

Efficacy and safety of furmonertinib in patients with EGFR-mutant advanced lung adenocarcinoma after failure of multiple lines of therapy: A single-center retrospective study

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Abstract. Currently, treatments for patients with non-small cell lung cancer harboring epidermal growth factor receptor (EGFR) mutations are limited after receiving multiple lines of therapy. Furmonertinib, a newly developed third-generation EGFR-tyrosine kinase inhibitor (TKI), has shown potential as a subsequent treatment. To explore efficacy and safety of furmonertinib, the present retrospective study analyzed patients with EGFR-mutant advanced lung adenocarcinoma (LUAD) who received furmonertinib after the failure of multiple lines of therapy at the China-Japan Friendship Hospital (Beijing, China) between December 2021 and April 2024. Data on patient demographics, treatment efficacy and safety outcomes were assessed until disease progression. A total of 25 patients with advanced LUAD were retrospectively included in the analysis. Among them, 15 (60.0%) harbored exon 19del, whilst 10 (40.0%) had exon21 L858R mutations. Pre-treatment genetic testing was performed in 14 patients (56.0%). Prior to furmonertinib therapy, 17, 5 and 19 patients had previously received first-, second- and third-generation EGFR-TKIs, respectively. The median line of treatment before furmonertinib was 3. The median progression-free survival was 5.73 (95% confidence interval, 4.30-not reached) months. The objective response rate was 16.0% (n=4) and the disease control rate was 88.0% (n=22). A total of 18 (72.0%) patients experienced at least one adverse event (AE). The rate of AEs was 80.0% (n=20) for grade 1-2, and 20.0% (n=5) for grade 3-4 AEs. No AEs led to treatment discontinuation, dose reductions or death. In conclusion, furmonertinib is a viable treatment

option for patients with EGFR-mutant advanced LUAD after the failure of multiple lines of therapy, even after resistance to treatment with third-generation EGFR-TKIs targeted agents. However, further large-scale clinical studies are warranted to validate these findings.

Introduction

Over the past two decades, notable advancements in the management of non-small cell lung cancer (NSCLC) have included the identification of oncogenic-driven subtypes and the development of targeted therapies (1). Among these subtypes, epidermal growth factor receptor (EGFR) is the most common driver mutation, present in ~51.4% of patients with lung adenocarcinoma (LUAD) in the Asian population. The predominant EGFR mutations, comprising exon 19 deletion (del) and exon 21 L858R mutation, account for ≤90% of cases (2,3). Furthermore, the introduction of EGFR-tyrosine kinase inhibitors (TKIs) has substantially improved clinical outcomes, with overall survival (OS) extending to 38.6 months in previously untreated patients with EGFR-mutant advanced NSCLC (4). The standard first-line therapy for patients with LUAD harboring EGFR mutations remains EGFR-TKIs (5). However, the emergence of resistance to EGFR-TKIs is inevitable, posing a marked therapeutic challenge across all generations of these inhibitors (6). Existing guidelines recommended a limited number of subsequent treatment options, such as chemotherapy and angiogenesis inhibitors, which are associated with modest limited clinical efficacy (7).

Furmonertinib is a newly developed irreversible third-generation EGFR-TKI with a trifluoroethoxypyridine-based molecular structure, designed to enhance target specificity and therapeutic efficacy. Emerging studies and case reports indicate that furmonertinib exerts favorable effects on patients previously treated with other EGFR-TKIs or those harboring uncommon EGFR mutations (8-10). Based on these findings, clinicians are increasingly considering furmonertinib as a potential therapeutic option in later-line therapy. Moreover, an increasing number of patients with EGFR-mutated LUAD, particularly those who have undergone multiple lines of

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therapy, are receiving furmonertinib as a novel treatment strategy (9,11).

Therefore, the present study aimed to retrospectively analyzed real-world data on furmonertinib use in patients with EGFR-mutant advanced NSCLC, to assess its efficacy, safety profile and potential predictors of treatment response after multiple lines of therapy.

Materials and methods

Participants and study design. Data from patients with EGFR-mutant advanced LUAD who received furmonertinib after the failure of multiple lines of therapy at the China-Japan Friendship Hospital (Beijing, China) from December 2021 to April 2024 were included. The final follow-up was performed in July 2024. Inclusion criteria were as follows: i) Histologically or cytologically confirmed unresectable locally advanced or metastatic LUAD; ii) presence of EGFR mutations confirmed through molecular testing; iii) failure of ≥ 2 prior lines of treatment; iv) treatment with furmonertinib either as a monotherapy or in combination with other anti-tumor treatments; and v) presence of ≥ 1 measurable target lesion as defined by the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 criteria (12). Exclusion criteria were as follows: i) Duration of furmonertinib treatment of < 1 month; ii) concurrent malignancies requiring active treatment; and iii) unavailable or incomplete medical records. The present retrospective study was approved by the Institutional Ethics Review Committee of the China-Japan Friendship Hospital (approval no. 2024-KY-104) and was performed according to the principles of the Declaration of Helsinki. Given the retrospective design of the study, the requirement for written informed consent was waived.

