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

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Summary

Background Furmonertinib (AST2818) is a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) targeting both sensitising *EGFR* and *EGFR* Thr790Met (T790M) mutations. This study aimed to assess the efficacy and safety of furmonertinib in patients with *EGFR* T790M mutated advanced non-small-cell lung cancer (NSCLC).

Methods This study was a single-arm, open-label, phase 2b study at 46 hospitals across mainland China. Patients with locally advanced or metastatic NSCLC with centrally confirmed *EGFR* T790M mutations in tumour tissue who progressed after first or second generation EGFR TKIs or with primary *EGFR* T790M mutations received furmonertinib 80 mg orally once daily. The primary endpoint was objective response rate. Efficacy was assessed by blinded independent central review as per the Response Evaluation Criteria in Solid Tumors (version 1.1) in all patients who had measurable disease at baseline and received at least one dose of furmonertinib. Safety was assessed as per the Common Terminology Criteria for Adverse Events (version 4.03) in all patients who received at least one dose of furmonertinib with at least one safety assessment during follow-up. This study is registered with ClinicalTrials.gov (NCT03452592) and is ongoing for survival follow-up.

Findings From Jun 4, 2018, to Dec 8, 2018, 220 patients received furmonertinib treatment. All 220 patients were included in the efficacy and safety analyses. At the data cutoff point of Jan 29, 2020, 71 (32%) patients remained on treatment. The median duration of follow-up was 9·6 months (range 0·7–19·4). The objective response rate was 74% (163 of 220 [95% CI 68–80]). Grade 3 or higher adverse events occurred in 58 (26%) patients and treatment-related grade 3 or higher adverse events occurred in 25 (11%) patients. The most common all-cause grade 3 or higher adverse events were increased γ-glutamyltransferase (five; 2%), increased aspartate aminotransferase, increased alanine aminotransferase, hyponatraemia, hypertension, pulmonary infection, hypermagnesaemia, and pericardial effusion (three each; 1%). Treatment-related diarrhoea was reported in ten (5%) patients and rashes were reported in 16 (7%) patients, all grade 1–2. Serious adverse events were reported in 52 (24%) patients, of which 12 (5%) were possibly treatment-related as evaluated by the investigator.

Interpretation Furmonertinib has promising efficacy and an acceptable safety profile for the treatment of patients with *EGFR* T790M mutated NSCLC. Furmonertinib is expected to become a new treatment option after first or second generation EGFR TKIs in the Chinese population.

Funding Shanghai Allist Pharmaceutical Technology, Ministry of Science and Technology of the People's Republic of China, and Chinese Academy of Medical Sciences.

Introduction

Lung cancer is the most prevalent malignancy worldwide and has the highest incidence and mortality rates.[1] Non-small-cell lung cancer (NSCLC) is the predominant histological type in which activating mutations of the epidermal growth factor receptor (*EGFR*) gene are one of the most pervasive driver mutations. *EGFR* mutations are found in approximately 10% of Caucasian and 30–40% of east Asian patients,[2] predominantly in lung adenocarcinoma.[3,4] Exon 19 deletions (19del) and exon 21 Leu858Arg (L858R) mutations account for approximately 90% of these activating alterations.[3,4] By targeting these alterations, first and second generation EGFR tyrosine kinase inhibitors (TKIs) have been approved as the standard first-line therapy for patients who have advanced NSCLC with *EGFR* mutations, based on the excellent efficacy in randomised controlled studies.[5–10] However, all patients who initially respond to these EGFR TKIs will inevitably experience acquired resistance, mainly caused by the appearance of an *EGFR* Thr790Met (T790M)

Lancet Respir Med 2021

Published Online March 26, 2021 https://doi.org/10.1016/S2213-2600(20)30455-0

For the Chinese translation of the abstract see Online for appendix 1

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Research in context

Evidence before this study

We searched PubMed for papers with the terms "*EGFR* tyrosine kinase inhibitors", "osimertinib", "advanced lung cancer", and "ctDNA" for clinical trials published between Jan 1, 2010, and Jan 29, 2020, in English. To our knowledge, osimertinib is the only third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) approved for *EGFR* Thr790Met (T790M) mutated advanced non-small-cell lung cancer (NSCLC) after first or second generation EGFR TKI treatment, with published results of phase 2 and phase 3 studies; and is also the current standard of care as first-line treatment for NSCLC with *EGFR*-sensitive mutations. Preclinical data have shown that furmonertinib (AST2818) and its main metabolite AST5902 have high activity for both *EGFR* sensitising and *EGFR* T790M mutations. The safety, tolerability, antitumour activity, and pharmacokinetic analysis of the phase 1 dose-escalation study and a subsequent phase 1/2 dose-expansion study provided the preliminary clinical evidence of furmonertinib for the treatment of advanced NSCLC with *EGFR* T790M mutation (including patients with CNS metastases). This phase 2b study aimed to further evaluate the efficacy and safety of furmonertinib in patients with *EGFR* T790M-mutated NSCLC.

Added value of this study

This study showed the clinical activity of furmonertinib in patients who had *EGFR* T790M mutated advanced NSCLC, including those with CNS metastases. Furmonertinib was associated with an acceptable safety profile regarding skin and gastrointestinal toxicities, which are very common in other EGFR TKIs irrespective of generation. Our results suggest several possible predictive factors in plasma circulating tumour DNA (ctDNA) for prognosis of these patients treated by a third-generation EGFR TKI.

