Review Article

Treatment of uncommon *EGFR* mutations in non-small cell lung cancer: new evidence and treatment

Tianli Zhang[1#], Bing Wan[2#], Yuan Zhao[3#], Chuling Li[4], Hongbing Liu[1,3,4], Tangfeng Lv[1,3,4], Ping Zhan[1,3,4], Yong Song[1,3,4]

[1]Department of Respiratory Medicine, Jinling Hospital, Medical School of Southeast University, Nanjing 210002, China; [2]Department of Respiratory and Critical Care Medicine, The Affiliated Jiangning Hospital of Nanjing Medical University, Nanjing 210002, China; [3]Department of Respiratory Medicine, Jinling Hospital, Nanjing University School of Medicine, Nanjing 210002, China; [4]Department of Respiratory Medicine, Jinling Hospital, Jinling Clinical College of Nanjing Medical University, Nanjing 210002, China

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#These authors contributed equally to this work.

Correspondence to: Ping Zhan; Yong Song, MD, PhD. Department of Respiratory Medicine, Jinling Hospital, Nanjing University School of Medicine, #305, East Zhongshan Road, Nanjing 210002, China. Email: zhanping207@163.com; yong_song6310@yahoo.com.

Abstract: Sensitizing mutations in epidermal growth factor receptor (EGFR) are associated with positive responses to anti-EGFR-targeted therapy, leading to a new era of treatment for non-small cell lung cancer (NSCLC). Exon 19 deletions and exon 21 L858R substitutions are the most common mutations, accounting for approximately 90% mutations in NSCLC; these are termed classic mutations and result in high sensitivity to tyrosine kinase inhibitors (TKIs). Other *EGFR* mutations are termed uncommon *EGFR* mutations, of which G719X, S768I, L861Q, exon 20 insertions, and complex mutations are the most frequent. G719X, S768I, and L861Q are point mutations and those that exist with complex mutations are sensitive to first-generation TKIs. A prospective analysis demonstrated that afatinib, a second-generation TKI, led to a better prognosis in some patients with NSCLC compared to first-generation TKIs. Chemotherapy used to be the traditional choice for patients carrying exon 20 insertions; however, with the development of novel targeted drugs, the role of chemotherapy is changing. Tremendous progress has also been made in clinical trials on immunotherapy treatment of uncommon *EGFR* mutations. The treatment for patients with NSCLC harboring uncommon *EGFR* mutations remains a subject of debate and the sensitivity of uncommon *EGFR* mutations to TKIs is still unclear. Here, we summarized recent data in the literature and provide an overview of the clinical characteristics, incidence, and outcomes of patients harboring G719X, S768I, L861Q, exon 20 insertions, and complex mutations who were treated with TKIs, chemotherapy, or immunotherapy.

Keywords: Non-small cell lung cancer (NSCLC); uncommon epidermal growth factor receptor mutations (uncommon *EGFR* mutations); tyrosine kinase inhibitors (TKIs); treatment; immunotherapy

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Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases and has high mortality worldwide (1,2). In China, it is also the most common cancer and leading cause of cancer-related deaths (3). Targeted therapy has led to a new era in the treatment of NSCLC with the development of detection techniques for epidermal growth factor receptor (EGFR)

