

EML4-ALK Rearrangement as a Mechanism of Resistance to Osimertinib in Metastatic Lung Adenocarcinoma: A Case Report



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ABSTRACT

Osimertinib, a third-generation *EGFR* tyrosine kinase inhibitor, is the preferred frontline therapy for *EGFR*-mutant advanced NSCLC. However, despite its high initial response rates, multiple *EGFR*-independent mechanisms of resistance have been reported in patients receiving osimertinib. One such mechanism is the emergence of acquired, targetable oncogenic fusion events. It has been documented in other case reports that combination therapies can be efficacious in these scenarios. In our case report, we present a patient with *EGFR*-mutant advanced NSCLC who developed an acquired *EML4-ALK* rearrangement mediating resistance to osimertinib, which was overcome by using a combination of osimertinib with the *ALK* tyrosine kinase inhibitor alectinib.

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Keywords: *EGFR*; *ALK*; Osimertinib; Case report

Introduction

EGFR tyrosine kinase inhibitor (TKI) therapy remains the standard frontline treatment for *EGFR*-mutant advanced NSCLC. Osimertinib, a third-generation *EGFR* TKI, improved both progression-free survival and overall survival when compared with first-generation *EGFR* TKIs,¹ establishing it as the preferred frontline treatment option. Whereas osimertinib is an effective treatment for *EGFR*-mutant NSCLC, acquired resistance is expected.² The mechanisms of resistance to frontline osimertinib are heterogenous and include secondary *EGFR*

mutations, activation of alternative signaling pathways, and histologic transformation.² Here, we report a case of an acquired *ALK* rearrangement mediating resistance to osimertinib that was overcome with a combination of osimertinib and the *ALK* TKI alectinib.

Case Presentation

A 78-year-old never-smoking woman presented with symptomatic left pleural effusion. A computed tomography (CT) scan was performed and revealed a lung mass in the left upper lobe (LUL). CT-guided biopsy was performed and pathological findings revealed poorly

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differentiated adenocarcinoma. Magnetic resonance imaging (MRI) of the brain was done and did not reveal any intracranial metastases. Positron emission tomography was done, which identified multiple pleural, osseous, and liver metastases. *EGFR* mutation analysis by Cobas real-time polymerase chain reaction (Roche diagnostics) revealed a sensitizing *EGFR* exon 19 deletion.

She enrolled in a clinical trial of osimertinib in combination with dasatinib, achieved a partial response, and was on the study for 20 months (Fig. 1). Blood-based next-generation sequencing (NGS) was performed 15 months into the clinical trial when initial signs of tumor growth were noted and revealed no detectable mutations (InVisionFirst-Lung, NeoGenomics, Research Triangle Park, NC). Brain MRI performed at the time of progression revealed no intracranial metastases. Subsequently, she received second-line osimertinib in combination with an *EGFR* monoclonal antibody on a clinical trial for 4 months before progression. Blood-based NGS obtained at progression revealed a *KRAS* G12V (variant allele frequency: 0.07%) without other genomic alterations including the original *EGFR* exon 19 deletion (InVisionFirst-Lung, NeoGenomics). She received third-line carboplatin plus pemetrexed with a mixed response followed by radiation to an oligoprogressive left adrenal gland lesion, which was given 3 months into chemotherapy. After four cycles of carboplatin (area under the curve 5) and pemetrexed (400 mg/m² except for cycle two when 500 mg/m² was given) given every 3 weeks, pemetrexed (400 mg/m²) was continued as maintenance therapy.

