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Afatinib Combined with Bevacizumab in the Treatment of Patients with Non-Small Cell Lung Cancer Harboring EGFR G719X, S768I or L861Q/P Mutations

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Purpose: To investigate the efficiency and safety of afatinib in combination with bevacizumab in patients with non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) G719X, S768I, and L861Q mutations.

Patients and Methods: We retrospective studied treatment naïve patients with local advanced or metastatic non-small cell lung cancer harboring EGFR G719X, S768I, and L861Q mutations from January 2017 to August 2021. EGFR tyrosine kinase inhibitors (TKIs) were the first-line treatment in all patients. The demographic, clinical data and treatment results were collected and analyzed.

Results: A total of 12 Chinese patients were studied. There were seven EGFR G719X mutations, three of the seven patients with single mutation and the others with compound mutations. Four patients had EGFR S768I mutations and one of them with single mutation. Four patients had EGFR L861Q/P mutations and one of them with compound mutations. The overall response rate of the EGFR TKIs treatment was 58.33% (7/12). The median progression-free survival (PFS) was 11.0 months, and median overall survival (OS) was 35.40 months. Two of five (40%) patients had required EGFR T790M mutations after TKIs were resistant. The side effects were mild to moderate hand-foot-syndrome, hypertension, and proteinuria.

Conclusion: Afatinib in combination with bevacizumab are effective and safe in the management of patients with NSCLC harboring EGFR G719X, S768I, L861Q/P single or compound mutations.

Keywords: epidermal growth factor receptor tyrosine kinase inhibitor, uncommon EGFR mutations, non-small-cell lung cancer, afatinib, bevacizumab

Introduction

Epidermal growth factor receptor (EGFR) gene somatic mutations in the kinase domain are found in approximately 40–58% and 17–21% of patients with non-small cell lung cancer (NSCLC) in Asians and in Caucasians, respectively.[1–3] The vast majority of EGFR mutations comprise exon 19 deletion (45–50%) and the Leu858Arg (L858R) point mutation in exon 21 (40–45%).[4] These mutations are called sensitive EGFR mutations and hereafter referred to as "common or classic EGFR mutations" which benefit from the treatment with EGFR tyrosine kinase inhibitors (TKIs).[5,6] The other uncommon EGFR mutations are insertions or duplications in EGFR exon 20, points mutations in EGFR exon 18 (eg, G719X, A, S or C), in EGFR exon 20 (eg, S768I) and in EGFR exon 21 (eg, L861Q). The proportion of uncommon EGFR mutations among EGFR-mutated NSCLC patients might be as high as 14%, but varies in different studies.[7–9] The uncommon EGFR mutations are not as sensitive as classic EGFR mutations especially in the single mutation other than compound mutations.[10–13] Due to the limited number of cases, no prospective and large-scale clinical trials have investigated the clinical activity of EGFR TKIs in patients with uncommon EGFR mutations.[10,11,13,14] Data from several retrospective studies remain controversial and

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insufficient.[9,15] Hence, we performed this study to evaluate the clinical features and the effect of first-line EGFR TKIs treatment with or without anti-angiogenesis therapy in patients with uncommon EGFR mutations.

Methods

Patients and Treatment

We have retrospectively analyzed a consecutive database of NSCLC patients hospitalized in Qingdao Central Hospital, University of Health and Rehabilitation Sciences during January 2017 to August 2021. All patients had histologically or pathologically confirmed locally advanced or metastatic NSCLC. Amplification refractory mutation system (ARMS) polymerase chain reaction (PCR) or next generation sequencing (NGS) with biopsied tissues were done and patients with EGFR G719X, S768I, L861Q/P mutations were selected into the study. Chest computed tomography scanning was performed every 6–8 weeks as a routine follow-up procedure and additionally as needed to confirm the patient response and assess the disease progression. Selected patients were required to have at least one measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter should be recorded) as ≥10 mm, using spiral computed tomography (CT) or magnetic resonance imaging (MRI). Furthermore, all patients were aged 18-years or older, with adequate organ and marrow function, and Eastern Cooperative Oncology Group (ECOG) performance status scores ≤2.

