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ORIGINAL ARTICLE

Uncommon mutation types of epidermal growth factor receptor and response to EGFR tyrosine kinase inhibitors in Chinese non-small cell lung cancer patients

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Abstract
Purpose Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) is the standard therapy for advanced lung adenocarcinomas with common *EGFR* mutations. However, the efficacy of EGFR-TKIs in patients with uncommon *EGFR* mutations (other than exon 19 deletions or exon 21 L858R mutation) remains undetermined.
Methods Seven hundred and fifty-five non-small cell lung cancer (NSCLC) patients with *EGFR* mutation analyses for TKI therapy were identified between October 2010 and December 2015 in East of China. And 66 patients bearing uncommon *EGFR* mutations were included to collect data from TKI response and prognosis. We categorised *EGFR* uncommon mutations as: sensitizing rare mutations (group 1: G719X, L861Q, S768I); Ex20 ins (group 2), or complex mutations (G719X + L861Q, G719X + S768I, 19 del + T790M, 19 del + L858R, L858R + S768I, and L858R + T790M; group 3).
Results Of 66 patients given EGFR-TKI treatment, rare sensitive mutations, Ex20 ins, and complex mutations were identified in 37 (56.1%), 9 (13.6%), and 20 (33.3%) cases, respectively. TKI efficacy in patients harboring uncommon *EGFR* mutations exhibited a tumor response rate of 28.8% and a median progression-free survival (PFS) of 4.8 months. Additionally, patients with complex *EGFR* mutations had significantly longer PFS when compared with the remaining sensitizing rare mutations or Ex20 ins cases (8.6 vs. 4.1 vs. 3.1 months; $p = 0.041$). Importantly, complex *EGFR* mutations were independent predictors of increased overall survival (Hazard Ratios = 0.31; 95% confidence intervals: 0.11–0.90; $p = 0.031$). Among them, patients harboring Del-19 combined with L858R mutations showed a tendency to have higher response rate (RR) and improved PFS than those with other complex mutation patterns (RR: 66.7 vs. 14.3%, $p = 0.021$; PFS: 10.1 vs. 8.6 months, $p = 0.232$).
Conclusions Personalized treatment should be evolving in different types of uncommon *EGFR* mutations. Clinical benefit from EGFR-TKIs was higher in NSCLC patients with complex *EGFR* mutations than those with other uncommon *EGFR* mutation types.

Keywords Non-small cell lung cancer · Epidermal growth factor receptor · Uncommon mutation · Tyrosine kinase inhibitors · Efficacy

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Introduction

As one of the most common malignant tumors, lung cancer is the leading cause of cancer-related mortality worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for 85% of primary lung cancer [2]. Regarding to patients with lung adenocarcinoma, around 50% cases are diagnosed with a somatic mutation of the epidermal growth factor receptor (*EGFR*) gene in East Asian [3, 4], while

mutations of *EGFR* were found in 10–20% of Caucasian patients [5, 6]. Therapies targeting driver mutations incorporate EGFR inhibitors such as gefitinib and erlotinib, resulting in extended survival in patients with NSCLC [7–9]. Icotinib also provides a similar efficacy to gefitinib, and with better tolerability in NSCLC patients [10].

The two most common *EGFR* mutations include deletions in exon 19 (Del-19) and L858R substitution in exon 21, which can be regarded as positive predictive biomarkers for response to EGFR tyrosine kinase inhibitors (TKIs) [6, 11]. Previous study has showed the response rate to EGFR TKIs was significantly higher in individuals with classic *EGFR* mutations than in those with uncommon mutations such as G719X, L861Q, S768I, Ex20 ins and so on [12]. However, *EGFR* uncommon mutation-positive cases are a heterogeneous group of molecular alterations with variable responses to EGFR-targeted drugs. Patients who had G719X, L861Q or S768I mutations could lead to favorable responses and longer progression-free survival (PFS) than the remaining rare mutation cases [13, 14], though not as favorable as for patients with classic mutations [12]. The 2017 NCCN guidelines Version 8. of NSCLC showed that there is a significant association between *EGFR* mutations-especially Del-19 and exon 21 (L858R, L861Q), exon 18 (G719X), and exon 20 (S768I) mutations-and sensitivity to EGFR TKIs [11, 15–17]. Moreover, the Ex20 ins predicts primary resistance to clinically achievable levels of TKIs [18, 19]. Collectively, studies characterizing the TKI sensitizing effect of individual rare mutations are indispensable to stagey patients who may benefit from anti-EGFR therapy.

