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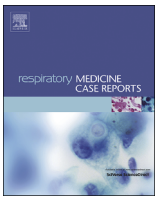

Case Report

Successful treatment of a patient with NSCLC carrying uncommon compound L861Q/G719X epidermal growth factor receptor mutations using Afatinib

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ABSTRACT

The availability of targeted therapies for molecular aberrations have substantially improved the outcomes of advanced non-small-cell lung cancer (NSCLC) patients harboring sensitive mutations. However, patients harboring uncommon epidermal growth factor receptor (EGFR) mutations such as G719X and L861Q often resulted in a lack of response to the first and third generation of EGFR TKIs. In this study, we reported a 64-year-old female patient, who initially presented with symptoms of pneumonia and showed positive response to anti-infection treatment, eventually diagnosed with stage IV lung adenocarcinoma (LUAD) harboring a rare EGFR G719X and L861Q compound mutations. The patient received 40 mg/day of afatinib and experienced no severe adverse events. As a result, partial response (PR) was observed based on CT scan and a progression free survival of 24 month was achieved. Her follow-up is still ongoing. The results of the present case support the effectiveness and safety of afatinib in LUAD patients carrying EGFR G719X and L861Q compound mutations.

1. Background

Adenocarcinoma, the most common histologic type of non-small cell lung cancer (NSCLC), shows high rates of somatic mutation and genomic rearrangement. Currently, the most established driver mutation in NSCLC is epidermal growth factor receptor (EGFR). Molecular therapies such as tyrosine kinase inhibitors (TKIs) targeting EGFR have changed the standard of care, with superior outcomes in patients with sensitive EGFR mutations compared with standard chemotherapy [1].

However, EGFR mutations are not created equal. Exon 19 deletion and exon 21 L858R point mutation are the two most common EGFR mutations, account for 60 % and 35 % of total mutations, respectively [2]. LUAD patients with rare or compound mutations (such as G719X in exon 18 and L861Q in exon 21) often had inferior response and shorter survival than those harboring exon 19 deletion or L858R mutation when treated with the first generation of EGFR TKIs [3,4]. Currently, third generation TKI osimertinib was developed as a mutant-sensitive therapy, showing superior efficacy in patients with common EGFR mutations over the first generation EGFR TKI. Nonetheless, the overall response rate (ORR) for osimertinib was only about 50.0 % for uncommon mutations, and the median progression-free survival (PFS) was only 8.2 months [5].

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In this study, we reported a patient with compound EGFR exon 18 G719X and exon 21 L861Q mutations was successfully treated with afatinib for 24 months.

2. Case presentation

A 64-year-old Chinese woman was referred to our hospital with cough and chest tightness in April 2021. She had a history of diabetes and hypertension. She was a non-smoker with no family history of malignances. Her performance status was zero. Upon admission, she had a body temperature of 36.3 °C, heart rate of 66 bpm, respiratory rate of 20 bpm, blood pressure of 130/70 mmHg. Physical examination of the chest revealed percussion dullness and diminished breath sounds at the left middle and lower lung fields. Hematological blood tests revealed a neutrophil count of 6620 cells/mm3 (83.6 % neutrophils and 86.5 % lymphocytes), a hemoglobin level of 130 g/dL, and a normal platelet count of 203,000/mm3. The C-reactive protein (CRP) was 7.41 mg/L. Notably, the level of tumor marker carcinoembryonic antigen (CEA) was elevated to 18.1 ng/ml (Table 1). Chest computer tomography (CT) scan revealed a massive amount of left pleural effusion and collapse consolidation of the adjacent left lung tissue. Importantly, multiple subpleural nodules were also found in the left lower lobe (Fig. 1A and B).

We performed thoracic puncture and drainage on April 16, and 2400 mL light red pleural fluid was drawn out. Cytological examination detected no tumor cells in the pleural effusion. To clarify the nature of the pulmonary lesion, fiberoptic bronchoscopy was performed on April 23, no malignant components were found in postoperative pathology, while the subsequent sputum culture and pathogenic microorganism next-generation sequencing (NGS) revealed Klebsiella pneumonia infection. According to the results of the antimicrobial susceptibility test, the patient received ceftazidime (2g three times a day) on April 25. One week later, the count and proportion of neutrophil and CRP level all fell to normal levels, and the symptoms of cough and chest tightness were significantly relieved.

Table 1
Patient characteristics.