Data collection. Data were extracted for each patient, including clinical characteristics and treatment-related information. The clinical characteristics included age, sex, surgical history, histological subtype, EGFR mutation status at initial diagnosis, clinical stage, presence of organ metastases (including pleura, bone, lung, brain, leptomeninges, adrenal gland and liver), gene mutation status before furmonertinib treatment and sites of disease progression before initiating furmonertinib treatment. Treatment-related information included previous administration of EGFR-TKIs, time to initiation of furmonertinib, duration of furmonertinib intake, use of combination therapies and occurrence of adverse events (AEs).

Efficacy and safety assessments. Efficacy was assessed according to the RECIST v1.1 criteria. The primary efficacy was progression-free survival (PFS), defined as the duration from initiation of furmonertinib to either documented disease progression or death from any cause. Safety assessments were performed using the National Cancer Institute-Common Terminology Criteria for Adverse Events version 5.0 (13).

Statistical analysis. Statistical methods were selected according to the data type. The Kolmogorov-Smirnov test was used to analyze the normality of data distribution. Quantitative variables were described as mean $\pm$ standard deviation or median (interquartile range) according to their distribution

(normal or non-normal, respectively). Categorical variables are presented as n (%). Kaplan-Meier survival curves were used to estimate the PFS, with differences in survival distributions assessed using the log-rank test. The median PFS (in months) and the corresponding 95% confidence interval (CI) were reported. All statistical analyses were performed using R software (version 4.0.3; The R Foundation). $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Baseline characteristics. The present study was a retrospective study involving 25 patients with EGFR-mutant advanced LUAD who received furmonertinib following the failure of multiple lines of therapy. The participants were treated at the China-Japan Friendship Hospital, between December 2021 and April 2024. The median age was 62.92 ± 12.56 years and 60.0% of the included patients were female. Additionally, 28.0% had a history of surgery and 96.0% were diagnosed with stage IV disease. The pathological subtype for all patients was adenocarcinoma. The most common sites of metastasis included the lung (52.0%), pleura (44.0%), brain (40.0%) and bone (40.0%). Further clinical assessments revealed that between the predominant EGFR mutations, 15 (60.0%) patients harbored exon 19del, whilst 10 (40.0%) patients harbored exon21 L858R mutations. Furthermore, 14 patients (56.0%) underwent genetic testing before receiving furmonertinib therapy, with the results revealing a diverse range of co-mutations, such as FGFR3/RB1, KRAS, MET, MET/18E709K, T790M and TP53.

The median number of prior lines of therapy before initiating furmonertinib treatment, either as a monotherapy or in combination with other therapies, was 3 (interquartile range, 2-4). Notably, one patient had undergone up to seven lines of systemic treatment before furmonertinib. Furmonertinib monotherapy was the most common (76.0%) treatment option. Among patients who received combination therapy, three patients (12.0%) underwent radiotherapy directed at the brain, two patients (8.0%) underwent chemotherapy, involving pemetrexed and carboplatin, and one patient (4.0%) underwent a combination of targeted therapy and chemotherapy. In terms of dosage, six patients were administered a double dose (160 mg), whilst 19 patients received a conventional dose (80 mg). The baseline demographics of the study population are presented in Table I.

A summary of previous treatments with EGFR-TKIs for patients receiving furmonertinib is presented in Table I and Fig. 1. Records indicated that 23 patients (92.0%) had previously received EGFR-TKI treatment. Specifically, 17 patients had previously received first-generation EGFR-TKIs, 5 had received second-generation, and 19 had received third-generation. Among these EGFR-TKI generations, gefitinib ($n=10$; 40.0%), afatinib ($n=3$; 12.0%) and osimertinib ($n=17$; 68.0%) were the most common treatments, respectively. Notably, the records revealed that prior to furmonertinib therapy, a marked proportion of patients ($n=12$) had received both first- and third-generation EGFR-TKIs. First-generation EGFR-TKIs were administered to three patients, second-generation EGFR-TKIs to one and third-generation EGFR-TKIs to three. Additionally,

Table I. Clinical characteristics of patients with advanced lung adenocarcinoma who received furmonertinib after multiline therapy failure (n=25).

Characteristic	Value
Age, years	62.92±12.56
Sex	
Female	15 (60.0)
Male	10 (40.0)
Surgical history	
Yes	7 (28.0)
No	18 (72.0)
Histological type	
Adenocarcinoma	25 (100.0)
Other	0 (0.0)
Clinical stage before furmonertinib	
IIIB	1 (4.0)
IVA	13 (52.0)
IVB	11 (44.0)
Organ metastasis	
Adrenal glands	2 (8.0)
Bone	10 (40.0)
Brain	10 (40.0)
Leptomeninges	3 (12.0)
Lung	13 (52.0)
Liver	2 (8.0)
Pleura	11 (44.0)
EGFR mutation status at diagnosis	
Exon 19del	15 (60.0)
Exon21 L858R	10 (40.0)
Combined mutations at diagnosis	
Unknown	23 (92.0)
KRAS	1 (4.0)
T790M	1 (4.0)
Genetic testing before furmonertinib	
Yes	14 (56.0)
No	11 (44.0)
EGFR mutation status before furmonertinib	
Exon 19del	8 (57.1)
Exon21 L858R	4 (28.6)
No mutation	2 (14.3)
Combined mutations	
FGFR3/RB1	1 (7.7)
KRAS	1 (7.7)
MET	1 (7.7)
MET/18E709K	1 (7.7)
T790M	3 (23.1)
TP53	1 (7.7)
No	5 (38.5)
First-generation EGFR-TKIs	
Gefitinib	10 (40.0)
Icotinib	7 (28.0)
No treatment	9 (32.0)

Table I. Continued.