Despite abundant literatures on common activating and secondary resistant *EGFR* mutations (T790M in exon 20), little is known about complex *EGFR* mutations due to the low incidence and complicated subtypes. And this gap in knowledge may constitute a challenge for the clinician in daily practice. To date, some studies showed that co-mutation might be associated with the primary resistance to TKIs [20, 21]. However, another study observed that patients with uncommon compound *EGFR* mutations (G719X + L861Q, G719X + S768I) had a significantly favorable PFS than did patients with a single mutation [22]. Therefore, comparative information about TKI efficacy within the *EGFR* co-mutated group is needed to optimise treatment.

In the present study, we aimed to investigate the clinical characteristics and efficacy of EGFR-TKIs in patients carrying uncommon *EGFR* mutations. The incidence of rare mutations varies in different ethnic groups and is also influenced by environmental factors. For this very reason, we informed the clinical decisions for the sensitivity of uncommon *EGFR* mutations to TKIs therapy in a Chinese cohort of advanced NSCLC patients. The results were discovered in a subset of NSCLC patients, which could help facilitate individual patient profiling and accurate prediction of response to EGFR TKIs therapy.

Materials and methods

Study design

Among 755 NSCLC patients with *EGFR* mutations, we retrospectively collected 66 patients with uncommon *EGFR* genotypes and treated for advanced NSCLC using EGFR-TKIs (Gefitinib, Erlotinib, Icotinib or Afatinib) during October 2010 and December 2015 at Zhejiang Cancer Hospital, China. Patients who harbored the acquired T790M substitution in exon 20 were excluded. Histological type and grade were decided based on lung tumor classification criteria of the World Health Organization (WHO). The TNM stages of patients were determined according to the 7th staging system of the International Association for the Study of Lung Cancer (IASLC). The protocol was approved by the institutional review board of Zhejiang Cancer Hospital, and all patients were provided informed consent.

EGFR mutational analysis

The tumor *EGFR* mutational status was determined by analyzing the DNA isolated from tumor specimens embedded in formalin-fixed and paraffin-embedded blocks. All samples were tested using an amplification refractory mutation system-based *EGFR* mutation detection kit (Amoy Diagnostics, Xiamen, People's Republic of China). The method enabled the detection of 29 mutations in exons 18, 19, 20, and 21. In exon 20, two mutations (S768I and T790M) and one insertion were included.

Clinical data collection and efficacy evaluations

All patients had complete clinicopathological data and follow-up information. Demographic data included age, gender, smoking history, and Eastern Cooperative Oncology Group performance status (ECOG PS). Clinicopathological factors included histological type, clinical stage, radical surgery experience, types of *EGFR* mutations, types of EGFR-TKIs, and treatment line. Patients were visited every 4 weeks, and tumor response were evaluated by enhanced computed tomography before treatment initiation and 1 month after therapy, then every 2–3 months according to NHI regulations. EGFR-TKI beyond progression was determined by the specialized physicians. Objective response rates (RRs) and disease control rates (DCRs) of the patients with measurable tumors were calculated according to response evaluation criteria in solid tumors 1.1. PFS was calculated from the date of initiation of EGFR-TKI treatment to the date

of disease progression or death. Overall survival (OS) was estimated from the date of initiation of EGFR-TKI treatment until death or last available follow-up. The median follow-up time of the 66 patients was 38 months.

Statistical analysis

Data were analyzed as categorical variables. Survival curves were plotted in a Kaplan–Meier method and compared using a log-rank test. Univariate and multivariate analyses of potential risk factors were performed using Cox proportional hazards regression model. Statistical analyses were performed using SPSS 13.0 for Windows (Chicago, IL). p value ≤ 0.05 in a two-tailed test was considered statistical significance.

Results

Demographics and clinical characteristics

The demographic characteristics of the patients with uncommon *EGFR* mutations are listed in Table 1. Among the 66 patients, 47.0% (31 patients) were male, 72.7% (48 patients) were younger than 65 years, and 45.5% (30 patients) had smoking experience. Most patients had good performance status with ECOG 0 or 1 ($N=57$, 86.4%). The majority of patients were stage IV ($N=50$, 75.8%) when receiving TKI treatment and diagnosed with NSCLC of predominantly adenocarcinoma histology ($N=63$, 95.5%). Thirteen patients (19.7%) received radical surgery when initially diagnosed with NSCLC at I–IIIa stage. Then they were treated with EGFR-TKIs once disease recurrence after surgery.

