Case Report

Durable clinical benefit from afatinib in a lung adenocarcinoma patient with acquired *EGFR* L718V mutation-mediated resistance towards osimertinib: a case report and literature review

Zizheng Song[1], Guanying Ren[1], Xiaolei Wang[1], Haiwei Du[2], Ying Sun[2], Ling Hu[1]

[1]Department of Medical Oncology, Affiliated Hospital of Hebei University, Hebei Key Laboratory of Cancer Radiotherapy and Chemotherapy, Baoding, China; [2]Burning Rock Biotech, Guangzhou, China

Correspondence to: Ling Hu. Department of Medical Oncology, Affiliated Hospital of Hebei University, Hebei Key Laboratory of Cancer Radiotherapy and Chemotherapy, 212 Yuhua East Road, Baoding 071000, China. Email: 57461548@qq.com.

Abstract: Osimertinib, as a third-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI), targeting *EGFR* exon 19 deletions, L858R, and T790M, has shown robust clinical efficacy and promising survival advantages in a subset of non-small cell lung cancer (NSCLC) patients. However, osimertinib-treated patients ultimately develop secondary resistance. Besides *EGFR* C797S mutation and *EGFR* amplification, a rare *EGFR* mutation, L718V, has been reported to confer osimertinib resistance in the literature, which is developed in about 8.0% of osimertinib-resistant NSCLC patients. Although the National Comprehensive Cancer Network or Chinese Society of Clinical Oncology NSCLC guidelines recommend radiotherapy, anti-angiogenesis therapy, chemotherapy and or immunotherapy for the treatment of NSCLC patients who acquire resistance to osimertinib, the feasible treatment options for patients harboring *EGFR* L718V remain elusive. There is an unmet need to develop effective strategies to treat *EGFR* L718X-positive NSCLC patients. Herein, we report that a lung adenocarcinoma patient with acquired *EGFR* L718V mutation-mediated resistance towards osimertinib derived durable response to the second-generation EGFR-TKI afatinib with a progression-free survival of 18 months and counting. Our work provides clinical evidence to administer afatinib in metastatic NSCLC patients who develop *EGFR* L718V at progression to osimertinib and paves the way for its potential clinical utilization.

Keywords: Afatinib; *EGFR* L718V; osimertinib; resistance; case report

Submitted Nov 29, 2021. Accepted for publication Jan 30, 2022.
doi: 10.21037/apm-21-3731
View this article at: https://dx.doi.org/10.21037/apm-21-3731

Introduction

Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) could be very effective for *EGFR* mutation positive patients. The third-generation EGFR-TKI osimertinib, targeting the *EGFR* T790M mutation which is related to about half of the acquired resistance cases, has further improved the efficacy (1). However, the majority of patients treated with osimertinib inevitably develop drug resistance. The heterogeneity of tumors leads to genetically distinctive mechanisms of acquired resistance to osimertinib, including the tertiary *EGFR* mutations, *EGFR* amplification and EGFR-independent bypass pathway activation (2,3). Nevertheless, the understanding of osimertinib resistance and subsequent treatment strategies are far from complete. The advent of next-generation sequencing (NGS) has significantly accelerated this process and been shown to bring benefit when NGS was done on rebiopsy samples at osimertinib resistance. Herein, we present the case of a metastatic lung adenocarcinoma (LUAD) patient who developed *EGFR* L718V at osimertinib resistance and derived a durable response to afatinib with a progression-free survival (PFS) of 18 months and counting.

We present the following article in accordance with the CARE reporting checklist (available at https://apm.

