mg), hypermagnesemia (grade 1, 160 mg), decreased white blood cell count and anemia (grade 2 and grade 3, 160 mg), and decreased platelet count (grade 2, 240 mg). Only one patient from the 80 mg dose group permanently

discontinued aflutininb owing to a grade 3 pleural effusion (assessed as possibly not related to treatment).

At the cutoff date, there were six deaths. Two deaths were due to disease progression, and three were due to hydrocephalus, multiple cerebral infarction, and sudden death. All of them were assessed as possibly not related to treatment except for the sudden death (assessed as uncertain). The cause for the sixth death was unknown, which occurred after voluntary withdrawal from the study treatment.

More detailed summaries on the AEs by dose, causality, and severity are included in [Supplementary Tables 1 to 3](#).

Efficacy

Study 1: Dose Escalation (n = 14). The overall investigator-assessed ORR was 50.0% (seven of 14, all had partial response), and the ORR in the 20 mg, 40 mg, 80 mg, 160 mg, and 240 mg groups were 50.0% (one of two), 66.7% (two of three), 66.7% (two of three), 66.7% (two of three), and 0% (zero of three), respectively. The overall DCR was 85.7% (12 of 14), and the remaining two patients (in 80 mg and 240 mg groups each) had stable disease but with a duration shorter than the predefined 12-week criterion. In addition, three of five patients (60.0%) with confirmed CNS metastases achieved partial response (in 20 mg, 40 mg, and 160 mg groups each). These promising results led to a quick start of study 2 (dose expansion).

Study 2: Dose Expansion (n = 116). According to the IRRC's assessment, the overall ORR was 76.7% (89 of 116; 95% CI: 68.0–84.1; all had partial response), and DCR was 82.8% (96 of 116; 95% CI: 74.6–89.1). The ORR in the 40 mg, 80 mg, 160 mg, and 240 mg groups were 83.3% (five of six), 77.8% (35 of 45), 78.0% (39 of 50), and 66.7% (10 of 15), respectively, and no apparent dose-response relationship was observed ([Table 3](#)). Subgroup analyses revealed similar high proportions of objective response on the basis of sex, age (<65 y versus ≥65 y), mutation type (*EGFR* T790M co-occurring with exon 19 deletion versus L858R), presence of CNS metastases, and duration of the most recent previous EGFR-TKI therapy (<6 mo versus ≥6 mo) ([Supplementary Fig. 1](#)).

At the cutoff date of October 30, 2018, among the 89 patients who achieved partial response, 16 patients (18%) had progressed status and two patients (2%) had died. The overall median DOR was not reached, and median PFS was 11.1 months (95% CI: 9.6–not reached; 39 patients [30%] had a progression event; [Table 3](#)). Both DOR and PFS in the 80 mg and higher dose groups were prolonged compared with the 40 mg dose group

Table 2. Summary of All-Cause and Treatment-Related AEs in the Overall Population ($n = 130$)

Adverse Event	All-Cause AE		Treatment-Related AE ^a	
	Grades 1-2	Grades 3-4	Grades 1-2	Grades 3-4
Decreased white blood cell count	34 (26%)	2 (2%)	29 (22%)	1 (1%)
Cough	25 (19%)	0		
Increased ALT	23 (18%) ^b	1 (1%)	22 (17%)	1 (1%)
Diarrhea	23 (18%)	2 (2%)	18 (14%)	1 (1%)
Proteinuria	21 (16%)	0	20 (15%)	0
Decreased neutrophil count	20 (15%)	4 (3%)	19 (15%)	3 (2%)
Increased serum creatinine	20 (15%)	0	16 (12%)	0
Anemia	19 (15%)	3 (2%)	14 (11%)	2 (2%)
Upper respiratory tract infection	19 (15%)	0		
Increased AST	15 (12%) ^b	0	15 (12%)	0
Rash	13 (10%)	0	12 (9%)	0
Urinary tract infection	12 (9%)	1 (1%)		
Hyperuricemia	7 (5%)	1 (1%)	0	1 (1%)
Prolonged electrocardiogram QT	8 (6%)	0	8 (6%)	0
Pleural effusion	7 (5%)	1 (1%)		
Decreased platelet count	7 (5%)	3 (2%)	5 (4%)	2 (2%)
Blood hypercoagulable state	7 (5%)	1 (1%)	3 (2%)	0
Acneiform dermatitis	7 (5%)	1 (1%)	7 (5%)	1 (1%)
Myalgia	4 (3%)	1 (1%)		
Chest discomfort	3 (2%)	2 (2%)		
Hyponatremia	3 (2%)	1 (1%)		
Hypertension	2 (2%)	1 (1%)	2 (2%)	1 (1%)
Hypokalemia	2 (2%)	1 (1%)	1 (1%)	1 (1%)
Pneumonia ^c	2 (2%)	1 (1%)	1 (1%)	0
Pneumonitis ^c	2 (2%)	1 (1%)	1 (1%)	0
Varicosity	1 (1%)	1 (1%)		
Bone pain	0	1 (1%)		
Cerebral infarction	0	1 (1%)		
Increased intracranial pressure	0	1 (1%)		
Hydrocephalus	0	1 (1%)		
Hypermagnesemia	0	1 (1%)	0	1 (1%)
Liver injury	0	1 (1%)	0	1 (1%)
Multidrug toxicity	0	1 (1%)		
Tumor lysis syndrome ^d	0	1 (1%)		