Implications of all the available evidence

The data from this study serve as evidence for the clinical benefit and potentially favourable safety profile of furmonertinib for patients with *EGFR* T790M-mutated advanced NSCLC with or without CNS metastases in a Chinese population. The study suggests that ctDNA is an option for molecular testing if tissue sample is unable to be collected and several factors in ctDNA can serve as predictors for prognosis. Ongoing studies are exploring overall survival in patients with NSCLC who have *EGFR* T790M mutations.

secondary mutation in exon 20.[11,12] This situation has led to the development of third-generation EGFR TKIs. Since Nov 13, 2015, osimertinib has gradually become a widely approved third-generation EGFR TKI that selectively blocks both *EGFR*-sensitive mutations and *EGFR* T790M resistance mutations. Besides acting against *EGFR* T790M mutations, osimertinib also works well against CNS lesions due to its good blood–brain penetration, whereas CNS progressions are more frequent when patients are treated with just first or second generation EGFR TKIs.[13] The resistance mechanism of osimertinib includes *EGFR*-dependent resistance alterations, such as *EGFR* mutations (mainly Cys797Ser), amplification and loss, and *EGFR*-independent resistance mechanisms, such as alternative kinase activation and small-cell transformation.[14]

Furmonertinib (AST2818) is a newly developed third-generation EGFR TKI. Preclinical studies have shown overall promising antitumour activity and selectivity of furmonertinib and its active metabolite AST5902 (unpublished). Phase 1 dose-escalation and phase 1/2 dose-expansion studies have also revealed that furmonertinib was clinically effective with acceptable toxicity in patients with *EGFR* T790M mutated advanced NSCLC.[15] Based on this evidence, a phase 2b study was designed to further assess the efficacy and safety of furmonertinib in patients with advanced NSCLC who have *EGFR* T790M mutations. Associations between furmonertinib efficacy and baseline *EGFR* T790M mutation status, as well as baseline blood tumour mutation burden (BTMB) and resistance mechanisms were also investigated.

Methods

Study design and participants

This study was a single-arm, open-label, phase 2b study at 46 hospitals across mainland China. Eligible patients were aged 18 years or older with histologically or cytologically confirmed locally advanced or metastatic NSCLC not suitable for operation or radiotherapy; had measurable disease according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1); Eastern Cooperative Oncology Group performance status of 0–2, without deterioration in the previous 2 weeks and at least a 12-week life expectancy; and radiological progression after first or second generation EGFR TKI therapy. All patients were required to be centrally confirmed *EGFR* T790M positive and *EGFR* 20 exon insertion negative by tumour tissue biopsy using the cobas *EGFR* Mutation Test (version 2, Roche Molecular Systems, Pleasanton, CA, USA). Patients with primary *EGFR* T790M mutations were included, whereas those who had previous treatment with third-generation EGFR TKIs were not included. Patients with asymptomatic stable CNS metastases not requiring steroids for at least 4 weeks before the first dose of furmonertinib were also included. Patients must have had adequate bone marrow reserve and organ function as defined by absolute neutrophil count $1{\cdot}5\times10^9$/L or higher, platelet count 75×10^9/L or higher, haemoglobin 90 g/L or higher, total bilirubin less than 1·5 times the upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) less than 2·5 times ULN (if liver metastases existed, total bilirubin ≤3×ULN, and ALT and AST ≤5×ULN were allowed), serum

creatinine less than 1·5 times ULN, or creatinine clearance 50 mL/min or higher according to the Cockcroft and Gault equation. All drug-related toxic effects (except for hair loss) had to be resolved to grade 1 according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 before starting furmonertinib. For platinum-based treatment-related neuropathy, the toxic effect could be relaxed to grade 2.

Key exclusion criteria included treatment with any cytotoxic chemotherapy or any other non-EGFR-TKI anticancer drugs within 14 days of the first dose of furmonertinib; treatment with any investigational drugs within 5 half-lives or 14 days of the first dose of furmonertinib; treatment with any EGFR TKIs within 5 half-lives; previous treatment with third-generation EGFR TKIs; any clinical evidence indicating severe or uncontrolled systemic disease, such as patients with uncontrolled hypertension, uncontrolled diabetes, coronary artery stenosis, aortic dissection, aortic aneurysm, active and haemorrhagic condition, or patients with hepatitis B virus (viral DNA ≥1000 copies per mL), hepatitis C virus, or HIV infection; any condition that possibly affects drug absorption; any factors that increased the risk of QTc prolongation or risk of arrhythmic events; medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis that required steroid treatment; patients with symptoms of acute or progressive lung disease or high risk factors that could lead to interstitial lung disease, in the judgment of the investigator; left ventricular ejection fraction less than 50% on echocardiography; pulmonary function test showing FEV_1/forced vital capacity ratio less than 70% and estimated percentage of FEV_1 less than 30%, or estimated percentage of carbon monoxide diffusing capacity less than 40%; and patients with *EGFR* 20 exon insertion mutation confirmed at any time since the initial diagnosis of NSCLC.

Written informed consent was obtained from all patients before enrolment in the study. This study was approved by the institutional review board or independent ethics committee associated with each study centre and done in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki.

Procedures

Patients were enrolled locally by investigators at participating sites. Eligible patients received furmonertinib 80 mg orally once daily on a continuous dosing schedule, until disease progression (defined according to RECIST 1.1), death, or treatment cessation for other reasons (including intolerable toxic effects or withdrawal from the study). The dose could be reduced to 40 mg per day for safety and tolerability, if necessary. Dose interruption was also permitted if a patient had a grade 3 or higher adverse events or unacceptable toxicity. If the adverse event resolved or returned to grade 2 or less within 21 days, furmonertinib treatment could be resumed at the same dose or a lower dose level. Otherwise, the patient should be discontinued from the study, and the adverse event should be followed up until recovery, stabilisation, or return to baseline. Treatment after disease progression was permitted in patients who continued to experience clinical benefits according to investigators. After disease progression, patients were followed up every 12 weeks until death, loss to follow-up, or withdrawal.