Afatinib (Giotrif, Boehringer-Ingelheim) was given orally at a dose of 40 mg daily, which could be adjusted to 30 mg oral daily or 30 mg oral every other day if patient was not tolerant to the toxicity. Bevacizumab (Avastin, Roche) at 15 mg/kg, dissolved in 250mL normal saline intravenous infusion was given every 21 days until tumor progression, patient death, uncontrolled toxicity or patient refusal.

Outcomes and Assessment

The progression-free survival (PFS), overall survival (OS), response rate, and toxicity were studied. Responders were defined as patients who had confirmed complete or partial response. The PFS was measured from the first day of TKI treatment until the first objective sign of disease progression or patient death; the overall survival was measured from the day of treatment to the day of patient death. Tumour responses, which was evaluated based on Response Evaluation Criteria in Solid Tumour, version 1.1 (RECIST, v1.1),[16] were observed during the trial period and classified as the following: complete response (disappearance of tumour lesions), partial response (a decrease of at least 30% in the sum of tumour lesion sizes), stable disease (steady state of disease), or progressive disease (an increase ≥20% in the sum of tumour lesion sizes). All adverse events were recorded and classified by grade, according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.[17]

Tumour measurements with thoracic CT or MRI were performed at baseline, and every 8–12 weeks thereafter. Patients' compliance, treatment safety, and side effects were assessed every 2–3 weeks, at each check-up.

Statistical Analysis

The response rate, symptom reduction, and treatment-related adverse events were assessed with Fisher's exact test. The Kaplan-Meier method was used for survival analyses, and the Log rank test was used to test for significance. Cox regression was used to analyze independent factors. $P < 0.05$ was considered statistically significant, and 95% confidence intervals (95% CIs) were calculated. Statistical analyses were conducted using Sigmaplot 14 (Systat software Inc., USA).

This study was approved by the Ethics Committee of the Qingdao Central Hospital, University of Health and Rehabilitation Sciences, and was performed in compliance with the provisions of the Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws.

Results

The demographic characteristics of the patients with uncommon EGFR mutations are listed in Table 1. Among the 12 patients, 41.7% (5/12) were male, 58.3% (7/12) were female. The median age was 57 year-old, and 75.0% (9/12) patients were younger than 65 year-old. Most patients had a performance status score of 1 or 2 accessed by ECOG; and most of

Table 1 Clinicopathological Features and Patients Factors

Factors	No. of Patients (n = 12) (%)
Gender	
Male	5 (41.7)
Female	7 (58.3)
Age (year)	
<65	9 (75.0)
≥65	3 (25.0)
Smoking	
Never	8 (66.7)
Ever/current	4 (33.3)
ECOG performance status	
0	1 (8.3)
1	7 (58.3)
2	4 (33.3)
Histology subtype	
Adenocarcinoma	11 (91.7)
Adenosquamous	1 (8.3)
Stage	
IIIb	1 (8.3)
IV	11 (91.7)
EGFR mutation	
G719X	3 (25.0)
G719X + S768I	2 (16.7)
G719X + L861Q	1 (8.3)
G719X + E20Ins	1 (8.3)
S768I	1 (8.3)
S768I + L858R	1 (8.3)
L861Q	2 (16.7)
L861P	1 (8.3)

Abbreviations: EGFR, epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group.

them were non-smokers with stage IV disease (91.7%, 11/12). All patients were newly diagnosed and treatment naïve. The patients' clinical data, EGFR mutations, therapy, and response are listed in Table 2. The objective response (complete or partial response) according to RECIST, version 1.1 was 58.33% (7/12), and the stable disease was

Table 2 Clinical Data on Patients, EGFR Mutations, and Response

list	Gender	Age	Smoking	Histology	Stage	EGFR Mutation	Response	PFS (m)
1	F	44	Never	Adenocarcinoma	IV	G719X	PR	21.0
2	M	63	Current	Adenocarcinoma	IV	G719A	PR	4.0
3	M	73	Ever	Adenosquamous	IV	G719X	PR	8.4
4	F	63	Never	Adenocarcinoma	IV	G719S, S768I	SD	46.0
5	F	65	Never	Adenocarcinoma	IV	G719X, S768I	PR	14.0
6	F	51	Never	Adenocarcinoma	IIIB	G719A, L861Q	PR	16.0
7	F	54	Never	Adenocarcinoma	IV	G719C, E20Ins	SD	5.5
8	F	53	Never	Adenocarcinoma	IV	S768I	PD	1.8
9	M	68	Current	Adenocarcinoma	IV	S768I, L858R	PR	15.5
10	M	58	Current	Adenocarcinoma	IV	L861P	SD	17.0
11	F	56	Never	Adenocarcinoma	IV	L861Q	SD	6.0
12	M	56	Never	Adenocarcinoma	IV	L861Q	PR	8.5

Abbreviation: PFS, progression-free survival.

