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LETTER TO THE EDITOR

A phase II study on Mefatinib as first-line treatment of patients with advanced non-small-cell lung cancer harboring uncommon *EGFR* mutations

Dear Editor,

Uncommon mutations in exons 18-21 of the epidermal growth factor receptor (*EGFR*) gene account for 10%–15% of all *EGFR* mutations when considered as a whole group [1, 2]. However, each variant confers heterogeneous clinical outcomes to different generations of EGFR tyrosine kinase inhibitors (TKIs) with G719X, L861Q, and/or S768I showing adequate sensitivity to EGFR inhibition [1–3]. Osimertinib, based on its superior survival outcomes, has become the preferred first-line treatment for patients diagnosed with advanced non-small cell lung cancer (NSCLC) harboring common *EGFR* mutations [4]; however, its efficacy in patients harboring G719X, S768I, and/or L861Q mutations was comparable or even inferior to Afatinib [5]. Afatinib, a second-generation EGFR-TKI, has received approval for extended clinical indication in treating previously untreated patients with metastatic NSCLC harboring G719X, L861Q, and/or S768I based on the findings from the pooled analysis of three clinical trials (LUX-Lung 2/3/6) [2]. The real-world clinical efficacy of Afatinib for treating this patient subset has been consistently demonstrated by two large retrospective studies [6, 7]. In China, chemotherapy remains a standard first-line treatment for this patient subset, with Afatinib available only as an off-label treatment option.

Mefatinib is a novel, second-generation EGFR-TKI with promising clinical efficacy and safety for patients with common *EGFR* mutations [8]. Here, we report the results of the phase II open-label, single-arm, multicenter study investigating the efficacy and safety of Mefatinib as first-line therapy for patients with NSCLC harboring uncommon *EGFR* mutations (ChiCTR2000029058). Details of the study methods are provided in the Supplementary Materials.

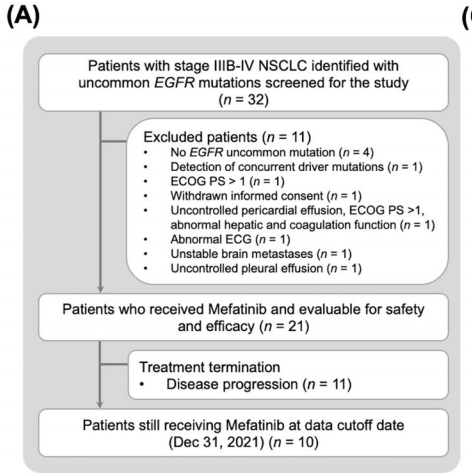
The pre-planned sample size was 50; however, patient recruitment was discontinued due to slow recruitment. Figure 1A illustrates the study flow diagram. Of the 32 patients screened between March 2019 and October 2019, 21 treatment-naïve patients with stage IIIB–IV NSCLC detected with at least 1 *EGFR* G719X, S768I, and/or L861Q mutations based on a central lab next-generation sequencing (Burning Rock Biotech, Guangzhou, China) analysis of tissue or malignant effusion samples were included in the study. Supplementary Table S1 summarizes the baseline characteristics of this cohort.

All 21 patients received Mefatinib at a daily oral dose of 80 mg as first-line therapy. The primary endpoint was objective response rate (ORR) by the investigator's assessment. Tumor shrinkage was observed in 20 patients (Figure 1B). Figure 1C summarizes the clinical outcomes of the cohort and subgroups of uncommon *EGFR* mutation types. ORR of the cohort was 85.7% (95% confidence intervals [CI]: 63.7-97.0). The respective ORR and median progression-free survival (PFS) was 94.1% and 20.6 months for patients with G719X ($n = 17$), 75.0% and 18.7 months for patients with L861Q ($n = 4$), and 71.4% and 20.6 months for patients with S768I ($n = 7$).

At the data cutoff date (December 31, 2021), the median duration of follow-up was 26.7 (range: 2.3-32.8) months. The median PFS was 20.6 months (95% CI: 8.3–NR) (Figure 1D). At 3 months and 6 months, 90.5% ($n = 19$) and 85.7% ($n = 18$) of patients remained progression-free; while 57.1% ($n = 12$) remained progression-free at 12 months. No patient died while receiving Mefatinib, with all patients alive at 12 months. The overall survival (OS) data remains immature (Figure 1E).

