Original Article

Efficacy of targeted therapy in patients with non-small cell lung cancer harboring very rare mutations in *EGFR* exon 18

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Background: Somatic mutations in epidermal growth factor receptor (*EGFR*) exon 18 are classified as uncommon or rare mutations in non-small cell lung cancer (NSCLC), in this context, other than G719X or E709X exon 18 mutations are even more rare and heterogeneous. In such scenario, first line treatment options are still debated. The aim of this study was to investigate the response of NSCLC patients harboring very rare exon 18 mutations to EGFR tyrosine kinase inhibitors (EGFR-TKIs).

Methods: This retrospective descriptive study included 105 patients with NSCLC harboring mutations in *EGFR* exon 18 diagnosed at West China Hospital. The clinical response to EGFR-TKIs was evaluated according to different classifications of mutations in 45 NSCLC patients: 39 harboring G719X or E709X mutations and 6 harboring very rare mutations in *EGFR* exon 18.

Results: Among 105 patients, 84% (88/105) harbored rare mutations in *EGFR* exon 18, including G719X and E709X mutations. The remaining 16% (17/105) had very rare mutations in *EGFR* exon 18, including E709_710delinsX and G724S. For the subsequent efficacy analysis of EGFR-TKI in 45 NSCLC patients, patients harboring very rare mutations achieved a favorable disease control rate (DCR) of 100% and had a median progression-free survival (PFS) of 17.2 months, which was not significantly different compared to patients harboring G719X or E709X (P=0.59).

Conclusions: EGFR-TKIs showed great efficacy in terms of responses and survival in patients harboring exon 18 *EGFR* rare mutations. This may justify the use of targeted therapies as a potential treatment strategy for these patients.

Keywords: Non-small cell lung cancer (NSCLC); epidermal growth factor receptor (EGFR); very rare mutations; targeted therapy; efficacy

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Introduction

Lung cancer is one of the most frequently diagnosed cancers and the leading cause of cancer-related deaths (1). Mutations in the epidermal growth factor receptor (*EGFR*) gene occur in more than 50% of Asian non-small cell lung cancer (NSCLC) patients (2). There are many *EGFR* mutation subtypes including common mutations, exon 19 deletions and L858R point mutation, which together account for approximately 85% of all *EGFR* mutations (3,4), and the remaining 15% are called uncommon or rare *EGFR* mutations, as represented by exon 18 mutations. Specifically, *EGFR* exon 18 mutations can be identified in 4.6% of east Asian patients with *EGFR* mutations (3,5).

The better clinical outcome of EGFR-TKIs in NSCLC patients harboring sensitive *EGFR* mutations has been demonstrated, including uncommon *EGFR* mutations such as G719X, S768I, and L861Q (6). Afatinib has been further approved for these patients (6-8), and was even a potential therapeutic option for patients harboring E709X in *EGFR* exon 18 (9). However, with the development of gene detection methods over the past decades, several very rare mutations have been found in exon 18 of the *EGFR*, including G721R, L718V/Q, and G724S (10-12). Due to the scarcity of these rare mutations, adequate treatment strategies for subgroups of patients are still debated. Recently, a few studies reported that targeted therapy was effective in very rare *EGFR* 18 exon mutations (12,13).

Highlight box

Key findings

- Patients with non-small cell lung cancer (NSCLC) harboring very rare mutations in epidermal growth factor receptor (*EGFR*) exon 18 have a potential to exhibit a clinically meaningful outcome with EGFR targeting therapy.

What is known and what is new?

- There is no consistent treatment strategy for NSCLC patients harboring very rare mutations in *EGFR* exon 18 due to the rarity of such mutations.
- In this study, we observed similar progression-free survival (PFS) and overall survival (OS) between NSCLC patients with very rare mutations in *EGFR* exon 18 and G719X and E709X group.

What is the implication, and what should change now?

- EGFR-tyrosine kinase inhibitors (TKIs) should be one of potential treatment strategies for NSCLC patients harboring very rare mutations in *EGFR* exon 18, and larger studies for the selection of treatment strategy for patient harboring very rare mutations in *EGFR* exon 18 are needed.

Here, we report clinical outcomes of patients with very rare *EGFR* 18 exon mutations who had received EGFR-TKIs. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-113/rc).

Methods

Patients and methods

Patients who underwent next-generation sequencing (NGS) and had detectable mutations in *EGFR* exon 18 from 2015 to 2020 at West China Hospital were retrospectively identified. A total of 105 patients were included in this study, all of whom had been pathologically confirmed as having NSCLC. Out of the initial cohort, a subset of 45 patients who received EGFR-TKIs for their advanced or metastatic NSCLC were included for further analysis. The inclusion criteria for this subsequent cohort were as follows: (I) advanced or metastatic NSCLC; (II) detected mutations in *EGFR* exon 18; (III) treatment with EGFR-TKIs; and (IV) availability of complete prognostic data. Clinical outcome to treatment, including disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). Tumor response was evaluated by Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1. The DCR was determined as the proportion of patients with complete response (CR), partial response (PR), or stable disease (SD). PFS was measured from the date of initiation of EGFR-TKI treatment until disease progression or death. OS was calculated from the date of initiation of EGFR-TKI to death due to any cause or at the follow up time. Patients were excluded from the subsequent analysis if they met the following criteria: (I) secondary mutations in *EGFR* exon 18; (II) had undergone surgery and/or perioperative maintenance treatment; (III) had received radiotherapy or chemotherapy only; and (IV) prognostic information for targeted therapy was missing (Figure S1). This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of West China Hospital of Sichuan University (No. 2022-0606), and the requirement for individual consent for this retrospective analysis was waived.