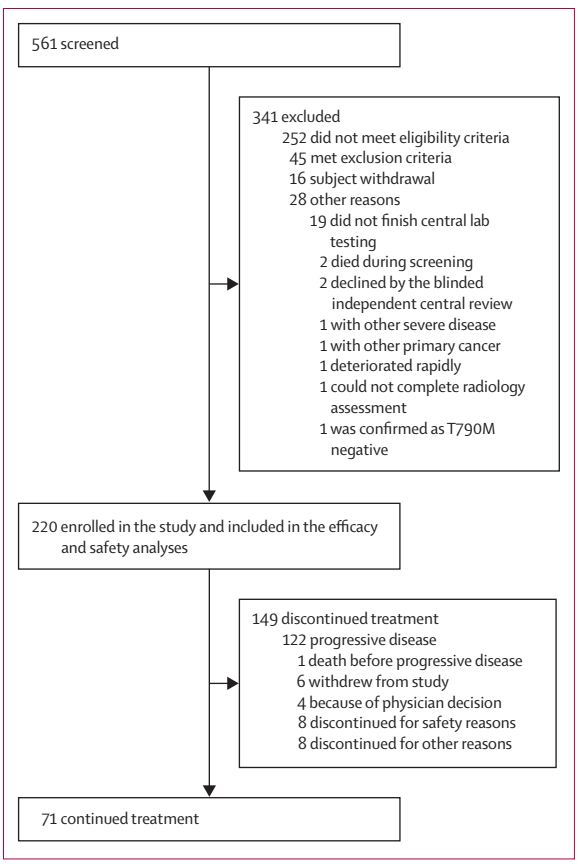

Figure 1: **Trial profile**

Tumour assessments with either CT or MRI scans of the chest, abdomen, pelvis, and any other suspected areas occurred at baseline every 6 weeks for the first 48 weeks, and then every 12 weeks until disease progression. In addition, CT or MRI of the brain was done at baseline; subsequent brain imaging was required with the same method used at baseline when clinically indicated and in patients with confirmed CNS metastases. Tumour response was assessed by investigators and blinded independent central review according to RECIST 1.1. The objective responses (complete response or partial response) were confirmed 6 weeks after an initial response was documented.

Adverse events were monitored throughout the study. Physical examinations, vital signs, Eastern Cooperative Oncology Group performance status scores, 12-lead electrocardiograms (ECGs), echocardiography,

For the **sambamba statistical software** see https://github.com/biod/sambamba

For the **VarDict statistical software** see https://github.com/AstraZeneca-NGS/VarDict

For the **CNVkit statistical software** see https://github.com/etal/cnvkit

	All patients (n=220)
Age, years	61 (29–80)
Sex	
Male	99 (45%)
Female	121 (55%)
Eastern Cooperative Oncology Group performance status	
0	41 (19%)
1	170 (77%)
2	9 (4%)
Smoking history	
Non-smoker	160 (73%)
Smoker	60 (27%)
Stage at enrolment	
III	8 (4%)
IV	212 (96%)
Previous lines of therapy	
0*	6 (3%)
1	163 (74%)
2	37 (17%)
3	9 (4%)
4	4 (2%)
>5	1 (1%)
Chemotherapy before entry	
Yes	75 (34%)
No	145 (66%)
EGFR mutations in tumour†	
T790M	220 (100%)
19del	136 (62%)
L858R	84 (38%)
Others	3 (1%)
CNS metastases‡	
Yes	105 (48%)
Previous brain radiotherapy	26 (12%)
No	115 (52%)

Data are median (range) or n (%). EGFR=epidermal growth factor receptor. *De-novo *EGFR* T790M mutation. †Three patients had both EGFR 19del and L858R mutations. ‡CNS metastases were determined from baseline data for the CNS lesion site, medical history, surgery, or radiotherapy.

Table 1: **Baseline clinical characteristics of patients in the full analysis set**

	Patients (n=220)
Complete response	0
Partial response	163 (74%)
Stable disease*	43 (20%)
Progressed disease	13 (6%)
Unevaluable	0
Not evaluated	1 (1%)
Objective response	74% (95% CI 68–80)
Disease control	94% (95% CI 90–97)

Data are n (%) or % (95% CI). *Stable disease of 6 weeks or more.

Table 2: **Summary of response to furmonertinib assessed by a blinded independent central review**

and laboratory tests were evaluated at baseline and protocol-specified time points.

Blood samples were collected for exploratory genetic analysis at baseline (after enrolment but before first dose of furmonertinib), 6 weeks after first study dose, and at the time of disease progression. Plasma samples were used for tumour DNA detection and leucocyte samples were used for normal DNA detection. The tumour and germline DNA from the same patient were detected by next-generation sequencing (Tongshu Biotech, Shanghai, China)—a target panel of 556 genes, with mean sequencing depths of more than 7000 times. The sequence data were aligned to the human reference genome (UCSC hg19) using Burrows-Wheeler Aligner (bwa-0.7.17.tar.bz2). Binary alignment or map format sorting and PCR duplication markings were done using sambamba. Simple somatic mutations were detected using VarDict with default parameters. Variants and polymorphisms were annotated with ANOVA. In-house post filtering was done to remove false positive mutations. Somatic copy number variations were analysed using CNVkit, using its threshold method to derive absolute integer copy number of each segment. Regions with a copy number of at least 3 were classified as amplifications. BTMB was calculated as number of non-synonymous mutations/1·4 MBASE.

Outcomes

The primary endpoint was the objective response rate, defined as the proportion of patients who had a complete or partial response as assessed by blinded independent central review. The secondary endpoints were disease control rate, duration of response, progression-free survival, overall survival, and safety. CNS response and CNS progression-free survival were also evaluated in patients with CNS lesions assessed by blinded independent central review at baseline. Efficacy was assessed with RECIST 1.1. Safety was assessed with CTCAE 4.03. Adverse events were judged to be treatment-related or not by investigators.

Disease control rate was defined as the proportion of patients with complete response, partial response, or stable disease. Duration of response was defined as the time from the date of first documented response with subsequent confirmation until the date of objective progression or death. Progression-free survival was defined as the time from the date of first study dose until the date of documented disease progression or all-cause death before disease progression. Overall survival was defined as the time from the date of first dose until the date of all-cause death.

The predictive role of some possible biomarkers, such as *EGFR* T790M mutation in baseline blood samples and baseline BTMB levels, in efficacy of furmonertinib were explored. Potential acquired resistance mechanisms of furmonertinib were analysed based on the

compared next-generation sequencing results of paired plasma samples at progression and baseline in patients who had baseline detectable circulating tumour DNA (ctDNA) *EGFR* mutations (exon 19 deletion, L858R, or T790M).