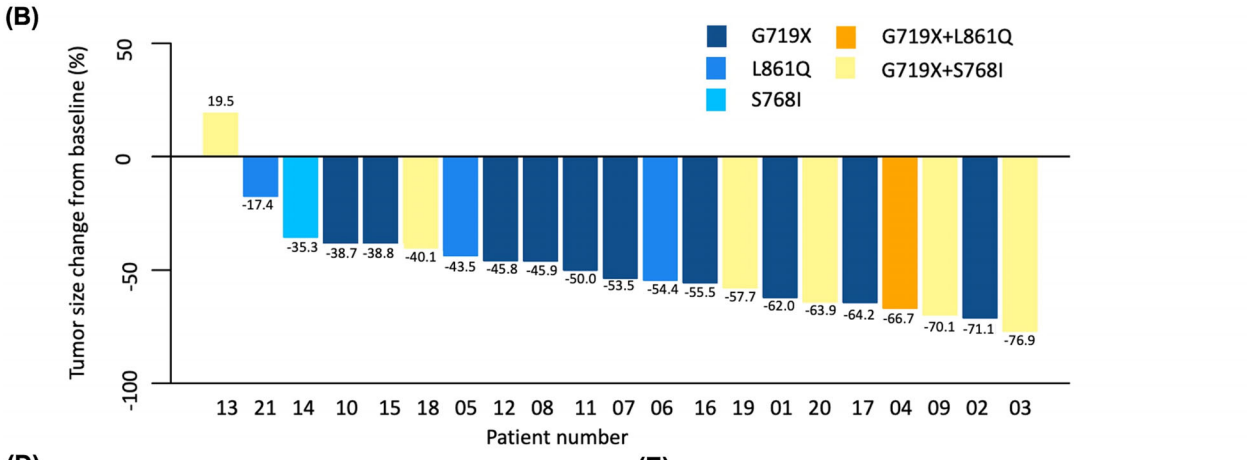
Based on these findings, Mefatinib had generally comparable ORR but had better PFS outcomes than those reported for Afatinib and Osimertinib [2, 5, 6, 9]; however, these comparisons should be considered with caution

Abbreviations: CI, confidence intervals; DCR, disease control rate; EGFR, epidermal growth factor receptor; NR, not reached; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.



(C)

Outcomes	All patients (*n* = 21)	G719X (*n* = 17)	L861Q (*n* = 4)	S768I (*n* = 7)
Treatment outcomes				
Complete response, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)
Partial response, *n* (%)	18 (85.7)	16 (94.1)	3 (75.0)	5 (71.4)
Stable disease, *n* (%)	3 (14.3)	1 (5.9)	1 (25.0)	2 (28.6)
Progressive disease, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)
Objective response rate, % (95% CI)	85.7 (63.7–97.0)	94.1 (71.3–99.9)	75.0 (19.4–99.4)	71.4 (29.0–96.3)
Disease control rate, % (95% CI)	100.0 (83.9–100.0)	100.0 (80.5–100.0)	100.0 (39.8–100.0)	100.0 (59.0–100.0)
Survival outcomes (months), median (95% CI)				
Progression-free survival	20.6 (8.3–NR)	20.6 (8.3–NR)	18.7 (7.0–NR)	20.6 (1.0–NR)
Duration of response	22.2 (8.4–NR)	18.7 (8.3–NR)	24.9 (9.7–NR)	NR (6.9–NR)