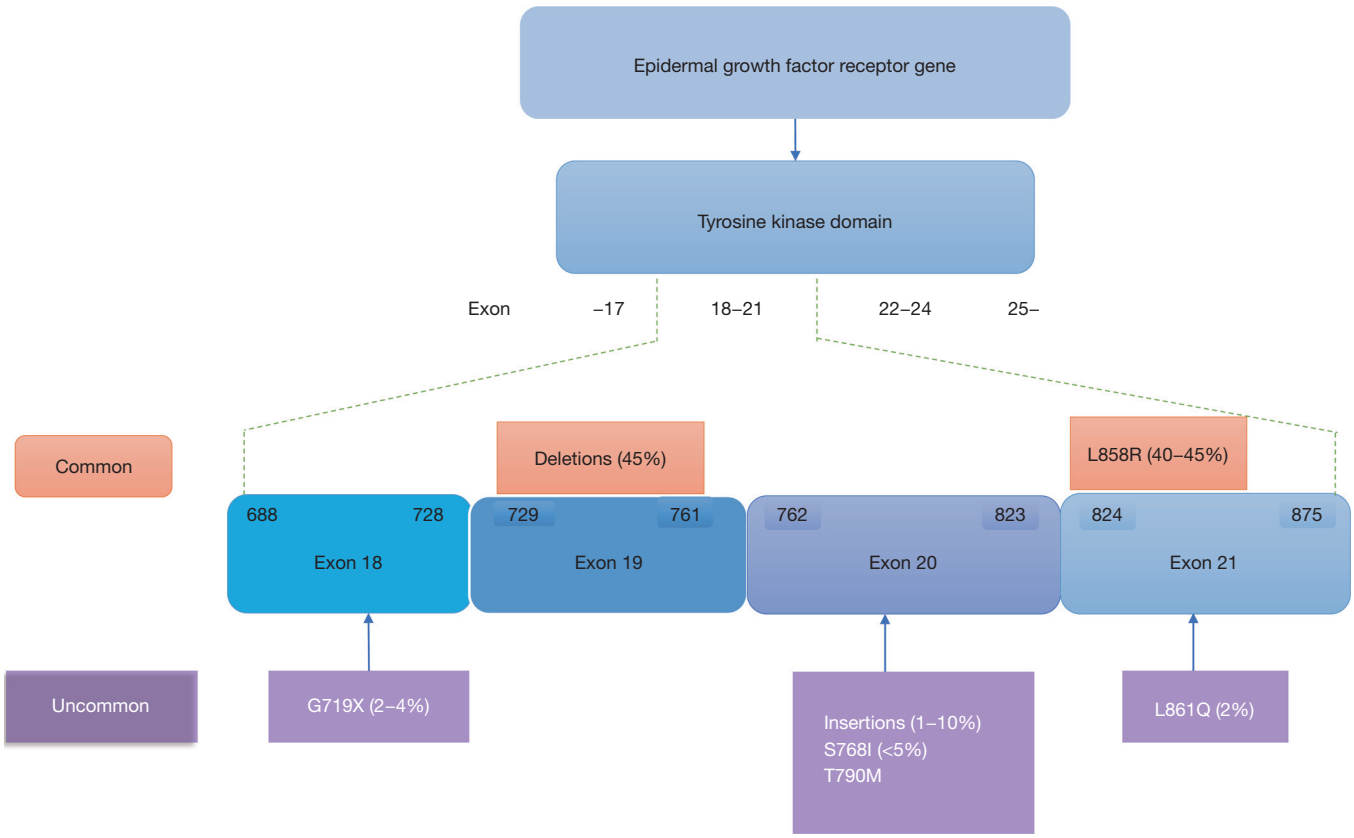

Figure 1 *EGFR* somatic mutations within exon 18–21 of the tyrosine kinase domain of the gene. Common and uncommon EGFR mutations are represented by orange and purple background respectively. EGFR, epidermal growth factor receptor.

mutations. NSCLC harboring *EGFR* mutations constitutes about 10–20% of all lung cancer cases in Europe and North America (4,5) and up to 50% of Asian patients with NSCLC (5). Exon 19 deletions and exon 21 L858R substitution are the most common mutations, accounting for approximately 90% of mutations in NSCLC; these are termed classic mutations and lead to high sensitivity to tyrosine kinase inhibitor (TKIs) (6-9). NSCLC patients with exon 19 deletions and exon 21 L858R substitution have longer progression-free survival (PFS) when treated with TKIs compared with traditional chemotherapy (10-12).

Other *EGFR* mutations are termed uncommon mutations, and account for 10–20% of all *EGFR* mutations (*Figure 1*) (10-13). Uncommon *EGFR* mutations show variable efficacy to EGFR-targeted drugs depending on the molecular alterations within exons 18–21, which are still not completely understood. The substitution mutations of G719X in exon 18, L861Q in exon 21, S768I in exon 20, and exon 20 insertions are the most frequent mutations among the uncommon mutations (14-16). Patients with these substitution mutations benefit from first-generation EGFR-TKIs such as erlotinib and gefitinib (14-17). The second-generation TKIs afatinib and dacomitinib have also demonstrated improved outcomes as first-line treatment of patients with classical *EGFR* mutations, which suggest that they may be the optimal therapy for this population (18,19). Increasing evidence has shown improved outcomes for patients with uncommon *EGFR* mutations such as G719X, L861Q, S768I, and complex mutations upon treatment with second-generation TKIs (17). However, there is no clear consensus on a treatment strategy for this population. The exon 20 mutation is traditionally considered to be insensitive to EGFR-targeted drugs (20-22). *Figure 2* compares the clinical outcome of EGFR-TKIs between common and uncommon *EGFR* mutation-positive patients (15,23-26). Recently, treatment with chemotherapy and immune checkpoint inhibitors (ICIs) has been reported in NSCLC patients with uncommon *EGFR* mutations (27-29).

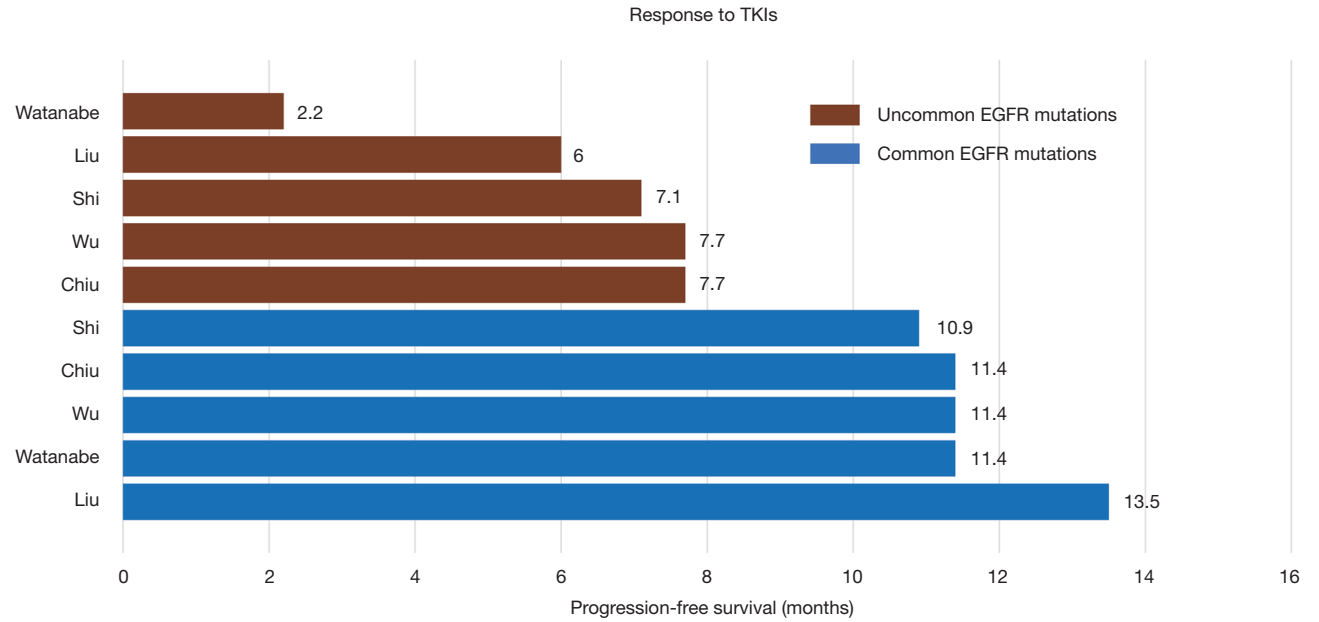

Figure 2 Progression-free survival to EGFR-TKI of NSCLC patients harboring common and common EGFR mutations. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer.