Statistical analysis

According to the results of previous phase 1/2 studies,[15] 55% of patients were estimated to have an objective response in this study. Thus, a sample size of 170 patients would be required to provide a lower limit of more than 45% for this estimation. Taking 15% dropouts into account, approximately 200 patients were planned to be enrolled in the study.

The efficacy analysis was done in the evaluable for response analysis set (ie, all patients who had measurable disease at baseline and received at least one dose of furmonertinib). The safety analyses were done in all patients who received at least one dose of furmonertinib with at least one safety assessment during follow-up. The objective response rate and disease control rate were calculated on the basis of the confirmed best overall response of tumours during the study, and the corresponding two-sided 95% CIs were determined using the Clopper-Pearson method. Prespecified subgroup analysis of objective response rate was done using the same method as the primary endpoint. For time-to-event efficacy analyses (duration of response, progression-free survival, and overall survival), median values and two-sided 95% CIs with Kaplan-Meier methods were used. SAS (version 9.4) was used for all statistical analyses. This study was registered with Clinical Trials.gov, NCT03452592.

Role of the funding source

The funder collaborated with the principal investigator (YS) to design the study and supervised the study throughout. They also provided funding and organisational support, collected the data, and were involved in the data analysis and interpretation. The medical writing was funded by the sponsor and reviewed and approved for publication by all co-authors and the sponsor.

Results

From June 4, 2018, to Dec 8, 2018, 561 patients were screened, of which 220 patients were enrolled and started on furmonertinib treatment (figure 1). Baseline characteristics are presented in table 1. All patients received at least one dose of furmonertinib, attended at least one safety follow-up, and no patients had inclusion criteria violations. Thus, all patients were included in analyses of efficacy and safety.

The efficacy was evaluated at the cutoff date of Jan 29, 2020. On this date, 71 (32%) of 220 patients remained on treatment. The median follow-up time was 9·6 months (range 0·7–19·4). Objective responses were found in 163 (74% [95% CI 68–80]) patients and disease control was achieved in 206 (94% [90–97]; table 2) patients. Objective responses were observed in all predefined subgroups (figure 2). Of the 163 patients deemed to have an objective response, 103 (63%) had subsequently progressed or died by the time of data cutoff. The median duration of response was 8·3 months (95% CI 8·3–11·1). Data for 60 (37%) patients were censored at data cutoff. The Kaplan-Meier curve for duration of response is shown in the appendix 2 (p 2). Tumour shrinkage was seen in 212 (96%) of 220 patients (figure 3).

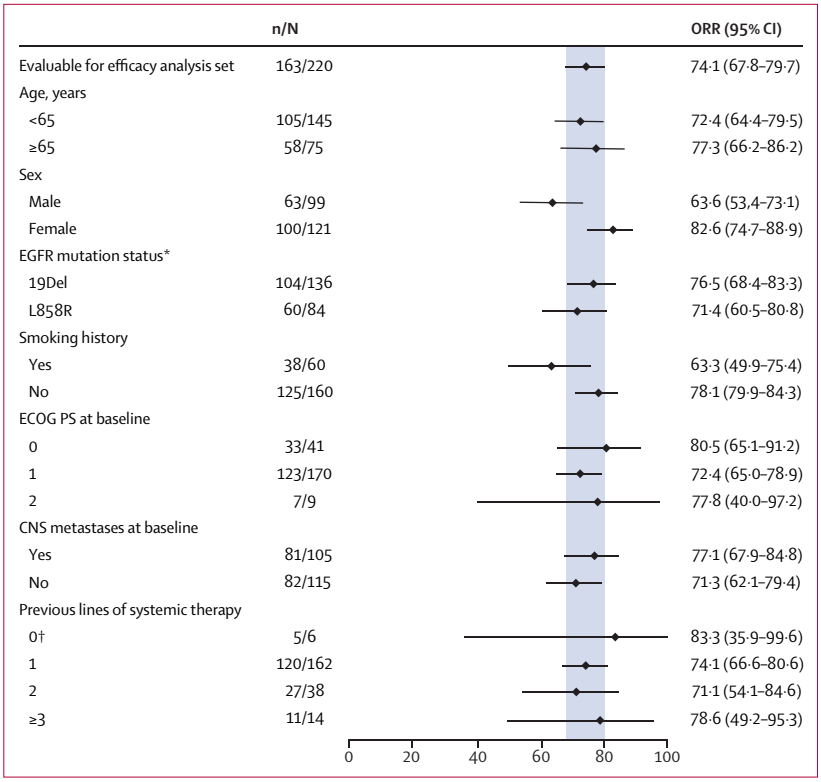

Figure 2: **Forest plot of subgroups of patients showing objective responses in the evaluable for efficacy analysis set**

ORR=objective response rate. EGFR=epidermal growth factor receptor. ECOG PS=Eastern Cooperative Oncology Group performance status. *Only patients with *EGFR* 19del and L858R mutations are reported; this includes three patients with both mutations and excludes three patients with other *EGFR* mutations. †De-novo *EGFR* T790M mutation.

At the cutoff date, 152 (69%) of 220 patients had progressed or died and data for the other 68 (31%) patients were censored. Median progression-free survival was 9·6 months (95% CI 8·2–9·7; figure 4). At the cutoff date, 54 (25%) patients had died. Thus, the median overall survival data were considered immature (appendix 2 p 2).