Table 1 Clinicopathological features of 66 NSCLC patients

Factors	No. of patients ($n=66$)	%
Gender		
Male	31	47.0
Female	35	53.0
Age (year)		
<65	48	72.7
≥ 65	18	27.3
Smoking		
Never	36	54.5
Ever/current	30	45.5
Performance status		
0–1	57	86.4
2	9	13.6
Histology subtype		
Adenocarcinoma	63	95.5
Non-adenocarcinoma	3	4.5
Radical surgery		
No	53	80.3
Yes	13	19.7
Stage		
IIIb	16	24.2
IV	50	75.8
Lines of EGFR-TKI		
First line	30	45.5
Second line	29	43.9
Third line	7	10.6
EGFR-TKI		
Icotinib	49	74.2
Gefitinib	11	16.7
Erlotinib	4	6.1
Afatinib	2	3.0

EGFR epidermal growth factor receptor, *TKI* tyrosine kinase inhibitor

EGFR mutation types and subtypes

Among the 755 patients with *EGFR* mutations, 66 (8.7%) cases had uncommon *EGFR* mutant. To further analyze the different responses of uncommon *EGFR* mutations to TKIs, when combining the effectiveness of EGFR-TKIs mentioned above in each mutation type, mutation variations were divided into three groups, such as rare sensitive mutations (group 1: G719X, L861Q, and S768I), Ex20 ins group 2, and complex mutations (G719X + L861Q, G719X + S768I, 19 del + T790M, 19 del + L858R, L858R + S768I, and L858R + T790M; group 3).

There were 46 patients had a single mutation [37 (56.1%) cases with sensitizing rare mutations, and 9 (13.6%) patients harboring Exon 20 ins], and 20 (30.3%) patients carried complex *EGFR* mutations (Table 2). Amino acid substitution mutations, G719X, L861Q, and S768I, were observed in 19 (28.8%), 16 (24.2%), and 2 (3.0%) patients, respectively. And Ex20 ins was noted in 9 (13.6%) patients (Fig. 1). Remaining 20 patients had co-mutations, which occurred in: G719X + L861Q (2 cases), G719X + S768I (2 cases), 19 del + T790M (1 cases), 19 del + L858R (6 cases), L858R + S768I (2 cases), and L858R + T790M (7 cases). EGFR-TKIs were used as first-line treatment for 30 (45.5%) patients. And Icotinib was prescribed more frequently in patients with EGFR-TKIs therapeutics.

Response to EGFR-TKIs treatment

Table 2 lists the treatment response of *EGFR* uncommon mutation types and subtypes to TKIs. Combining the response rate and sample number of patients with uncommon mutations, the efficacy of TKIs in each mutation types was showed in Fig. 2. The RR of the individuals with uncommon *EGFR* mutations was 28.8% (19 of 66) and the DCR was 81.8% (54 of 66). In subgroup analyses, patients

Table 2 EGFR-TKIs response in each uncommon subtypes of *EGFR* mutations

	Objective response						
	No. of patients	CR	PR	SD	PD	RR (%)	DCR (%)
Rare sensitive mutations							
G719X	19	0	7	11	1	36.8	94.7
L861Q	16	0	5	6	5	31.3	68.8
S768I	2	0	0	2	0	0.0	100.0
Subtotal	37	0	12	19	6	**32.4**	**83.8**
Resistance mutation							
Ex20 ins	9	0	1	6	2	**11.1**	**77.8**
Complex mutations							
G719X + L861Q	2	0	0	2	0	0.0	100.0
G719X + S768I	2	0	0	2	0	0.0	100.0
19 del + T790M	1	0	1	0	0	100.0	100.0
19 del + L858R	6	0	4	2	0	66.7	100.0
L858R + S768I	2	0	0	0	2	0.0	0.0
L858R + T790M	7	0	1	4	2	14.3	71.4
Subtotal	20	0	6	10	4	**30.0**	**80.0**
Total	66	0	19	35	12	28.8	81.8

Bold values showed the EGFR-TKIs response in each uncommon subtypes of EGFR mutations, such as sensitizing rare mutations (group 1), Ex20 ins (group 2), and complex mutations (group 3)

EGFR epidermal growth factor receptor, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NA* not available, *RR* response rate, *DCR* disease control rate