Controversy over the treatment of uncommon *EGFR* mutation-positive patients still remains despite completed and ongoing clinical trials. This review provides an overview of the treatment of patients with G719X, S768I, L861Q, exon 20 insertions, and complex mutations based on existing clinical data.

Literature search

We conducted a systemic review in PubMed using the terms "NSCLC," "EGFR," "uncommon mutations," "rare mutations," "G719X," "S768I," "L861Q," "exon 20," and references from relevant articles. T790M mutations were excluded from uncommon *EGFR* mutations. Only articles in English were included and the search had no date limit. Some unpublished studies were searched online in the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology, and results were obtained from conference abstracts. We included diverse study types including clinical trials, retrospective and prospective studies, case reports, preclinical research, and systemic reviews. The details are shown in *Figure 3*.

Incidence and clinical characteristics

The G719X mutation in *EGFR* has alanine (A), serine (S), cysteine (C), or aspartic acid (D) in the position of the glycine residue, and is the most frequent point mutation in exon 18, representing 2–4% of all *EGFR* mutations (30,31). The exon 20 S768I substitution accounts for approximately less than 5% of all *EGFR* mutations and often exists with other mutations such as G719X and L861Q (31-33). L861Q in exon 21 consists of approximately 2% of *EGFR*-positive mutations, and is sometimes compounded with other mutations (34,35). G719X, L861Q, and S768I are thought to sensitize *EGFR* mutations to TKIs, just inferior to the prognosis of classical mutations, exon 19 deletions and exon 21 L858R substitution (17,23,24,36). Exon 20 insertions account for approximately 1–10% of all *EGFR* mutations (37). A multicenter observational study by Beau-Faller *et al.* (31) reported that A767V769dupASV was the most frequent variant, accounting for 12% of exon 20 insertions, which differs from a previous study that reported that V769_D770insASV is the most common mutation, constituting 22% of exon 20 insertions. Sasaki's study (38) demonstrated that exon 20 insertions are more common in non-smokers and females. However, in a study involving 367 *EGFR*-positive patients, exon 20 insertions represented 9% (33/367) of mutations with more females (67%) and more smokers (52%) affected, consistent with another study (37). However, there was no significant difference in age, sex, ethnic origin, or stage at diagnosis

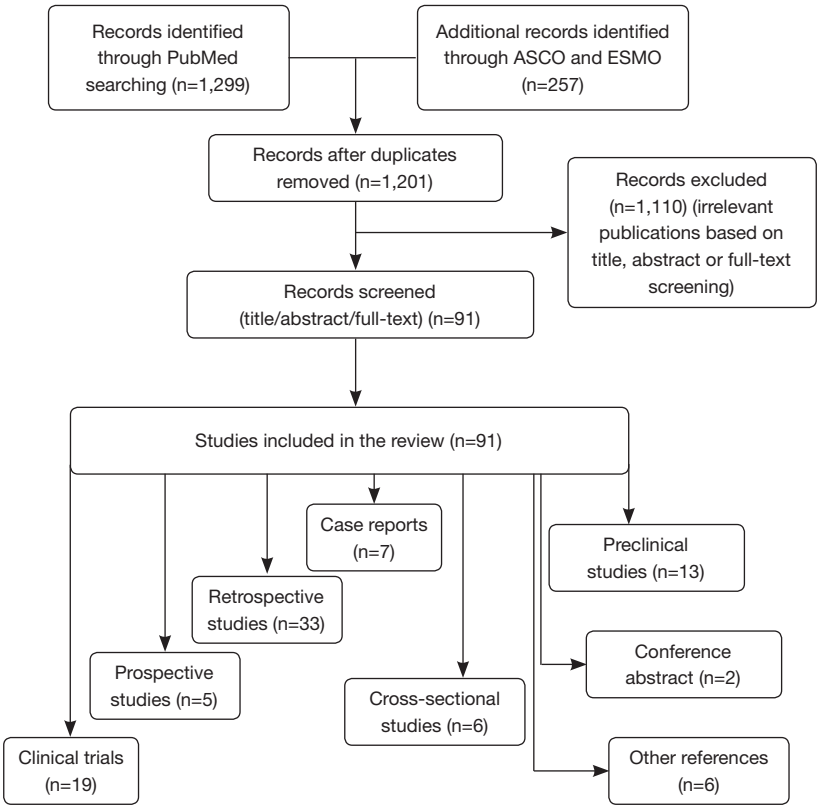

Figure 3 Flow diagram of the study selection. Other references include reviews and meta-analysis.

(37,39). A comprehensive view of uncommon *EGFR* mutations from five studies (14,15,17,40,41) (*Figure 4*) demonstrated that the exon 18 G719X mutation was the most frequent point mutation, representing approximately 26% of uncommon *EGFR* mutations, followed by exon 21 L861Q mutation and exon 20 S768I mutation. Exon 20 insertions accounted for 9% of uncommon *EGFR* mutations (71/382). Complex mutations were not listed alone and were included as part of the other mutations.