After 9 months of chemotherapy, the patient developed confusion. A brain MRI was performed and revealed numerous metastases; CT was also done and revealed extracranial progression. Circulating tumor DNA (ctDNA) testing (Guardant360 CDx, Redwood City, CA) was done, which revealed an *EGFR* exon 19 deletion (variant allele frequency: 11.5%), *EGFR* amplification (plasma copy number: 2.5), and *TP53* mutations (Y163C, Y327*, R273H, splice site SNV). Pemetrexed was stopped and osimertinib 80 mg daily was restarted in the hopes

of improved central nervous system (CNS) control. After 1 month, a repeat brain MRI revealed a mixed response, and osimertinib was increased to 160 mg daily. Another CT was done and revealed progression of extracranial disease. Tissue NGS (DNA- and RNA-based) (Caris Life Sciences, Phoenix, AZ) from a bronchoscopic biopsy was performed, exhibiting the original *EGFR* exon 19 deletion, an acquired *EML4-ALK* gene fusion (on RNA sequencing), *NSD1* R375fs, and *TP53* mutations. Alectinib at a dose of 450 mg twice daily was added to osimertinib 80 mg daily. Alectinib 450 mg twice daily was chosen instead of the full dose (600 mg twice daily) owing to concerns about potential adverse effects of the combination. After 5 days, a brain MRI was performed and revealed a CNS response (Fig. 2). After 1 month, she was admitted with dyspnea and symptomatic anemia with a hemoglobin of 6.6 g/dL (her hemoglobin ranged from 7.3–7.9 g/dL before the admission). She was transfused and a source was not identified. A CT was performed and revealed a response in the left paramediastinal mass and pleural metastases (Fig. 3), but LUL opacities were noted. Treatment was held and she was treated with broad-spectrum antibiotics with improvement in the LUL opacities. An echocardiogram was performed, which revealed a normal ejection fraction, and coronavirus disease 2019 testing revealed negative results. On hospital day 13, she had an aspiration event in the setting of a known medical history of severe oral and pharyngeal dysmotility, leading to acute hypoxia. Subsequently, she was found to have had type II non-ST segment elevation myocardial infarction resulting in cardiogenic shock. Her clinical status declined, and she transitioned to comfort care.

Discussion

Here we describe a patient whose tumor developed an *EML4-ALK* rearrangement as a mechanism of resistance to osimertinib. It is unclear when the *EML4-ALK* rearrangement developed in this patient. Although the three ctDNA tests obtained around the time of disease

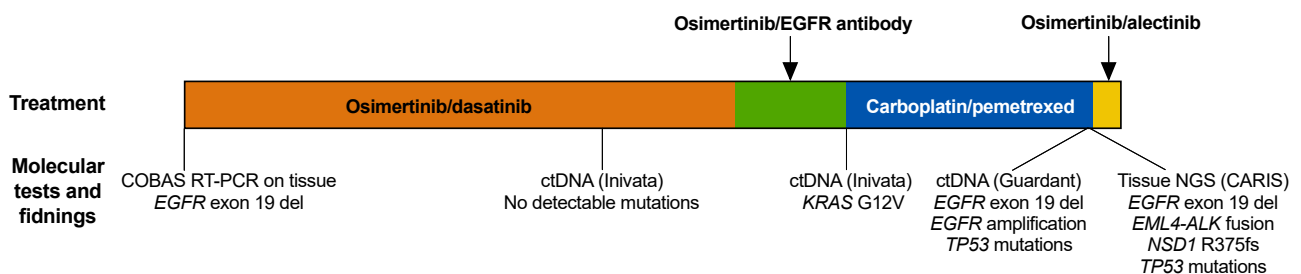


Figure 1. The timeline illustrates the treatments received by the patient for *EGFR*-mutant NSCLC and the types and findings of molecular tests. The length of the bar corresponds to the duration of each treatment. ctDNA, circulating tumor DNA; exon 19 del, exon 19 deletion; NGS, next-generation sequencing; RT-PCR, real-time polymerase chain reaction.