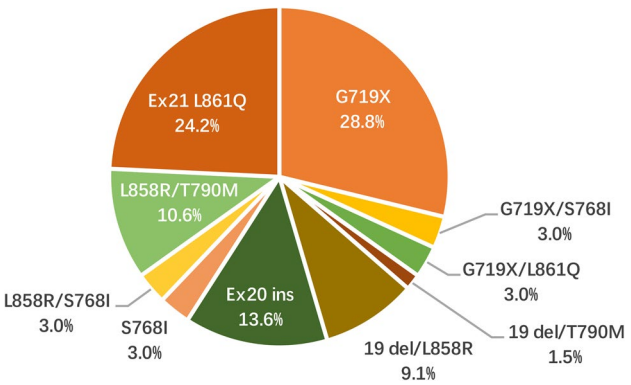

Fig. 1 Distribution of the uncommon and complex *EGFR* mutations in 66 NSCLC patients. Amino acid substitution mutations, G719X, L861Q, and S768I, were observed in 19 (28.8%), 16 (24.2%), and 2 (3.0%) patients, respectively. And Ex20 ins were noted in 9 (13.6%) patients. Remaining 20 patients were had co-mutations, which occurred in: G719X + L861Q (2 cases), G719X + S768I (2 cases), 19 del + T790M (1 cases), 19 del + L858R (6 cases), L858R + S768I (2 cases), and L858R + T790M (7 cases)

carrying complex mutation had a RR of 30.0% and DCR of 80.0%. Of them, patients harboring Del-19 and L858R mutations showed a RR of 66.7% (4 of 6), which was significantly higher than those with other complex mutations patterns (RR = 14.3%, 2 of 14, $p = 0.021$). Regarding to the patients carrying *de novo* T790M combined with 19del or L858R mutation, the RR displayed 25.0% (2 of 8), and the DCR was 75.0% (6 of 8). In addition, patients in rare sensitive mutation group (G719X, L861Q, and S768I) had the RR of 32.4% and DCR of 83.8%, while a RR of 11.1% and a DCR of 77.8% were observed in Ex20 ins group.

Survival

After EGFR-TKIs treatment, patients with uncommon mutations had a median PFS of 4.8 months [95% confidence intervals (CI) 3.5–6.1, Fig. 3] and a median OS of 15.7 months (95% CI 11.6–19.7). In the subset analysis, patients with compound mutations had the most favorable PFS, followed by those with rare sensitive mutations and Ex20 ins (median PFS: 8.6 vs. 4.1 vs. 3.1 months, $p = 0.041$). We also detected an OS difference between them (median OS: 20.5 vs. 15.2 vs. 16.1 months), although no significant difference was reached ($p = 0.271$).

Interestingly, in the tumors harboring co-mutation, longer PFS was found for patients with Del-19 occurred with L858R mutation that the median PFS reached 10.1 months compared with 8.6 months for those with other co-mutation patterns, although exhibited nonsignificant differences ($p = 0.232$, Fig. 4). And the median OS was 20.5 months and 17.8 months, respectively ($p = 0.713$). Moreover, the median PFS and OS of patients occurred with de novo T790M combined Del-19 or L858R mutation was 8.6 and 21.6 months, respectively.