33.33% (4/12), which were assessed by the study investigators. The median depth of remission rate of tumor (maximum percentage change in tumor size compared with baseline) was 33.0% (Figure 1).

Of the enrolled 12 patients, the median PFS (Figure 2A) was 11.0 months (95% CI: 7.98–27.61), and median OS (Figure 2B) was 35.40 months (95% CI: 24.17–46.24). The PFS was 9.60 months (95% CI: 2.48–14.46) for patients harboring a single mutation, and was 18.50 months (95% CI: 3.58–25.52) for patients harboring compound mutations (p = 0.162) (Figure 3A); OS was not reached or 35.40 months (p = 0.279) (Figure 3B). Eight patients progressed on 1st line therapy and five of them had re-biopsies on the newly developed lesions. NGS was done with re-biopsied tissues and two (2/5, 40%) patients had acquired EGFR T790M mutations. Treatments and outcomes are shown in Figure 4.

The side effects were mild to moderate hand-foot-syndrome, hypertension, and proteinuria. One patient developed grade 3 proteinuria on the 21st cycle, and permanently discontinued bevacizumab. Hand-foot-syndrome was mainly caused by afatinib use. Five patients acquired paronychia; all of them were improved by dose reduction and lotion embrocation (Table 3).

Discussion

EGFR mutations are considered the most robust predictive biomarker for the clinical and radiographic responses attained by EGFR TKIs in clinical practice. Single EGFR mutations or compound mutations can be identified by the sequencing

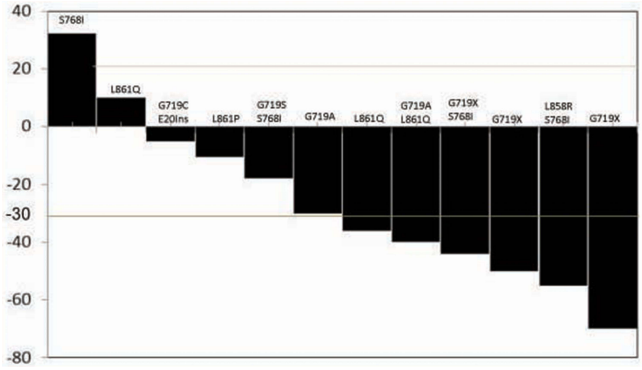

Figure 1 Depth of remission according mutation sites and treatment methods.

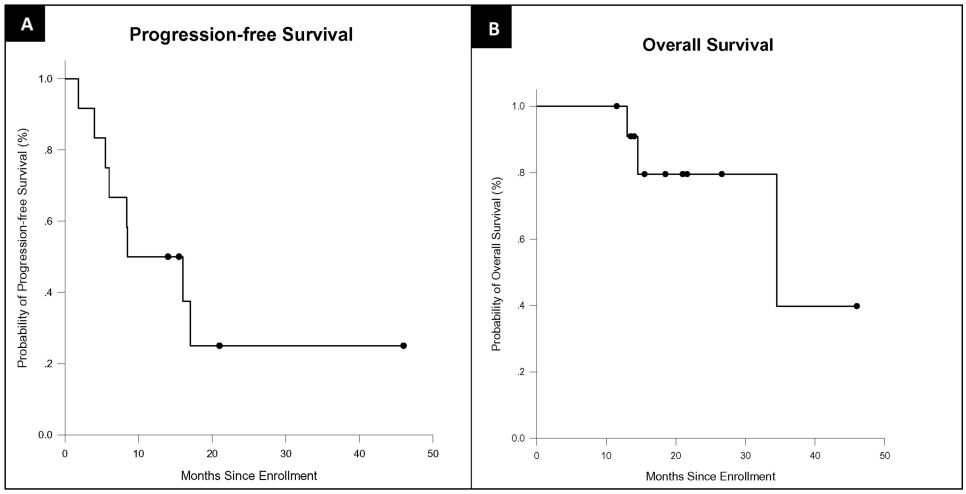

Figure 2 Kaplan-Meier analysis of progression-free survival (PFS) and overall survival (OS). Of the enrolled 12 patients, the median PFS (**A**) was 11.00 months (95% CI: 7.98–27.61), and median OS (**B**) was 35.40 months (95% CI: 24.17–46.24).