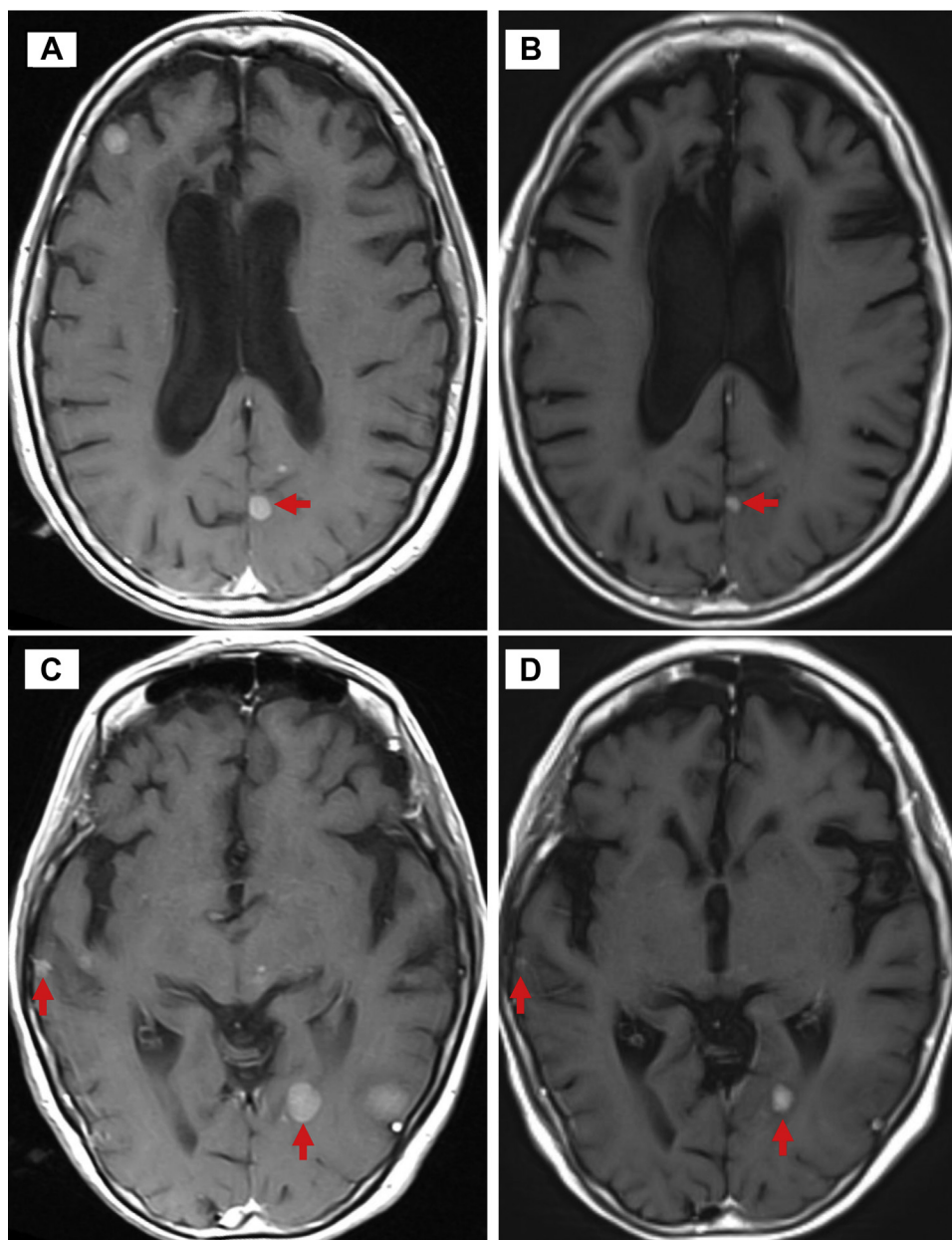


Figure 2. (A, C) The brain MRI obtained while the patient was taking osimertinib 80 mg daily revealed numerous brain lesions. Shortly after the brain MRI was obtained, osimertinib was increased to 160 mg daily. Subsequently, treatment was switched to osimertinib 80 mg daily plus alectinib 450 mg daily. (B, D) Brain MRI obtained 5 days after initiation of the combination therapy revealed shrinkage of brain lesions. MRI, magnetic resonance imaging.

progression on first-, second-, and third-line treatment did not exhibit the *EML4-ALK* rearrangement, given the moderate sensitivity of liquid biopsy, it is possible that the *EML4-ALK* rearrangement developed earlier in the course of treatment. The second ctDNA test revealed a *KRAS* G12V mutation. It is unclear whether the *KRAS* mutation represents a mechanism of resistance to osimertinib, clonal hematopoiesis of indeterminate potential, or a sequencing error.