Data are number of patients (%). This table included grade 1-2 AEs that occurred in at least 10% of patients and all grade 3-4 events.

^aTreatment-related AEs were defined as an AE related or possibly related to treatment, as assessed by the investigator.

^b95% of these events were of grade 1.

^cInvestigators confirmed that these AEs were not interstitial lung disease.

^dThe patient experienced grade 3 tumor lysis syndrome during the follow-up period (9 d after the treatment discontinuation), which was considered as definitely not related to the study drug by the investigator.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

(Fig. 3A and B). The tumor shrinkage was observed in most patients (Fig. 4), and the overall mean best percentage change in the target lesion size from baseline was -51% (range: -100% to 37%).

In 17 patients with CNS metastases, both overall IRRC-assessed ORR and DCR were 70.6% (12 of 17), and three patients (18.0%) achieved stable disease but with a duration of less than 12 weeks. The ORR in the 40 mg, 80 mg, 160 mg, and 240 mg groups was 50.0% (one of two), 100.0% (four of four), 66.7% (six of nine), and 50.0% (one of two), respectively. The overall median DOR and PFS were 8.4 and 9.9 months, respectively (Table 3). Similar trends for DOR and PFS were also

observed in patients with CNS metastases: 80 mg and higher dose groups had prolonged effect than the 40 mg dose group. For exploratory purpose, the CNS objective response was also evaluated on the basis of investigator's assessment: the overall CNS ORR was 58.8% (10 of 17). Specifically, two had complete response (intracranial lesions completely disappeared), eight had partial response, and seven had stable disease.

Pharmacokinetics ($n = 38$)

AUC₀₋₂₄ and C_{max} of alflutinib increased in a slightly less than dose-proportional manner over a daily dose

Table 3. Summary of IRRC-Assessed Efficacy End Points by Dose and the Presence of CNS Metastases ($n = 116$, Dose-Expansion Study)

Dose Group	40 mg	80 mg	160 mg	240 mg	Total
All patients (n)	6	45	50	15	116
Objective response	5 (83.3%)	35 (77.8%)	39 (78.0%)	10 (66.7%)	89 (76.7%)
Disease control	5 (83.3%)	38 (84.4%)	41 (82.0%)	12 (80.0%)	96 (82.8%)
DOR (mo)					
DOR ≥ 6 mo	2 (40%)	20 (57%)	18 (46%)	4 (40%)	44 (49%)
Median (95% CI)	4.1 (2.8, NA)	NA (8.4, NA)	NA	NA (4.2, NA)	NA (9.7, NA)
PFS (mo)					
Number of events ^a	4 (67%)	16 (36%)	14 (28%)	5 (33%)	39 (34%)
Median (95% CI)	4.9 (2.7, NA)	11.1 (8.2, NA)	NA (6.9, NA)	NA (4.1, NA)	11.1 (9.6, NA)
Patients with CNS metastases (n)	2	4	9	2	17
Objective response	1 (50.0%)	4 (100.0%)	6 (66.7%)	1 (50.0%)	12 (70.6%)
Disease control	1 (50.0%)	4 (100.0%)	6 (66.7%)	1 (50.0%)	12 (70.6%)
DOR (mo)					
DOR ≥ 6 mo	0	2 (50%)	4 (67%)	0	6 (50%)
Median (95% CI)	2.8	6.3 (2.4, 8.4)	NA	NA	8.4 (2.8, NA)
PFS (mo)					
Number of events ^a	2 (100%)	3 (75%)	3 (33%)	1 (50%)	9 (53%)
Median (95% CI)	3.4 (2.7, 4.2)	7.8 (3.7, NA)	NA (2.7, NA)	NA (1.5, NA)	9.9 (3.7, NA)