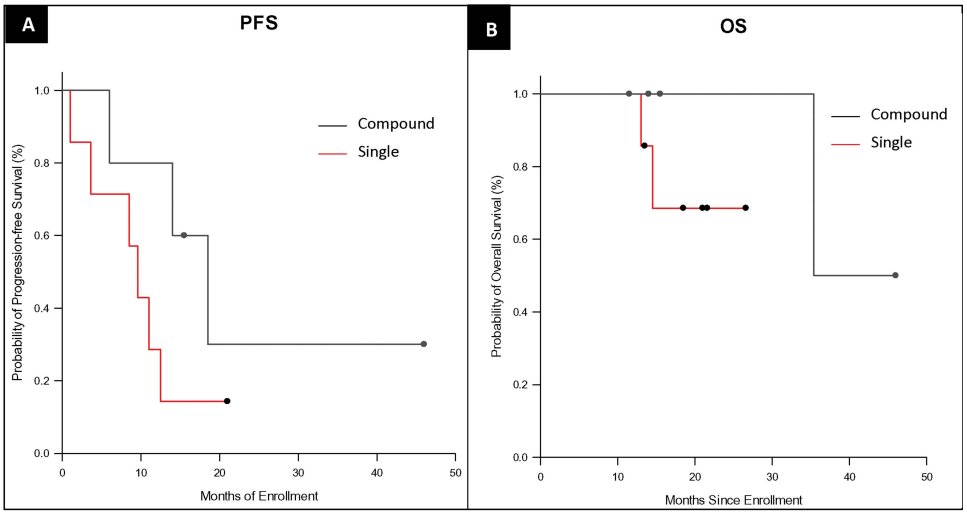

Figure 3 Kaplan-Meier analysis of Progression-Free Survival (PFS) according to single or compound mutations. The PFS was 9.60 months (95% CI: 2.48–14.46) for patients harboring single mutation and was 18.50 months (95% CI: 3.58–25.52) for patients harboring compound mutations (p = 0.162) (**A**); OS was not reached or was 35.40 months (p = 0.279) (**B**).

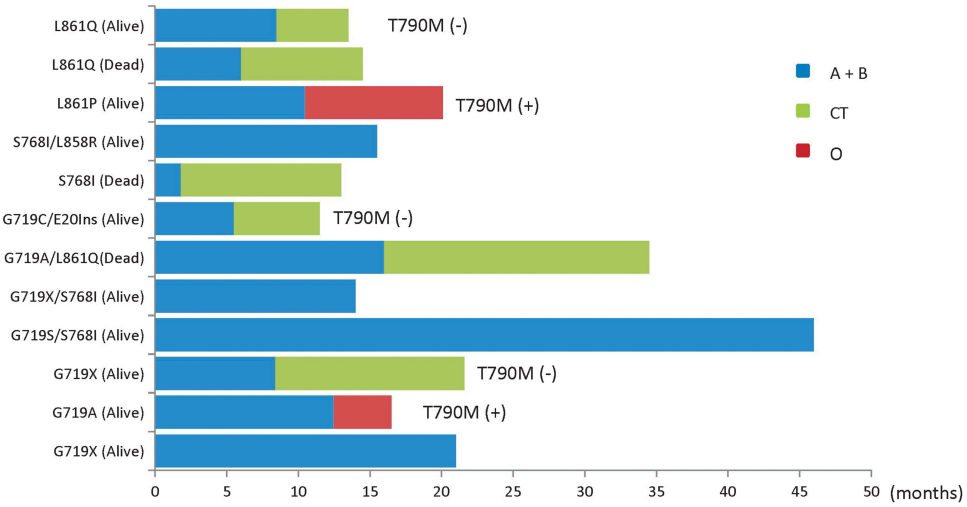

Figure 4 Treatment and outcomes.
Abbreviations: A, afatinib; B, bevacizumab; CT, chemotherapy; O, Osimertinib.