Characteristic	Value
Second-generation EGFR-TKIs	
Afatinib	3 (12.0)
Dacomitinib	2 (8.0)
No treatment	20 (80.0)
Third-generation EGFR-TKIs	
Almonertinib	1 (4.0)
Osimertinib	17 (68.0)
Rezivertinib	1 (4.0)
No treatment	6 (24.0)
Combination therapy	
Monotherapy	19 (76.0)
Chemotherapy	2 (8.0)
Radiotherapy	3 (12.0)
Targeted + chemotherapy	1 (4.0)
Treatment line	3.00 (2.00-4.00)
Medication dosage	
Normal dose (80 mg)	19 (76.0)
Double dose (160 mg)	6 (24.0)

Data are presented as mean ± standard deviation, median (interquartile range) or n (%). EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

two patients received sequential treatment with EGFR-TKIs, spanning from the first to the third generation. Furthermore, two patients had no history of prior treatment involving EGFR-TKIs.

Survival analysis. Using a data cut-off of July 2024, disease progression or death was observed in 16 patients (64.0%), whilst 9 patients (36.0%) remained progression-free. The median (m)PFS was 5.73 months [95% CI, 4.30-not reached (NR)] for the 25 patients with EGFR-mutant advanced NSCLC (Fig. 2A). Moreover, among the 25 patients included in the present study, the best response was partial response (PR) in 4 patients (16.0%), stable disease (SD) in 18 patients (72.0%) and progressive disease in 3 patients (12.0%), with no patient achieving a complete response. The objective response rate was 16.0% (n=4) and the disease control rate was 88.0% (n=22). Notably, one patient who received four cycles of furmonertinib combined with chemotherapy, followed by furmonertinib monotherapy as maintenance, achieved sustained SD for ~30.3 months. Furthermore, in the subgroup of 19 patients who had previously developed resistance to third-generation EGFR-TKIs, the median PFS was also 5.73 months (95% CI, 4.30-NR; Fig. 2B). Among these patients, 17 had previously received treatment with osimertinib. Similarly, the median PFS for this subgroup remained at 5.73 months (95% CI, 4.20-NR; Fig. 2C). Only nine patients reached the mortality endpoint for OS, and four were lost to follow-up by the cut-off date. Consequently, the survival rate was 57.1%. However, the OS data are not yet mature enough for analysis.



Figure 1. Sunburst of previous epidermal growth factor receptor-tyrosine kinase inhibitor treatments received before furmonertinib. The inner to outer circles represent the first, second and third generations of EGFR-TKIs. The numbers refer to the number of patients who received EGFR-TKI. No, the patient did not receive the corresponding EGFR-TKIs. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

Subgroup analysis. The present study aimed to assess whether certain clinical characteristics influence the efficacy of furmonertinib as a subsequent treatment. To achieve this, subgroup analyses were performed based on clinical characteristics, EGFR mutation status at initial diagnosis and previous treatment agents. The results indicated that the number of treatment lines may be a significant negative prognostic factor [hazard ratio (HR)=1.54; P=0.029]. However, the reliability of these findings is limited by the relatively small sample size. Beyond this observation, the results did not reveal any other significant differences in the subgroup analyses (Fig. 3).

To validate the aforementioned findings, a sensitivity analysis was performed, excluding patients who received combination therapy (Table SI). Additionally, Bonferroni's

correction was applied to the multiplicity test. However, the association between the number of treatment line and survival outcome did not remain significant after adjustment for multiple comparisons.

Furthermore, to evaluate potential prognostic factors influencing the efficacy of furmonertinib, subgroup analyses were performed considering the influence of distant organ metastases and other clinical factors. The patients were classified into four groups based on the existing published literature (9,14) and clinical experience: i) Based on the metastatic site, patients were divided into two groups based on whether the metastatic lesions were localized in the chest region. The results revealed that patients with metastasis localized in the chest region had notably longer mPFS compared