Of the 220 enrolled patients, 105 (48%) patients had CNS metastases at baseline. 87 (40%) patients who had measurable or non-measurable CNS lesions were defined as the CNS full analysis set, and 29 (13%) patients who had one or more measurable CNS lesions were defined as the CNS evaluable for response set. By Jan 29, 2020, in

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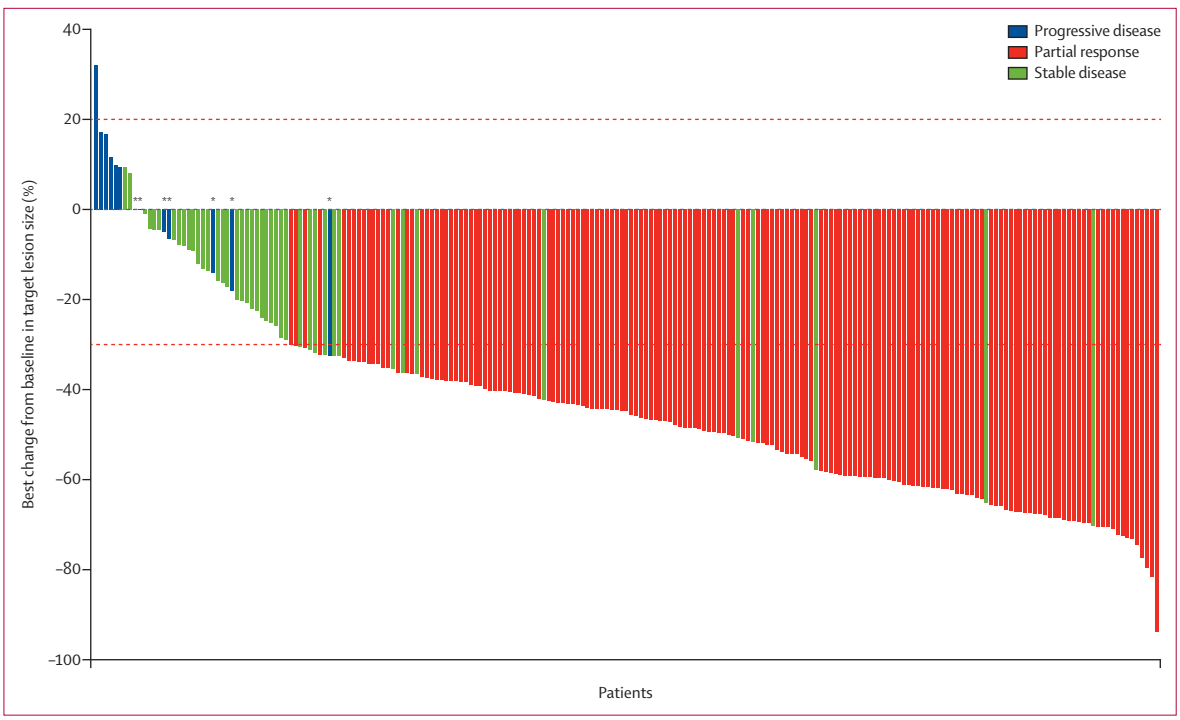

Figure 3: **Waterfall plot for best percentage change in target lesion size for all patients**
The dashed line at 20% represents the boundary for determination of progressive disease, and the dashed line at −30% represents the boundary for determination of partial response. *Patients with shrinkage of target lesion size but enlargement of other lesions, resulting in disease progression.

the CNS evaluable for response set, CNS objective responses were found in 19 (66% [95% CI 46–82]) patients and CNS disease control was found in all 29 (100%) patients. In the CNS full analysis set, the CNS objective response rate was 34% (30 of 87 [25–45]), the CNS disease control rate was 98% (85 of 87 [92–100]), and the median progression-free survival was 11·6 months (8·3–13·8).

At the cutoff date, the median duration of exposure to furmonertinib, irrespective of dose interruptions, was 9·7 months (range 0·7–19·4). 214 (97%) of 220 enrolled patients were reported to have at least one adverse event and 171 (78%) patients were reported to have at least one treatment-related adverse event as assessed by investigators (table 3). 58 (26%) patients had grade 3 or higher adverse events and 25 (11%) patients had grade 3 or higher treatment-related adverse events. The most common all-cause adverse events of grade 3 or higher were increased γ-glutamyltransferase, increased AST, increased ALT, hyponatraemia, hypertension, pulmonary infection, hypermagnesaemia, and pericardial effusion (appendix 2 pp 8–10). The most common treatment-related adverse events of grade 3 or more were increased ALT, increased AST, and increased γ-glutamyltransferase (table 4).

19 (9%) of the 220 patients reported diarrhoea and in ten (5%) patients it was considered treatment-related by investigators. 18 (8%) patients reported a rash and in 16 (7%) patients this was considered treatment-related by investigators. No grade 3 or higher treatment-related diarrhoea or rashes were observed in all 220 patients. Detailed information about other treatment-emergent adverse events is shown in appendix 2 (pp 8–10).

Grade 3 interstitial lung disease was observed in one (<1%) patient after 46 weeks of treatment with furmonertinib. Prolonged ECG QT interval was reported in 34 (15%) patients, all grade 1–2 adverse events. No patients had prolonged ECG QT interval of more than 500 ms. No patients had dose reduction or discontinuation of furmonertinib due to a prolonged ECG QT interval.

Doses of furmonertinib were reduced at least once in five (2%) patients and interrupted in 24 (11%) patients. Discontinuation of furmonertinib occurred in eight (4%) patients. Reasons for discontinuation were interstitial lung disease (n=1, possibly treatment-related), decreased platelet count (n=1, possibly treatment-related), gastric perforation (n=1, possibly treatment-related), embolism (n=1, possibly treatment-related), hypacusia (n=1, possibly not treatment-related), epilepsy (n=1, possibly not treatment-related), chest discomfort (n=1, possibly not treatment-related), and pulmonary embolism (n=1, possibly not treatment-related).

52 (24%) patients had serious adverse events; 12 (5%) patients had possibly treatment-related serious adverse events, which were abnormal liver function (two patients, 1%), vomiting, gastric perforation, gastritis, elevated ALT, elevated AST, decreased platelet count, hypertension, embolism, hyperuricemia, acute pyelonephritis, and interstitial lung disease (one patient each, <1%).