Data are number of patients (%).

^aSubjects who had progressed or died.

CI, confidence interval; DOR, duration of response; IRRC, independent radiological review committee; n , number of patients; NA, not available; PFS, progression-free survival.

range from 20 mg to 240 mg, whereas AUC_{0-24} and C_{max} of AST5902 increased in an approximately dose-proportional manner. Steady-state exposures to alflutinib and AST5902 were comparable and achieved after 7 days and 14 days of dosing, respectively. The accumulation of alflutinib exposure at steady state tended to decrease as the dose increased (e.g., AUC_{0-24} : 3.1-fold to 1.3-fold), whereas the accumulation of AST5902 exposure remained similar (e.g., AUC_{0-24} : 7.6-fold to 9.1-fold). More details are included in [Supplementary Table 4](#). The mean concentration-time profiles of alflutinib and AST5902 at 80 mg dose and individual AUC_{0-24} of alflutinib and AST5902 by dose are presented in [Supplementary Figures 2 and 3](#), respectively.

Discussion

Our studies revealed that alflutinib was safe and well tolerated at daily doses up to 240 mg in patients with advanced NSCLC with confirmed *EGFR* T790M mutation. Most AEs were manageable and mild in severity. All-cause and treatment-related grade 3 or higher AEs occurred in 19% (25 of 130) and 8% (11 of 130) of patients, respectively. As noted earlier, three of four patients with dose reduction owing to treatment-related AEs were from the 160 mg and 240 mg dose groups. The incidence rates of decreased white blood cell count, decreased platelet count, and increased AST tended to increase slightly with the dose. Nonetheless, no apparent relationships between the dose and the severity or

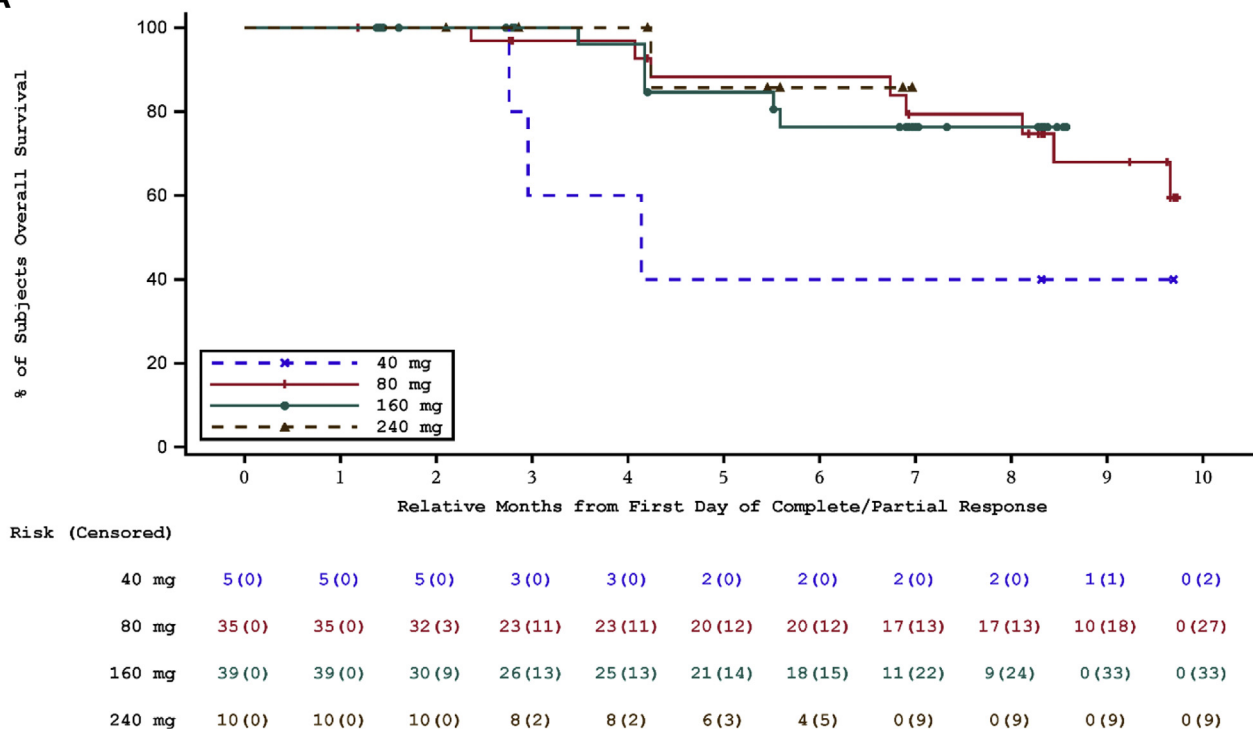
frequency of AEs were identified ([Supplementary Tables 2 and 3](#)).