More importantly, the combination of osimertinib and alectinib resulted in a response of the thoracic disease, suggesting potential clinical efficacy of the combination in this setting. It is difficult to determine whether the decrease in size of brain lesions was because of the higher dose osimertinib 160 mg daily or the combination of osimertinib and alectinib, as both have good CNS penetration. The combination treatment was associated with low-grade diarrhea and anemia but was otherwise

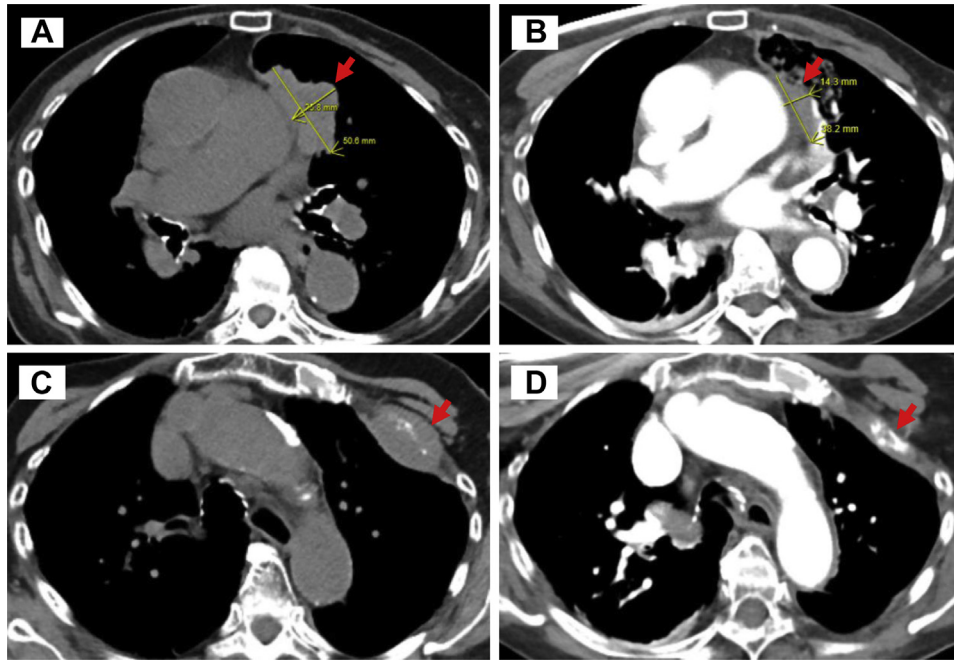


Figure 3. A lobulated soft tissue mass along the left paramediastinal pleura seen on CT (A) before initiation of alectinib and osimertinib, and is smaller on CT (C) obtained 4 weeks after initiation of the combination treatment. (B, D) Similarly, a left-sided pleural-based mass has reduced in size with treatment. CT, computed tomography.

well tolerated. It is unlikely that the treatment was the culprit for the patient's cardiac events given the normal ejection fraction at the time of admission and the temporal association between the aspiration event resulting in acute hypoxia and the development of the cardiac events.

Fusion events have been described as an EGFR-independent mechanism of acquired resistance in patients with *EGFR*-mutant NSCLC receiving osimertinib.² These oncogenic fusion events likely behave as oncogenic drivers, and reported examples include *FGFR3-TACC3*, *RET-ERC1*, *CCDC6-RET*, *NTRK1-TPM3*, *NCOA4-RET*, *GOPC-ROS1*, *AGK-BRAF*, *ESYT2-BRAF*, *SPTBN1-ALK*, *PLEKHA7-ALK*, *EML4-ALK*,^{2,3} and *STRN-ALK*.⁴