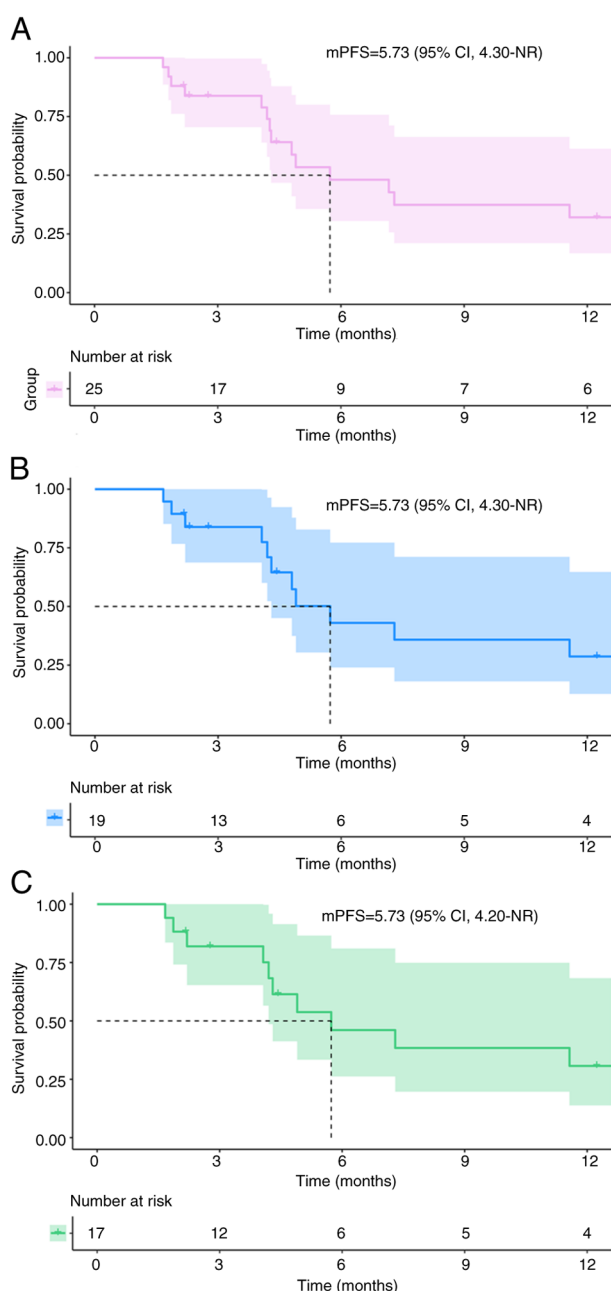


Figure 2. Kaplan-Meier survival curves of mPFS in patients who received furmonertinib. mPFS of (A) 25 patients with EGFR mutated lung adenocarcinoma after the failure of multiple lines of therapy; (B) 19 patients who were previously resistant to third-generation EGFR-tyrosine kinase inhibitor-targeted agents; and (C) 17 patients who had previously received treatment with osimertinib. mPFS, median progression-free survival; EGFR, epidermal growth factor receptor; CI, confidence interval; NR, not reached.

with those with extra chest metastases (4.9 vs. 13.0 months; HR=0.43; 95% CI, 0.16-1.15; P=0.102; Fig. 4A); ii) based on the mode of disease progression before furmonertinib initiation, patients were categorized into brain metastases (BM) and other metastases (OM) groups. Individuals in the OM group exhibited markedly longer mPFS compared with those in the BM group (5.3 vs. 7.2 months; HR=1.26; 95% CI, 0.43-3.69; P=0.687; Fig. 4B); iii) based on the EGFR mutation subtype, patients with EGFR exon21 L858R mutation exhibited notably longer mPFS compared with those with EGFR 19del (4.9 vs. 7.3 months; HR=0.78; 95% CI, 0.29-2.10; P=0.628; Fig. 4C);

and iv) based on furmonertinib dosage, patients who received 80 mg had markedly longer mPFS compared with those receiving 160 mg (7.3 vs. 5.7 months; HR=1.02; 95% CI, 0.33-3.19; P=0.968; Fig. 4D). However, there was no statistically significant difference in survival for these subgroups.

Safety. A total of 18 patients (72.0%) experienced at least one AE over the treatment course. Among these patients, four received combination therapy, while 14 received monotherapy with furmonertinib. A total of 25 AEs were reported across 16 distinct categories, with an 80.0% rate (n=20) in grade 1-2 and 20.0% (n=5) in grade 3-4. The incidence of AEs was 72.0% (n=18) in the monotherapy group and 28.0% (n=7) in the combination therapy group. The incidence of suspected drug-related AEs was 48% (n=12). The majority of AEs (17/25; 68.0%) were managed with supportive care. All grade 3-4 AEs were treated accordingly. Notably, no AEs required dose reductions or treatment discontinuation, which may be due to the conventional application of supportive care measures. The distribution of AEs is presented in Table II.

Discussion

The present retrospective study summarized the efficacy and safety profiles of furmonertinib therapy in patients with EGFR-mutant advanced LUAD following the failure of multiple lines of therapy. The majority of patients harboring the EGFR-sensitizing mutations are inevitably faced with the challenge of receiving effective subsequent treatment options after the failure of multiple-line therapies. Notably, furmonertinib therapy was initiated in most patients as a subsequent treatment option after multiple progression of the disease. Furmonertinib is a third-generation EGFR-TKI designed to target both the EGFR-sensitizing mutations and the T790M resistance mutation. It was independently developed in China (15). Additionally, furmonertinib has exhibited promising efficacy and an acceptable safety profile in patients with central nervous system (CNS) metastases (16). It has been approved as the first-line treatment for patients with LUAD harboring EGFR-sensitizing mutations. Clinical data indicate that furmonertinib can prolong PFS to 20.8 months, exceeding the PFS observed with other EGFR-TKIs (17). Additionally, a real-world retrospective study reported an mPFS of 19.5 months in patients with NSCLC with EGFR mutations who received furmonertinib as the initial therapy (18).