The following information was collected from the medical records of patients retrospectively: age, sex, performance status, smoking history, *EGFR* mutational status, tumor-node-metastasis (TNM) stage of the primary tumor, pathology, treatment regimen, distant metastasis, and survival status. The pathological sections were reviewed

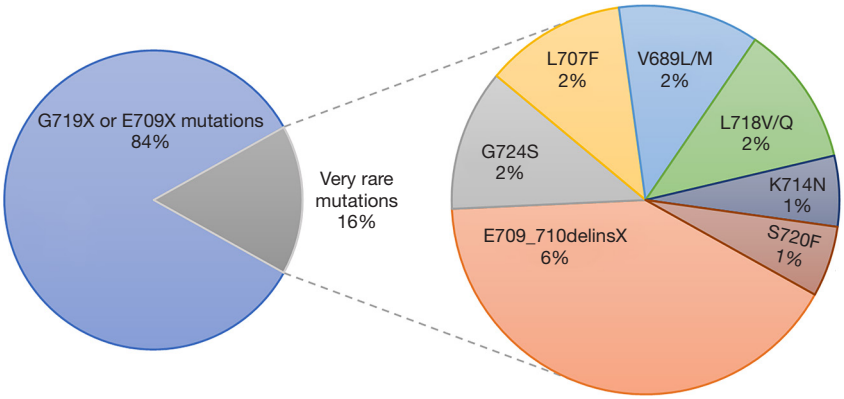

Figure 1 Distribution of different *EGFR* mutations in exon 18 in 105 NSCLC patients. *EGFR* mutations were subdivided into G719X or E709X group (88/105, 84%) and very rare mutation group (17/105, 16%) (left). Very rare mutations in *EGFR* exon 18 included E709_710delinsX, G724S, L707F, V689L/M, L718V/Q, K714N, and S720F (right). NSCLC, non-small cell lung cancer.

independently by an experienced pathologist.

Definition of very rare mutations in exon 18

In our retrospective study, we defined very rare mutations in *EGFR* exon 18 as follows: mutations other than G719X or E709X. Very rare mutations in *EGFR* exon 18 include point mutations, deletions, and others, which were observed in approximately 15% of NSCLC patients with *EGFR* exon 18 mutations.

Statistical analysis

The comparison of clinical characteristics between G719X or E709X group and the very rare mutation group was performed using Fisher's exact test. Survival time was estimated using the Kaplan-Meier method, and groups were compared using log-rank tests. All statistical analyses were conducted with SPSS (version 26; IBM Corp, Armonk, NY, USA) and R software (version 4.0.3 or version 4.2.2; The R Foundation for Statistical Computing, Vienna, Austria).

Results

Identification and distribution of different subtypes of EGFR exon 18 mutations in 105 NSCLC patients

A summary of the distribution of the *EGFR* exon 18 mutations in 105 NSCLC patients is provided in *Figure 1*. Most of the patients (88/105, 84%) had G719X or E709X mutations, including G719A, G719C, G719D, G719S, E709A, E709G, E709K, E709Q, and E709V. On the other hand, 17 (16%) had very rare mutations in exon 18, among whom 7 patients had E709_710delinsX, followed by L707F, G724S, V689L/M, L718V/Q, S720F, and K714N. The baseline characteristics of NSCLC patients harboring G719X or E709X and very rare mutations were compared. We found no significant difference between these two groups (Table S1).

Clinical characteristics and the efficacy of targeted therapy in NSCLC patients harboring very rare EGFR exon 18 mutations

Patient characteristics for the subsequent analysis are shown in *Table 1*. Among the 45 NSCLC patients, 39 had G719X or E709X, and the remaining 6 had very rare mutations. All these patients had lung adenocarcinoma, and their pathological images were presented in Figure S2. Five of them were stage IVA NSCLC, and the remaining one was stage III. The median age was 60.5 years, male patients were predominant (5/6, 83.3%), most of them were non-smokers, and the median follow-up time was 27.6 months. In the very rare mutation group, 5 (5/6, 83.3%) patients received first-generation EGFR-TKIs, and the remaining 1 (1/6, 16.7%) patient received second-generation EGFR-TKI; 5 of them received targeted therapy as first-line therapy. The baseline characteristics were identical between patients with G719X or E709X and those with very rare mutations (*Table 1*).