Clinical evidence

G719X, S768I, L861Q mutations

It has been reported that G719X in exon 18 is responsive to EGFR-TKIs (35,42). A combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 clinical trials demonstrated that NSCLC patients harboring G719X had an objective response rate (ORR) of 77.8% to afatinib, with a PFS of 13.8 months, which was longer than that with chemotherapy, but a shorter overall survival (OS) than that with chemotherapy (17). A retrospective study by Chiu *et al.* (25) demonstrated higher sensitivity to TKIs in patients with complex mutations (G719X+ L861Q and G719X+ S768I) than with a single G719X mutation (PFS: 11.9 *vs.* 6.5 m, respectively, P=0.010). However, the ORR in Zhang's study (14) was only 22.7% compared with a retrospective study by Xu (16), which showed an ORR of 42.9% with TKIs. By contrast, the PFS for patients harboring the G719X mutation in Zhang's study (14) was longer than that in Xu's study (16) (7.6 *vs.* 5.98 m, respectively) (*Table 1*).

The S768I in exon 20 is a rare mutation that commonly exists with L858R, G719X, and other mutations (43). Several small case studies have demonstrated the clinical efficacy of EGFR-TKIs in NSCLC patients harboring S768I mutations (44,45). Two small retrospective studies by Shi (15) and Chen (46) reported moderate clinical efficacy inferior to that of other common mutations, but better than that of other exon 20 mutations, with a PFS of 3.4 months and 2.7 months, respectively. Zhang's study (14) showed a longer PFS of 8.0 months, although the ORR was only

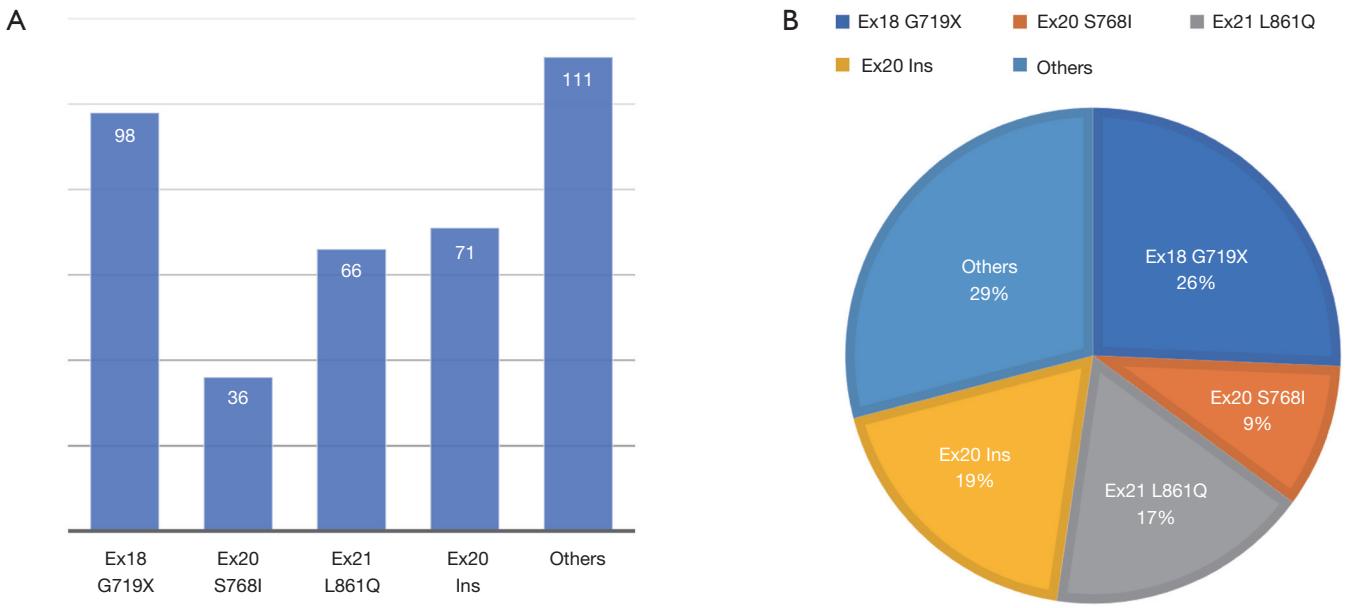

Figure 4 A comprehensive view of uncommon EGFR mutations from five studies: (A) a summary of frequency of G719X, S768I, L861Q, Exon 20 insertions and other mutations (complex mutations included); (B) a summary of these single point mutations and exon 20 insertions. EGFR, epidermal growth factor receptor.

Table 1 Clinical outcomes in exon 18 G719X treated with TKI

Article reference	Research type	N, cases in the study	TKI therapy	ORR (%)	Median PFS (month)	Median OS (month)
Yang, 2015 (2)	Prospective	N=18	18	77.80%	13.8 (6.8–NE)	26.9 (16.4–NE)
		G719X [8]	2nd			
		G719X + Others [10]*				
Zhang, 2017 (14)	Retrospective	N=22	22	22.70%	7.6 (4.9–10.4)	NR
		G719X [14]	1st			
		G719X + Others [8]				
Wu, 2011 (24)	Retrospective	N=15	15	53.30%	8.1	16.4
		G719X/G719X + Others [15]	1st			
Xu, 2016 (16)	Retrospective	N=14	14	42.90%	5.98 (1.53–10.42)	19.81 (16.8–22.81)
		G719X [14]	1st			
Chiu, 2015 (25)	Retrospective	N=97	78			NR
		G719X [78]	1st	36.80%	6.3	
		G719X + L861Q [9]		88.90%	11.9	
		G719X + S768I [10]		50%	6.5	
Shi, 2017 (15)	Retrospective	N=27	27	NR	8.2	NR
		G719X [27]	1st			

NR, not reported; NE, not estimable; TKI, tyrosine kinase inhibitor; ORR, objective response rate; PFS, progression-free survival. *, means complex mutation involves T790M.