Furmonertinib has also demonstrated a survival advantage as a salvage therapy. A retrospective study involving 39 patients with advanced NSCLC who had developed resistance to third-generation EGFR-TKIs reported that 160 mg furmonertinib was a viable treatment option, with an mPFS of 4.70 months and OS of 7.73 months (9). In the present study, the median PFS was 5.73 months in patients with EGFR-mutant advanced LUAD, with one patient achieving sustained SD for ~30.3 months. Notably, among the 19 patients previously treated with third-generation EGFR-TKIs, the mPFS remained at 5.73 months. Whilst patients in the present study received several previous lines of systemic therapy, only nine patients reached the mortality endpoint and four were lost to follow-up at the cut-off date, rendering the analysis of the OS data immature. Future studies with longer follow-up periods are

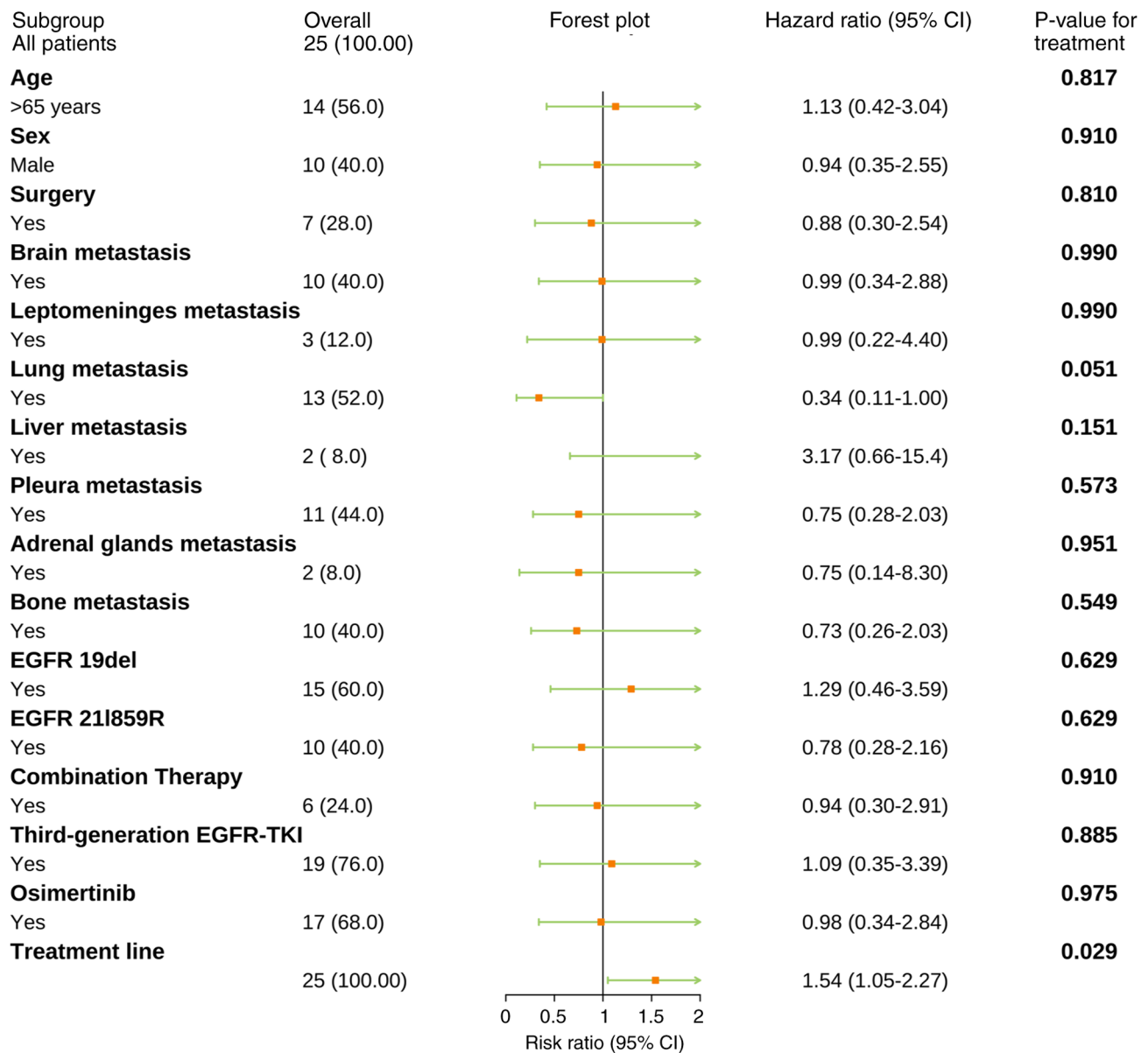


Figure 3. Forest plot of subgroup analysis for progression-free survival in 25 patients who received furmonertinib. CI, confidence interval; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

warranted to confirm these initial observations and address potential attrition bias.