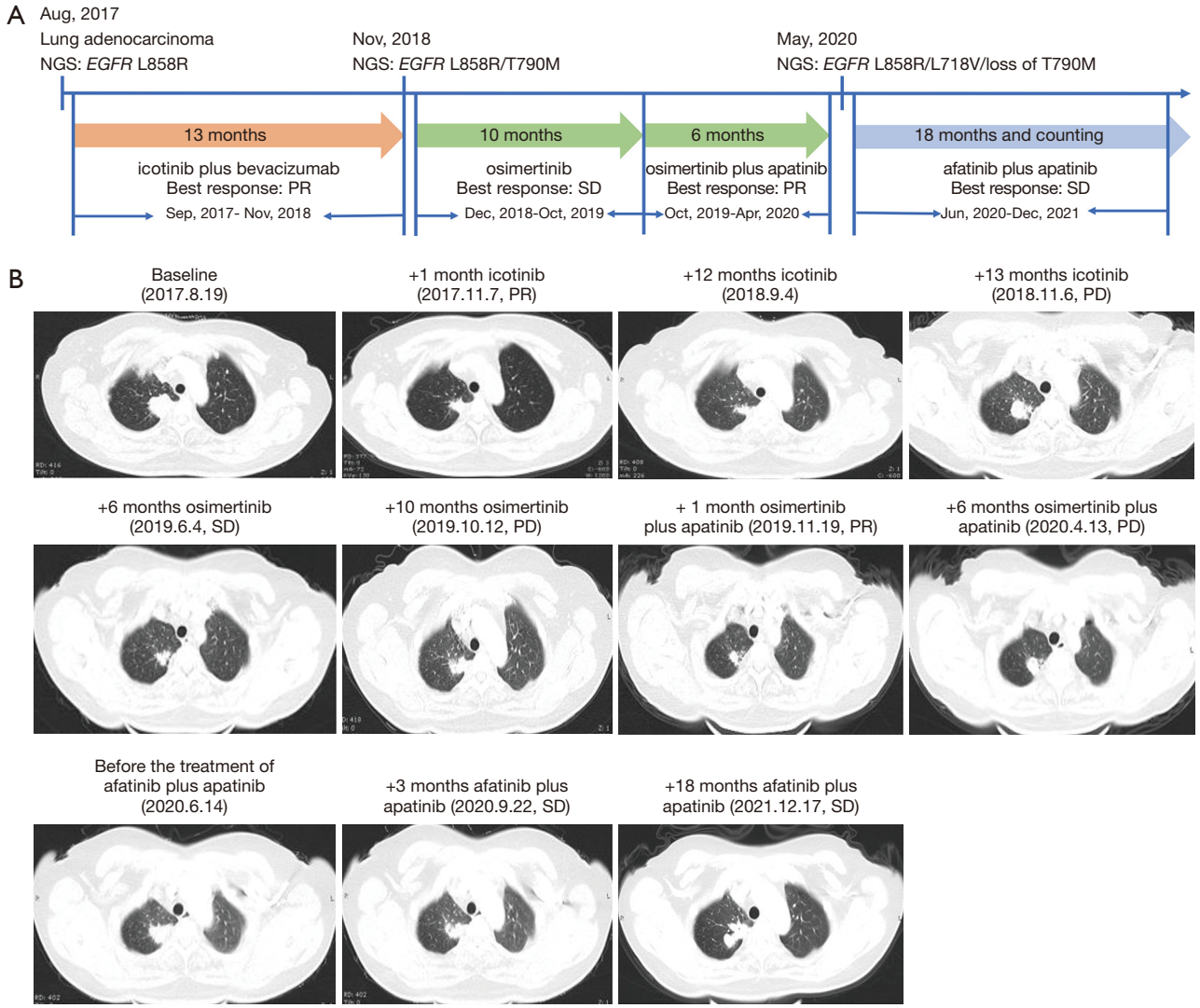

Figure 1 Summary of disease course, therapies, and molecular findings. (A) The entire treatment procedure; (B) CT scan of the primary lung tumor at treatment milestones. CT, computed tomography; NGS, next-generation sequencing; *EGFR*, epidermal growth factor receptor; PR, partial response; SD, stable disease; PD, progressive disease.

amegroups.com/article/view/10.21037/apm-21-3731/rc).