Table 2 Clinical outcomes in exon 20 S768I treated with TKI

Article reference	Research type	N, cases in the study	TKI therapy	ORR (%)	Median PFS (month)	Median OS (month)
Yang, 2015 (2)	Prospective	N=8	8	100%	14.7 (2.6–NE)	NE (3.4–NE)
		S768I [1]	2nd			
		S768I + Others [7]				
Zhang, 2017 (14)	Retrospective	N=11	11	27.30%	8.0 (4.3–11.8)	NR
		S768I [4]	1st			
		S768I + Others [7]				
Shi, 2017 (15)	Retrospective	N=9	9		3.4	NR
		S768I [9]				
Chen, 2016 (44)	Retrospective	N=10	10	20%	2.7	14.5
		S768I [3]				
		S768I + Others [7]				

NR, not reported; NE, not estimable; TKI, tyrosine kinase inhibitor; ORR, objective response rate; PFS, progression-free survival.

27.3%. Surprisingly, a post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 clinical trials of NSCLC patients carrying S768I with complex mutations showed the longest PFS of 14.7 months among the uncommon *EGFR* mutations (17). A female patient with advanced NSCLC harboring a single S768I mutation achieved 6-month survival from afatinib after showing no response to gefitinib (47). These results suggest that afatinib may be a more effective treatment for NSCLC patients carrying the S768I mutation compared to first-generation TKIs (*Table 2*).

The exon 21 L861Q mutation is the second most frequent uncommon mutation, representing approximately 2% of all *EGFR* mutations. Some preclinical trials have demonstrated low efficacy or complete resistance of the L861Q mutation to EGFR-TKIs (48-50), suggesting a poor prognosis for these patients. However, a large retrospective study by Chiu *et al.* reported a response rate (RR) of 39.6% and a PFS of 8.1 months, demonstrating a moderate response to TKIs, but the OS was not followed (25). Wu and Xu obtained similar data as Chiu, although with smaller cases (24). In the prospective clinical trial by Yang (17), high afatinib activity was observed in patients harboring the EGFR-L861Q mutation, with an ORR of 56.3%, median PFS of 8.2 months, and median OS of 17.1 months (*Table 3*).

Exon 20 insertions

Several retrospective studies have reported that EGFR-targeted drugs are ineffective in NSCLC patients with exon 20 insertions (16,24,36). The work by Wu (24) demonstrated that NSCLC patients harboring exon 20 insertions had a much shorter PFS than those with exon 19 deletions and exon 21 L858R substitution (1.4 *vs.* 8.5 m, P<0.001) (24). In addition, a study involving 12 NSCLC cases harboring exon 20 insertions reported that TKIs might not be the first choice of therapy for these patients (16). In this study, the ORR and PFS were 8.3% and 2 months, respectively. It has been suggested that NSCLC patients who harbor exon 20-ins mutation should be treated with traditional therapy, similar to NSCLC patients with EGFR wild-type. Thus, platinum-based chemotherapy might be the preferred treatment choice rather than TKIs (51). The combined post-hoc analysis of Lux-Lung 2, Lux-Lung 3, and Lux-Lung 6 clinical studies is currently the largest prospective study on the efficacy of EGFR-TKI in patients harboring uncommon *EGFR* mutations. The study divided patients with rare *EGFR* mutations into three groups: point mutations or duplications in exons 18–21 (Group 1), *de novo* Thr790Met mutations in exon 20 alone or in combination with other mutations (Group 2), and exon 20 insertions (Group 3). Patients with exon 20 insertions treated with afatinib had an ORR of less than 10% and a median PFS of 2.7 months, representing the lowest efficacy with afatinib compared to Group 1, Group 2, Group 3, and the chemotherapy-treated group (PFS: 10.7, 2.9, 2.7, and 8.2 months, respectively) (17). Similar results were found in other three studies with a PFS of 2.9, 3.1, and 3.0 months for exon 20ins groups, respectively (*Table 4*) (36,41,52).

Table 3 Clinical outcomes in exon 21 L861Q treated with TKI

Article reference	Research type	N, cases in the study	TKI therapy	ORR (%)	Median PFS (month)	Median OS (month)
Yang, 2015 (2)	Prospective	N=16	16	56.30%	8.2 (4.5–16.6)	17.1 (15.3–21.6)
		L861Q [12]	2nd			
		L861Q + Others [4]				
Zhang, 2017 (14)	Retrospective	N=5	5	0.00%	5.7 (1.6–9.8)	NR
		L861Q [4]	1st			
		L861Q + Others [1]				
Wu, 2011 (24)	Retrospective	N=15	15	60.00%	6.0	15.2
		L861Q/L861Q + Others [15]	1st			
Xu, 2016 (16)	Retrospective	N=15	15	46.70%	8.9 (4.47–13.34)	21.98 (12.35–31.61)
		L861Q [15]	1st			
Chiu, 2015 (25)	Retrospective	N=66	66			NR
		L861Q [57]	1st	39.60%	8.1	
		L861Q + G719X [9]		88.90%	11.9	

NR, not reported; TKI, tyrosine kinase inhibitor; ORR, objective response rate; PFS, progression-free survival.