Treatment options are limited for patients with LUAD harboring EGFR-sensitizing mutations after failure of multiple-lines of therapy. In clinical practice, patients usually receive platinum-based doublet chemotherapy, either as a monotherapy or in combination with anti-angiogenic therapy, with the observed mPFS being ~5 months after treatment (19,20). The advancement of immune checkpoint inhibitors has led to a paradigm shift in the management of NSCLC. However, previous studies reported that patients harboring the EGFR mutation who received immunotherapy exhibited suboptimal clinical outcomes, with an mPFS ranging between 1.3-2.1 months (21,22); however, improvement in the outcomes was observed in those patients who received immunotherapy in combination with other treatment options. Specifically, this combination treatment resulted in an mPFS ranging from 3.6-7.6 months (23,24). Moreover,

treatment involving sunvozertinib yielded an mPFS of 5.9 months in patients with NSCLC with EGFR-sensitizing mutations following the failure of EGFR-TKIs treatment (25). A meta-analysis assessing the efficacy of immunotherapy in combination with chemotherapy along with antiangiogenic therapy suggested that this approach conferred notably superior survival benefits on PFS in patients with NSCLC with EGFR mutations, especially those who had previously undergone EGFR-TKI therapy (26). However, these combination therapies also exhibit an elevated risk of toxicity, thereby exacerbating the treatment burden (23,26). By contrast, furmonertinib therapy exhibits a superior efficacy and safety profile, and an optimal treatment burden with an mPFS of 5.73 months in this study. Meanwhile, Ding *et al* (11) reported that furmonertinib may be a promising prospect to treat the vast majority activating EGFR-mutant NSCLC. However, existing clinical studies have failed to perform comparative analyses of furmonertinib with chemotherapy

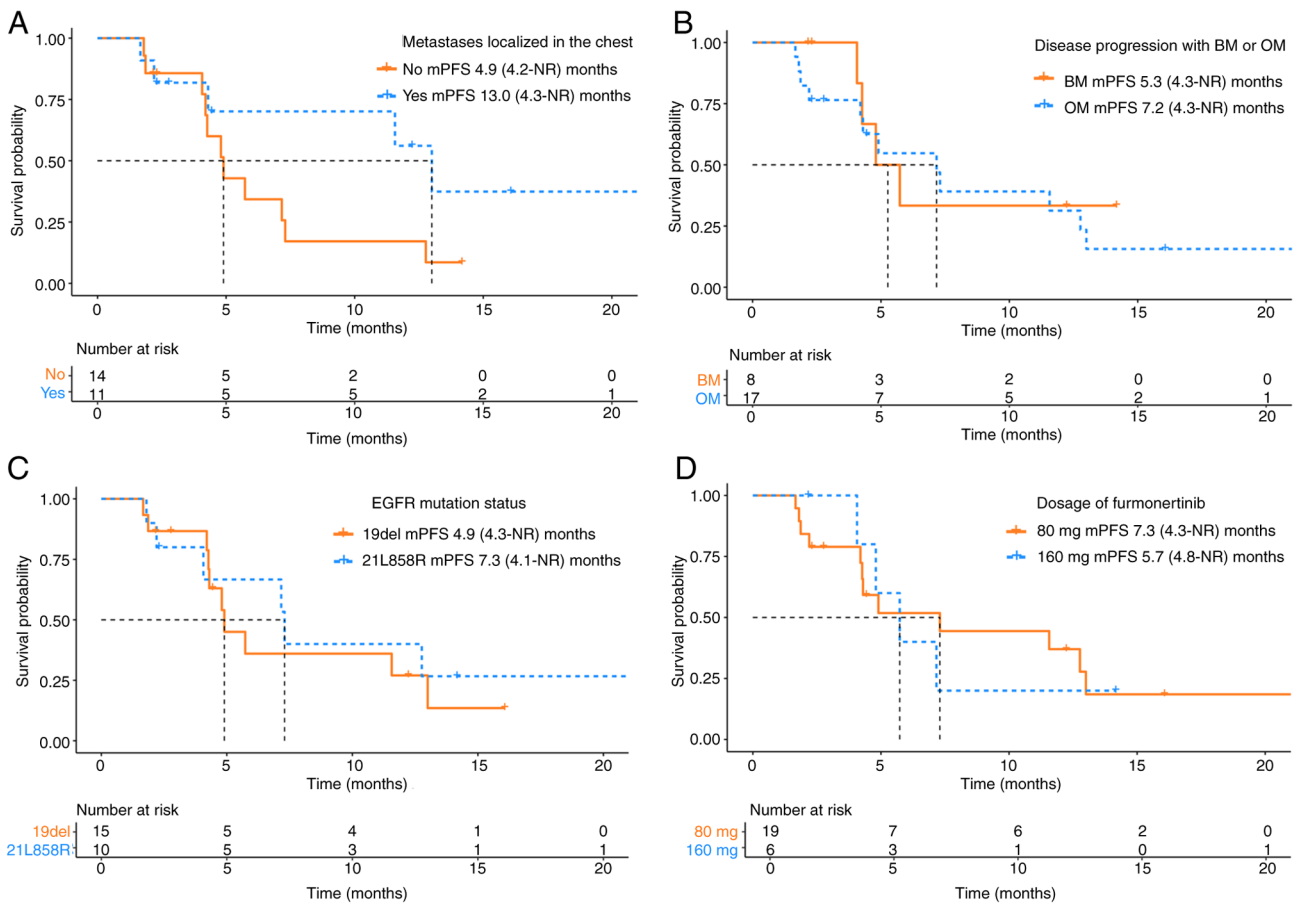


Figure 4. Kaplan-Meier survival curves of the mPFS of patients who received furmonertinib. (A) Metastases localized in the chest; (B) Disease progression with BM or OM; (C) EGFR mutation status; and (D) Dosage of furmonertinib. mPFS, median progression-free survival; EGFR, epidermal growth factor receptor; NR, not reached; BM, brain metastases; OM, other metastases.