Alflutinib also had favorable antitumor activity with a wide therapeutic range (i.e., effective at all dose levels evaluated). The 80 mg and higher dose groups had prolonged effect than the 40 mg dose group on the basis of DOR and PFS data, but doses higher than 80 mg may not further improve the antitumor activity substantially in patients with NSCLC ([Fig. 3A and B](#)). Furthermore, clinical effectiveness of alflutinib on intracranial lesions has been demonstrated in our studies, and this is consistent with the preclinical findings that alflutinib and AST5902 could penetrate into the brain. Although the sample size was small, the responses observed in patients with CNS metastases were comparable to those in patients without CNS metastases ([Table 3](#)).

Overall, on the basis of the benefit and risk assessment for long-term treatment with alflutinib, an 80 mg daily dose was selected for subsequent phase IIb and III studies to maximize the treatment benefit and minimize any potential safety risk.

Our study population consisted of patients with locally advanced or metastatic NSCLC with confirmed *EGFR* T790M mutation, whose status progressed after the first- or second-generation *EGFR*-TKI therapy. This population is similar to that enrolled in AURA studies of osimertinib.^{14,19-21} In the AURA studies, most of the patients received a daily dose of 80 mg osimertinib, reported ORR ranged from 61% to 71%, and median PFS ranged from 9.6 to 12.3 months. The clinical activity of osimertinib at