Table 4 Clinical outcomes in exon 20 insertion treated with TKI

Article reference	Research type	N, cases in the study	TKI therapy	ORR (%)	DCR (%)	Median PFS (month)	Median OS (month)
Yang, 2015 (2)	Prospective	23	2nd	9%	65%	2.7 (1.8–4.2)	9.2 (4.1–14.2)
Wu, 2011 (24)	Retrospective	11	1st	0.00%	NR	1.4	4.8
Xu, 2016 (16)	Retrospective	12	1st	8.30%	58.30%	2.0 (0–5.41)	16.69 (13.93–19.45)
Kuiper, 2016 (36)	Retrospective	16	1st	0%	56%	2.9 (2.3–3.6)	9.7 (0–21.1)
Chen, 2017 (41)	Retrospective	9	1st	11.10%	77.80%	3.1 (1.6–4.6)	6.1 (4.4–27.8)
Tu, 2017 (52)	Retrospective	12	1st	0%	NR	3.0 (1.3–4.7)	12.5 (0–25.5)

NR, not reported; NE, not estimable; TKI, tyrosine kinase inhibitor; PFS, progression-free survival; ORR, objective response rate; DCR, disease control rate.

Complex mutations

The occurrence and application of new mutational detection techniques s uch as direct sequencing, multiplex PCR systems, and next-generation sequencing have resulted in an increased number of cases with complex mutations. Complex *EGFR* mutations reportedly account for approximately 3–14% of all *EGFR*-positive mutations (13,24,53-55). Complex and classical mutations showed similar treatment efficacy toward EGFR-TKIs as that of classical mutations alone in a large retrospective study by Keam (55), demonstrating a RR of 74.8% and 68.8% and a median PFS of 11.9 months and 8.1 months, respectively. Hata *et al.* also reported similar results on complex mutations, but patients harboring L858R plus G719S mutations did not show a response to gefitinib (56). NSCLC patients harboring uncommon complex mutations without classical mutations (G719X + L861Q and G719X + S768I) had a significantly longer PFS than patients with a single rare mutation (11.9 *vs.* 6.5 months, respectively) (25). A retrospective multicenter study in 18 Italian institutions by Passaro *et al.* (57) demonstrated that TKI treatment of patients with complex mutations had superior efficacy than treatment with exon 18 mutation with regard to median PFS (mPFS) and OS (57). Yu *et al.* (58) reported a worse

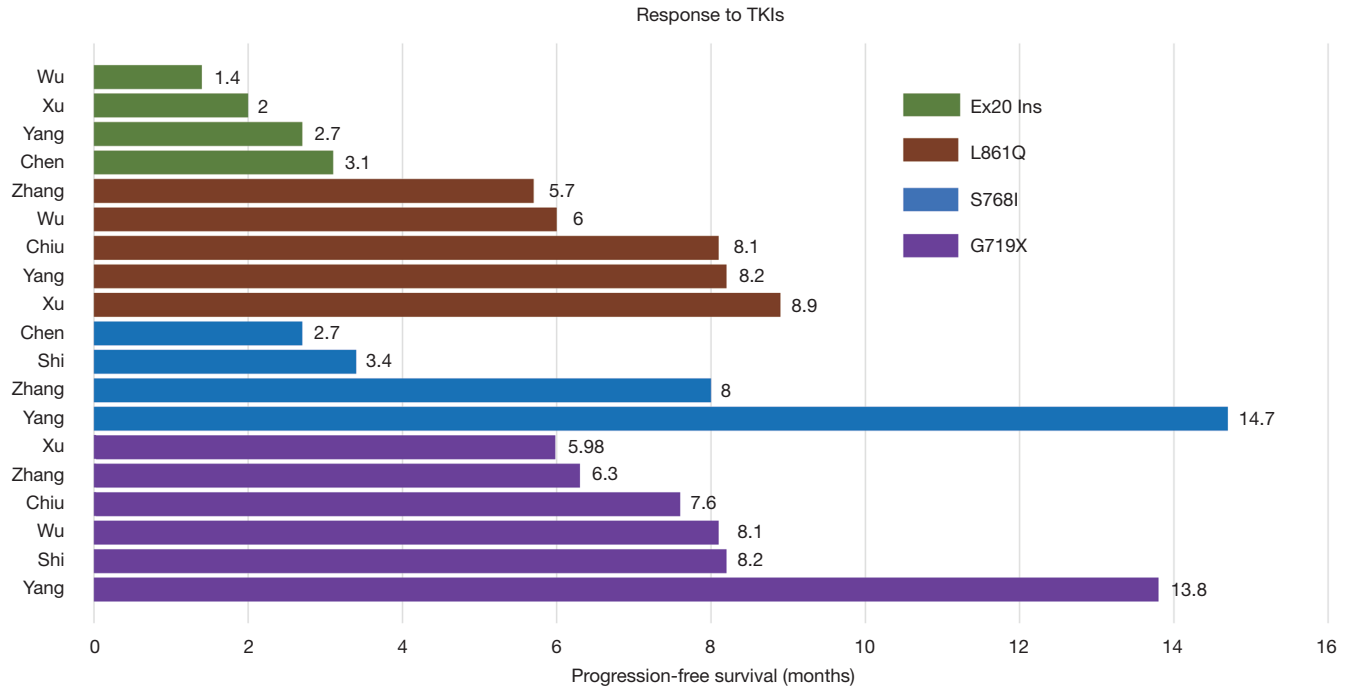

Figure 5 Efficacy of EGFR-TKIs in each uncommon EGFR mutation in different studies. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

outcome for compound mutations with exon 20 compared to compound mutations without exon 20 and single common *EGFR* mutation (mPFS: 6.5, 9.1, and 13 months, respectively, P=0.002). Interestingly, Passaro and colleagues did not observe differences between compound mutation exon 20-positive and exon 20-negative patients with a mPFS of 10 months and 12 months, respectively (P=0.9), in contrast to Yu's results (57,58). A summary of the efficacy of EGFR-TKIs in patients with each uncommon *EGFR* mutation is shown in *Figure 5*. As depicted, the PFS in patients with exon 20 insertions was significantly shorter than that in patients with G719X, S768I, or L861Q mutations. However, inconsistent efficacy to EGFR-TKIs has been shown in different studies of patients with G719X, S768I, or L861Q mutations (2,14-16,24,25,41).