or immunotherapy in patients with EGFR-mutant advanced NSCLC who progressed on EGFR-TKI treatment, to the best of our knowledge.

Furmonertinib exhibits favorable clinical activity in patients with BM due to its ability to penetrate the blood-brain barrier. Notably, a previous study reported that furmonertinib levels in the brain were higher compared with those in the plasma (27). The FURLONG Study reported that CNS PFS was 20.8 months in the furmonertinib group and 9.8 months in the gefitinib group (HR=0.40; P=0.001) (16). Another study reported that high-dose furmonertinib in combination with intraventricular chemotherapy as salvage treatment for patients with leptomeningeal metastases (LM) harboring EGFR ex20ins mutations had promising clinical benefits and a modest safety profile (8). Additionally, Hu *et al* (28) performed a pooled analysis of two Phase II studies and reported that furmonertinib exhibited promising CNS efficacy in patients with EGFR T790M-mutated NSCLC when administered orally at a dose of ≥ 80 mg once daily. These findings indicate that furmonertinib exhibits promising potential in treating CNS metastases. However, its clinical advantages in the BM population have not been validated in this study.

Patients with tumors localized to the lung may represent a population that could potentially benefit from furmonertinib treatment as the clinical efficacy of furmonertinib may be

associated with its pharmacological properties. In a study where a single oral dose of [14C]-furmonertinib was administered to rats, lung tissue had the highest levels of radioactivity, with the total radioactivity concentration ~ 100 -fold greater than that in the plasma (29). In the present study, patients with metastasis localized in the chest exhibited a prolonged mPFS. Moreover, these findings indicate that patients harboring the EGFR exon 21 L858R mutations had longer mPFS, which was a favorable outcome for this subgroup. Notably, previous studies have suggested that patients with the EGFR L858R mutation typically have a worse PFS compared with those with exon 19del (4,30,31). Additionally, in the present study, subgroup analysis suggested that a higher number of prior treatment lines may be a negative prognostic factor. However, the sample size in the subgroup analysis was too small, thereby limiting the reliability of these findings. Consequently, large-scale studies are needed to validate these findings these trends.

Furmonertinib exhibits a superior clinical safety profile and a wider dosage range compared with other EGFR-TKIs (11). According to previously reported data, treatment-related AEs of grade ≥ 3 occurred in 11% of 178 patients with NSCLC who received 80 mg furmonertinib once daily as first-line therapy (17). Regarding the toxicity of high-dose furmonertinib (dosages of ≥ 160 mg), existing studies suggest that it exhibits a favorable tolerability profile. Xu *et al* (14) enrolled 28 patients with advanced NSCLC with BM/LM and

Table II. Adverse events in patients who received furmonertinib monotherapy or combination therapy as subsequent treatment (n=25).

Adverse event	Monotherapy		Combination therapy	
	Grade 1-2 (n=16)	Grade 3-4 (n=2)	Grade 1-2 (n=4)	Grade 3-4 (n=3)
Cough	2 (8.0)	-	-	-
Diarrhea	1 (4.0) ^a	-	-	1 (4.0) ^a
Dizziness	1 (4.0)	-	-	-
Dry eye	2 (8.0) ^a	-	-	-
Dry skin	-	-	1 (4.0) ^a	-
Fatigue	2 (8.0)	-	-	-
Headache	1 (4.0)	-	-	-
Hemoptysis	1 (4.0)	-	-	-
Mucositis oral	1 (4.0) ^a	-	-	-
Nail changes	-	-	1 (4.0) ^a	-
Neutrophil count decreased	-	-	1 (4.0) ^a	-
Pain	1 (4.0)	1 (4.0)	1 (4.0)	-
Palpitations	1 (4.0) ^a	-	-	-
Paronychia	1 (4.0) ^a	-	-	1 (4.0)
Shingles	1 (4.0)	1 (4.0)	-	-
Decreased white blood cell count	1 (4.0) ^a	-	-	1 (4.0) ^a

Data are presented as n (%). ^aSuspected drug-related adverse events.

