

## CASE REPORT

**ALK rearrangements as mechanisms of acquired resistance to osimertinib in *EGFR* mutant non-small cell lung cancer**Helei Hou<sup>†</sup>, Dantong Sun<sup>†</sup>, Chuantao Zhang, Dong Liu & Xiaochun Zhang

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Thoracic Cancer **12** (2021) 962–969**Abstract**

Non-small cell lung cancer (NSCLC) patients harboring *EGFR* sensitive mutations may benefit from treatment with *EGFR* TKIs. Osimertinib, which is an irreversible third-generation *EGFR* TKI, has demonstrated a convincing efficacy, irrespective of whether it is used in first- or second-line treatment. The acquired resistance mechanisms to osimertinib are highly complicated, and a variety of potential molecular mechanisms have been discovered, including C797S. Here, we determined that *ALK* rearrangement might be an underlying mechanism contributing to acquired resistance to osimertinib. In our report, a 60-year-old female patient with lung adenocarcinoma with an *EGFR* mutation was administered multiple treatments, including first-line gefitinib and second-line osimertinib. According to the next-generation sequencing (NGS) assay after osimertinib failure, the emergence of an *ALK* rearrangement was considered to be a potentially acquired resistance mechanism to osimertinib. The combination of osimertinib and crizotinib then maintained a six-month stable disease. *VEGFA* amplification was identified after osimertinib plus crizotinib treatment, and chemotherapy plus bevacizumab achieved a continuous stable disease over 21 months. In this study, we also summarized previously reported cases and concluded that *ALK* rearrangement is a rare but critical resistance mechanism to osimertinib. After failure of combined treatment with osimertinib plus crizotinib, comprehensive molecular profiling should be performed, and chemotherapy plus bevacizumab might be an optimal treatment especially for patients harboring *VEGFA* amplification.

**Introduction**

Lung cancer is one of the most common malignancies and ranks first as a cause of cancer-related mortality.<sup>1</sup> Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases, and the early stage of the disease is usually asymptomatic, which results in difficulties in early diagnosis.<sup>2</sup> With the development of molecular detection technologies, patients harboring sensitive driver gene mutations might benefit from targeted therapy. Epidermal growth factor receptor (*EGFR*) plays an important role in the carcinogenesis of lung cancer, and approximately 50% of Asian patients harbor *EGFR* sensitive mutations, mainly including the deletion mutation in *EGFR* exon 19 (19 del) and the substitution of leucine for arginine (L858R) in *EGFR* exon 21.<sup>3,4</sup> According to the results of the IRESSA

Pan-Asia Study, the first-generation *EGFR* tyrosine kinase inhibitor (TKI) caused NSCLC patients harboring *EGFR* sensitive mutations to have significantly longer progression-free survival (PFS), which was maintained for 9.5 months (9.5 months vs. 6.3 months) compared with the regular regimen of chemotherapy.<sup>5</sup> However, primary or acquired resistance to first-generation *EGFR* TKIs leads to the failure of targeted therapy that targets *EGFR* sensitive mutations. Therefore, three or more generations of *EGFR* TKIs were explored in the clinical treatment of NSCLC patients.