A



B

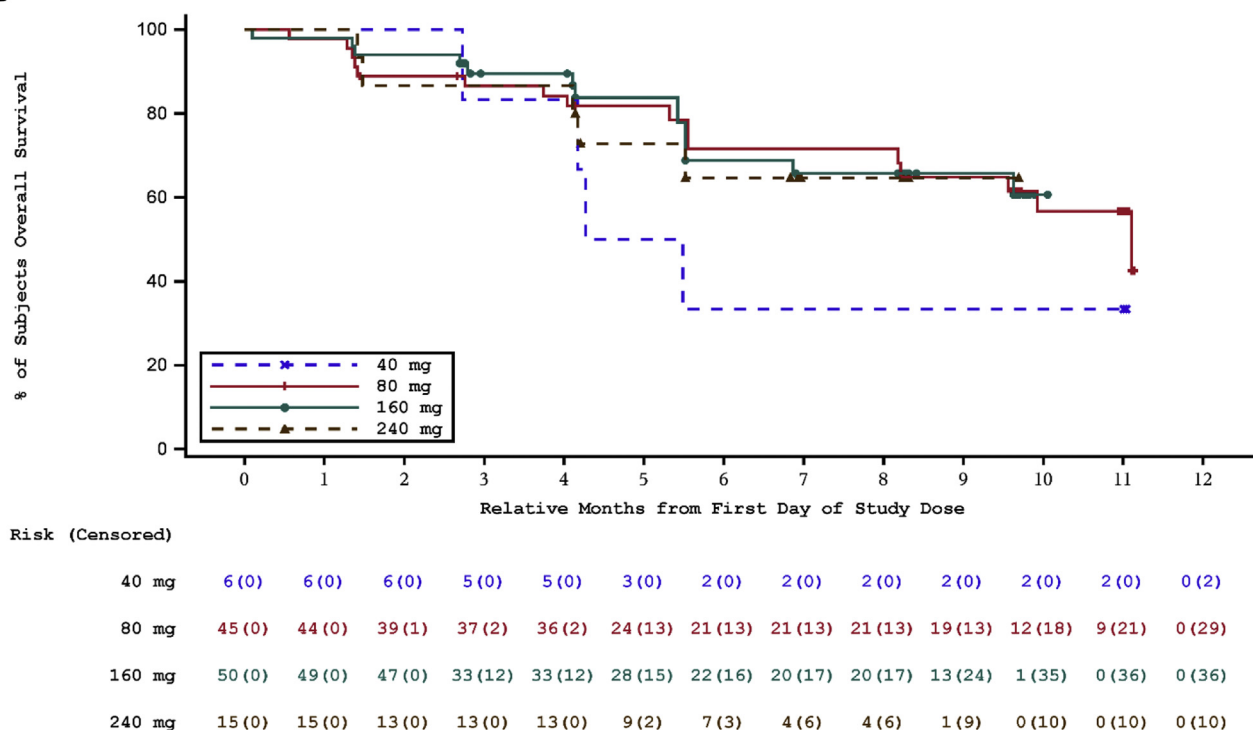


Figure 3. (A) Independent radiological review committee-assessed duration of response in patients who responded ($n = 89$, study 2); (B) Independent radiological review committee-assessed progression-free survival in all patients ($n = 116$, study 2).

80 mg daily dose has also been demonstrated in patients with confirmed CNS metastases, with a reported ORR of 54% (27 of 50).²² In comparison, alflutinib had similar response rates (based on IRRC assessment) in study 2:

overall ORR was 76.7% (89 of 116); ORR in patients with CNS metastases was 70.6% (12 of 17); at 80 mg alflutinib daily dose, ORR was 77.8% (35 of 45), and median PFS was 11.1 months (Table 3).