administered 160 mg furmonertinib, either as a monotherapy or in combination with anti-angiogenic agents. The results indicated that 14.3% of these patients (n=4) who had grade ≥ 3 AEs experienced controlled outcomes with no dose reductions or therapeutic suspension (14). Another prospective real-world study involving 48 patients with EGFR-mutated NSCLC and LM, who were administered a high-dose furmonertinib (240 mg once daily), either as a monotherapy or in combination with other treatment agents, reported that 22 (45.8%) had AEs possibly related to furmonertinib, and 3 (6.3%) had a grade 3 AEs leading to a dose reduction to 160 mg daily (32). In summary, a double dose of furmonertinib (160 mg) exhibits a favorable tolerability profile, and this observation extends to a daily dose of up to 240 mg, where the response is both safe and tolerable for patients with NSCLC (27). The aforementioned studies demonstrate that a higher dose of furmonertinib may have a greater efficacy with a favorable safety profile compared with the conventional dose. In the present study, 76% of patients received a conventional dose of furmonertinib, with no AEs observed in association with dose reductions or discontinuation, which may be attributed to the implementation of conventional supportive care measures. Additionally, the present study assessed the dose-response relationship and demonstrated that the group administered 80 mg furmonertinib had longer mPFS; however, this observation was not statistically significant.

The findings regarding genetic testing must be interpreted with caution. First, the proportion of patients who underwent repeat genetic testing was relatively small, which may be attributed to limiting factors such as the high cost and availability

of biopsy specimens. Specifically, only 14 patients (56.0%) underwent genetic testing prior to furmonertinib, potentially introducing selection bias. Untested patients may harbor undetected driver mutations. They were highly likely to exhibit drug-resistant mutations, such as MET amplification, EGFR C797S and TP53 mutations (33,34). These could confound the observed association between genetic profiles and treatment outcomes, leading to an underestimation of the efficacy of furmonertinib in the present study. Secondly, the majority of specimens for genetic testing were peripheral blood samples rather than tissue specimens, which inherently exhibit a high false-negative rate (35,36). These findings present a common clinical obstacle in the subsequent treatment of patients with cancer. With an extended treatment period, the proportion of genetic mutations also increases (37), which may lead to underestimation of targetable mutations and misclassification of true responders. Ultimately, as patients progress to the terminal phase, they may opt for essential genetic testing rather than comprehensive genomic profiling. Consequently, future studies should require tissue-based next-generation sequencing (NGS) to mitigate the influence of potential confounding factors associated with co-mutations and to improve the detection of more potential therapeutic targets to guide clinical decisions.

Currently, studies focusing on furmonertinib involving specific gene mutations in LUAD can be divided into two categories. First, furmonertinib has been explored in patients with EGFR ex20ins with an encouraging antitumor activity (38). In multiple retrospective studies, furmonertinib demonstrated promising antitumor and CNS activity in patients with advanced NSCLC with EGFR ex20ins (8,39,40). A phase-III trial of furmonertinib

vs. chemotherapy as first-line treatment for advanced NSCLC with EGFR ex20ins mutations (FURMO-004) is ongoing (41). Additionally, furmonertinib has demonstrated clinical efficacy in patients with uncommon EGFR mutations, such as L861Q/G719X (42), exon 18 (G719X) and 20 (S768I) (10), EGFR kinase domain duplication (EGFR-KDD) (43), exon 20 R776S, C797S, exon 21 L858R compound EGFR mutations (44) and HER2 T8962A and L869R (45). These suggest that furmonertinib may have suppressive effects on EGFR resistance mutations; however, the clinical evidence primarily stems from case reports.

The present study has certain limitations. Firstly, the sample size included is relatively small to ensure the generalizability of the study findings. The findings from the subgroup analyses should serve as exploratory foundations rather than definitive due to the inherent limitations of the sample size. In the future, multicenter and prospective studies should be performed, expanding the sample size to acquire higher-level evidence, thereby clearly identifying the patient population that derives clinical benefit from furmonertinib therapy. Secondly, the immature OS data, involving only 9 mortality events, limits the robustness of the survival analysis and the ability to establish definitive conclusions on the long-term outcomes. The low event rate notably reduces the statistical power to detect clinically meaningful survival differences. Furthermore, the loss of four patients to follow-up introduces the potential for attrition bias. These limitations underscore the necessity of future studies with extended follow-up periods to validate the preliminary findings of the present study. Ultimately, not all patients included underwent genetic testing before treatment with furmonertinib. Most patients had only a single gene mutation, and EGFR mutational status varied. Therefore, establishing an association between available genetic data and treatment outcomes was challenging. This highlights the fact that the current level of genetic testing availability is insufficient for clinicians. To identify actionable targets and address the effects of potential co-mutation confounders, future studies should incorporate tissue-based NGS for more comprehensive molecular profiling.

In conclusion, furmonertinib is a viable treatment option for patients with EGFR-mutant advanced LUAD following the failure of multiple lines of therapy, even after resistance to third-generation EGFR-TKIs targeted agents. The clinical application of furmonertinib is continuously advancing from first-line to subsequent treatment. In the future, clinical research with a large sample size is needed to enhance the robustness and generalizability of the findings of the present study.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YZ and HC designed the study. YZ and XL were responsible for the writing of the original draft of the manuscript and data analyses. JL, HD, YS and ZL contributed to data collection, data analyses and manuscript preparation. YZ and HC confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present retrospective study was approved by the Institutional Ethics Review Committee of the China-Japan Friendship Hospital (approval no. 2024-KY-104). The requirement for informed consent for participation was waived due to the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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