Among NSCLC patients harboring very rare *EGFR* exon 18 mutations, all 4 patients who received EGFR-TKIs as the first-line therapy experienced SD, and 1 patient experienced PR. The objective response was not

Table 1 Baseline characteristics of patients harboring mutations in *EGFR* exon 18 and who received EGFR-TKIs

Characteristics	Overall (N=45)	G719X or E709X mutations (N=39)	Very rare mutations (N=6)	P value
Presence of common mutation, n (%)				0.742
Yes	9 (20.0)	7 (17.9)	2 (33.3)	
No	36 (80.0)	32 (82.1)	4 (66.7)	
L858R or 19del, n (%)				
L858R	7 (15.6)	6 (15.4)	1 (16.7)	1.000
19del	2 (4.4)	1 (2.6)	1 (16.7)	0.252
Follow-up time (months), median (IQR)	25.60 (16.97, 39.17)	25.07 (15.03, 39.25)	27.63 (23.87, 28.40)	0.570
Age (years), median (IQR)	60.00 (55.00, 73.00)	60.00 (55.00, 73.00)	60.50 (52.25, 67.25)	0.514
Age (years), n (%)				1.000
<60	19 (42.2)	16 (41.0)	3 (50.0)	
≥60	26 (57.8)	23 (59.0)	3 (50.0)	
Gender, n (%)				0.488
Female	17 (37.8)	16 (41.0)	1 (16.7)	
Male	28 (62.2)	23 (59.0)	5 (83.3)	
Smoking, n (%)				0.832
Current/former smoking	11 (24.4)	10 (25.6)	1 (16.7)	
Never smoking	29 (64.4)	25 (64.1)	4 (66.7)	
Unknown	5 (11.1)	4 (10.3)	1 (16.7)	
Smoking index, n (%)				0.631
≤200	32 (71.1)	27 (69.2)	5 (83.3)	
>200	5 (11.1)	5 (12.8)	0 (0.0)	
Unknown	8 (17.8)	7 (17.9)	1 (16.7)	
ECOG PS, n (%)				0.871
≥2	5 (11.1)	4 (10.3)	1 (16.7)	
0–1	26 (57.8)	23 (59.0)	3 (50.0)	
Unknown	14 (31.1)	12 (30.8)	2 (33.3)	
Pathology, n (%)				1.000
Adenocarcinoma	43 (95.6)	37 (94.9)	6 (100.0)	
Squamous cell carcinoma	2 (4.4)	2 (5.1)	0 (0.0)	
Stage, n (%)				0.122
III	5 (11.1)	4 (10.3)	1 (16.7)	
IVA	23 (51.1)	18 (46.2)	5 (83.3)	
IVB	17 (37.8)	17 (43.6)	0 (0.0)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Overall (N=45)	G719X or E709X mutations (N=39)	Very rare mutations (N=6)	P value
Metastases, n (%)				0.405
Multiple organ metastasis	17 (37.8)	16 (41.0)	1 (16.7)	
Single organ metastasis	20 (44.4)	17 (43.6)	3 (50.0)	
No organ metastasis	8 (17.8)	6 (15.4)	2 (33.3)	
Treatment lines, n (%)				0.620
First-line	43 (95.6)	38 (97.4)	5 (83.3)	
Second-line	2 (4.4)	1 (2.6)	1 (16.7)	
EGFR-TKIs, n (%)				0.065
First-generation	18 (40.0)	13 (33.3)	5 (83.3)	
Second-generation	24 (53.3)	23 (59.0)	1 (16.7)	
Third-generation	3 (6.7)	3 (7.7)	0 (0.0)	
Response, n (%)				0.622
PD	1 (2.2)	1 (2.6)	0 (0.0)	
PR	14 (31.1)	13 (33.3)	1 (16.7)	
SD	19 (42.2)	15 (38.5)	4 (66.7)	
Unknown	11 (24.4)	10 (25.6)	1 (16.7)	

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; PS, performance status; common mutation, *EGFR* 19del and L858R; PD, progressive disease; PR, partial response; SD, stable disease.

available in the remaining one patient. A waterfall plot of the tumor retraction rate (TRR) is shown in *Figure 2A*. The DCR was 100% in NSCLC patients harboring very rare mutations in *EGFR* exon 18 and 97.4% in patients with G719X or E709X mutations, and there was no significant difference in these two groups (P>0.99) (*Figure 2B*). *Figure 3* shows the duration of the treatment and survival time after EGFR-TKI treatment. The median PFS of NSCLC patients with very rare mutations in *EGFR* exon 18 was 17.2 months, which was not significantly different from that of patients with G719X or E709X group [17.2 *vs.* 14.9 months, P=0.59, hazard ratio (HR) =1.301, 95% confidence interval (CI): 0.488–3.472, P=0.599] (*Figure 4A*). For OS, as shown in *Figure 4B*, the very rare mutation group had a similar OS compared with G719X or E709X group (89.8 *vs.* not reached, P=0.42, HR =2.515, 95% CI: 0.244–25.958, P=0.439).