of exon 18 to 21 of EGFR. EGFR mutations except L858R mutation and exon 19 deletion, are considered uncommon mutations, which account for approximately 5.9% to 14.0% of all EGFR mutations, depending on the detection methods and different studies.[7,10,12,18,19] Of the group with uncommon EGFR mutations, EGFR G719 and L861Q represent a major portion and the single uncommon mutation and compound uncommon mutation are presented equally.[10,12,18,20] The prevalence of exon 20 insertions in all EGFR mutations range between 1% and 10% and generally falls between 4% to 5%.[19,21,22] The most frequently found insertion site is between Asp770 and Asn771, followed by Val769_Asp770, the two insertion sites account for around 50% of exon 20 insertions.[21,22] EGFR exon 20 insertions are highly diversified in terms of insertion patterns and co-occurring mutations and these insertion variants show different clinical responses to various EGFR TKIs.[22] Patients with single EGFR exon 20 insertions were not included in this respective study.

The objective response rate (ORR), mPFS, and mOS in patients harboring uncommon mutations treated with first-generation TKIs (gefitinib or erlotinib) are in high variation, and are all inferior compared to the classical EGFR L858R or exon 19 deletions.[5,12,15,23] Patients with EGFR G719X, S768I, or L861Q single mutation have low response rates and short PFS and OS compared to compound mutations.[12,24,25]

Table 3 Summary of Adverse Events

Adverse Events Case (%) (N = 12)		
	All Grade	**Grade 3–4**
Nausea	3 (25.0)	0 (0)
Loss of appetite	3 (25.0)	0 (0)
Stomatitis	4 (33.3)	0(0)
Diarrhea	5 (41.7)	0 (0)
Paronychia	5 (41.7)	0 (0)
Hypertension	2 (16.7)	0 (0)
Hand-foot syndrome	9 (75.0)	1 (8.3)
Gingiva bleeding	3 (25.0)	0 (0)
Proteinuria	4 (33.3)	1 (8.3)
Headache	2 (16.7)	0 (0)
Faintness	2 (16.7)	0 (0)

In this study, the ORR was 58.33% (7/12), the median PFS was 11.0 months and the median OS was 35.40 months. These results were comparable to the patients harboring sensitive EGFR mutations treated with 1st generation EGFR TKIs and bevacizumab.[26]

Furthermore, from post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 clinical trials on afatinib, the reported ORRs were from 8.7% to 71.1%, and median PFS were from 2.7 months to 10.7 months, with remarkable inconsistency.[12,27] Results in this study also showed combined mutations of EGFR uncommon mutations have high response rates and longer PFS than single mutations.

First generation EGFR TKIs were not enough to suppress the activity of single uncommon EGFR mutations in patients with non-small cell lung cancer. It also had been reported that 1st generation EGFR TKIs alone had low response rates, short mPFS and mOS in patients with a single uncommon EGFR mutation.[12,15,28] In this study, patients with an EGFR single uncommon mutation, the median PFS was 9.60 months and was 18.50 months with compound mutations. It indicated that, EGFR uncommon mutations were sensitive to afatinib combined with bevacizumab therapy, while, compound mutation was more sensitive.

There were five patients re-biopsied with newly developed lesions after disease progression, two (40%) of them acquired EGFR T790M mutations tested by NGS, hence, acquired EGFR T790M mutation could happen in a reasonable rate in patients with uncommon EGFR mutation resistant to 1st or 2nd generation EGFR TKIs and bevacizumab.

To our knowledge, this was the first report on afatinib in combination with bevacizumab in the management of uncommon EGFR mutations in non-small cell lung cancer. It had a high response rate and durable PFS and OS. The present study, however, did have some limitations. This was a respective study with a relatively small sample size, which can potentially cause selection bias. The relatively short follow-up period compared to other studies can affect the statistical power. The predictive value of afatinib in combinations with bevacizumab in the treatment of uncommon EGFR mutations in this study should be further explored in randomized settings.