Sex	Female
Age	64
Smoking history	no
Medical history	Hypertension、diabetes、Non-STEMI
Vital signs	T:36.3 °C P:66 bpm R:20 bpm BP:130/70 mmHg
Laboratory examination	CRP:7.41mg/L BNP:26.3pg/mL CEA:18.1ng/mL
biochemistry analysis(hydrothorax)	TP:45.3g/L LDH:141U/L ADA:4.6U/L

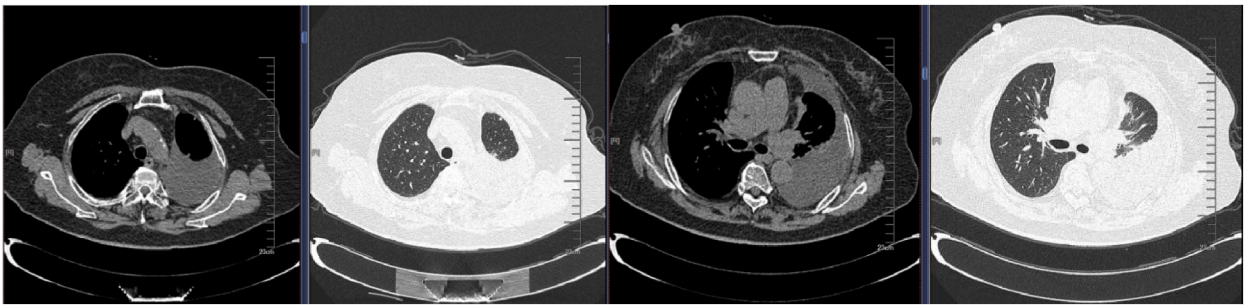

Fig. 1A. CT images taken on 15 April 2021 revealed a massive amount of left pleural effusion and collapse consolidation of the adjacent left lung tissue.

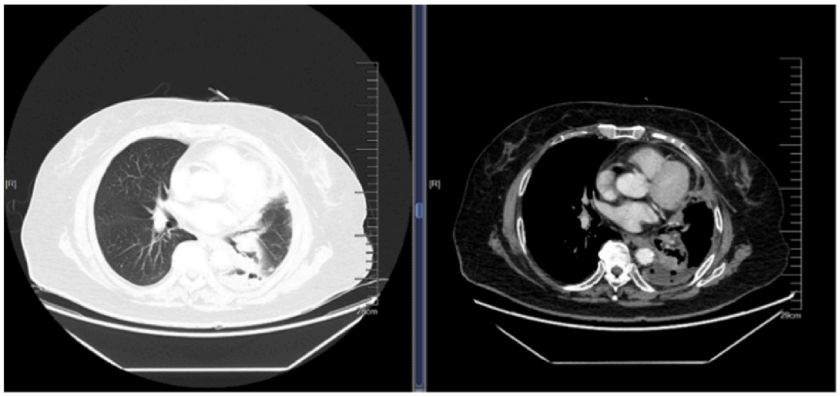

Fig. 1B. Contrast-enhanced CT images taken on 21 April 2021 showed a patchy high-density shadow in the left lower lobe and multiple pleural nodules.

However, elevated CEA level might indicated the possibility of neoplasms. PET-CT scan was performed and the result showed that there was a 1.9*1.5cm nodule in the lower left lobe of the patient, with an SUV value of 9.34 (Fig. 2). CT-guided percutaneous lung biopsy was performed, and the lesion were pathologically confirmed as lung adenocarcinoma with TTF1(+), P40 (−) and PD-L1 (22C3) (TPS <1 %) (Fig. 3). Genetic tests showed that EGFR 18 exon (G719X) and 21 exon (L861Q) mutations. Magnetic resonance imaging (MRI) shown no evidence of cerebral metastases. Thus, the patient was diagnosed with lung adenocarcinoma, stage IVa (cT2N3M1a).

The patient began to be treated with afatinib 40mg daily in May 2021 (Fig. 4). She was followed up at outpatient visits every two months and achieved a PR until May 2023, the latest return visit. Afatinib treatment is ongoing. The major treatment-related side effects observed were grade 1 skin adverse events. As shown in Fig. 5, the flowchart illustrates the process of patient's treatment.