New evidence

G719X, S768I, L861Q, and complex mutations

A retrospective study including 95 NSCLC patients harboring uncommon EGFR mutations conducted by Brindel *et al.* (27) in France demonstrated an OS of 16.9 months in patients treated with first-line TKIs compared to an OS of 27.7 months in patients treated with first-line chemotherapy. In this study, patients with the exon 21 L861Q mutation had a poor prognosis compared to those with exon 18 and exon 20 mutations (27).

Neratinib, an irreversible pan-ErbB receptor TKI, showed great response in patients harboring a G719X point mutation in exon 18 in a phase II clinical trial, achieving a median PFS of 52.7 weeks (90% confidence interval: 25.6–57.0 weeks) (59). In contrast, low activity was observed in patients with other *EGFR* mutations. However, another second-generation EGFR-TKI, afatinib, showed high efficacy in the largest prospective study conducted on the efficacy of EGFR-TKI in patients harboring uncommon EGFR mutations, namely a combined post-hoc analysis of the Lux-Lung 2, Lux-Lung 3, and Lux-Lung 6 clinical trials (2,17). More clinical evidence is required to determine whether afatinib should be the first treatment choice for NSCLC patients harboring G719X, S768I, and/or L861Q mutations. A 72-year-old female diagnosed with advanced NSCLC carrying complex exon 18 G719X plus exon 20 S768I mutations reportedly exhibited a good response without progression for 12 months (26). Another patient harboring compound L861Q and L858M

mutations experienced tumor regression with afatinib after treatment failure with erlotinib and chemotherapy (60). A retrospective analysis of a Caucasian population in Germany by Kauffmann-Guerrero *et al.* (61) showed that a patient with G719X mutation achieved a durable partial response (PR) to afatinib that remained after 26 months. In a retrospective analysis, Passaro (57) found good afatinib activity when treating four patients with G719X mutations, all of whom achieved a PR. A large retrospective study (62) demonstrated that patients with uncommon mutations lacking exon 19 deletions or L858R had a significantly longer PFS with afatinib treatment than those who received gefitinib or erlotinib (18.3 *vs.* 2.8 months, P=0.07). However, compared with gefitinib or erlotinib, patients with complex and classical mutations receiving afatinib exhibited a higher albeit insignificant mPFS (11 *vs.* 8.2 months, P=0.24). In a small study by Tanaka (63) of patients harboring uncommon *EGFR* mutations (except exon 19 deletions or exon 21 L858R substitution), afatinib showed superior efficacy over first-generation EGFR-TKIs with an ORR of 75.0% versus 40.0% and PFS of 17.1 versus 5.5 months, respectively (P=0.0481). Therefore, second-generation TKIs might become an optimal choice for patients harboring these mutations.

Osimertinib, a third-generation TKI, has also shown promising results in some cases and studies with small sample sizes. It was confirmed to be effective for treating patients with uncommon *EGFR* mutations in an open-label, multicenter, phase II single arm trial that included 36 patients (64). A total of 77.8% of patients harboring the L861Q mutation achieved a PR with osimertinib treatment, followed by G719X (52.5%) and S7681 (37.5%). The overall mPFS was 9.5 months and the median duration of response (mDoR) was 7.0 months. Thus, this is a promising drug worth studying.

Exon 20 insertions

Previous studies have demonstrated that NSCLC patients with A763_Y764insFQEA, achieved a PR to treatment with gefitinib and erlotinib (22,65). In another study, two patients carrying N771_P772insNand H773_V774insQ mutations achieved a moderate response to those TKIs (52). The differences in TKI efficacy might be due to the diversity of exon 20 insertions. Comprehensive genomic profiling may allow the detection of a broad spectrum of *EGFR* exon 20 insertions associated with co-occurring genomic alterations, which will provide insights into effective treatments for improving clinical outcomes in this population (66). In addition, some cases have reported high efficacy to second- and third-generation TKIs (67,68). In a preclinical study, Floc'h and colleagues (69) showed that osimertinib and its metabolite AZ5104 had anti-tumor activity indifferent exon 20 insertion PDX models in vivo, which suggests that its will be efficacious in patients harboring exon 20 insertions. In clinical practice, one NSCLC patient carrying H773L/V774M in exon 20 demonstrated sustained disease control to osimertinib, which suggests that patients with this mutation may clinically benefit from treatment with this TKI (67,68). Nazartinib, a covalent EGFR inhibitor similar to osimertinib, has also exhibited potential benefits for exon 20 insertions in preclinical studies (70). A clinical trial of this drug is ongoing in NSCLC patients with common *EGFR* mutations, but effects in patients with exon 20 insertions have not been observed. Clinical trials are needed to confirm the role of osimertinib in this patient population.