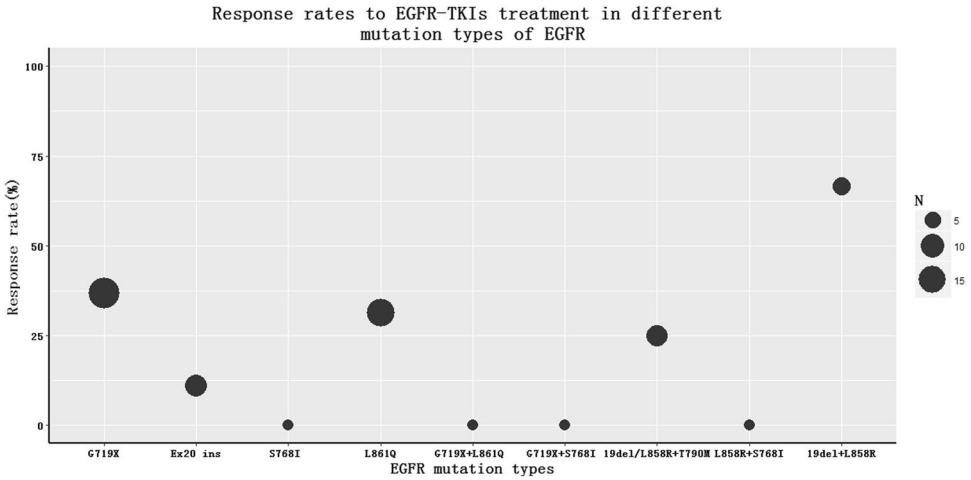

Fig. 2 Response rates to EGFR-TKIs treatment in different mutation types of EGFR. Combining the response rate and sample number in NSCLC patients with uncommon mutations, the efficacy of each mutation types was showed in 9 groups. The size of the circle represents the sample number in each mutation types, while color depth also indicates the sample number. G719X: RR = 36.8%, $N = 19$; Ex20 ins: RR = 11.1%, $N = 9$; S768I: RR = 0.0%, $N = 2$; L861Q: RR = 31.3%, $N = 16$; G719X + L861Q: RR = 0.0%, $N = 2$; G719X + S768I: RR = 0.0%, $N = 2$; 19 del or L858R + T790M: RR = 25.0%, $N = 8$; L858R + S768I: RR = 0.0%, $N = 2$; 19 del + L858R: RR = 66.7%, $N = 6$

In the multivariate analysis (Table S1), performance status, radical surgery, the types of *EGFR* mutation, and line of EGFR-TKI therapy were identified as independent predictors for OS after adjusting by clinicopathological factors. First, complex *EGFR* mutations were independent predictor of increased OS [Hazard ratio (HR) = 0.31; 95% confidence interval (CI): 0.11–0.90; $p = 0.031$]. Second, patients with worse performance status were more likely to have shorter OS than those with better performance status (HR = 9.38; 95% CI 1.41–62.2; $p = 0.020$). Compared with patients who did not go through radical surgery, those who underwent it were at lower risk for disease death (HR = 0.16; 95% CI 0.06–0.48; $p = 0.001$). Finally, NSCLC patients with *EGFR* uncommon mutations who received EGFR-TKIs as their second-line or third-line treatment had reduced risk for death (HR = 0.32; 95% CI 0.15–0.72; $p = 0.006$; for second-line; and HR = 0.20; 95% CI 0.06–0.66; $p = 0.008$; for third-line).

Discussion

In the present study, 8.7% (66/755) of NSCLC patients carrying uncommon *EGFR* mutant, similar to East-Asian studies where the incidence of rare mutations was ranging from 7 to 8% [13], while the incidence in Caucasian cohort was only 1.9–2.7% [23, 24]. Then we observed a RR of 28.8% and a median PFS of 4.8 months in our patients after receiving TKIs treatments, and both results were inferior to the patients with common *EGFR* mutations that the RR was 70–80% and the median PFS was 9.4–11.9 months [22, 25, 26]. The RR of 28.8% in our study was in accordance with the 31% demonstrated in Johnson's study [27], and the PFS of 4.8 months was comparable to the 5-month PFS in a East-Asian study performed by Wu et al. [12]. Moreover, the OS of 15.7 months in our cohort was also similar with 15.0 months in Wu's study [12]. Considering the patients with uncommon *EGFR* mutant showed a worse efficacy than those with classic mutations after TKIs treatment, additional subtypes analyses in therapeutic responses among uncommon *EGFR* mutations should be urgent warranted.

Subgroup analysis showed patients with rare sensitive *EGFR* mutations (G719X, L861Q, and S768I) exhibited a RR of 32.4% and a median PFS of 4.1 months. The RR of 32.4% was consistent with data previously reported of 35.9% (51/142, $p > 0.05$), while the PFS of 4.1 months was shorter than 6.5 months observed in their study [22]. Previous researches have indicated that tumor with S768I mutation showed a variable response to TKIs treatment [28, 29], which might result in the shorter PFS among our patients with G719X, L861Q, and S768I mutant. Furthermore, in a post hoc analysis from three clinical trails on Afatinib (LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6), 14 (77.8%) patients with G719X had an objective response, as did nine (56.3%) with L861Q, and eight (100.0%) with S768I [30, 31]. Notably, the median PFS of them was reached to 10.7 months [30], which was inconsistent with our findings. The potential reasons might be listed as follows. First, Afatinib as a second-generation irreversible TKI could combine the targeted gene more firmly, inducing its favorable responses in G719X/L861Q/S768I [31]. Second, the scale of these two cohorts was not large enough (37 vs. 31 cases) to elucidate this problem, resulting in the different responses to