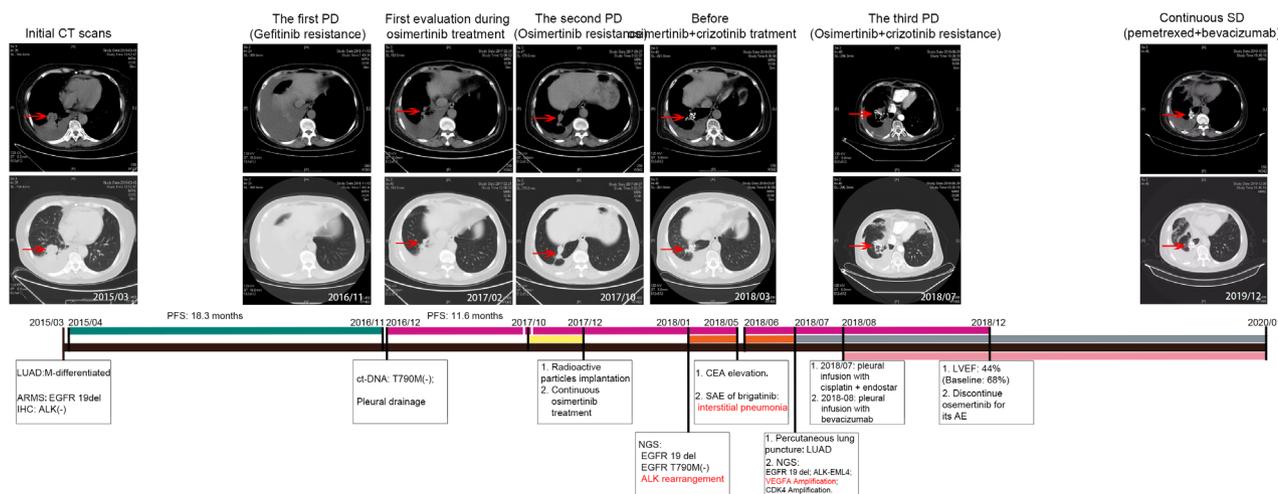
The Thr790Met point mutation (T790M) in *EGFR* exon 20 is a primary contributor to the acquired resistance to first-generation *EGFR* TKIs. Osimertinib is an irreversible third-generation *EGFR* TKI that is selective for both *EGFR*

sensitizing and T790M resistance mutation.<sup>6</sup> Both primary and metastatic lesions, including metastases in the central nervous system (CNS), respond well to osimertinib treatment.<sup>7</sup> In addition, recent clinical trials have confirmed the role of osimertinib as a first-line treatment of NSCLC patients harboring *EGFR* mutations.<sup>8,9</sup> Despite the efficacy of osimertinib, its resistance was unavoidable, and the related mechanisms were demonstrated to be highly heterogeneous.<sup>10</sup> *EGFR* gene point mutations, *MET* or *HER2* gene amplification<sup>10–12</sup> and the activation of RAS mitogen-activated protein kinase (MAPK) or RAS phosphatidylinositol-3 kinase (PI3K) pathways<sup>10</sup> have all been confirmed to be associated with resistance to osimertinib. In addition, a few cases have suggested that an emerging *ALK* rearrangement was detected after resistance to osimertinib treatment,<sup>13–17</sup> but the role of *ALK* rearrangement in resistance to osimertinib remains unclear. Here, we report an NSCLC patient who experienced osimertinib resistance who was shown to harbor the emerging *ALK* rearrangement and explored the available treatment strategies for patients after osimertinib resistance mediated by *ALK* arrangements.