Discussion

In this study, we reported clinical efficacy of EGFR-TKIs in NSCLC patients harboring very rare mutations in *EGFR* exon 18; although no patients achieved a CR, 4 of 6 patients achieved SD. In addition, we observed no significant difference in PFS and OS between NSCLC patients harboring very rare *EGFR* exon 18 mutations and those with G719X or E709X mutations, suggesting that EGFR-TKI should be considered during treatment of NSCLC patients harboring any *EGFR* exon 18 mutations.

With the increasing use of NGS-based analysis in clinical practice of NSCLC patients, we often observe patients with very rare mutations in *EGFR* exon 18 (14). In this descriptive study, we investigated the distribution of mutations in *EGFR* exon 18 in a Chinese NSCLC cohort from a single center. We identified that the incidence of very rare mutations in exon 18 was 16% (17/105), and the majority of the very rare mutations were E709_710delinsX (N=7). In addition, there were other very rare mutations in *EGFR* exons 18, including G724S, L707F, K714N, L718V/Q, V689L/M, and S720F mutations. Previous work has reported a frequency of 0.44% (26/5905) for E709_710delinsX mutations in *EGFR* mutant lung cancer

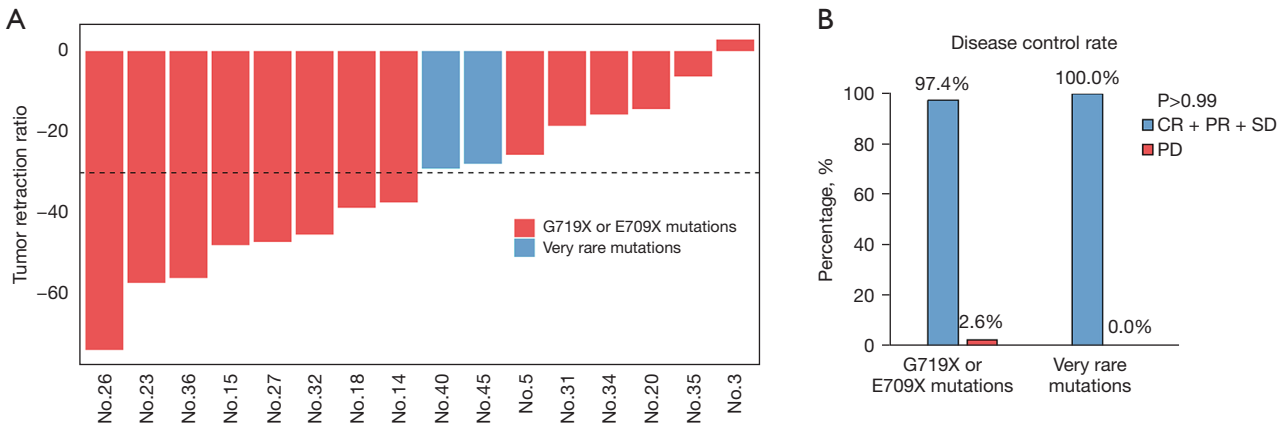

Figure 2 Clinical response in patients harboring G719X or E709X and those harboring very rare mutations in *EGFR* exon 18. (A) A waterfall plot showing the tumor retraction ratio of patients who received EGFR-TKIs; (B) histogram showing the proportions of patients with controlled disease with G719X or E709X and very rare mutations. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; *EGFR*, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