Case presentation

A 55-year-old Chinese female without smoking history was diagnosed with stage IV LUAD in August 2017. The computed tomography (CT) scan indicated a nodular lesion (4.1 cm × 3.3 cm, *Figure 1A*,*1B*) in the right upper lung, and pleural metastases. The patient had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 1. A percutaneous needle lung biopsy was performed and the NGS analysis (168 solid cancer-related genes panel, Burning Rock Biotech, Guangzhou, China) revealed an *EGFR* L858R mutation. After 3 rounds of circular intrapleural hyperthermic perfusion, the patient was started on icotinib, 125 mg 3 times per day on 26 September 2017, together with bevacizumab (500 mg every 3 weeks). A CT scan after 5 weeks of this treatment showed obvious shrinkage of the nodular lesion (2.4 cm × 2.1 cm), which was assessed as a partial response (PR) on 7 November 2017 (*Figure 1B*). The lesion size remained stable until the follow-up examination on 13 August 2018. Enlargement of the lesion was observed between 13 August 2018 and 3 September 2018 (from 2.2 cm × 1.5 cm to 2.3 cm × 1.6 cm).

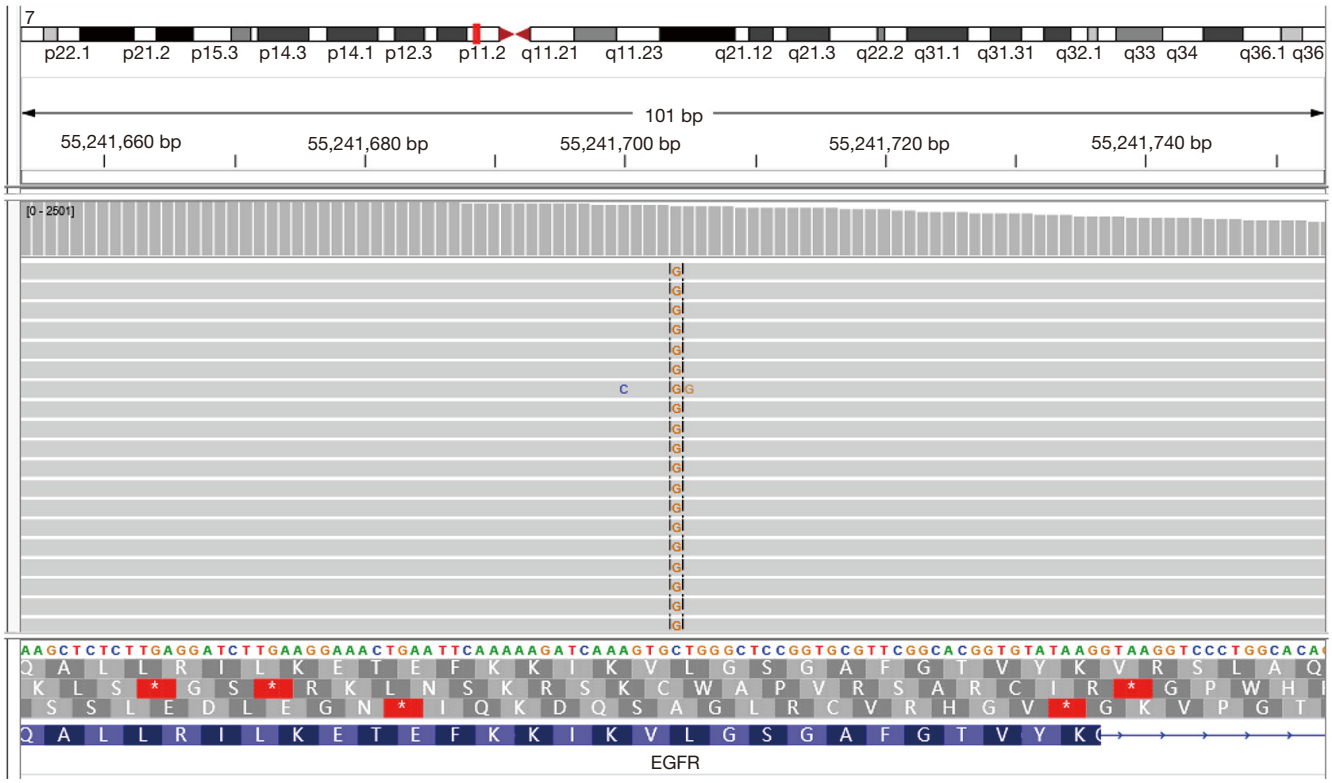

Figure 2 The integrative genomics viewer (IGV) screenshots revealed the harboring of *EGFR* exon 18 L718V. * indicates a stop codon. *EGFR*, epidermal growth factor receptor; NGS, next-generation sequencing.

The patient continued on the treatment of icotinib. The NGS test with biopsy sample confirmed the emergence of *EGFR* T790M mutation on 19 November 2018 (*Figure 1A*). The patient received osimertinib (80 mg/day) as second-line treatment on 10 December 2018, following which, stable disease (SD) was achieved for 10 months. A CT scan on 12 October 2019 indicated progressive disease (PD) (*Figure 1B*). The patient commenced on apatinib (250 mg/day) and osimertinib (80 mg/day) as the third-line treatment. The CT scan after 1 month of combination treatment showed obvious lesion size decrease, contributing to PR (*Figure 1B*). The treatment lasted for 6 months until PD in April 2020 (*Figure 1B*).