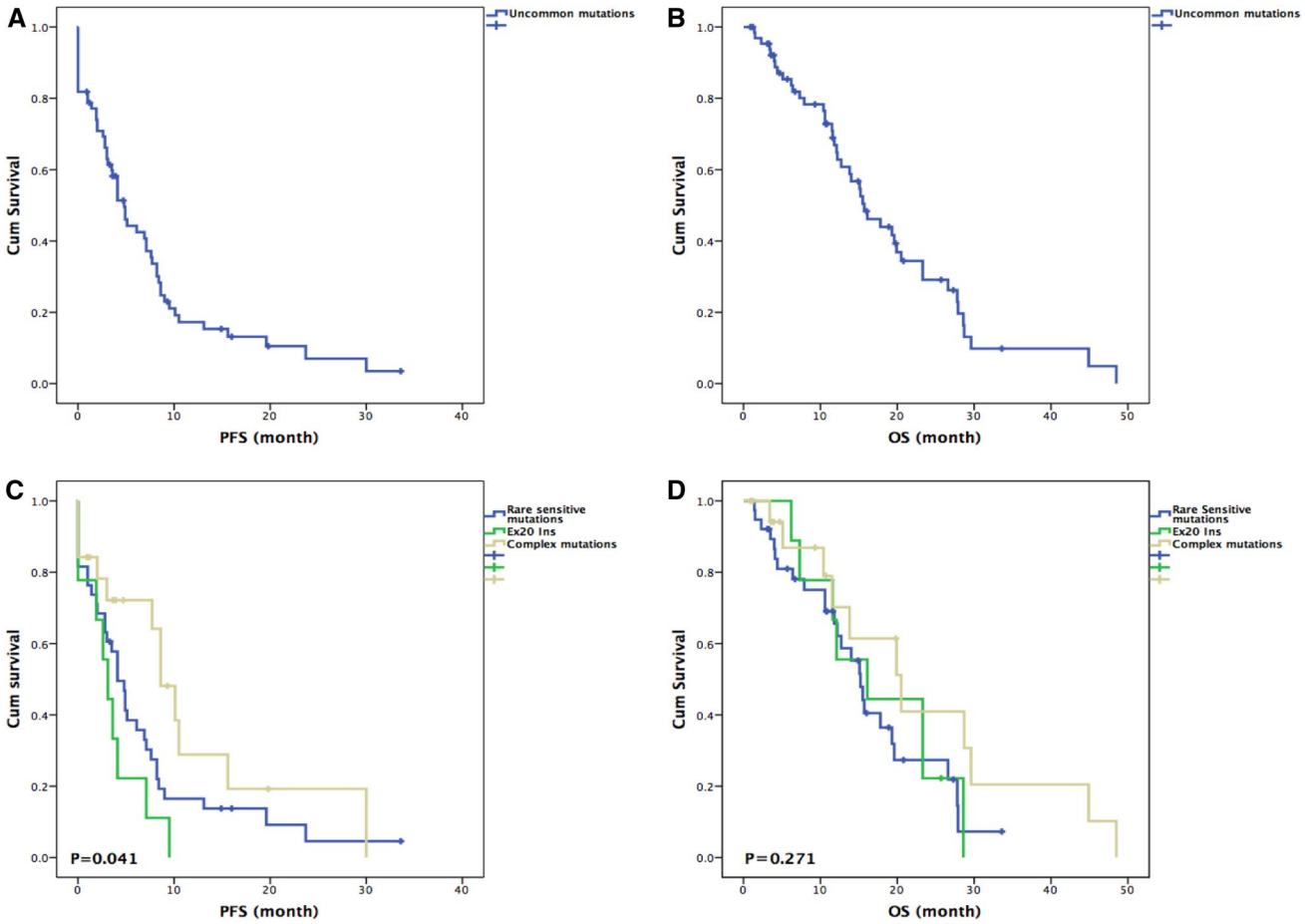

Fig. 3 Kaplan–Meier curves of PFS and OS in *EGFR* uncommon mutation types and subtypes in NSCLC after EGFR-TKI therapy. **a, b** Patients with uncommon mutations had a median PFS with 4.8 months (95% CI 3.5–6.1); median OS with 15.7 months (95% CI 11.6–19.7). **c** Patients with compound mutations had the longest median PFS of 8.6 months (95% CI 6.1–11.1), followed by those with rare sensitive mutations (median PFS = 4.1 months; 95% CI 2.7–5.5) and Ex20 ins (median PFS = 3.1 months; 95% CI 1.6–4.6, $p = 0.041$). **d** Patients with compound mutations had the longest median OS of 15.2 months (95% CI 12.7–17.6), followed by those with rare sensitive mutations (median OS: 15.2 months; 95% CI 12.7–17.6) and Ex20 ins (median OS: 6.1 months; 95% CI 4.4–27.8, $p = 0.271$)

EGFR-TKIs in these two studies. Collectively, first-generation TKIs demonstrated certain efficacy in patients with G719X, L861Q, and S768I mutations, while Afatinib might be a priority choice in these individuals.