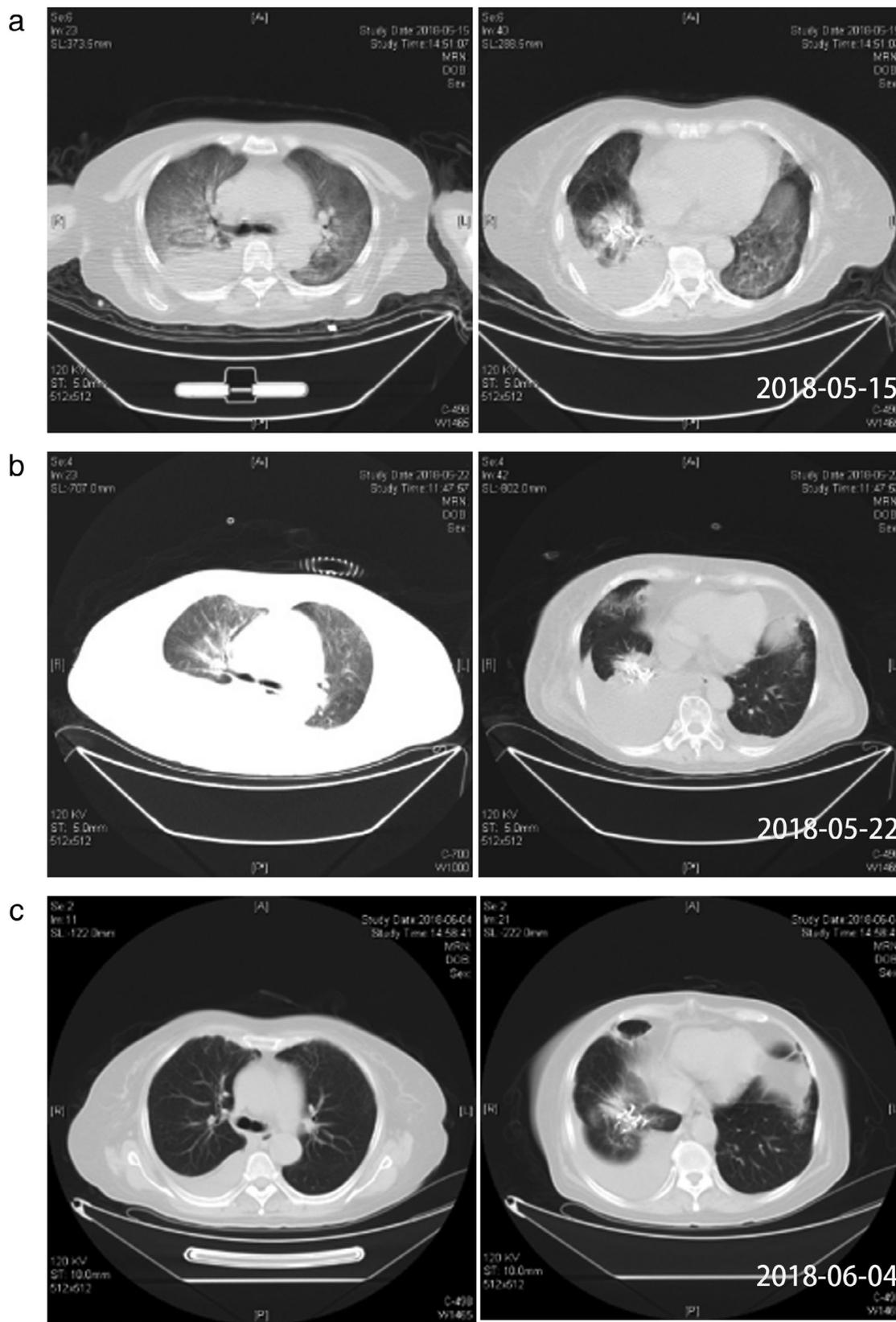
### Case report

A 60-year-old female first presented in March 2015 with symptoms of chest distress for one month. Computed tomography (CT) scan showed a space-occupying lesion in her right lung combined with pleural effusion. Through percutaneous lung puncture and pathological diagnosis, the patient was diagnosed with stage IV moderately differentiated invasive lung adenocarcinoma (LUAD). No other metastatic lesions were found after systematic examination. Amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) examination of