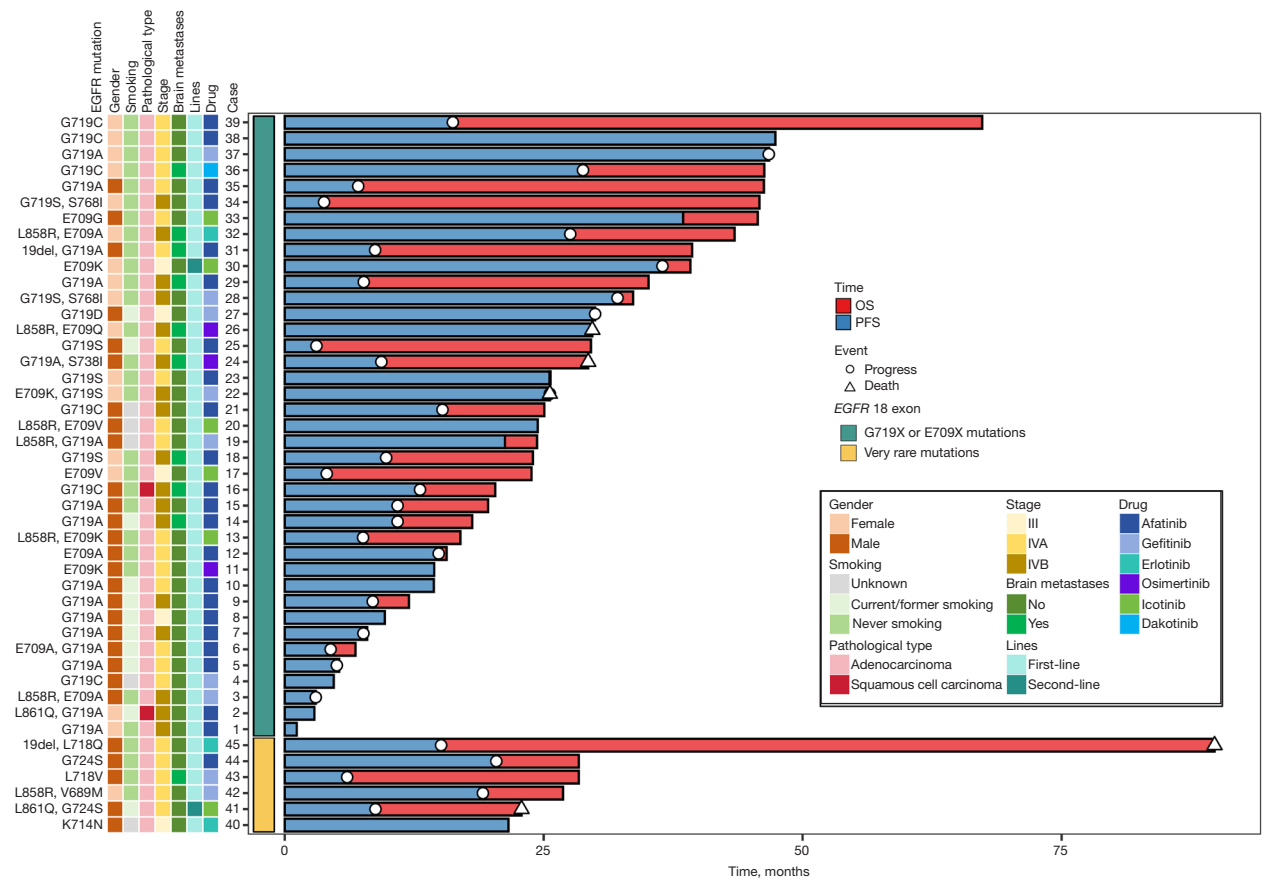

Figure 3 Duration of survival status to EGFR-TKIs. A swimming chart showing the survival status of patients with G719X or E709X mutations and very rare mutations. *EGFR*, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; OS, overall survival; PFS, progression-free survival.

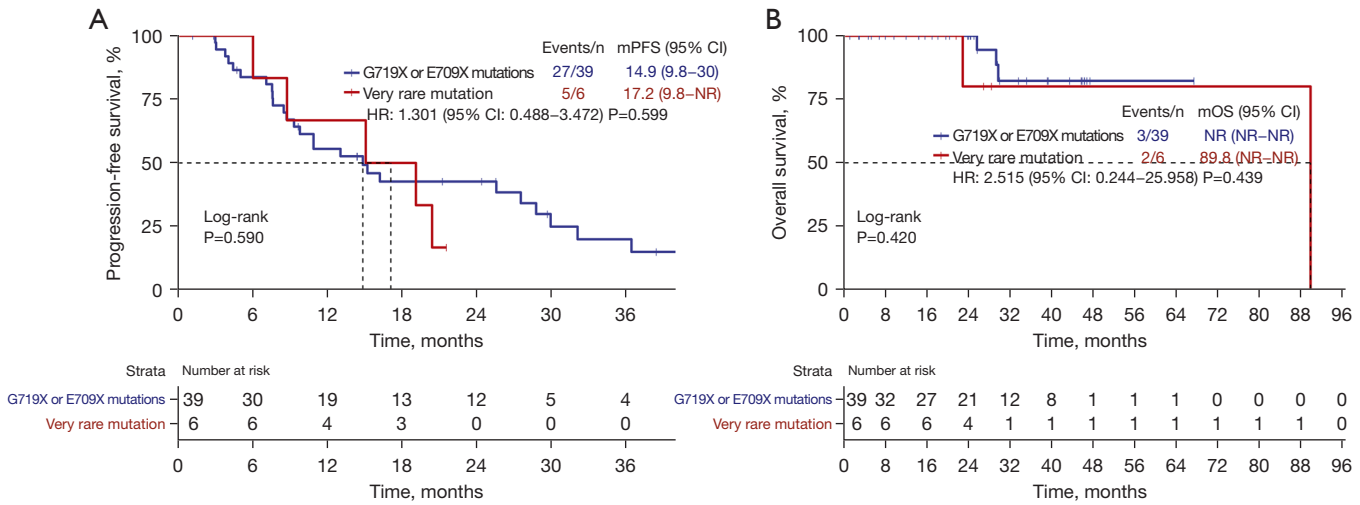

Figure 4 Clinical outcome in the different types of mutations in *EGFR* exon 18. (A) Kaplan-Meier curve of PFS of *EGFR*-TKI treatment in 45 NSCLC patients with G719X or E709X mutations in *EGFR* exon 18 and very rare mutations in *EGFR* exon 18; (B) Kaplan-Meier curve of OS of *EGFR*-TKI treatment in 45 NSCLC patients with G719X or E709X mutations in *EGFR* exon 18 and very rare mutations in *EGFR* exon 18. *EGFR*, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; PFS, progression-free survival; CI, confidence interval; OS, overall survival; NR, not reached; NSCLC, non-small cell lung cancer.

patients (15). Another study reported that 4.9% (4/82) had *EGFR* G724S in exon 18 (16), which was more than the incidence of *EGFR* G724S we identified in our study. Due to the low incidence of NSCLC patients with very rare *EGFR* mutations in exon 18, the information on their epidemiology is still inconsistent and incomplete, and a large cohort study of patients harboring *EGFR* mutations is warranted.