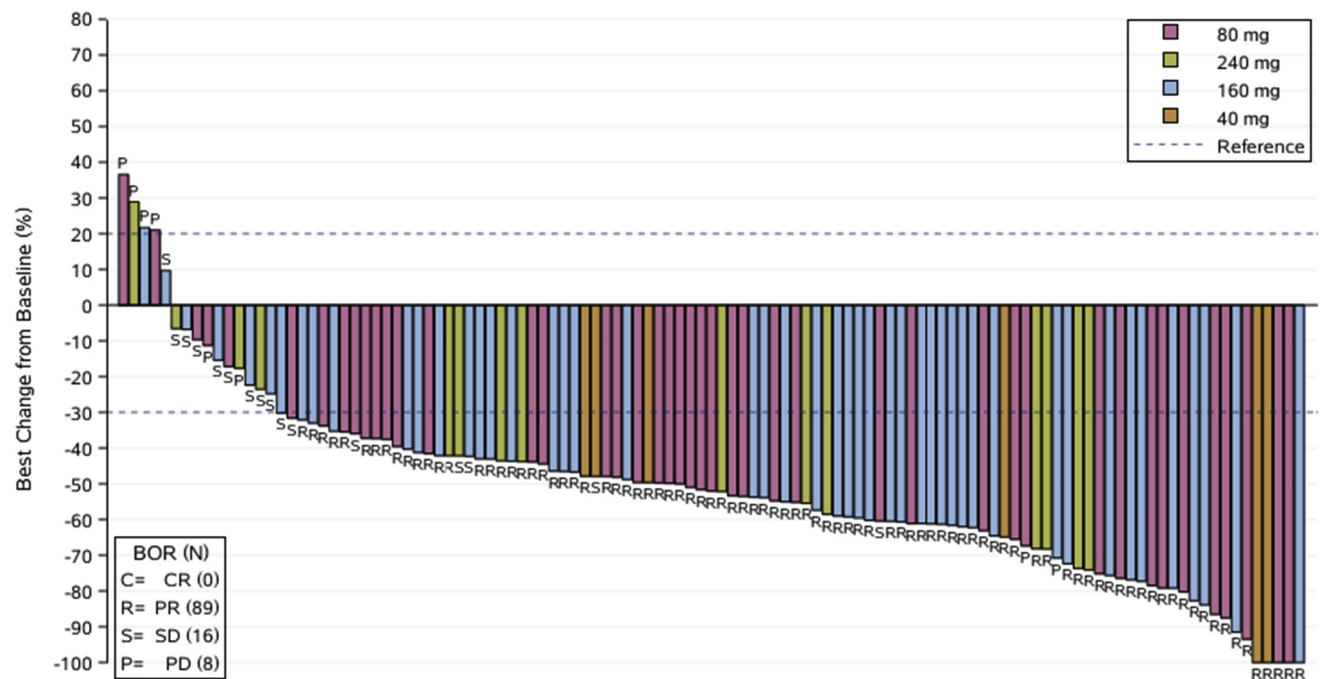


Figure 4. IRRC-assessed best percentage change from baseline in target lesion size for all patients ($n = 113$). Note: Of the 116 patients, two patients did not have postbaseline data owing to early death, and one patient did not have the data on the target lesion for central review. BOR, best objective response; CR, complete response; IRRC, independent radiological review committee; PD, progressive disease; PR, partial response; SD, stable disease.

The median treatment duration of alflutinib in our studies was 7.4 months (range: 0.1–16.9), which is similar to the treatment duration of osimertinib in the AURA3 study (median: 8.1 mo, range: 0.2–18.5).¹⁴ The most common AEs of osimertinib (80 mg daily) reported in patients with NSCLC with T790M mutation in the AURA3 study ($n = 279$) included diarrhea (41%), rash (34%), dry skin (23%), paronychia (22%), nausea (16%), stomatitis (15%), constipation (14%), pruritus (13%), and vomiting (11%).¹⁴ These patients also experienced hematological abnormalities (thrombocytopenia [10%], neutropenia, leukopenia, and anemia [8% each]) and abnormal liver function tests (increased alanine aminotransferase [6%] and increased AST [5%]); grade 3 or higher AEs were reported in 23% of patients (63 of 279).¹⁴ The AEs of special interest for osimertinib include ILD, QT prolongation, cardiomyopathy, and keratitis according to its product label.

In general, the safety profile of alflutinib seemed to be similar to that of osimertinib. As skin and gastrointestinal disorders are known as the typical EGFR-associated toxicities, a comparison was made between alflutinib and osimertinib: the relevant all-cause AEs reported for alflutinib in at least 5% of patients included rash (10%), acneiform dermatitis (6%), diarrhea (19%), nausea (7%), vomiting, stomatitis, and constipation (5% each), which were much lower than those reported in the

osimertinib AURA3 study.¹⁴ We also noted that no patients experienced ILD and grade 3 or higher eye disorders in our studies. This indicates that alflutinib may have a better tolerability profile than osimertinib in several aspects; however, more clinical data of alflutinib will be needed to confirm these observations.

Given the lower rates of skin and gastrointestinal disorders and no occurrence of ILD for alflutinib treatment, it is speculated that this may be related with its weak inhibitory activity on the wild-type EGFR. As described earlier, alflutinib is a trifluoroethoxy pyridine-based irreversible EGFR-TKI, which is structurally distinct from other pyrimidine-based irreversible EGFR-TKIs, including osimertinib. Investigations are ongoing to further understand the mechanism from the molecular structure level.

Limitations of our studies include that both were of single-arm design and investigations of alflutinib response are limited without a comparator arm. All the analyses are presented descriptively. In addition, to accommodate quick decision making during the early development stage, the tumor response was not assessed by the IRRC in study 1 (dose escalation). Furthermore, our studies were conducted in Chinese patients only, and caution should be taken when extrapolating the safety and efficacy data to other patient populations.

In summary, on the basis of the initial evidence, alflutinin could potentially be another effective and safe treatment option for patients with advanced NSCLC with *EGFR* T790M mutation. It is currently being investigated in a phase IIb study (NCT 03452592) to assess the efficacy and safety of alflutinin in patients with locally advanced or metastatic NSCLC with T790M mutation and in a randomized phase III study (FLAG, NCT03787992) to compare alflutinin with gefitinib as the first-line treatment in patients with locally advanced or metastatic NSCLC.

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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.2020.01.010>.

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