Regarding to the TKI activity in NSCLC patients with Ex20 ins, we detected a RR of 11.1% and a median PFS of 3.1 months. The PFS was line with the 2.7 months reported previously [30]. However, the outcome was worse than that of the cisplatin-pemetrexed combination regimen treating lung adenocarcinoma with *EGFR* mutations (median PFS: 6.9 months; RR: 23%) in LUX-Lung 2 clinical trial [32]. As a result, first-line chemotherapy rather than EGFR-TKIs treatment seems to achieve a better efficacy in Ex20 ins mutated cases.

Consistent with previously published data [13], 20 (2.6%) individuals carried complex *EGFR* mutations. And our further subtype analysis suggested these patients had a longer PFS than those with G719X/L861Q/S768I mutations or Ex20 ins, indicating those patients may benefit more from first-line EGFR-TKIs treatment. Similar to the findings by Johnson et al. [27], multivariate analysis demonstrated complex *EGFR* mutations could be an independent predictor of increased OS in NSCLC patients carrying uncommon *EGFR* mutations.

EGFR compound mutations were composed of heterogeneous groups, resulting in the different responds to TKIs treatment. Further precise definition is crucial for individualized therapy in *EGFR* mutant lung adenocarcinoma. Analysis on PFS revealed that patients combined Del-19 and L858R mutations had significantly higher RR and a trend toward longer PFS than those carrying other patterns of complex *EGFR* mutations. Considering the median PFS of 10.1 months and the RR of 66.7% were in line with the effectiveness of TKIs in patients harboring classic mutations [25,