*EGFR* mutations based on blood samples and immunohistochemistry (IHC) testing of *ALK* were performed to guide the molecular targeted therapy of this patient. The IHC test suggested a wild-type *ALK* protein. Given the confirmation of *EGFR* 19 del through ARMS-PCR, treatment with gefitinib was initiated in this patient who experienced a rapid partial response (PR). The detailed treatment regimen for this patient are described in Fig 1. After 18.3 months of gefitinib treatment, a CT scan of this patient revealed progressive disease (PD). The patient suffered serious pleural effusion, and pleural drainage was performed to alleviate the clinical symptoms. A droplet digital-PCR (dd-PCR) assay performed on the patient's blood for the *EGFR* T790M mutation was negative in December 2016. Given the baseline mutation status of *EGFR* and the false-negative possibility of ct-DNA examination, osimertinib was then administered. Fortunately, the patient achieved stable disease (SD) during osimertinib treatment, and pleural effusion gradually decreased. After 11.6 months of treatment in October 2017, the lesions on the right lung enlarged, and the osimertinib response was evaluated as PD. Due to local progression of the primary tumor, the patient was then given radioactive particle implantation treatment of the primary lesion combined with continuation of osimertinib, which maintained SD until December 2017. Although the CT scan demonstrated SD, the concentration of carcinoembryonic antigen (CEA) was significantly elevated from 5.5 to 13.0 ng/mL. Therefore, tissue samples obtained from percutaneous lung puncture before radioactive particle implantation treatment were examined by targeted next-generation sequencing (NGS) in December 2017, which revealed a de novo *ALK* rearrangement (*EML4-ALK*) in addition to *EGFR* 19del. Consequently, the patient received osimertinib plus crizotinib



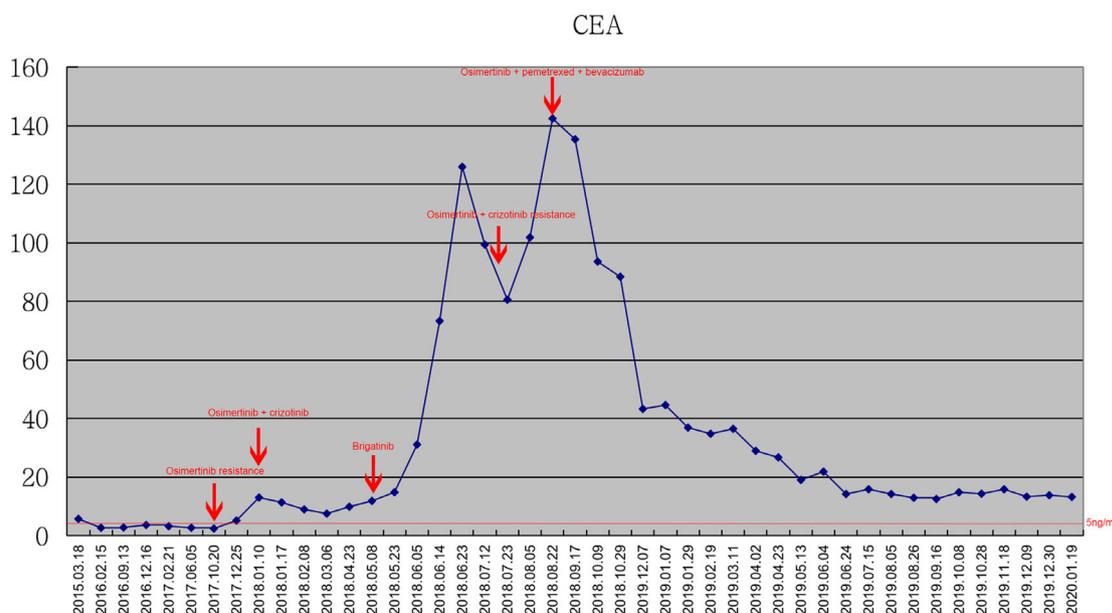
**Figure 1** Treatment history of the patient in the study. —, Gefitinib; —, Osimertinib; —, Radioactive particles implantation; —, Crizotinib; —, Chemotherapy; —, Bevacizumab.