Conclusions

Afatinib in combination with bevacizumab is effective and safe in the management of patients with NSCLC harboring EGFR G719X, S768I, L861Q/P single or compound mutations. 40% patients have acquired EGFR T790M mutation after resistant afatinib plus bevacizumab therapy. Continuous follow-up is needed, and randomized studies with more patients enrolled is needed in the future.

Data Sharing Statement

The dataset generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval

This study was approved by the Ethics Committee of the Qingdao Central Hospital, University of Health and Rehabilitation Sciences.

Consent for Publication

Informed consent s were obtained from all patients.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declared there was no conflict of interest.

References

1. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA*. 2014;311(19):1998–2006. doi:10.1001/jama.2014.3741
2. Sholl LM, Aisner DL, Varella-garcia M, et al. Multi-institutional oncogenic driver mutation analysis in lung adenocarcinoma: the lung cancer mutation consortium experience. *J Thorac Oncol*. 2015;10(5):768–777.
3. Yatabe Y, Kerr KM, Utomo A, et al. EGFR mutation testing practices within the Asia pacific region: results of a multicenter diagnostic survey. *J Thorac Oncol*. 2015;10(3):438–445. doi:10.1097/JTO.0000000000000422
4. Murray S, Dahabreh IJ, Linardou H, Manoloukos M, Bafaloukos D, Kosmidis P. Somatic mutations of the tyrosine kinase domain of epidermal growth factor receptor and tyrosine kinase inhibitor response to TKIs in non-small cell lung cancer: an analytical database. *J Thorac Oncol*. 2008;3(8):832–839. doi:10.1097/jto.0b013e31818071f3
5. Mok TS, Wu Y, Thongprasert S, et al. Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma. *N Eng J Med*. 2009;361(10):947–957. doi:10.1056/NEJMoa0810699
6. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, EGFR -mutated advanced NSCLC. *N Engl J Med*. 2020;382(1):41–50. doi:10.1056/NEJMoa1913662
7. Kobayashi S, Canepa HM, Bailey AS, et al. Compound EGFR mutations and response to EGFR tyrosine kinase inhibitors. *J Thorac Oncol*. 2013;8(1):118–122. doi:10.1097/JTO.0b013e3182781e35
8. Wu S, Chang Y, Hsu Y, et al. Good response to gefitinib in lung adenocarcinoma of complex Epidermal Growth Factor Receptor (EGFR) mutations with the classical mutation pattern. *Oncologist*. 2008;13(12):1276–1284. doi:10.1634/theoncologist.2008-0093
9. Keam B, Kim DW, Park JH, et al. Rare and complex mutations of epidermal growth factor receptor, and efficacy of tyrosine kinase inhibitor in patients with non-small cell lung cancer. *Int J Clin Oncol*. 2014;19(4):594–600. doi:10.1007/s10147-013-0602-1
10. Kuiper JL, Hashemi SMS, Thunnissen E, et al. Non-classic EGFR mutations in a cohort of Dutch EGFR-mutated NSCLC patients and outcomes following EGFR-TKI treatment. *Br J Cancer*. 2016;115(12):1504–1512. doi:10.1038/bjc.2016.372
11. Gx EM. Effectiveness of gefitinib against non – small-cell lung cancer with the uncommon. *J Thorac Oncol*. 2014;9:189–194.
12. Chen K, Yu X, Wang H, et al. Uncommon mutation types of epidermal growth factor receptor and response to EGFR tyrosine kinase inhibitors in Chinese non-small cell lung cancer patients. *Cancer Chemother Pharmacol*. 2017;80(6):1179–1187. doi:10.1007/s00280-017-3464-9
13. Shi J, Yang H, Jiang T, et al. Uncommon EGFR mutations in a cohort of Chinese NSCLC patients and outcomes of first-line EGFR-TKIs and platinumbased chemotherapy. *Chin J Cancer Res*. 2017;29(6):543–552. doi:10.21147/j.issn.1000-9604.2017.06.09
14. Kobayashi Y, Togashi Y, Yatabe Y, et al. EGFR Exon 18 mutations in lung cancer: molecular predictors of augmented sensitivity to afatinib or neratinib as compared with first- or third-generation TKIs. *Clin Cancer Res*. 2015;21(23):5305–5313. doi:10.1158/1078-0432.CCR-15-1046
15. Wu TH, Hsiue EHC, Lee JH, Lin CC, Yang JCH. New data on clinical decisions in NSCLC patients with uncommon EGFR mutations. *Expert Rev Respir Med*. 2017;11(1):51–55. doi:10.1080/17476348.2017.1267569
16. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1. 1). *Eur J Cancer*. 2008;45(2):228–247. doi:10.1016/j.ejca.2008.10.026