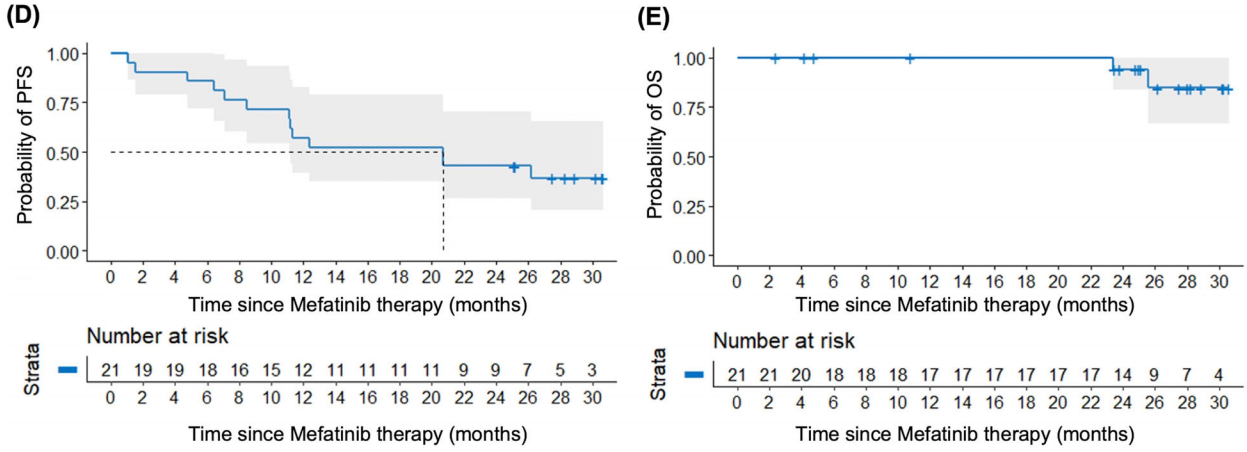


FIGURE 1 First-line Mefatinib therapy is associated with a high ORR and longer PFS in patients with stage IIIB–IV NSCLC harboring *EGFR* G719X, S768I, and/or L861Q mutations ($n = 21$). (A). Study flow chart. (B). Waterfall plot illustrating the best percentage change in target lesion size after Mefatinib therapy (relative to baseline). Measurable lesions were assessed at baseline and after 1 cycle of Mefatinib therapy based on RECIST version 1.1. Tumor shrinkage of 30% from baseline is evaluated as partial response. An increase of > 20% from baseline was evaluated as progressive disease. Color denotes the *EGFR* mutation of each patient. (C). Table summarizing the treatment and survival outcomes of the cohort and subgroups of uncommon *EGFR* mutation types. Treatment outcomes were presented as the number of cases and the corresponding percentage of patients whose disease was evaluated as a partial response or stable disease. PFS was calculated for all patients, whereas the duration of response was only calculated among Mefatinib responders. (D–E). Kaplan-Meier curves illustrating the PFS (D) and OS (E) of 21 patients with uncommon *EGFR* mutations who received Mefatinib as first-line therapy. Gray shadow represents 95% CI. The dotted line indicates the median survival. Tick marks denote censored events. The risk table below the plot shows the number of events/patients included in the survival analysis per time point.

Abbreviations: CI, confidence intervals; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria of Solid Tumors.

due to the difference in sample size and overall treatment history of the patients. As summarized in Supplementary Table S2, the ORR and PFS with different EGFR-TKIs were heterogeneous for the three subtypes of uncommon *EGFR* mutations, but the long-term efficacy of Mefatinib was demonstrated by its durable disease control and promising OS benefit. The results of our current study were also consistent with the efficacy of first-line Mefatinib therapy in patients with common *EGFR* mutations [8]. Our previous phase II study reported an ORR of 84.9%, DCR of 97.2%, median PFS of 15.4 months, and median OS of 31.6 months with common *EGFR* mutations with consistent long-term efficacy regardless of *EGFR* mutation subtypes (i.e., L858R, common and uncommon 19del), and concurrent *TP53* mutation status [8]. Together, our current clinical findings suggest that Mefatinib is active across common and uncommon *EGFR* subtypes. Based on its promising benefit for survival outcomes, Mefatinib may potentially serve as a best-in-class EGFR-TKI for uncommon *EGFR* mutations.