Furthermore, due to the low incidence of *EGFR* exon 18 mutations observed in approximately 5% of *EGFR*-mutant NSCLC patients and because *EGFR* mutations cause inconsistent responses to EGFR-TKIs, many clinical trials have been conducted to explore the efficacy of diverse treatments for *EGFR* exon 18-mutant NSCLC patients (17). Xu *et al.* discovered that there was no significant difference in PFS between second-generation EGFR-TKIs and first-generation EGFR-TKIs (16). Passaro *et al.* found that *EGFR* exon 18 and combination mutations could be considered potentially sensitive rare mutations because of a similar survival compared with common *EGFR* mutations (18). Currently, afatinib, a second-generation irreversible ErbB family blocker, has been sufficiently validated to have clinical activity in NSCLC patients harboring major rare mutations and compound *EGFR* mutations (7,19). The efficacy of osimertinib for NSCLC patients with these rare *EGFR* mutations has also been studied, and in a single arm phase II study, Cho *et al.* demonstrated favorable activity in patients with NSCLC harboring uncommon *EGFR* mutations (20), and other studies also found similarly favorable clinical activities (21-24).

However, the efficacy of EGFR-TKIs for NSCLC patients harboring very rare *EGFR* mutations is still unclear due to the exclusion of patients harboring very rare *EGFR* mutations from many previous studies and the low incidence of these mutations (23,25-27). For patients with very rare mutations in *EGFR* exon 18, there was no consensus concerning the treatment outcome and treatment strategy of these patients, and only some case reports and small sample studies had reported diverse therapeutic strategies and clinical outcomes (10,12,15,28). Lee *et al.* reported a patient harboring the *EGFR* G724S mutation who was susceptible to gefitinib and observed a long-term response (12). Jelli *et al.* reported a NSCLC patient harboring the *EGFR* E709_710delinsD mutation who achieved a complete response to afatinib (13). However, in addition to the favorable response reported in the above cases, some case reports have described that patients with very rare mutations in *EGFR* exon 18 did not experience clinical benefit from EGFR-TKIs. Furthermore, some case studies have demonstrated that *EGFR* L718V/Q is a mechanism of resistance to osimertinib but potentially retains sensitivity to afatinib (10,29-31). To identify the efficacy of targeted

therapy in patients harboring very rare mutations in *EGFR* exon 18, we initiated the first descriptive study to investigate the therapeutic responses in these patients. In the present study, we found that patients with very rare *EGFR* exon 18 mutations achieved a favorable DCR (100%) and a median PFS of 17.2 months, which was identical to that of patients harboring G719X or E709X mutations. Furthermore, in a previous study, some patients with uncommon *EGFR* alterations were reported to derive clinical benefit from immune checkpoint inhibitors and patients with uncommon *EGFR* mutations had high rates of programmed cell death ligand 1 (PD-L1) expression and $CD8^+$ tumor infiltrating lymphocytes (TILs) (32). Thus, to date, the predominant treatment strategy for patients with very rare *EGFR* exon 18 has remained uncertain; our study found that EGFR-TKIs could serve as a potential treatment strategy for patients harboring very rare mutations in *EGFR* exon 18 despite the quite limited number of patients.

This retrospective study is subject to several inherent limitations that warrant consideration. First, the present study included only 6 patients who harbored very rare mutations in *EGFR* exon 18 and received EGFR-TKIs. Since the very rare *EGFR* exon 18 mutations were heterogeneous mutations, the therapeutic strategy selected for patients with these mutations was diverse, resulting in a limited number of patients receiving EGFR-TKIs. However, appropriate selections of treatment are important, and retrospective studies are the first step in establishing effective treatment strategies. Another limitation could have been the use of first- and second-line EGFR-TKIs since nowadays osimertinib could be considered the standard in first-line treatment, and in the present study, there were no patients harboring very rare mutations received osimertinib. Additionally, a significant limitation is that we did not analyze the influence on the treatment outcome of compound mutations, defined as harboring sensitive *EGFR* 19 del or L858R missense mutations in exon 21. Attili *et al.* reported that NSCLC patients with combined common plus uncommon *EGFR* mutations achieved response rates of 40–80% and 100% with first-generation EGFR-TKIs and afatinib, respectively (33), and another study identified that complex mutations are similarly sensitive to EGFR-TKIs treatment as are classical mutations (8). This lack of compound mutation data creates a challenge to draw definitive conclusions about the response rate impact of very rare mutations in *EGFR* exon 18 in this population. We acknowledge that these limitations may affect the robustness of our results and the strength of our conclusions. Therefore, the outcomes of this study should be interpreted cautiously and further validated in a large cohort study with exclusion of the impact of compound mutations.