3. Discussion and conclusions

3.1. Prevalence of uncommon mutation

G719X is the most commonly reported uncommon mutation, comprising 0.9–4.8 % of all EGFR mutations across eight studies. Ex20ins has a similar prevalence range to G719X, reported in 0.8–4.2 % of all EGFR mutations across ten studies. L861X and S768I

Fig. 2. PET-CT images showed that there was a 1.9*1.5cm nodule in the left lower lobe of the patient with an SUV value of 9.34.

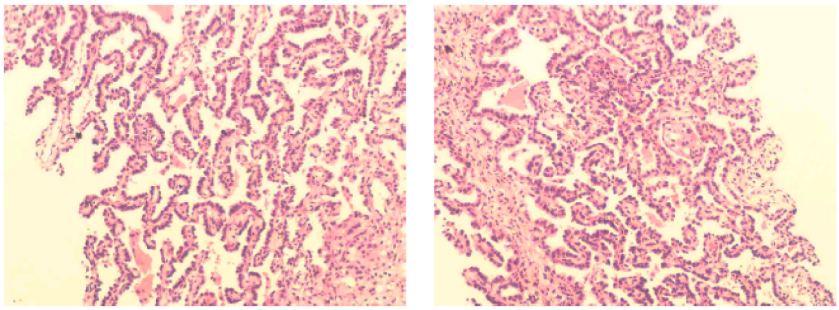

Fig. 3. Hematoxylin and eosin staining of lung tissue showed that the lesion was lung adenocarcinoma.

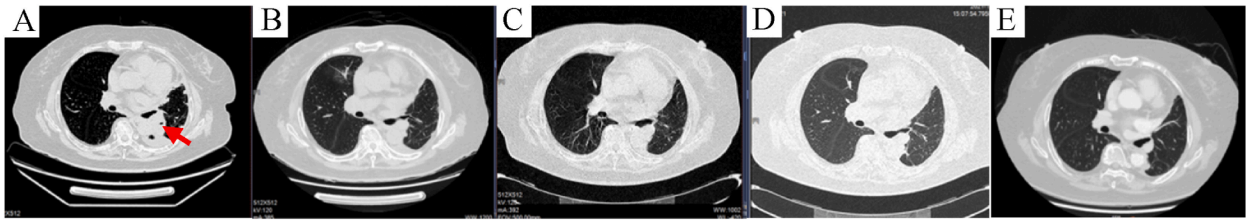

Fig. 4. Chest CT scan for the patient during treatment with Afatinib showed continuous shrinkage of leision.

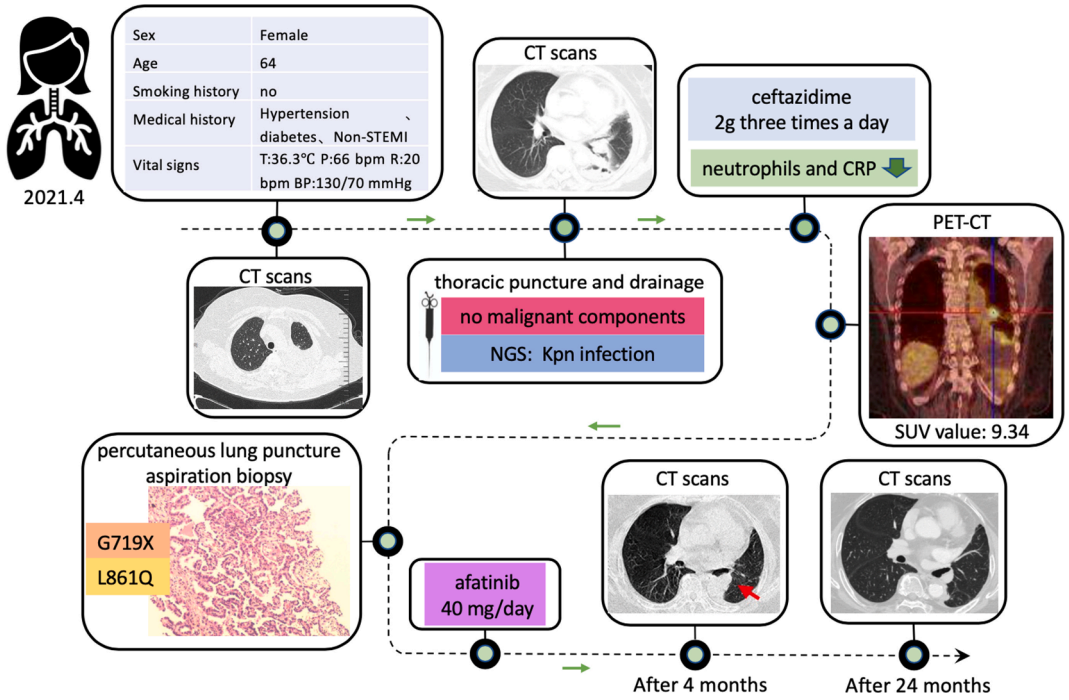

Fig. 5. A summary of the patient's treatment history.