17. Constable EC, Daniels MAM, Drew MGB, Tocher DA, Walker JV, Wood PD. Mono-and di-nuclear helical complexes of 2, 2′: 6′, 2 ″: 6 ″, 2‴: 6‴, 2â —-quinquepyridine (qpy) and its 4′, 4‴-disubstituted derivatives; crystal and molecular structures of [Co (bcpqpy)(H 2 O)(MeOH)][PF 6] 2 and [Ni 2 (bmtqpy) 2 (O 2 CMe)][PF 6] 3 [bcpqpy and bmtqpy= bis (p-chlorophenyl) and bis (methylthio) derivatives]. *J Chem Soc Dalt Trans*. 1993;13:1947–1958. doi:10.1039/DT9930001947
18. Alizade- Harakiyan M, Jangjoo AG, Jafari-Koshki T, Fatemi A, Mesbahi A. Radiobiological modeling of acute esophagitis after radiation therapy of head, neck, and thorax tumors: the influence of chemo-radiation. *J Cancer Res Ther*. 2018;14(7):1525–1534. doi:10.4103/jcrt.JCRT
19. Arrieta O, Cardona AF, Corrales L, et al. The impact of common and rare EGFR mutations in response to EGFR tyrosine kinase inhibitors and platinum-based chemotherapy in patients with non-small cell lung cancer. *Lung Cancer*. 2015;87(2):169–175. doi:10.1016/j.lungcan.2014.12.009
20. Lohinai Z, Hoda MA, Fabian K, et al. Distinct epidemiology and clinical consequence of classic versus rare EGFR mutations in lung adenocarcinoma. *J Thorac Oncol*. 2015;10(5):738–746. doi:10.1097/JTO.0000000000000492
21. Yasuda H, Kobayashi S, Costa DB. EGFR exon 20 insertion mutations in non-small-cell lung cancer: preclinical data and clinical implications. *Lancet Oncol*. 2012;13(1):e23–e31. doi:10.1016/S1470-2045(11)70129-2
22. Qin YR, Jian H, Tong X. Variability of EGFR exon 20 insertions in 24 468 Chinese lung cancer patients and their divergent responses to EGFR inhibitors. *Mol Oncol*. 2020;14(8):1695–1704. doi:10.1002/1878-0261.12710
23. Kutsuzawa N, Takahashi F, Tomomatsu K, et al. Successful treatment of a patient with lung adenocarcinoma harboring compound egfr gene mutations, g719x and s768i, with Afatinib. *Tokai J Exp Clin Med*. 2020;45(3):113–116.
24. Li K, Yang M, Liang N, Li S. Determining EGFR-TKI sensitivity of G719X and other uncommon EGFR mutations in non-small cell lung cancer: perplexity and solution. *Oncol Rep*. 2017;37(3):1347–1358. doi:10.3892/or.2017.5409
25. Zhu X, Bai Q, Lu Y, et al. Response to tyrosine kinase inhibitors in lung adenocarcinoma with the rare epidermal growth factor receptor mutation S768I: a retrospective analysis and literature review. *Target Oncol*. 2017;12(1):81–88. doi:10.1007/s11523-016-0455-4
26. Saito H, Fukuhara T, Furuya N, et al. Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small-cell lung cancer (NEJ026): interim analysis of an open-label, randomised, multicentre, Phase 3 trial. *Lancet Oncol*. 2019;20(5):625–635. doi:10.1016/S1470-2045(19)30035-X
27. Yang JCH, Sequist LV, Geater SL, et al. Clinical activity of Afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. *Lancet Oncol*. 2015;16(7):830–838. doi:10.1016/S1470-2045(15)00026-1
28. Zhang T, Wan B, Zhao Y, et al. Treatment of uncommon EGFR mutations in non-small cell lung cancer: new evidence and treatment. *Transl Lung Cancer Res*. 2019;8(3):302–316. doi:10.21037/tlcr.2019.04.12