**Figure 2** Computed tomography (CT) scan evolution of the patient who suffered from interstitial pneumonia caused by brigatinib. (a) 17 hours after brigatinib treatment. (b) 1 week after brigatinib treatment. (c) the patient recovered from the SAE induced by brigatinib.

for the following treatment since January 2018 according to the NGS assay. During the treatment with dual TKIs, including osimertinib plus crizotinib, the CEA concentration was reduced from 13.0 to 7.5 ng/mL, and the CT scan also demonstrated SD. However, in May 2018, the CEA concentration increased again and reached 11.8 ng/mL. Given the SD condition evaluated by CT scan, the treatment using the original dual TKI regimen was recommended, but the patient opted to try the second-generation *ALK* inhibitor brigatinib. Only 12 hours after the first treatment with brigatinib, the patient suffered polypnea and weakness, and 17 hours after treatment, the patient slipped into a coma and was sent to the emergency intensive care unit (EICU). Following CT scan,

the patient was diagnosed with serious interstitial pneumonia, most likely induced by brigatinib (Fig 2). After tracheal intubation and treatment with glucocorticoids, on 4 June 2018, the patient recovered from the serious adverse event (SAE) and continued to receive treatment with osimertinib plus crizotinib. During treatment, the CEA concentration increased continuously to 125.9 ng/mL, and the CT scan suggested PD in July 2018. A third biopsy was then obtained, and *VEGFA* gene amplification was detected through NGS examination in addition to *EGFR* 19del and *ALK* arrangement. According to the NGS results, it was thought that *VEGFA* gene amplification might be involved in the acquired resistance of combination therapy of osimertinib plus



**Figure 3** Dynamic change in carcinoembryonic antigen (CEA) of the patient during various treatments. ◆, CEA.

**Table 1** Molecular detection during treatment of the patient in the study

Detection time	Samples	Methods	Mutation (abundance %)
03/2015	Blood	ARMS-PCR	EGFR 19 del
First diagnosis	Tumor tissue	IHC	ALK (-)
12/2016	Blood	dd-PCR	EGFR T790M (-)
Gefitinib resistance			
10/2017	Tumor tissue	NGS	EGFR 19 del (16.69%); ALK rearrangement (22.29%); CDK4 amplification (CN = 16.67); NOTCH1 missense mutation (12.88%)
Osimertinib resistance			
	Blood	NGS	NA
07/2018	Tumor tissue	NGS	EGFR 19 del (15.85%); ALK rearrangement (27.79%); VEGFA amplification (CN = 3.95); CDK4 amplification (CN = 12.94)
Osimertinib + crizotinib resistance			
	Blood	NGS	NA
05/2019	Blood	NGS	NA
Post pemetrexed + bevacizumab treatment			

**Table 2** Patient treatment information

Treatment methods	Regimen	PFS (months)	Adverse events (Grade)
First generation EGFR TKI	Gefitinib	18.3	Rash (II)
Third generation EGFR TKI	Osimertinib	11.6	Rash (II); Skin hyperpigmentation (I)
Third generation EGFR TKI + radioactive particles implantation	Osimertinib + particles implantation	2.1	Rash (II)
Third generation EGFR TKIs + first generation ALK TKIs	Osimertinib + crizotinib	6.0	Rash (II); paronychia (II)
Third generation EGFR TKIs + second generation ALK TKIs	Osimertinib + brigatinib	NA	Interstitial pneumonia (IV)
Third generation EGFR TKIs + chemotherapy + antiangiogenic therapy	Osimertinib + pemetrexed/carboplatin + bevacizumab	4.2	Rash (II); Asymptomatic, absolute decrease in LEVF (44%)
Chemotherapy + antiangiogenic therapy	Pemetrexed/carboplatin + bevacizumab	16.8 (last CT scan: SD)	Anemia (II)

crizotinib. The patient was then administered PP regimen chemotherapy (pemetrexed plus carboplatin) combined with bevacizumab and continuation of osimertinib. After treatment with six-cycle PP regimen chemotherapy plus bevacizumab and osimertinib, the patient maintained SD. Thereafter, pemetrexed plus bevacizumab and osimertinib treatment was maintained, and the last evaluation of the disease follow-up in October 2019 indicated that the patient was still in SD. Notably, osimertinib treatment was discontinued in December 2018 as a result of the asymptomatic absolute decrease in the left ventricular ejection fraction (LEVF), which was lower than 50% (LVEF = 44%) according to the instructions of osimertinib. The patient is now in good condition and has a good quality of life. The variation trend of carcinoembryonic antigen (CEA) of the patient during the treatment is shown in Fig 3. Detailed information on the molecular detection and the treatment process is presented in Tables 1 and 2, respectively.