each constitute 0.5–3.5 % and 0.5–2.5 % of all EGFR mutations, respectively [6]. For cases with compound mutations, EGFR G719X was more frequently identified as a compound mutation than L861Q (73.2 %, 52/71 for G719X; 29.8 %, 14/47 for L861Q). Moreover, among patients with compound L861Q mutation, 78.6 % (11/14) had concurrent exon 18 mutations (G719X: n = 9, S720F: n = 2) [7]. A systematic literature review of 25 studies showed that for patients receiving first-line EGFR-TKIs, those with common mutations had a PFS ranging from 8.3 months to 19.1 months/not reached, while those with uncommon mutations (excluding Ex19del, L858R, and T790M) had a PFS ranging from 2.1 months to 19.7 months/not reached. A shorter PFS of 1.2 months was reported in a subgroup with exon 20 mutations. In later/mixed lines, PFS ranged from 3.0 to 18.0 months for common mutations and 1.0–9.0 months for uncommon mutations, but this trend appeared to be dependent on the specific type of uncommon mutation [6].

3.2. Mechanism of compound mutations

Some studies have explored the mechanism of compound mutations. Kancha et al. transferred Wt (wild type), G719S, L861Q and L858R mutant genes into Ba/F3 cells, and used ELISA to detect the degree of EGFR protein self-phosphorylation and downstream signal molecule phosphorylation. It was found that the cells with L861Q mutation had the highest degree of phosphorylation, followed by L858R and G719S [8]. Hence, we can deduce that G719X frequently occurs as a compound mutation because a single mutation may be insufficient to initiate tumorigenesis. Compound mutations can enhance kinase phosphorylation activity and activate downstream signaling pathways, thereby regulating cell division, inhibiting apoptosis, stimulating angiogenesis, and promoting tumorigenesis and tumor formation. Kohsaka et, performed gDNA or cDNA-based amplicon sequencing or Droplet Digital PCR and observed that all compound mutations were present in cis alleles in all cases analyzed. Consequently, the transforming potential of compound mutations may be stronger than that of minor mutations alone [9].

In the study of Sato et, focused on the functional properties of L861Q mutation in exon 21 and detailed mechanisms of its response to EGFR TKIs, they found that EGFR is strongly co-immunoprecipitated with ERBB2 in cells expressing L861Q by co-immunoprecipitation analysis. Meanwhile, they observed the suppression of ERK and AKT phosphorylation in cells carrying L861Q when ERBB2 has been knocked down. The result suggests that ERBB2 plays an important role in cells with EGFR L861Q mutation. However, compared to osimertinib, afatinib is more potently inhibited phosphorylation of AKT and ERK in cells expressing L861Q by examining their effect on phosphorylation of EGFR, ERBB2, and other downstream signaling proteins [7,10].

3.3. Efficiency of first-generation EGFR TKIs against uncommon mutations

Several real-world studies have assessed the activity of first-generation EGFR TKIs against major uncommon mutations. In a retrospective multicenter study conducted in the Republic of China, erlotinib/gefitinib treatment outcomes were analyzed for patients with G719X (n = 78), L861Q (n = 57), or S768I (n = 7) mutations. The results showed moderate activity, with response rates of 37 %, 40 %, and 33 % for G719X, L861Q, and S768I mutations, respectively. The median PFS for all patients was 6.5 months [11]. For another instance, a retrospective single-center analysis compared outcomes between erlotinib/gefitinib (n = 14) and afatinib (n = 10) in patients with G719X/L861Q/S768I [12]. Despite the limited patient numbers, the results showed that patients treated

with afatinib had a longer PFS (18.3 mo; p = 0.12) than those treated with erlotinib/gefitinib (2.6 mo), while the response rates were 57 % and 70 %, respectively. Among cases with compound mutations, in a group of 46 patients with complex mutations were treated with gefitinib (n = 25), erlotinib (n = 10), or afatinib (n = 11), the median PFS was 12.3 months and median OS was 31.0 months [13].