The repeated NGS with CT-guided biopsy sample indicated the presence of *EGFR* L718V (*Figure 2*) in conjunction with *EGFR* L858R, as well as the disappearance of *EGFR* T790M. Based on the findings of previous studies, the patient was shifted to afatinib (40 mg/day) and apatinib (250 mg/day) as fourth-line treatment on 14 June 2020. The CT scan after 3 months' treatment showed obvious lesion size reduction (from 2.5 cm × 2.2 cm to 2.0 cm × 1.9 cm, *Figure 1B*). The clinical response assessment was SD with a ECOG PS of 0. The patient continued on the treatment with no evidence of progression and a PFS of more than 18 months (the data cut-off date: 17 December 2021). Besides loss of appetite and grade I nausea that did not require medical treatment, the patient reported no other complaints. She had good adherence to the treatment of afatinib plus apatinib.

We also reviewed 9 previously reported cases harboring *EGFR* L718X. Among 4 cases who received afatinib treatment, 3 showed a response to it. The clinical characteristics and outcomes of non-small cell lung cancer (NSCLC) patients with acquired *EGFR* L718X to osimertinib in our and previous studies are summarized in *Table 1*.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written

Table 1 Clinical characteristics and outcomes of NSCLC patients harboring *EGFR* L718X in our and previous studies

Patient No.	Publication	Year of publication	Age (years)	Smoking	Gender/ ethnicity	Diagnosis/ stage	Original *EGFR*	Treatment history	Concurrent mutations	Best response to EGFR-TKI	PFS (months)
1	Raez *et al.*	2021	NA	No	Female/ Asian	NSCLC/IV	L858R	Osimertinib (L858R)/1st line; 3 of the 4 patients were started on afatinib (L718V)/2nd line	NA	SD/PR; two of the 3 patients responded to afatinib with disease stabilization	5–20
2	Raez *et al.*	2021	NA	No	Female/ White	NSCLC/IV	L858R		NA		NA
3	Raez *et al.*	2021	NA	Yes	Male/ Hispanic	NSCLC/IV	L858R				
4	Raez *et al.*	2021	NA	No	Male/ White	NSCLC/IV	L858R				
5	Fang *et al.*	2019	45	Yes	Male/ Chinese	LUAD/IV	L858R	Gefitinib (L858R)/1st line		NA	20
								Osimertinib (L858R + T790M)/2nd line		NA	9.5
								Afatinib (L858R + L718V + loss of T790M)/3rd line	*EGFR* amplification	NA	More than 6 months
6	Liu *et al.*	2018	67	Yes	Male/ Chinese	LUAD/IIB	L858R	Chemotherapy/1st line		NA	7
								Gefitinib (L858R)/2nd line		PR	13.5
								Osimertinib (L858R + T790M)/3rd line		PR	17.7
								Erlotinib (L718V + L858R + loss of T790M)/4th line		PD	3
								Chest radiotherapy (C797S mutation in cis + L858R + T790M)/5th line		SD	NA