Furthermore, first-line Mefatinib therapy demonstrated a manageable toxicity profile. Grade 3 treatment-related adverse events (TRAEs) primarily involved gastrointestinal and skin disorders, including diarrhea ($n = 8$), rash ($n = 5$), and oral mucositis ($n = 1$) (Supplementary Table S3). All patients reported at least 1 TRAE, but no unexpected and Grade 4-5 TRAEs were observed (Supplementary Table S4). Intolerable grade 1-3 toxicities were observed in 57.1% (12/21), which were managed by treatment interruption and/or dose modifications (Supplementary Table S5).

In vitro assays have also demonstrated that treatment with Mefatinib or Afatinib effectively inhibited the proliferation of cell lines expressing G719S, S768I, or L861Q (Supplementary Figure S1, Supplementary Table S6). An unpublished pharmacokinetic dose-escalation study demonstrated a Mefatinib exposure (measured as the area under the plasma concentration-time curve over the time interval from 0 to 24 hr post-dose [$AUC_{0\text{-}24}$]) of 4393 ng·h/mL for 80 mg Mefatinib. The $AUC_{0\text{-}24}$ observed for Mefatinib was much higher than the reported $AUC_{0\text{-}24}$ of 498 ng·h/mL for Afatinib 40 mg daily [10], which may explain the better clinical efficacy observed with Mefatinib therapy.

The main limitation of this study is its small cohort, which severely limits further subgroup analysis. Our study on patients with common *EGFR* mutations found that a lower 60 mg dose had comparable efficacy but was more tolerable than the higher 80 mg dose [8]; however, Mefatinib was only administered at one dose level due to the small cohort of our study. The rarity of G719X, S768I, and/or L861Q mutations severely limited patient recruitment. Although patient recruitment was initiated in multiple institutions, the uncertainty in clinical outcomes associated with investigational drugs and the availability of approved treatment options might have influenced the treatment decisions of some patients. The third limitation is the absence of an assessment of Mefatinib's efficacy in the central nervous system (CNS) for patients with uncommon *EGFR* mutation. All patients enrolled in this study were not detected with CNS metastasis at initial diagnosis. Our earlier observation on the efficacy of first-line Mefatinib in NSCLC patients harboring common *EGFR* mutations with CNS metastasis at baseline [8] raises the possibility of Mefatinib's CNS activity in patients with uncommon *EGFR* mutations; however, clinical data is needed to support this speculation.

In conclusion, our study provides preliminary clinical evidence that first-line Mefatinib therapy was effective, provides durable PFS, and has a manageable toxicity profile in patients with stage IIIB–IV NSCLC harboring *EGFR* G719X, S768I, and/or L861Q mutations. This study did not reach the planned accrual; hence, clinical evidence from a larger cohort is needed to establish Mefatinib efficacy in this patient subset. Based on these encouraging clinical and survival outcomes from a small cohort, Mefatinib could potentially serve as an alternative treatment regimen to target both common and uncommon *EGFR* mutations in advanced NSCLC.

DECLARATIONS

AUTHOR CONTRIBUTIONS

Yong Song and Kai Wang contributed to the study design. Pingli Wang, Liming Cao, Panwen Tian, Shengxiang Ren, Liyun Miao, Chengzhi Zhou, Yun Fan, Yuping Li, Dongqing Lv, Xin Zhao, Yong Song, and Kai Wang provided study participants. All authors contributed to data analysis and data interpretation, manuscript revision and editing. All authors reviewed and approved the final version of the manuscript. The corresponding authors take full responsibility for the credibility of the descriptions of data presented in this work.

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CONFLICT OF INTEREST STATEMENT

Mei Yang, Chaonan Zhu, Bing Yu, and June Xu are employees of Hangzhou Zhongmei Huadong

Pharmaceutical Company. All the other authors declare no conflict of interest.

FUNDING INFORMATION

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ETHICS APPROVAL STATEMENT

The study protocol was approved by the institutional ethics board of The Second Affiliated Hospital Zhejiang University School of Medicine (Approval number: 2018-0216) and the ethics board of the other participating centers.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from all study participants.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

CLINICAL TRIAL REGISTRATION

This phase II study on Mefatinib was registered on the Chinese Clinical Trial Registry (ChiCTR2000029058).

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available from the corresponding authors upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.