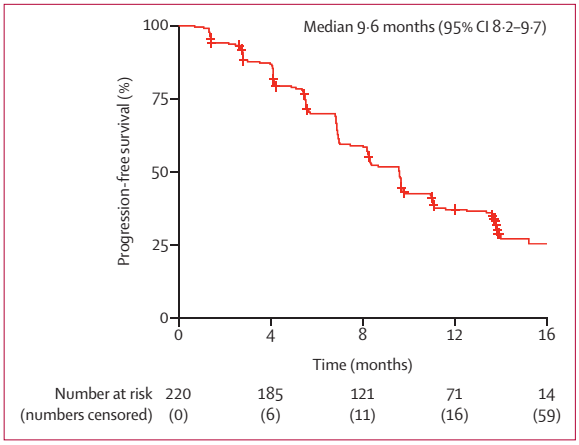

Figure 4: **Kaplan-Meier estimates of progression-free survival in all patients**

	Patients (n=220)
Any adverse event	214 (97%)
Treatment-related adverse event*	171 (78%)
Grade ≥3 adverse event	58 (26%)
Treatment-related grade ≥3 adverse event*	25 (11%)
Dose interruption due to adverse event	24 (11%)
Dose reduction due to adverse event	5 (2%)
Discontinuation due to adverse event	8 (4%)
Discontinuation due to treatment-related adverse event*	4 (2%)
Any serious event	52 (24%)
Treatment-related serious event*	12 (5%)
Any adverse event with outcome of death	4 (2%)
Any treatment-related adverse event with outcome of death*	1 (<1%)

Data are n (%). *Assessed by investigator.

Table 3: **Overview of adverse events**

	Grade 1–2	Grade 3–4	Grade 5
Prolonged electrocardiogram QT interval	34 (15%)	0	0
Increased aspartate aminotransferase	32 (15%)	3 (1%)	0
Increased alanine aminotransferase	31 (14%)	3 (1%)	0
Decreased white blood cell count	27 (12%)	0	0
Decreased platelet count	14 (6%)	1 (<1%)	0
Hyperuricemia	11 (5%)	2 (1%)	0
Decreased neutrophil count	10 (5%)	2 (1%)	0
Vomiting	8 (4%)	2 (1%)	0
Abnormal liver function	8 (4%)	1 (<1%)	0
Anorexia	8 (4%)	1 (<1%)	0
Increased γ-glutamyltransferase	6 (3%)	3 (1%)	0
Increased blood uric acid	6 (3%)	1 (<1%)	0
Hypertension	3 (1%)	2 (1%)	0
Hypokalaemia	3 (1%)	1 (<1%)	0
Hypertriglyceridaemia	3 (1%)	1 (<1%)	0
Hypermagnesaemia	3 (1%)	1 (<1%)	0
Hyponatraemia	2 (1%)	2 (1%)	0
Gastritis	1 (<1%)	1 (<1%)	0
Urinary tract infection	1 (<1%)	1 (<1%)	0
Gastric perforation	0	1 (<1%)	0
Acute pyelonephritis	0	1 (<1%)	0
Interstitial lung disease	0	1 (<1%)	0
Embolism	0	1 (<1%)	0
Death (reason indeterminable)	0	0	1 (<1%)

Data are n (%). Treatment-related adverse events in 220 patients were assessed by an investigator. Grade 1 or 2 treatment-related adverse events of 10% or higher and all grade 3–5 treatment-related adverse events are reported.

Table 4: **Treatment-related adverse events**

Four adverse events with an outcome of death were recorded, including CNS metastases (n=2), respiratory failure (n=1), and death of unknown cause (n=1). The causality between the study drug and the first three adverse events were assessed as probably not related by investigators, whereas the fourth adverse event could not be assessed due to the indeterminable cause of death.

Of the 220 enrolled patients, 167 (76%) patients provided plasma samples for ctDNA testing at baseline, 154 (70%) patients after 6 weeks of treatment, and 144 (65%) patients at disease progression. The flow of patients who received ctDNA next-generation sequencing is shown in appendix 2 (p 3).

At baseline, 132 (79%) patients were identified as plasma *EGFR* T790M positive and 35 (21%) patients were plasma *EGFR* T790M negative. Median progression-free survival was similar between these two groups of patients (6·9 [95% CI 6·9–8·3] months *vs* 6·8 [4·1–12·5] months; hazard ratio [HR] 0·99 [95% CI 0·65–1·49], p=0·96; appendix 2 p 5). After 6 weeks of treatment with furmonertinib, *EGFR* T790M clearance was tested in 123 patients and 105 (85%) patients had complete clearance (appendix 2 p 4). The median progression-free survival of patients still harbouring plasma *EGFR* T790M mutation after 6 weeks of treatment (n=18, 15%) was shorter than those with complete clearance of *EGFR* T790M (n=105, 85%) but with no statistical significance (6·9 [95% CI 5·6–9·7] months *vs* 8·2 [6·9–9·6] months; HR 1·48 [0·89–2·51], p=0·14; appendix 2 p 6). 142 patients were analysed to further reveal the prognostic value of baseline BTMB in *EGFR* T790M mutated advanced NSCLC treated with furmonertinib (appendix 2 p 3). Objective cut-points for BTMB are not yet well established. Most clinical studies use median BTMB as study-specific cut-points or divide patients in tertiaries or quartiles accordingly to measured BTMB.[16] In this specific population, the first quartile BTMB was 2·23. When dividing these patients into BTMB high group (BTMB ≥2·23, n=106, 75%) and BTMB low group (BTMB <2·23, n=36, 25%), the median progression-free survival was 7·0 (95% CI 6·9–8·3) months versus 9·6 (6·9–15·2) months (HR 1·73 [1·10–2·71], p=0·017;

appendix 2 p 6). The 142 patients were then separated into two subgroups according to the presence (n=69, 49%) or absence (n=73, 51%) of additional gene aberrations (including tumour suppressor genes *TP53*, *RB1*, *PTEN*, oncogenic drivers, *MET*, *ERBB2*, *KRAS*, *BRAF*, *RET*, *ROS1*, and *EGFR* amplification). The median progression-free survival was 7·0 (6·8–8·3) months for the presence group and 8·3 (6·9–9·7) months for the absence group (HR 1·26 [0·87–1·82], p=0·21; appendix 2 p 7). Another analysis for prediction of prognosis was bypass pathway amplification, these 167 patients were separated into two other subgroups based on the presence (n=52, 31%) or absence (n=115, 69%) of additional gene amplifications (including *EGFR*, *MET*, *CCNE1*, *MYC*, *ERBB2*, *PIK3C2B*, and *RET* amplifications). The median progression-free survival was 5·6 (5·4–7·0) months in the additional gene amplification presence group and 8·3 (7·0–9·6) months in the absence group (HR 1·46 [1·02–2·09], p=0·032; appendix 2 p 7).