3.4. Efficiency of second-generation EGFR TKIs against uncommon mutations

The combined post-hoc analysis of the Lux-Lung 2, Lux-Lung 3 and Lux-Lung 6 studies included 18 G719X patients and 16 L861Q patients with PFS of 13.8 and 8.2 months, respectively, after treatment with afatinib [14]. Yang et al. investigated the activity of afatinib in 272 EGFR TKI–naive patients, of those, median time to treatment failure (TTF) was 14.7, 10.0, and 15.6 months in patients with G719X, L861Q, and S768I mutations. Additionally, patients with compound mutations had the longest TTF (median 14.7 months), especially when one of the mutations involved a major uncommon mutation (median 16.6 months; uncommon mutations included G719X, L861Q, and S768I mutations) [15].

Second-generation EGFR TKIs demonstrate a wider range of activity across compound mutations compared to first or third-generation TKIs, according to preclinical observations [16]. In a comprehensive analysis of compound EGFR mutations, erlotinib and gefitinib were found to be effective against 37 of the 69 sensitivities tested. Afatinib is recommended for complex mutations involving E709X, S768I, or G719X, while osimertinib is recommended for complex mutations involving T790M in a resistance setting. The majority of the compound mutations (62 out of 69) were highly sensitive to afatinib, with the exception of those involving T790M, while 45 were highly sensitive to osimertinib [9].

However, afatinib appears to have higher rates of certain adverse events (AEs), such as diarrhea and rash/acne, compared to first- or third-generation TKIs [17]. In the LUX-Lung 7 trial, 57 % of patients experienced treatment-related AEs, with 13 % and 9 % experiencing grade greater than or equal to 3 diarrhea and rash/acne, respectively [18]. Nevertheless, dose reductions and supportive care can effectively manage AEs in patients treated with afatinib [17].

3.5. Efficiency of third-generation EGFR TKIs against uncommon mutations

A phase II trial involving 35 patients with uncommon mutations demonstrated that osimertinib achieved an ORR of 50.0 %, with the highest ORRs observed in patients with L861Q (77.8 %) and G719X (52.6 %) mutations, while patients with S768I mutation had an ORR of 37.5 %. The median duration of response (DoR) was 9.8 months, and the median PFS was 8.2 months (95 % CI: 5.9–10.5 months). These findings suggest that osimertinib may be a treatment option with limited activity against afatinib [19,20]. The UNICORN case series investigated the efficacy of osimertinib as a first-line EGFR-TKI in 60 patients with uncommon mutations, including T790M. The highest RR was observed in patients with L861Q (80 %), followed by G719X (47 %) and T790M (44 %). The median PFS for the study cohort was 9.5 months (95 % CI: 8.5–17.4 months), 16 and 8.8 months for L861Q and G719X [21]. Considering the potential activity in the central nervous system (CNS) is crucial, especially since a recent study, although small, revealed that uncommon mutations of the EGFR gene are relatively frequent (54 %) in CNS metastases of patients who have NSCLC with EGFR mutations [22]. Although osimertinib and afatinib have demonstrated clinical efficacy against brain metastases in patients with EGFR mutation-positive NSCLC and can lower the risk of CNS progression, there is insufficient data on their effectiveness against brain metastases carrying rare mutations [23–25].

In general, afatinib has demonstrated efficacy in treating NSCLC patients with rare mutations according to certain reports [26,27], however, the population of patients with such mutations appears to be heterogeneous and the underlying mechanisms of these mutations have yet to be fully understood. To confirm its effectiveness, large-scale multi-center studies are required. In addition, the responsiveness of compound mutations to EGFR TKIs is heavily impacted by the accompanying mutation. If both mutations are sensitive to a specific EGFR TKI, the effectiveness is typically similar to that against a single uncommon mutation. However, if there is a combination of a sensitive and resistant mutation, it diminishes the efficacy [28]. Therefore, when dealing with compound mutations, the choice of treatment should be informed by the sensitivity or resistance of the individual mutations, especially the accompanying mutation.

In conclusion, we have noted a significant positive response to afatinib in an advanced NSCLC patient with rare mutations affecting EGFR exon 18 G719X and exon 21 L861Q. Our results indicate that afatinib could be a viable treatment alternative for such patients.

Ethics approval and consent to participate

The treatment was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patient provided written informed consent for publication of this case report and all the accompanying images.