Table 1 (*continued*)

Table 1 (*continued*)

Patient No.	Publication	Year of publication	Age (years)	Smoking	Gender/ ethnicity	Diagnosis/ stage	Original *EGFR*	Treatment history	Concurrent mutations	Best response to EGFR-TKI	PFS (months)
7	Yang *et al.*	2019	59	No	Male/ Chinese	LUAD/IV	L858R	Concurrent chemoradiotherapy/1st line		NA	NA
								Icotinib (L858R)/2nd line		PD	2
								Osimertinib (L858R)/3rd line	*MAP3K1* K1342E and *NSD1* K513R	PR	10.4
								Erlotinib (L718V+L858R)		PD	2
8	Li *et al.*	2021	72	No	Female/ Chinese	LUAD/IV	L858R	Gefitinib (L858R)/1st line		PR	6
								Osimertinib (L858R+T790M)/2nd line		SD	27
								Dacomitinib (L858R+L718Q+loss of T790M)/3rd line		PD	1
9	Li *et al.*	2021	45	Yes	Male/ Chinese	LUAD/IV	L858R	Chemotherapy/1st line		SD	4
								Osimertinib/2nd line		PR	5
								Dacomitinib (L758R+L718Q)/3rd line		PD	1
10	Our study	2022	55	No	Female/ Chinese	LUAD/IIIB	L858R	Icotinib (L858R) + chemotherapy/1st line		PR	13
								Osimertinib (L858R + T790M)/2nd line		SD	10
								Osimertinib (L858R + T790M) + apatinib/3rd line		PR	6
								Afatinib (L858R + L718V+ loss of T790M) + apatinib/4th line		SD	18 months and counting

EGFR, epidermal growth factor receptor; PD, progressive disease; PR, partial response; SD, stable disease; NA, not available; No., number; LUAD, lung adenocarcinoma; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer.

consent is available for review by the editorial office of this journal.

Discussion

It has been well documented that acquired resistance to osimertinib is mainly mediated by *EGFR* C797S mutation or loss of *EGFR* T790M in patients with *EGFR*-T790M-positive NSCLC. Herein, we have presented that *EGFR* L718V also contributed to resistance to osimertinib and retention of sensitivity to afatinib in a LUAD patient with a PFS of 18 months and counting. To the best of our knowledge, this is the longest PFS among all reported studies.

EGFR-mutated NSCLC is a genetically heterogeneous disease that includes more than 200 distinct mutations. The most common *EGFR* mutations—exon 19 deletions or L858R mutations, which account for approximately 50% of all NSCLC in Asians and 10-15% in Western patients (4,5), predict sensitivity to EGFR-TKI. Gefitinib, icotinib, and osimertinib as EGFR-TKIs have been used as first-line treatment for NSCLC patients bearing *EGFR* sensitizing mutations based on the results from clinical trials as previously reported indicating that EGFR-TKI has significantly improved clinical outcomes compared with chemotherapy (1,6,7). However, NSCLC patients with *EGFR* mutations inevitably develop acquired resistance to EGFR-TKI. The common cause of the failure of EGFR-TKI is the emergence of new actionable alterations, while in up to 30% of cases, the mechanisms underlying acquired resistance remain unknown (8,9). Recent studies have revealed that epigenetic factors are involved in the acquired mechanisms to EGFR-TKI, such as epigenetic regulation of *EGFR*, epigenetic silencing of microRNA-483-3p, and epigenetic repression of DUSP1 (10-12). Further studies are needed to investigate whether epigenetic factors are implicated in the resistance mechanisms to osimertinib.