Acquired *EML4-ALK* rearrangements have been identified in patients receiving an EGFR TKI including osimertinib³⁻⁵ (Table 1). In a case report of two patients with *ALK* fusion-mediated resistance, osimertinib was combined with crizotinib or alectinib, and the combination provided benefit to both patients.³ A separate case report documented resistance to gefitinib owing to *EML4-ALK* rearrangement.⁵ The patient received gefitinib plus crizotinib, osimertinib plus crizotinib (owing to the development of *EGFR* T790M), and osimertinib plus brigatinib (owing to the development of secondary *ALK* mutations), suggesting that serial molecular testing could guide the choice of specific targeted therapy agents. In another case report, an acquired *STRN-ALK* fusion was identified as a resistance mechanism to osimertinib, and switching the treatment regimen to

gefitinib and crizotinib combination achieved a partial response.⁴ The true activity of these combinations is difficult to ascertain, acknowledging selection bias associated with case reports. Our case is unique in that *ALK* fusion occurred in the setting of the first-line use of osimertinib. Notably, the patient's *ALK* fusion was detected on tissue NGS, but not on ctDNA testing, highlighting the use of tissue-based RNA sequencing for detection of fusion events and the need for highly sensitive blood-based NGS assays.

Conclusion

Our case adds to the limited body of literature illustrating *ALK* rearrangement as a mechanism of resistance to osimertinib in advanced *EGFR*-mutant NSCLC, and the addition of *ALK* TKI therapy to osimertinib could serve as a viable therapeutic strategy in this setting. A biomarker-directed phase 2 platform study in patients with advanced NSCLC whose disease has progressed on first-line osimertinib therapy, ORCHARD (NCT03944772), will assess the combination of osimertinib and alectinib in patients with *EGFR*-mutant NSCLC whose disease progresses on frontline osimertinib and will provide more information on the safety and efficacy of the combination.

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Table 1. Reported Cases of Osimertinib Resistance Owing to ALK Fusion Treated With ALK Inhibitor Therapy

	Case 1 ³	Case 2 ³	Case 3 ⁵	Case 4 ⁴	Case 5 (Current Case Report)
Age	65	68	43	43	81
Sex	F	F	M	M	F
Smoking	Former (9-pack-year)	Never smoker	Never smoker	Current smoker	Never smoker
Organs involved	Lung, liver	Lung, brain	Lung, brain, adrenal gland, liver	Lung, liver, bone	Lung, brain, bone, liver
Systemic therapies before ALK fusion detection	Erlotinib osimertinib/necitumumab	Erlotinib osimertinib	Gefitinib	Gefitinib osimertinib	Osimertinib/dasatinib Osimertinib/EGFR monoclonal antibody Carboplatin/pemetrexed
ALK fusion detected	<i>EML4-ALK</i>	<i>EML4-ALK</i>	<i>EML4-ALK</i>	<i>STRN-ALK</i>	<i>EML4-ALK</i>
Other genomic alterations	<i>EGFR</i> exon 19 deletion <i>EGFR</i> T790M	<i>EGFR</i> L858R <i>EGFR</i> T790M	<i>EGFR</i> exon 19 deletion	<i>EGFR</i> exon 19 deletion	<i>EGFR</i> exon 19 deletion <i>NSD1</i> R375fs <i>TP53</i> mutations
Treatment regimen	Osimertinib 80 mg QD/crizotinib 200 mg twice daily	Osimertinib 80 mg QD/alectinib 300 mg twice daily	GC OC OB	GC	Osimertinib 80 mg QD/alectinib 450 mg twice daily
Duration of treatment	6 mo ^a	1 mo ^a	5 mo with GC 5 mo with OC 16 mo with OB	6 mo ^a	1 mo
Tumor response	Stable disease	Stable disease ^b	Partial response	Partial response	Partial response
Adverse events	No reported toxicities	No reported toxicities	Rash with GC, OC Rash and diarrhea with OB	Rash	Anemia, diarrhea

^aOngoing treatment at the time of writing.

^bA –25% reduction by RECIST version 1.1.

F, female; GC, Gefitinib/crizotinib; M, male; OB, osimertinib/brigatinib; OC, osimertinib/crizotinib; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.1

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