## Discussion

*EGFR* and *ALK* are both key driver genes contributing to the carcinogenesis of NSCLC. According to previous studies, *EGFR* mutations and *ALK* rearrangements share the same downstream signaling pathways, such as the PI3K/AKT pathway, JAK/STAT pathway and MAPK pathway, through the phosphorylation of tyrosine kinase.<sup>18–20</sup> Therefore, targeted TKIs demonstrate convincing efficacy in NSCLC patients harboring *EGFR* mutations or *ALK* rearrangements. However, the mutual downstream signaling pathways might also explain the mechanisms of TKI resistance induced by the activation of the other driven genes. Previous studies clarified the role of *EGFR* bypass pathway activation in resistance to *ALK* TKIs in vitro,<sup>21,22</sup> but whether emerging *ALK* rearrangement is involved in acquired resistance to *EGFR* TKIs, especially osimertinib,

remains unknown. In Table 3, we summarize seven cases that might indicate the novel mechanism of *ALK* rearrangement involvement in acquired resistance to osimertinib. According to NGS testing after osimertinib resistance, all these patients harbored an emerging *ALK* rearrangement. The dual TKI treatment, including *EGFR* TKI plus crizotinib or crizotinib monotherapy, had a therapeutic effect on patients. As a result, our report suggests that *ALK* rearrangement participates in acquired resistance to osimertinib, although this only occupies a small fraction.

It has been previously reported that approximately 1.3% to 1.6% of NSCLC patients harbor concomitant *EGFR* mutations and *ALK* rearrangements.<sup>23,24</sup> For patients with concomitant alterations at baseline, a previous study suggested a standard therapy based on the phosphorylation level of both *EGFR* and *ALK*. Previous research reported that only 0.13% of NSCLC patients harboring *EGFR* mutations acquired *EGFR* TKI resistance mediated by emerging *ALK* rearrangement.<sup>25</sup> Nevertheless, no studies have established a standard treatment regimen for NSCLC patients harboring *EGFR* mutations and *EGFR* TKI resistance induced by adaptive *ALK* rearrangement. Here, for the first time, our report reveals an underlying regimen for this group of patients. As listed in Table 3, the regimen of osimertinib combined with crizotinib achieved a more satisfactory efficacy than monotherapy. This result suggested that dual TKI treatment might benefit *EGFR* TKI-acquired resistant NSCLC patients induced by *ALK* rearrangement rather than *ALK* inhibitor alone (Cases No. 2, 3, 4, 5 and 7 in Table 3), which warrants further study.

The dual TKI treatment achieved a six-month PFS in the patient reported here as the third-line treatment. Through NGS examination, *VEGFA* amplification was identified in a rebiopsy sample, which might contribute to resistance to osimertinib plus crizotinib treatment. VEGF was indicated to be upregulated after *EGFR* TKI resistance,