A female with advanced NSCLC harboring an EGFR exon 20 insertion mutation (A767_S768insSVA tandem duplication) achieved a long survival of 54 months with afatinib after increased pulmonary metastasis with first-generation TKI (67,68). As reported by van Veggela *et al.* (71) from Netherlands, four progressed patients with NSCLC who had received platinum-based chemotherapy or first-generation TKI with EGFR exon 20 insertion were treated with afatinib 40 mg once daily and cetuximab 250–500 mg/m^2 every two weeks. Surprisingly, three patients experienced a radiological response, with significant shrinkage of tumor size. The mPFS for the four patients was 5.4 months, with the longest PFS of 17.6 months. The results of this study provide clinical evidence for the treatment of advanced NSCLC patients harboring *EGFR* exon 20 insertion with the combination of afatinib plus cetuximab. The efficacy of the combined treatment might be due to the dual blockade of *EGFR* by the second-generation EGFR-TKI afatinib and the EGFR monoclonal antibody cetuximab, according to previous studies (72,73). This is the same theory underlying the effects of osimertinib plus cetuximab (74). Thus, clinical trials on osimertinib plus monoclonal antibodies should be conducted.

In contrast to classical EGFR-TKIs, new EGFR-TKIs are emerging, and being studied in preclinical studies or clinical trials. Poziotinib is a pan-human epidermal growth factor receptor 2 (HER2) TKI, which was confirmed to be effective in treating advanced or metastatic lung adenocarcinoma that has progressed on erlotinib or gefitinib in a phase II study (75). Robichaux *et al.* (76) demonstrated

that 64% (7/11) of NSCLC patients carrying exon 20 insertion had a confirmed objective partial radiological response based on response evaluation criteria in solid tumors (RECIST) that was due to poziotinib. They also confirmed that poziotinib could overcome changes within the drug-binding pocket induced by insertions in exon 20 by its structural features (76). These results suggest that poziotinib might be a promising TKI for this population both preclinically and clinically, who are considered to be highly resistant to standard therapy. In addition to poziotinib, Ap32788 is a new EGFR or HER2 TKI that has entered into clinical trials in the United States. The latest ASCO meeting reported the preliminary results of safety, pharmacokinetics, and anti-tumor activity of AP32788 in a phase 1/2 clinical trial of NSCLC patients harboring exon 20 insertions (77). This study demonstrated that the ORR was 39% with six of 18 patients achieving a PR and a disease control rate of 94% when the dosage was 80–160 mg. The latest data about the efficacy of AP73288 in treating NSCLC patients with exon 20 insertions was expected to report.

Chemotherapy and uncommon EGFR mutations

Chemotherapy has been demonstrated to have a statistically significant inferior efficacy than EGFR-TKIs in patients with common *EGFR* mutations (8,11,12,78-81). However, little was concerned about chemotherapy and uncommon *EGFR* mutations. Brindel *et al.* (27) found that, compared with first-line TKIs, first-line chemotherapy showed superior efficacy with a longer OS in patients with uncommon *EGFR* mutations, especially for mutations in exon 18 and exon 20. A real-world study in China had a similar conclusion, showing that chemotherapy led to a better prognosis with an OS of 20.7 months compared to the EGFR-TKI group, which had an OS of 14.3 months (29). Future studies are needed with a larger sample size, and the prognosis and mutation type needs further investigations.

Immunotherapy and uncommon EGFR mutations

The development of ICIs has led to a new era in the treatment of NSCLC. ICIs such as pembrolizumab, nivolumab, and atezolizumab have shown promising results by restoring antitumor activity in clinical trials (82-85). However, it is not recommended that NSCLC patients with *EGFR* mutations be treated with immunotherapy agents. A meta-analysis reported that ICIs as second-line therapy for *EGFR*-mutated NSCLC patients did not improve clinical outcome compared to docetaxel (86). The lower expression of PD-L1 and tumor mutation burden in NSCLC patients with *EGFR* mutations might be associated with a poor prognosis compared to *EGFR* wild-type patients (82,83, 87-89). Akbay *et al.* (90) found that oncogenic EGFR signaling was related to the change of the tumor microenvironment, which induced immune escape, resulting in a low response to ICIs. However, according to the results of the IMpower150 study, the combination of atezolizumab, bevacizumab, and chemotherapy conferred significant PFS and OS benefits compared to combined treatment without atezolizumab in patients with metastatic nonsquamous NSCLC including patients with *EGFR* mutations or anaplastic lymphoma kinase (ALK) translocations (91). In subgroup analysis of patients with *EGFR* mutations or ALK translocations, the PFS was 9.7 months in the group treated with atezolizumab, longer than the PFS of 6.1 months in group of bevacizumab plus chemotherapy. This finding offers a new perspective on the treatment of patients with *EGFR* mutations using combination therapy including immunotherapy.

Yamada *et al.* (28) demonstrated that patients with uncommon EGFR mutations, including G719X in exon 18 and insertion in exon 20, showed statistically significant superiority to ICIs compared to those with common *EGFR* mutations (PFS: 256 *vs.* 50 days, respectively; P=0.003). These results indicate that immunotherapy might be a potent treatment for NSCLC patients with uncommon *EGFR* mutations; further studies are needed for confirmation.

Conclusions

G719X, S768I, L861Q, complex mutations, and exon 20 insertions are the most frequent uncommon *EGFR* mutations. NSCLC patients harboring G719X, S768I, L861Q, and some complex mutations are sensitive to TKIs, but are not sensitive to common mutations (exon 19 deletions and exon 21 L858R substitution). Patients treated with afatinib or osimertinib have a better prognosis than first-generation TKIs, which suggests that second- or third-generation TKIs may be the preferred choice of treatment for this population. More evidence has demonstrated a moderate response to TKIs in NSCLC patients with exon 20 insertions. Novel targeted drugs including poziotinib and Ap32788 have reached late phase clinical trials and achieved good results. Immunotherapy has

also achieved promising results for uncommon EGFR mutations. Future research is needed to help determine the treatment choice for NSCLC patients with uncommon EGFR mutations.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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