CASE REPORT

# Novel *MRPL13-ALK* and *PPP1CB-ALK* Double Fusion As a Potential Mechanism of Acquired Resistance to First-Line Osimertinib in *EGFR*-Mutant High-Grade Neuroendocrine Tumor of the Lung

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## Introduction

Osimertinib, a third-generation EGFR tyrosine kinase inhibitor, is approved for the treatment of NSCLC with *EGFR*-activating mutations and *EGFR* T790M mutations. However, acquired resistance eventually develops. Current reports have described different resistance mechanisms emerging in first-line osimertinib treatment, including pathologic trans-acquired *EGFR* mutations and other gene mutations.[1] *ALK* fusion, as an acquired resistance mechanism to osimertinib, has been reported in individual cases.[2,3] Here, we report *MRPL13-ALK* and *PPP1CB-ALK* double fusions detected in a patient with lung cancer harboring *EGFR* L858R, who developed resistance to first-line osimertinib.

## Case Report

An 80-year-old man presented to our hospital for systemic bone pain. Magnetic resonance imaging of the thoracolumbar spine was performed, which revealed multiple destructions of the thoracolumbar and lumbosacral vertebrae; thus, a metastatic tumor was considered. Moreover, an enhanced computed tomography (CT) scan of the chest revealed lung cancer in the right upper lobe, and an enhanced CT scan of the whole abdomen exhibited multiple metastatic tumors in the liver; a CT scan of the brain exhibited possible multiple metastatic tumors in the brain. The patient refused biopsy, so the pathologic classification was uncertain. *EGFR* L858R (allele frequency [AF] 92.04%) was identified in plasma circulating tumor DNA by next-generation sequencing 10-gene panel profiling. As brain metastasis was considered, osimertinib (80 mg once a day) was administered. After 2 months, a CT of the chest revealed that lesions in the upper lobe of the right lung and right hilar lymph node metastasis had considerable shrunk.

However, after 7 months, enlargement of the lung lesions was detected, and the disease progressed. Dynamic imaging by CT scan at different stages of treatment is illustrated in Figure 1*A–C*. The results of histopathologic stains from the liver puncture biopsy were the following: cytokeratin (CK)-positive, CK7-positive, CK8/18-positive, hepatocyte paraffin 1–negative, CK19-positive, thyroid transcription factor-1–positive, Napsin A–negative, P40-negative, Syn-positive, CD56-negative, and Ki-67 positive index 70%;—this established the diagnosis of high-grade neuroendocrine carcinoma of lung origin (Fig. 2*A–G*). Owing to the limited amount of puncture biopsy sample, plasma

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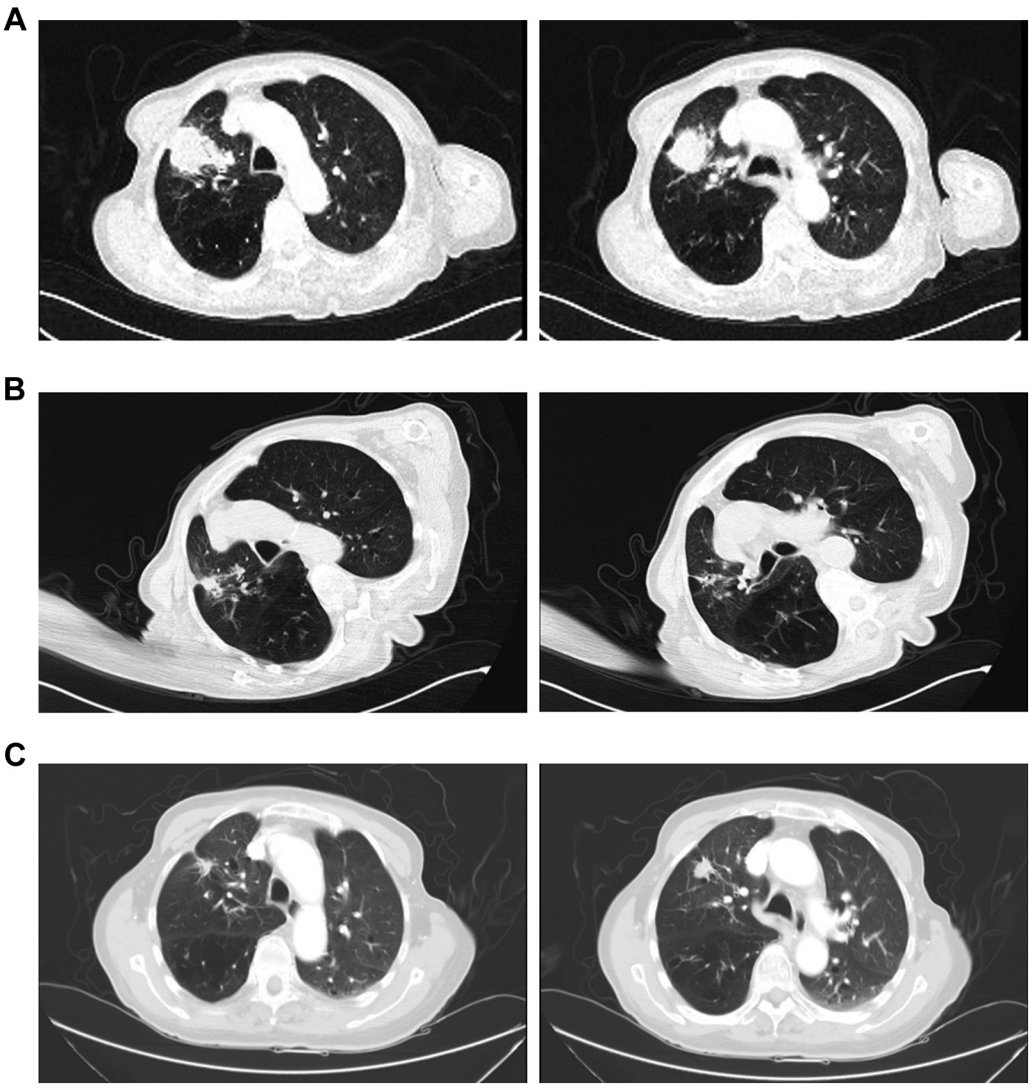