Osimertinib, a third-generation EGFR-TKI, could be used as the preferred first-line treatment for *EGFR* mutation-positive NSCLC patients, and also as a salvage therapy with the presence of *EGFR* T790M mutation (1,13). Despite the efficacy of osimertinib exerted *in vitro* and in the clinical setting, the inevitable drug resistance poses a challenge due to the paucity of post-osimertinib pharmacological strategies available to date. Besides the most common *EGFR* exon 20 C797S mutation (1), the acquired mutations in L718 have been reported to be related with osimertinib resistance (14,15). The residue L718 is located at the adenosine triphosphate (ATP) binding site in EGFR, and it would induce the spatial confliction for osimertinib binding (16). Previous *in vitro* studies have demonstrated that those with mutation in L718X (L718Q and L718V) might remain sensitive to afatinib, especially with the concurrent loss of *EGFR* T790M (15,16).

National Comprehensive Cancer Network guidelines (NCCN) and Chinse Society of Clinical Oncology (CSCO) recommend immunotherapy, radiotherapy, continuing osimertinib, anti-angiogenesis therapy, and chemotherapy as palliative treatment options for NSCLC patients who progress on osimertinib (17,18). In the present work, the patient who acquired *EGFR* L718V resistant to osimertinib was challenged with afatinib based on the previous studies indicating that NSCLC patients who acquired *EGFR* L718V might derive durable response to afatinib. Afatinib has been indicated for the first-line treatment of patients with metastatic NSCLC whose tumors have non-resistant *EGFR* mutations based on the results from clinical trial LUX-Lung 3 (NCT00949650) that patients with *EGFR* mutation-positive, metastatic NSCLC who receive afatinib as the first-line treatment have a significantly longer PFS than those receiving pemetrexed/cisplatin (19). Afatinib is also indicated for the treatment of patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy according to its promising efficacy in clinical trial LUX-Lung 8 [NCT01523587] that previously treated, metastatic squamous NSCLC who receive afatinib have a significantly longer overall survival than those receiving erlotinib (20).

The current literature on the treatment option for NSCLC patients with *EGFR* L718X conferring resistance to osimertinib is limited. To our knowledge, there are 5 case reports in the literature. Due to the lack of the standard-of-care, patients who developed *EGFR* L718X at progression on osimertinib were treated with EGFR-TKI erlotinib or dacomitinib in 3 previous case reports; however, they failed to respond to those 2 EGFR-TKIs (21-23). In another 2 case reports in the literature, LUAD patients who developed *EGFR* L718V/Q at progression on osimertinib could respond to afatinib treatment (24,25).

Raez *et al.* demonstrated that 2 of 3 NSCLC patients with *EGFR* L718V respond to afatinib with disease stabilization (25) and Fang *et al.* revealed that the use of afatinib in an *EGFR*-mutated LUAD patient with acquired L718V mutation yielded a PFS of at least 6 months (24). Consistent with these 2 previous case reports, our case with *EGFR* L718V and loss of T790M responded to afatinib.

Furthermore, this patient showed a durable response to afatinib with a PFS of 18 months and counting, which is obviously longer than that of 6 months as previously reported (24). Among the 5 cases who developed *EGFR* L718V at the progression to osimertinib as reported in the previous and our study, 4 cases responded to afatinib, achieving an objective response rate (ORR) of 80.0%. The most common adverse reactions of afatinib as first-line treatment reported in clinical trial LUX-Lung 3 are diarrhea, rash, stomatitis, paronychia, and dry skin (19). In addition, the most common adverse reactions of afatinib for the treatment of metastatic squamous NSCLC patients progressing after platinum-based chemotherapy reported in clinical trial LUX-Lung 8 are diarrhea, rash, stomatitis, and decreased appetite (20). In the present work, the patient reported decreased appetite and nausea that did not require medical treatment during the treatment of afatinib. These findings suggest that afatinib serves a crucial role in overcoming the acquired resistance caused by *EGFR* L718V. Our work highlights that dynamically monitoring the mutation status could improve progression survivals of NSCLC patients.