Conclusions

Our study is the first descriptive study examining the response of patients with very rare *EGFR* mutations in exon 18 to EGFR-TKIs. EGFR-TKIs showed promising results in the treatment of very rare mutations in *EGFR* exon 18. Further studies, especially on the selection of treatment strategies, are needed.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-113/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-113/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-113/coif). K.S. has received research grant from AstraZeneca, and has received honoraria from AstraZeneca, Chugai, Boehringer Ingelheim, and Taiho, outside the submitted work. M.S. reported speakers bureaus from ROCHE, BMS, ASTRA ZENECA and NOVARTIS. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of West China Hospital of Sichuan University (No. 2022-0606), and the requirement for individual consent for this retrospective analysis was waived.

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Supplementary

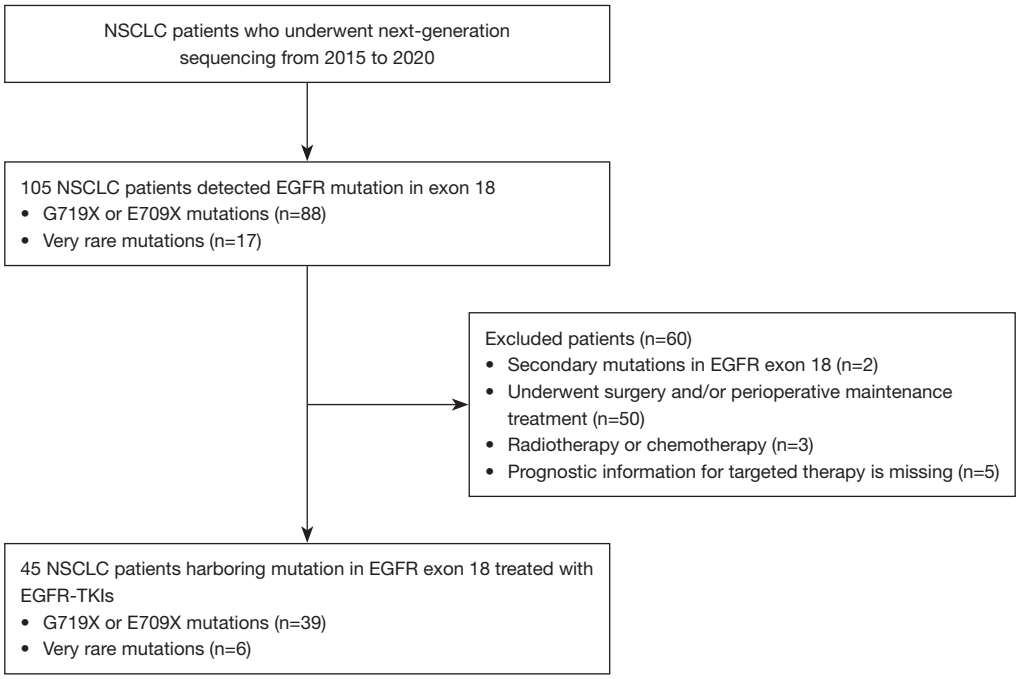

Figure S1 Flow diagram of the study design. NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

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Table S1 Baseline characteristics of 105 NSCLC patients harboring mutations in *EGFR* exon 18

Characteristics	Overall (N=105)	G719X or E709X mutations (N=88)	Very rare mutations (N=17)	P value
Presence of common mutation, n (%)				>0.99
Yes	15 (14.3)	13 (14.8)	2 (11.8)	
No	90 (85.7)	75 (85.2)	15 (88.2)	
L858R or 19del, n (%)				
L858R	13 (12.4)	12 (13.6)	1 (5.9)	0.688
19del	2 (1.9)	1 (1.1)	1 (5.9)	0.299
Age (years), median (range)	60.00 (53.00, 68.00)	60.00 (53.00, 70.50)	56.00 (51.00, 65.00)	0.377
Age (years), n (%)				0.510
<60	51 (48.6)	41 (46.6)	10 (58.8)	
≥60	54 (51.4)	47 (53.4)	7 (41.2)	
Gender, n (%)				0.830
Female	55 (52.4)	47 (53.4)	8 (47.1)	
Male	50 (47.6)	41 (46.6)	9 (52.9)	
Smoking, n (%)				0.854
Current/former smoking	20 (19.0)	16 (18.2)	4 (23.5)	
Never smoking	77 (73.3)	65 (73.9)	12 (70.6)	
Unknow	8 (7.6)	7 (8.0)	1 (5.9)	
Smoking index, n (%)				0.708
≤200	80 (76.2)	67 (76.1)	13 (76.5)	
>200	14 (13.3)	11 (12.5)	3 (17.6)	
Unknown	11 (10.5)	10 (11.4)	1 (5.9)	
ECOG PS, n (%)				0.998
≥2	6 (5.7)	5 (5.7)	1 (5.9)	
0–1	80 (76.2)	67 (76.1)	13 (76.5)	
Unknown	19 (18.1)	16 (18.2)	3 (17.6)	
Pathology, n (%)				>0.99
Adenocarcinoma	102 (97.1)	85 (96.6)	17 (100.0)	
Squamous cell carcinoma	3 (2.9)	3 (3.4)	0 (0.0)	
Stage, n (%)				0.518
I–II	43 (41.0)	35 (39.8)	8 (47.1)	
III	11 (10.5)	9 (10.2)	2 (11.8)	
IVA	26 (24.8)	21 (23.9)	5 (29.4)	
IVB	22 (21.0)	21 (23.9)	1 (5.9)	
Unknown	3 (2.9)	2 (2.3)	1 (5.9)	
Metastases, n (%)				0.356
Multiple organ metastasis	20 (19.0)	19 (21.6)	1 (5.9)	
No organ metastasis	57 (54.3)	45 (51.1)	12 (70.6)	
Single organ metastasis	26 (24.8)	22 (25.0)	4 (23.5)	
Unknown	2 (1.9)	2 (2.3)	0 (0.0)	