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Authors' contributions

Conception and design: Z.Z., J.H., Y.L., S.H.; data acquisition or data analysis/interpretation: Z.Z., J.H., Y.L., S.H., M.D., J.H., Q.W.; Final approval of manuscript: All authors; Manuscript drafting or manuscript revision: Z.Z., J.H., Y.L.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Availability of data and materials

All data and material are available for sharing if needed.

Declaration of competing interest

The authors declare that they have no competing interests.

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Abbreviations

NSCLC	non-small-cell lung cancer
EGFR	epidermal growth factor receptor
LUAD	lung adenocarcinoma
PR	partial response
TKIs	kinase inhibitors
ORR	overall response rate
PFS	progression-free survival
CRP	C-reactive protein
CEA	carcinoembryonic antigen
CT	computer tomography
NGS	next-generation sequencing
MRI	Magnetic resonance imaging
TTF	time to treatment failure
AEs	adverse events
CNS	central nervous system

References

[1] Comprehensive molecular profiling of lung adenocarcinoma, Nature 511 (7511) (2014) 543–550, https://doi.org/10.1038/nature13385.
[2] R. Rosell, T. Moran, C. Queralt, et al., Screening for epidermal growth factor receptor mutations in lung cancer, N. Engl. J. Med. 361 (10) (2009) 958–967, https://doi.org/10.1056/NEJMoa0904554.
[3] Klughammer Barbara, Wolfram, et al., Examining treatment outcomes with erlotinib in patients with advanced non–small cell lung cancer whose tumors harbor uncommon EGFR mutations - ScienceDirect, J. Thorac. Oncol. 11 (4) (2016) 545–555.
[4] J.Y. Wu, C.J. Yu, Y.C. Chang, et al., Effectiveness of tyrosine kinase inhibitors on "uncommon" epidermal growth factor receptor mutations of unknown clinical significance in non–small cell lung cancer, Clin. Cancer Res. 17 (11) (2011) 3812–3821.
[5] J.H. Cho, S.H. Lim, H.J. An, et al., Osimertinib for patients with non-small-cell lung cancer harboring uncommon EGFR mutations: a multicenter, open-label, phase II trial (KCSG-LU15-09), J. Clin. Oncol. 38 (5) (2019) JCO1900931.
[6] T. John, A. Taylor, H. Wang, et al., Uncommon EGFR mutations in non-small-cell lung cancer: a systematic literature review of prevalence and clinical outcomes, Cancer Epidemiol. 76 (2022) 102080, https://doi.org/10.1016/j.canep.2021.102080.
[7] H. Sato, M. Offin, D. Kubota, et al., Allele-specific role of ERBB2 in the oncogenic function of EGFR L861Q in EGFR-mutant lung cancers, J. Thorac. Oncol. 16 (1) (2021) 113–126, https://doi.org/10.1016/j.jtho.2020.09.019.
[8] R.K. Kancha, C. Peschel, J. Duyster, The epidermal growth factor receptor-L861Q mutation increases kinase activity without leading to enhanced sensitivity toward epidermal growth factor receptor kinase inhibitors, J. Thorac. Oncol. 6 (2) (2011) 387–392, https://doi.org/10.1097/JTO.0b013e3182021f3e.
[9] S. Kohsaka, M. Nagano, T. Ueno, et al., A method of high-throughput functional evaluation of EGFR gene variants of unknown significance in cancer, Sci. Transl. Med. 9 (416) (2017), https://doi.org/10.1126/scitranslmed.aan6566.
[10] H. Wecker, C.F. Waller, Afatinib. Recent Results Cancer Res. 211 (2018) 199–215, https://doi.org/10.1007/978-3-319-91442-8_14.
[11] C.H. Chiu, C.T. Yang, J.Y. Shih, et al., Epidermal growth factor receptor tyrosine kinase inhibitor treatment response in advanced lung adenocarcinomas with G719X/L861Q/S768I mutations, J. Thorac. Oncol. 10 (5) (2015) 793–799, https://doi.org/10.1097/jto.0000000000000504.
[12] Y.C. Shen, G.C. Tseng, C.Y. Tu, et al., Comparing the effects of afatinib with gefitinib or Erlotinib in patients with advanced-stage lung adenocarcinoma harboring non-classical epidermal growth factor receptor mutations, Lung Cancer 110 (2017) 56–62, https://doi.org/10.1016/j.lungcan.2017.06.007.
[13] A. Passaro, A. Prelaj, L. Bonanno, et al., Activity of EGFR TKIs in caucasian patients with NSCLC harboring potentially sensitive uncommon EGFR mutations, Clin. Lung Cancer 20 (2) (2019) e186–e194, https://doi.org/10.1016/j.cllc.2018.11.005.
[14] J.C. Yang, L.V. Sequist, S.L. Geater, 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. 16 (7) (2015) 830–838, https://doi.org/10.1016/s1470-2045(15)00026-1.
[15] J.C. Yang, M. Schuler, S. Popat, et al., Afatinib for the treatment of NSCLC harboring uncommon EGFR mutations: a database of 693 cases, J. Thorac. Oncol. 15 (5) (2020) 803–815, https://doi.org/10.1016/j.jtho.2019.12.126.
[16] V. Gristina, U. Malapelle, A. Galvano, et al., The significance of epidermal growth factor receptor uncommon mutations in non-small cell lung cancer: a systematic review and critical appraisal, Cancer Treat Rev. 85 (2020) 101994, https://doi.org/10.1016/j.ctrv.2020.101994.
[17] R. Shah, J.F. Lester, Tyrosine kinase inhibitors for the treatment of EGFR mutation-positive non-small-cell lung cancer: a clash of the generations, Clin. Lung Cancer 21 (3) (2020) e216–e228, https://doi.org/10.1016/j.cllc.2019.12.003.
[18] K. Park, E.H. Tan, K. O'Byrne, et al., Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial, Lancet Oncol. 17 (5) (2016) 577–589, https://doi.org/10.1016/s1470-2045(16)30033-x.
[19] J.H. Cho, S.H. Lim, H.J. An, et al., Osimertinib for patients with non-small-cell lung cancer harboring uncommon EGFR mutations: a multicenter, open-label, phase II trial (KCSG-LU15-09), J. Clin. Oncol. 38 (5) (2020) 488–495, https://doi.org/10.1200/jco.19.00931.