Immune checkpoint inhibitors (ICIs) have emerged as a pillar in the management of advanced malignancies, which could be used as palliative treatments for NSCLC patients who acquire osimertinib resistance. Positive expression of programmed cell death ligand-1 (PD-L1) predicts favorable prognosis in NSCLC patients who received ICIs. However, of the patients who initially respond, some develop resistance at a later time and experience tumor relapse, leading to a poor survival (26). The emergence of new actionable alterations or mechanisms contributing to the acquired resistance to EGFR-TKIs and ICIs could promote the development of efficacious strategies for NSCLC patients. Collectively, drug resistance is the key clinical barrier to further improve outcomes of patients with metastatic NSCLC and developing treatment strategy to overcome drug resistance for NSCLC patients is an unmet need.

A few limitations are associated with our study. Due to the nature of our work, only 1 patient was involved in the study. More evidences or clinical trials are needed to evaluate the efficacy and safety of afatinib in NSCLC patients harboring *EGFR* L718V.

Our case not only supports that the *EGFR* L718V mutation is responsible for osimertinib resistance, but also provides clinical evidence that patients harboring *EGFR* L718V mutation and the loss of T790M might derive a durable response to afatinib. Our study suggests that afatinib might be an effective treatment option for NSCLC patients harboring the uncommon *EGFR* L718V.

Acknowledgments

We would like to express our sincere gratitude to the patient and her family. We also thank all investigators, coordinators, and operating staff for their contribution and efforts in this project.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-21-3731/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-21-3731/coif). HD and YS were employed by the company Burning Rock Biotech Ltd. at the time of writing this report. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