**Figure 1.** CT scan of the chest. CT scan with dynamic imaging of the patient at different stages of treatment. *(A)* Before osimertinib treatment. *(B)* After 2 months of osimertinib treatment. *(C)* After 7 months of osimertinib treatment. CT, Computed tomography.

circulating tumor DNA was again tested by next-generation sequencing (Simcere Diagnostics 69-gene panel), and the following mutations were detected: *EGFR* L858R (AF 86.75%), amplification of *EGFR* (5.28-fold) and *RET* (9.79-fold), copy number loss of *CDKN2A* (0.49-fold), and *MRPL13-ALK* (AF 5.73%) and *PPP1CB-ALK* (AF 12.80%) double fusion (Fig. 3*A–D*). The 69-gene panel is declared on the web link (http://www.simceredx.com/sixNight). The mutation profile of the patient is described in Table 1. Osimertinib (80 mg once a day) and crizotinib (250 mg twice a day) were then administered; however, owing to the severe adverse effects like asthenia and anorexia, osimertinib was stopped. Unfortunately, the patient died after 1 month. Informed consent was obtained from the family for the publication of this case.

## Discussion

To our knowledge, this is the first report to state that that *EGFR* L858R and *ALK* double fusion were found in a high-grade neuroendocrine tumor of the lung. The rare *ALK* double fusion may be the potential reason for