In this study, next-generation sequencing data at disease progression (n=116, 53%) revealed possible *EGFR*-dependent and *EGFR*-independent resistance mechanisms of furmonertinib. The most frequent gene aberrations were acquired *EGFR* mutations, including Cys797Ser/Gly (C797S/G; 11, 9%), Leu792Phe/Tyr/His (seven, 6%), Leu718Gln (two, 2%), and Gly796Ser (two, 2%). All these patients harboured *EGFR* T790M mutations at progression and all C797S/G mutations are in cis with *EGFR* T790M mutations. Other possible acquired resistance mechanisms are listed in the appendix 2 (p 10).

Discussion

This study represents the phase 2b data with furmonertinib, the newly developed third-generation EGFR TKI to treat patients with advanced NSCLC who have confirmed *EGFR* T790M mutations. High objective response rates and disease control rates with clinically significant duration of response and progression-free survival were observed in this study, including in patients with CNS metastases. The safety profile with furmonertinib in this study was acceptable and manageable. These findings are consistent with the previous phase 1/2 study of furmonertinib in patients with *EGFR* T790M-positive tumours,[15] and support the recommendation of furmonertinib for the treatment of patients with *EGFR* T790M-positive advanced NSCLC after progression with previous first or second generation EGFR TKI therapy.

To our knowledge, the objective response rate (74%) and disease control rate (94%) with furmonertinib recorded in this study remain numerically the highest among third-generation EGFR TKIs in patients with *EGFR* T790M-positive advanced NSCLC. In the AURA17 study,[17] which was also done in an Asian population, osimertinib had an objective response rate of 62% and a disease control rate of 88%. In a pooled analysis of two phase 2 studies (AURA extension and AURA2) and in the AURA3 study, osimertinib had an objective response rate of 66% and 71%, and a disease control rate of 91% and 93%, respectively.[18,19] The objective response rate and disease control rate for almonertinib in Asian patients were 68·4% and 93·4% in a phase 2 study;[20] for lazertinib were 54% and 87% across all doses in a phase 1/2 study;[21] nazartinib were 51% and 89% across all doses in a phase 1 study.[22] The high outcomes for furmonertinib might be related to the fact that both furmonertinib and its metabolite AST5902 can irreversibly inhibit both *EGFR*-sensitive mutations and the *EGFR* T790M mutation.[15] The median progression-free survival (9·6 months) with furmonertinib was also comparable with osimertinib (9·7 months in AURA17,[17] 9·9 months in the AURA pooled analysis,[18] and 10·1 months in AURA3[19]).

Notably, a high proportion of patients with CNS metastases and *EGFR* L858R mutations were enrolled in this study. The proportion of patients with CNS metastases was 48% in this study, 33% in AURA3,[19] 37% in AURA17,[17] 39% in the AURA pooled analysis,[18] and 37% in the almonertinib phase 2 study.[20] Patients with CNS metastases usually have shorter progression-free survival compared with those without.[18,23] Additionally, the prognosis of patients with *EGFR* L858R mutations is usually worse than those with *EGFR* 19del.[18,23] Although the L858R mutation rate in this study (38%) is higher compared with the AURA series studies (AURA pooled analysis 29%,[18] AURA3 study 31%,[19] and AURA17 study 35%),[17] there is only a slight difference. In total, the higher proportion of these patients might be closer to real clinical practice but might be negatively associated with the efficacy of EGFR TKIs. Despite these baseline differences, furmonertinib still had an encouraging objective response rate and disease control rate as well as a comparable progression-free survival with other third-generation EGFR TKIs.

Patients with CNS metastases usually have a worse prognosis even when treated with EGFR TKIs. In this study, furmonertinib showed clinically meaningful activity in patients with *EGFR* T790M-positive NSCLC and CNS metastases. The CNS objective response rate of 66% and CNS disease control rate of 100% in patients evaluable for response and median CNS progression-free survival of 11·6 months in the full analysis set were consistent with that reported for the overall patient population. These data again show that third-generation EGFR TKIs share a good CNS activity due to their good blood–brain penetration in addition to activity against *EGFR* T790M.

In this study population, furmonertinib was well tolerated with low incidence of grade 3 or worse adverse events that were possibly related to treatment. This finding is consistent with previous phase 1/2 studies.[15] Diarrhoea and rashes are common adverse events of EGFR TKIs and were also reported in 29–39% and 28–42% of patients in the AURA series studies;[18,19]

approximately 1% of these patients had grade 3 or more adverse events.[18,19] In our study, treatment-related diarrhoea and rash were reported in only 5% and 7% patients, but none of these adverse events were grade 3 or higher. These data show the high selectivity of furmonertinib with *EGFR* of sensitive mutations against *EGFR* of wild type. In our study, only one patient (<1%) had interstitial lung disease of grade 3 after 46 weeks of furmonertinib treatment, which was not observed in the phase 1/2 study even at the dose of 240 mg per day (n=18).[15] AURA17[17] and AURA3[19] studies of osimertinib reported interstitial lung disease in 1% and 3% patients. The phase 1 study of nazartinib also reported pneumonitis or interstitial lung disease in 2% of patients.[22] There is currently no evidence of a higher risk of interstitial lung disease of furmonertinib compared with other third-generation EGFR TKIs. Another important adverse event was prolonged ECG QT interval, which was reported in 15% patients in our study. However, there were no grade 3 or higher prolonged ECG QT interval (>500 ms) and no case was led to dose reduction or discontinuation. The overall impact of furmonertinib on QT interval seems mild and manageable. Data from this study indicate furmonertinib has an overall acceptable and manageable safety profile from a purely clinical perspective. However, data on health-related quality of life were not collected in our study. Therefore, even though the initial safety profile has been shown on a small number of highly selected patients in a single health-care system over a short period of follow-up from this study, the safety profile largely remains to be shown. The data of health-related quality of life are being collected in the ongoing phase 3 study of furmonertinib (NCT03787992) and will be reported in the planned publications.