[20] J.C. Soria, Y. Ohe, J. Vansteenkiste, et al., Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer, N. Engl. J. Med. 378 (2) (2018) 113–125, https://doi.org/10.1056/NEJMoa1713137.
[21] J. Bar, N. Peled, S. Schokrpur, et al., UNcommon EGFR mutations: international case series on efficacy of osimertinib in real-life practice in first-LiNe setting (UNICORN), J. Thorac. Oncol. 18 (2) (2023) 169–180, https://doi.org/10.1016/j.jtho.2022.10.004.
[22] C. Ma, J. Zhang, D. Tang, et al., Tyrosine kinase inhibitors could Be effective against non-small cell lung cancer brain metastases harboring uncommon EGFR mutations, Front. Oncol. 10 (2020) 224, https://doi.org/10.3389/fonc.2020.00224.
[23] M. Schuler, Y.L. Wu, V. Hirsh, et al., First-line afatinib versus chemotherapy in patients with non-small cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases, J. Thorac. Oncol. 11 (3) (2016) 380–390, https://doi.org/10.1016/j.jtho.2015.11.014.
[24] T. Reungwetwattana, K. Nakagawa, B.C. Cho, et al., CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer, J. Clin. Oncol. (2018) Jco2018783118, https://doi.org/10.1200/jco.2018.78.3118.
[25] P. Hoffknecht, A. Tufman, T. Wehler, et al., Efficacy of the irreversible ErbB family blocker afatinib in epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)-pretreated non-small-cell lung cancer patients with brain metastases or leptomeningeal disease, J. Thorac. Oncol. 10 (1) (2015) 156–163, https://doi.org/10.1097/jto.0000000000000380.
[26] Y. Kobayashi, Y. Togashi, Y. Yatabe, 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. 21 (23) (2015) 5305–5313, https://doi.org/10.1158/1078-0432.Ccr-15-1046.
[27] D.F. Heigener, C. Schumann, M. Sebastian, et al., Afatinib in non-small cell lung cancer harboring uncommon EGFR mutations pretreated with reversible EGFR inhibitors, Oncol. 20 (10) (2015) 1167–1174, https://doi.org/10.1634/theoncologist.2015-0073.
[28] A. Russo, T. Franchina, G. Ricciardi, et al., Heterogeneous responses to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in patients with uncommon EGFR mutations: new insights and future perspectives in this complex clinical scenario, Int. J. Mol. Sci. 20 (6) (2019), https://doi.org/10.3390/ijms20061431.