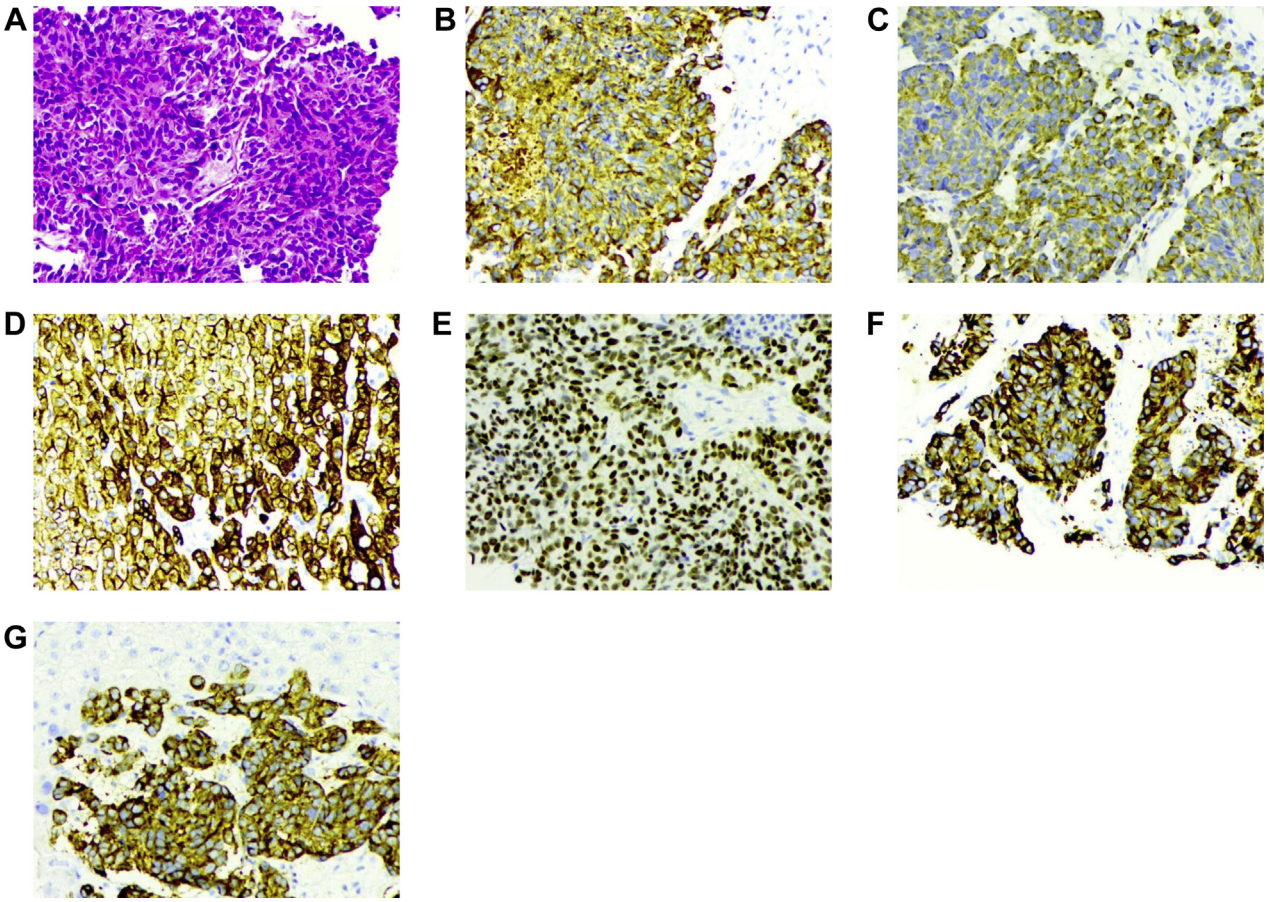


**Figure 2.** Histopathologic stains from the liver puncture biopsy. *(A)* hematoxylin and eosin; *(B)* CK; (*C*), CK7; *(D)* CK8/18; *(E)* thyroid transcription factor-1; *(F)* CK19; (*G*), synaptophysin (×200). CK, cytokeratin.

osimertinib resistance. Serine/threonine-*PPP1CB (PPP1CB-ALK)* fusion has already been reported in individual cases in glioma of infancy and leiomyosarcoma, but none in lung cancer.[4] *MRPL13-ALK* is a novel fusion, which has never been reported yet. Both fusions retain the complete kinase domain of *ALK*. Furthermore, the resistance to EGFR tyrosine kinase inhibitors was inevitable, with receptor tyrosine kinase (RTK) fusions reported as the emerging rare mechanism. RTK fusions are the actionable resistance, which can be suppressed by dual blockade of the RTK fusion and *EGFR* mutation.[5] Unfortunately, because of the patient's advanced age, he was unable to withstand the adverse effects of osimertinib combined with crizotinib.

One of the limitations of the study is that the patient refused a lung biopsy, which caused histopathologic uncertainty. A previous study has reported that de novo high-grade neuroendocrine carcinomas of the lung harboring *EGFR* mutations lack response to EGFR inhibitors,[6], and given that progression-free survival of osimertinib lasts for 7 months, a mixed tumor or adenocarcinoma may be considered at the beginning. In conclusion, transformation to high-grade neuroendocrine carcinoma of the lung and double *ALK* fusions may be coexisting mechanisms of acquired resistance to osimertinib in this patient. It was also suggested that the amplification of *RET* could be a potential resistance mechanism for osimertinib.