Safety data for osimertinib, furmonertinib, lazertinib, nazartinib, and almonertinib have been published. Although all these drugs are third-generation EGFR TKIs and some of their data are preliminary, some information of interest can be found. For example, serum creatine phosphokinase elevation was reported in 46 (19%) of 244 patients in the phase 2 study of almonertinib and 15 (6%) of these patients had grade 3–5 events;[20] peripheral oedema was observed in 22 (12%) of 180 patients in a phase 1 study of nazartinib across all doses.[22] Both these events were much less reported for other EGFR TKIs, including osimertinib, furmonertinib, and lazertinib.

Compared with tumour tissues, ctDNA is easily obtained non-invasively (or minimally) and can be a specific and sensitive biomarker for the detection of *EGFR* mutations in patients with NSCLC. Therefore, a plasma ctDNA assay could be used to identify *EGFR* mutations, when tissue is limited or insufficient for molecular testing. In our study, ctDNA was also used to identify the plasma *EGFR* mutation status and BTMB and evaluate whether these factors could predict the prognosis of advanced NSCLC with *EGFR* T790M mutation treated with furmonertinib. Plasma versus tissue *EGFR* T790M detection showed a high consistency, which was similar with previous studies.[24] The median progression-free survival was similar between patients with and without plasma *EGFR* T790M mutation, indicating that patients with a plasma *EGFR* T790M-negative result who progressed on previous first or second generation EGFR TKIs should try tissue biopsy to seek the treatment chance of third-generation EGFR TKIs, if possible. Median progression-free survival was longer in patients with plasma *EGFR* T790M clearance than those without at 6 weeks, but did not show any statistical significance. However, other studies had shown that patients with early ctDNA clearance had a significantly longer progression-free survival than those without.[25,26] The different results of our study versus other studies[25,26] might be caused by the different patient population, treatment, and sample size, which need further exploration. Patients with lower BTMB at baseline had significantly better outcomes (longer median progression-free survival), which indicated that patients with high BTMB might need more effective treatment. The impact of high BTMB on progression-free survival could be caused by an increased pace with which a resistance mechanism would lead to progression under the selective pressure of EGFR TKIs.[26] Additionally, combinative bypass gene amplifications had predictive effects on poor prognosis in patients with advanced NSCLC who had *EGFR* T790M mutations. Similarly, the BENEFIT study[27] showed poor predictive effects of accompanying gene aberrances on prognosis of gefitinib. These studies suggest that additional gene aberrations should be detected at baseline to find patients who might need combined treatment approaches other than EGFR TKI monotherapy.

Similar to earlier generation EGFR TKIs and osimertinib, resistance to furmonertinib would inevitably occur. In our study, *EGFR*-dependent and *EGFR*-independent resistance mechanisms were found. Within the patients who still had *EGFR* T790M mutations at the time of resistance, acquired *EGFR* C797X presented in 11 patients in our study, which is also the most common tertiary *EGFR* mutation that occurred in the resistance to osimertinib treatment.[28] Further deeper analysis of possible resistance mechanisms of furmonertinib in *EGFR* T790M-mutated advanced NSCLC is ongoing.

After the release of FLAURA study,[23] osimertinib has become a new standard of care for first-line treatment of NSCLC. Based on the encouraging data of furmonertinib in patients with advanced *EGFR* T790M-positive NSCLC, a first-line phase 3 study of furmonertinib (NCT03787992) is ongoing.

This study has several limitations. First, it is a single-arm study and the subgroup analysis is not prespecified and, therefore, the subgroup results are descriptive and have no comparator group. Second, the study was done in one country within one single ethnicity so the comparison between different studies should be

done cautiously as ethnicity might have a potential effect on the results.[29] Third, for some analyses, significance might not have been reached as blood samples for next-generation sequencing were not collected from all patients and some potential bias could have played a part.

Furmonertinib showed promising clinical antitumor activity in patients with *EGFR* T790M-mutated NSCLC, including those with CNS metastases. Furmonertinib also showed an acceptable and manageable safety profile. Therefore, furmonertinib is expected to become a new treatment option for NSCLC patients with *EGFR* T790M mutation after first and second generation EGFR TKIs in the Chinese population.

Contributors

YS was the leading principal investigator and designed the study with the funder. YS, XH, SZ, DL, LW, QY, YZ, LL, XW, YC, ZM, HN, DW, JF, CH, CL, HZ, JL, and XZ were investigators and involved in patient recruitment and data acquisition. YJ and CG did the data analysis and interpretation. All authors reviewed and approved the final version of the manuscript. YS and CG verified the data. All authors had full access to the data in the study and final responsibility for the decision to submit for publication.

Declaration of interests

YJ and CG are employees and shareholders of Shanghai Allist Pharmaceutical Technology. All other authors declare no competing interests.

Data sharing

Data generated and analysed in this study are on file with Shanghai Allist Pharmaceutical Technology and are not publicly available according to the company.

Acknowledgments

This study was funded by Shanghai Allist Pharmaceutical Technology and was also supported by the China National Major Project for New Drug Innovation (grant numbers 2017ZX09304015, 2018ZX09301014009, and 2019ZX09201–002) and the Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (2016-I2M-1–001). We appreciate all the sites that contributed to recruitment, the patients and their families who participated in this study, and participating study teams. Medical writing assistance for this manuscript was provided by Ying Du from Tongshu Biotech and was funded by Shanghai Allist Pharmaceutical Technology. We thank Shiyu Jiang (National Cancer Center and National Clinical Research Center for Cancer and Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College) for editorial assistance.

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