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status; common mutation, *EGFR* 19del and L858R.

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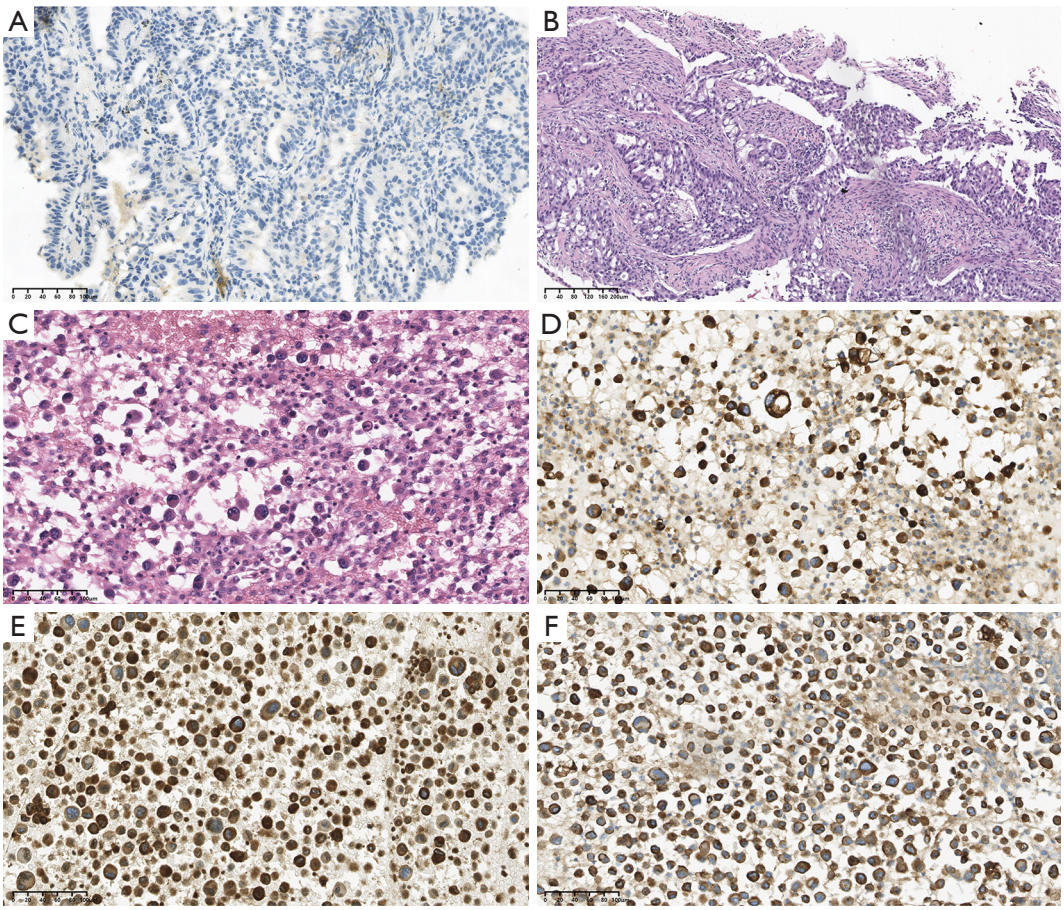

Figure S2 Pathological images of NSCLC patients with very rare mutations. (A-C) Hematoxylin and eosin section of patient 44 (HE staining, ×200), patient 40 (HE staining, ×100), and patient 43 (HE staining, ×200), respectively. And their pathologic types were all adenocarcinoma. (D-F) Immunohistochemistry examinations on NapsinA, CEA, E-C for patient 43, respectively. NapsinA, CEA and E-C were positive for patient 43. NSCLC, non-small cell lung cancer; HE, hematoxylin and eosin.

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