**Table 3** Summary of osimertinib acquired resistant NSCLC patients induced by ALK rearrangement

Contributors	Case	Gender	Age	First-line treatment		Second-line treatment		Third-line treatment		Ongoing treatment	
				Molecular detection; treatment	PFS (months)	Molecular detection; treatment	PFS (months)	Molecular detection; treatment	PFS (months)	Molecular detection; treatment	PFS (months)
Zhang, <i>et al.</i> <sup>13</sup>	#1	Male	66	EGFR 19 del; gefitinib	18	EGFR T790M (+); osimertinib	14	EGFR 19del, T790M(+), C797G in cis(+), EML4-ALK; crizotinib	1	No molecular detection; pemetrexed + bevacizumab	NA <sup>#</sup>
Zhou, <i>et al.</i> <sup>14</sup>	#2	Male	42	EGFR 19 del; gefitinib	10	EGFR T790M (+); osimertinib	5	EGFR19del, T790M(-), STRN-ALK; gefitinib + crizotinib	6	—	—
Hou, <i>et al.</i>	#3	Female	60	EGFR 19 del; gefitinib	18.3	EGFR T790M (-); osimertinib	11.6	EGFR 19del, T790M (-), CDK4 Amp, EML4-ALK; osimertinib + crizotinib	6	EML4-ALK, EGFR 19del, VEGFA Amp; osimertinib* + chemotherapy + bevacizumab	Over 17 months
Schrock <i>et al.</i> <sup>15</sup>	#4	Female	70	EGFR L858R; erlotinib	12	EGFR T790M (+); afatinib	2	EGFR T790M (+); osimertinib	10	EGFR L858R, EGFR T790M (+), PLEKHA7-ALK; osimertinib + alectinib	6
Offin <i>et al.</i> <sup>16</sup>	#5	Female	65	EGFR 19 del; erlotinib	19	EGFR T790M (+); osimertinib + necitumumab	9	EGFR 19del, T790M(+), EML4-ALK; osimertinib + crizotinib	NA <sup>#</sup>	—	—
Offin <i>et al.</i> <sup>16</sup>	#6	Female	68	EGFR L858R; erlotinib	15	EGFR T790M (+); osimertinib	6	EGFR L858R, T790M (+), EML4-ALK; alectinib	NA <sup>#</sup>	—	—
Liang <i>et al.</i> <sup>17</sup>	#7	Female	46	EGFR 19 del; erlotinib	4	No molecular detection; pemetrexed + bevacizumab	0	No molecular detection; osimertinib (followed 2-cycle GP regimen chemotherapy)	2	EGFR 19 del, EGFR L747S, EML4-ALK; osimertinib + crizotinib/brigatinib*	NA <sup>#</sup>

\*Case 3: Osimertinib was discontinued as a result of its cardiac toxicity as shown in Table 2. \*Case 7 was evaluated as progressive disease after two months of osimertinib plus crizotinib treatment and the regimen was changed to osimertinib plus brigatinib. #NA, not available. Patients maintained a continuous stable disease.

and the combination treatment of anti-VEGF therapy plus TKIs has been previously reported to demonstrate a synergistic antitumor efficacy.<sup>26,27</sup> In our report, the patient achieved a satisfactory exceptional response by treatment with osimertinib plus chemotherapy and bevacizumab. In addition, as shown in Table 3, two previously reported patients (Cases 1 and 3) were administered chemotherapy plus bevacizumab, and all three achieved continuous SD even without VEGFA amplification (Case 1), which indicated that chemotherapy plus bevacizumab might serve as the optimal regimen for EGFR TKI plus ALK inhibitor treatment-resistant lung cancer patients.

The AEs or even SAEs of targeted therapy in this patient are worth noting. Regardless of the grade II AEs, including rash, paronychia and grade I skin hyperpigmentation induced by EGFR TKIs, grade IV interstitial pneumonia induced by brigatinib must be noted. From the results of the previous study, ALK TKIs demonstrated significant respiratory toxicity. A total of 5.09% and 4.29% of patients might suffer pneumonia and dyspnea/respiratory failure induced by brigatinib, respectively.<sup>2</sup> In addition, the risk of cardiac toxicity induced by long-term use of osimertinib might be involved in the evaluation, especially the asymptomatic decrease in LVEF or even congestive heart failure.

In conclusion, ALK rearrangement probably serves as a rare molecular mechanism underlying acquired resistance to osimertinib. The dual TKI treatment targeting EGFR and ALK might benefit osimertinib-resistant NSCLC patients induced by ALK rearrangement. VEGFA amplification might contribute to acquired resistance to combined osimertinib and crizotinib therapy, and chemotherapy plus bevacizumab might be an optimal treatment strategy.

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## Disclosure

The authors declare that there are no conflicts of interest.

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