References

1. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med 2017;376:629-40.
2. Oxnard GR, Hu Y, Mileham KF, et al. Assessment of Resistance Mechanisms and Clinical Implications in Patients With EGFR T790M-Positive Lung Cancer and Acquired Resistance to Osimertinib. JAMA Oncol 2018;4:1527-34.
3. Nukaga S, Yasuda H, Tsuchihara K, et al. Amplification of EGFR Wild-Type Alleles in Non-Small Cell Lung Cancer Cells Confers Acquired Resistance to Mutation-Selective EGFR Tyrosine Kinase Inhibitors. Cancer Res 2017;77:2078-89.
4. Lynch T J, Bell D W, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129-39.
5. Shi Y, Au JS, Thongprasert S, et al. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). J Thorac Oncol 2014;9:154-62.
6. Chang CH, Chen KY, Young-Xu Y, et al. The safety and efficacy of gefitinib versus platinum-based doublets chemotherapy as the first-line treatment for advanced non-small-cell lung cancer patients in East Asia: a meta-analysis. Lung Cancer 2008;62:242-52.
7. Shi Y K, Wang L, Han BH, et al. First-line icotinib versus cisplatin/pemetrexed plus pemetrexed maintenance therapy for patients with advanced EGFR mutation-positive lung adenocarcinoma (CONVINCE): a phase 3, open-label, randomized study. Ann Oncol 2017;28:2443-50.
8. Westover D, Zugazagoitia J, Cho BC, et al. Mechanisms of acquired resistance to first- and second-generation EGFR tyrosine kinase inhibitors. Ann Oncol 2018;29:i10-9.
9. Leonetti A, Sharma S, Minari R, et al. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. Br J Cancer 2019;121:725-37.
10. Peralta-Arrieta I, Trejo-Villegas OA, Armas-López L, et al. Failure to EGFR-TKI-based therapy and tumoural progression are promoted by MEOX2/GLI1-mediated epigenetic regulation of EGFR in the human lung cancer. Eur J Cancer 2022;160:189-205.
11. Yue J, Lv D, Wang C, et al. Epigenetic silencing of miR-483-3p promotes acquired gefitinib resistance and EMT in EGFR-mutant NSCLC by targeting integrin β3. Oncogene 2018;37:4300-12.
12. Chen Z, Chen Q, Cheng Z, et al. Long non-coding RNA CASC9 promotes gefitinib resistance in NSCLC by epigenetic repression of DUSP1. Cell Death Dis 2020;11:858.
13. Ramalingam S S, Yang J C, Lee C K, et al. Osimertinib As First-Line Treatment of EGFR Mutation-Positive Advanced Non-Small-Cell Lung Cancer. J Clin Oncol 2018;36:841-9.
14. Finlay MR, Anderton M, Ashton S, et al. Discovery of a potent and selective EGFR inhibitor (AZD9291) of both sensitizing and T790M resistance mutations that spares the wild type form of the receptor. J Med Chem 2014;57:8249-67.
15. Yang Z, Yang N, Ou Q, et al. Investigating Novel Resistance Mechanisms to Third-Generation EGFR Tyrosine Kinase Inhibitor Osimertinib in Non-Small Cell Lung Cancer Patients. Clin Cancer Res 2018;24:3097-107.
16. Bersanelli M, Minari R, Bordi P, et al. L718Q Mutation as New Mechanism of Acquired Resistance to AZD9291 in EGFR-Mutated NSCLC. J Thorac Oncol 2016;11:e121-3.
17. NCCN. NCCN Clinical Practice Guidelines in Oncology Non-Small Cell Lung Cancer. 2021.
18. CSCO. Guidelines of Chinese Society of Clinical Oncolgy Non-Small Cell Lung Cancer. 2021.
19. Yang JC, Wu YL, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol 2015;16:141-51.
20. Soria J C, Felip E, Cobo M, et al. Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. Lancet Oncol 2015;16:897-907.
21. Li HS, Yang G J,Wang Y. Case Report: Dacomitinib May Not Benefit Patients Who Develop Rare Compound Mutations After Later-Line Osimertinib Treatment. Front Oncol 2021;11:649843.
22. Yang Z, Yang J, Chen Y, et al. Acquired EGFR L718V Mutation as the Mechanism for Osimertinib Resistance in a T790M-Negative Non-Small-Cell Lung Cancer Patient. Target Oncol 2019;14:369-74.
23. Liu Y, Li Y, Ou Q, et al. Acquired EGFR L718V mutation mediates resistance to osimertinib in non-small cell lung cancer but retains sensitivity to afatinib. Lung Cancer

2018;118:1-5.
24. Fang W, Gan J, Huang Y, et al. Acquired EGFR L718V Mutation and Loss of T790M-Mediated Resistance to Osimertinib in a Patient With NSCLC Who Responded to Afatinib. J Thorac Oncol 2019;14:e274-5.
25. Raez LE, Carracedo C, Drusbosky LM, et al. EGFR L718V (+)/T790M (-) as a Mechanism of Resistance in Patients with Metastatic Non-small-cell Lung Cancer with EGFR L858R Mutations. Clin Lung Cancer 2021;22:e817-9.
26. Jenkins RW, Barbie DA, Flaherty KT. Mechanisms of resistance to immune checkpoint inhibitors. Br J Cancer 2018;118:9-16.

(English Language Editor: J. Jones)

Cite this article as: Song Z, Ren G, Wang X, Du H, Sun Y, Hu L. Durable clinical benefit from afatinib in a lung adenocarcinoma patient with acquired EGFR L718V mutation-mediated resistance towards osimertinib: a case report and literature review. Ann Palliat Med 2022;11(3):1126-1134. doi: 10.21037/apm-21-3731