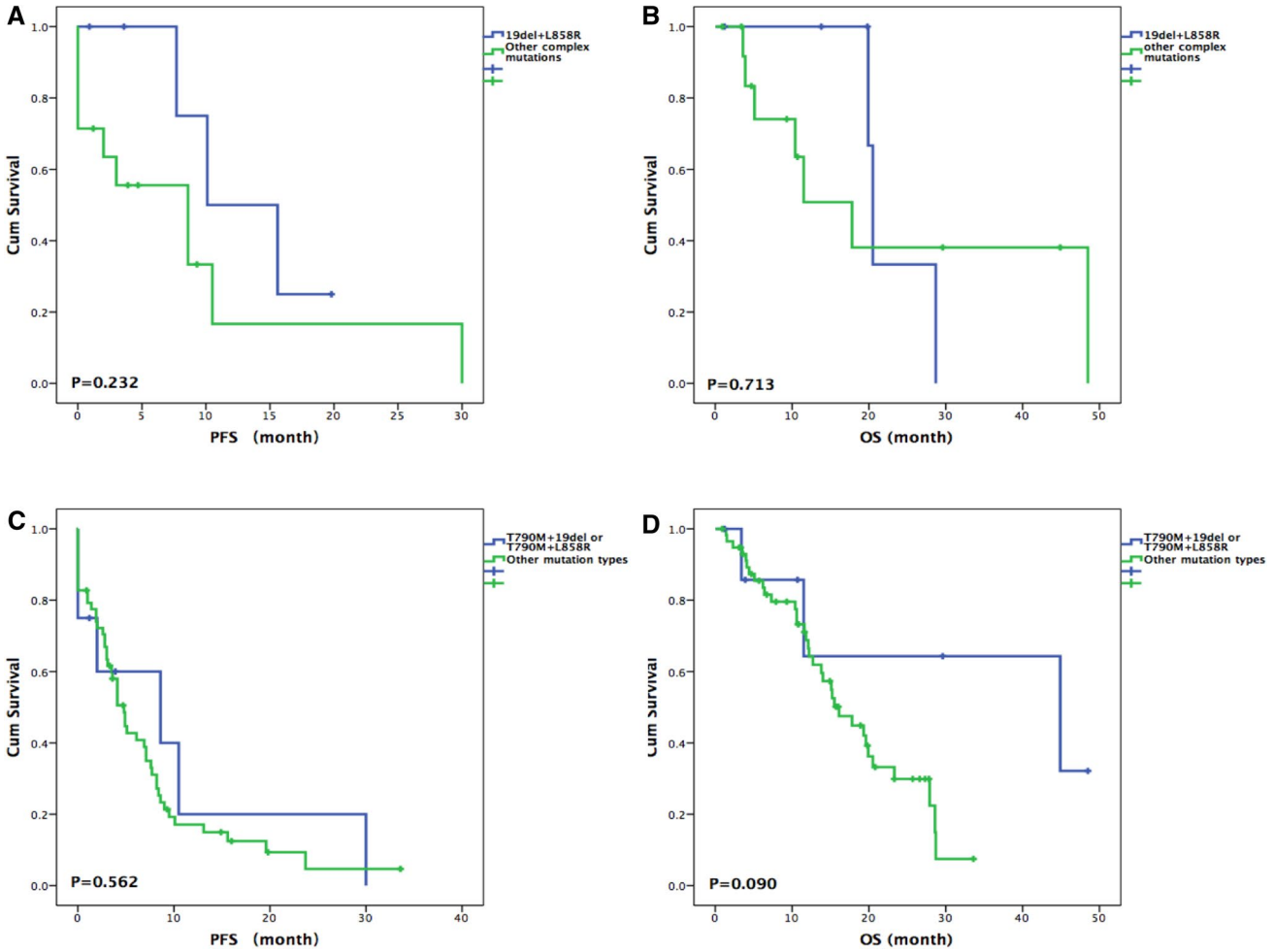

Fig. 4 Kaplan–Meier curves of OS and PFS in *EGFR* uncommon mutation subtypes in NSCLC after EGFR-TKI therapy. **a** Patients with 19del and L858R mutations had the median PFS of 10.1 months (95% CI 2.4–17.8), while those with other complex mutations types had the mPFS of 8.6 months (95% CI 1.4–15.8), although exhibited nonsignificant differences ($p=0.232$). **b** Patients with 19del and L858R mutations had the median OS of 20.5 months (95% CI 19.5–21.5); while those with other complex mutations types had the mOS = 17.8 months (95% CI 8.4–27.2), although exhibited non-significant differences ($p=0.713$). **c, d** The PFS and OS in patients with de novo T790M and 19del or L858R mutations was similar with patients with other uncommon *EGFR* mutations (median PFS: 8.6 vs. 4.8 months; median OS: 21.6 vs. 32.9 months; $p>0.05$)

26], patients with Del-19 and L858R are strongly recommended to receive EGFR-TKIs as their first-line treatment.

Complex mutations of de novo T790M combined with other mutation types (such as Del-19 or L858R) were also detected in this study. Notably in these patients, the RR to EGFR-TKIs was 25.0%, and the median PFS was 8.6 months. Consistent with previous report [33], the efficacy of complex mutations including de novo T790M to first-generation and second-generation TKIs was inferior to the classic *EGFR* mutations. However, third-generation agent (Osimertinib) has proved to be effective in NSCLC cell lines with *EGFR* sensitizing and T790M resistant mutations [34]. Moreover, Osimertinib has been approved by FDA and EMA for the treatment of patients with advanced *EGFR* T790M mutated NSCLC who have disease progressed during first-generation or second-generation TKI therapeutics [35, 36]. Another research indicated that Osimertinib as first-line therapy for advanced NSCLC patients harboring *EGFR* mutation (including 5 patients with *de novo* T790M mutation) resulted in a high RR, favorable PFS and manageable tolerability profile [37]. Therefore, Osimertinib has being investigated its efficacy in patients with de novo T790M mutation as a first-line treatment (versus gefitinib) in the phase 3 FLAURA trial (NCT02296125), then the results are worth looking forward to. In conclusion, distinct clinical features of different *EGFR* co-mutations were displayed. A further crystal structure analysis of the compound *EGFR* mutations is required to elucidate the mechanisms underlying these observations. Our findings of these complex mutations and their association to EGFR-TKIs, help to

guide the application of EGFR-TKIs in patients with *EGFR* co-mutations.

This study provided the systematical treatment options for the sensitivity of uncommon *EGFR* mutations types and subtypes, especially the complex mutations to EGFR-TKIs therapy. Personalized treatment should be applied to different types of uncommon *EGFR* mutations in NSCLC patients. EGFR-TKIs as first-line treatment seems to achieve certain effectiveness in patients harbored types of G719X, L861Q, and S768I mutations, but Afatinib might be a priority selection for these patients. However, less benefit from TKIs treatment was gained in Ex20 ins mutated cases. Moreover, different responds to TKIs were existed in *EGFR* compound mutations subtypes. It is strongly recommended TKIs as first-line therapy in patients harboring Del-19 compound L858R mutations; while might not be effective in patients with de novo T790M combined with other mutation types. Collectively, our study indicated the predictive and prognostic values of uncommon *EGFR* mutations with regard to TKI therapy in a cohort of East-Asian population, which should be evaluated in wide multinational studies. Then the integrated data could help inform clinical decisions for patients in different ethnic groups with NSCLC harboring uncommon *EGFR* mutations.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standard of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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