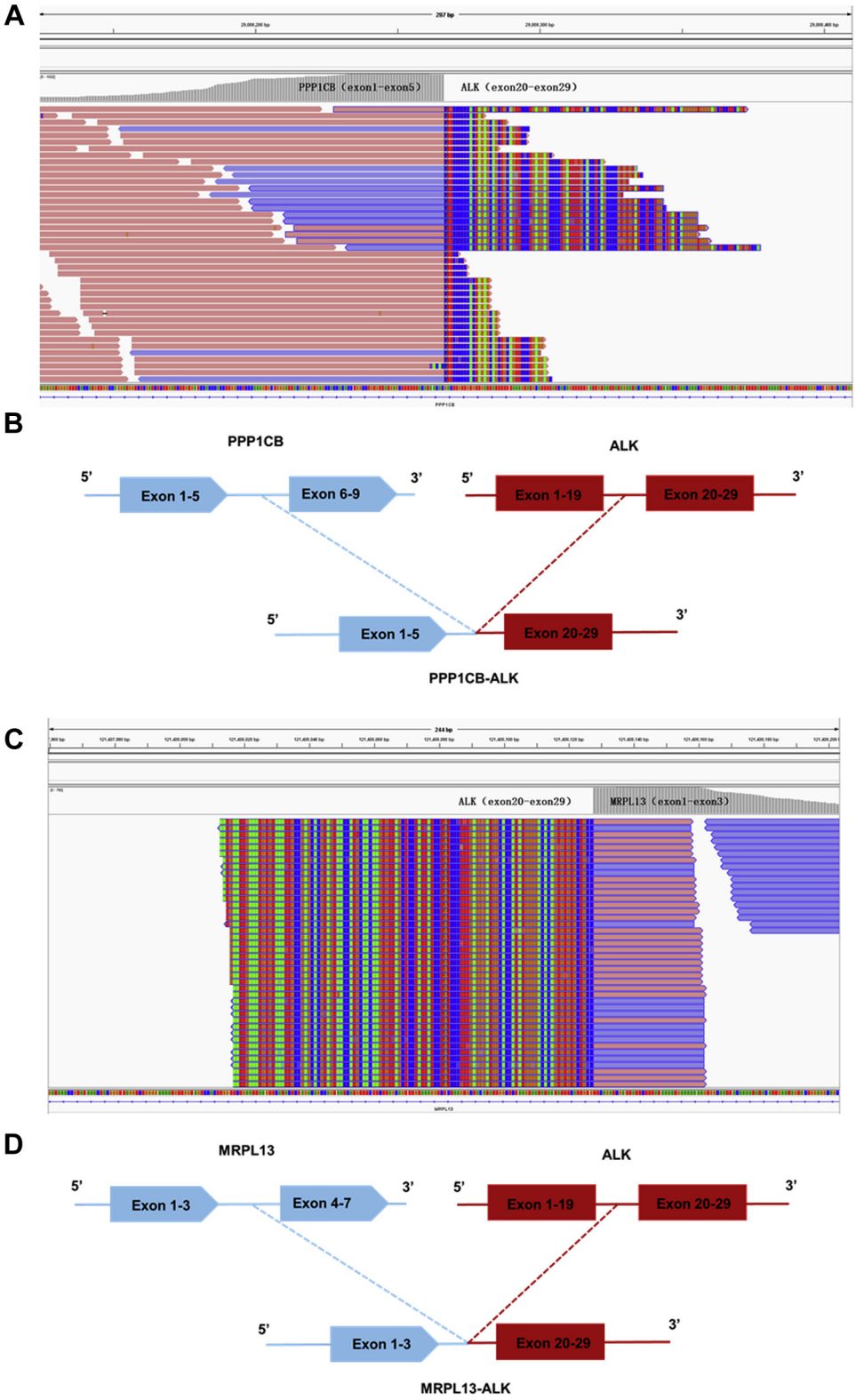


**Figure 3.** The findings of NGS. The Integrative Genomics Viewer screenshot of *(A) PPP1CB-ALK* and *(C) MRPL13-ALK* fusion are displayed. The schematic diagram represents the *(B) PPP1CB-ALK* and *(D) MRPL13-ALK* fusion protein domain structure. ALK, anaplastic lymphoma kinase; NGS, next-generation sequencing.

**Table 1.** NGS Findings of the Plasma ctDNA

| Time of Sampling | Gene | Mutation Style | Frequency (%) or Copy Number |
|---|---|---|---|
| Before osimertinib (10-gene panel) | *EGFR* | p. L858R | 92.04% |
| After resistance to osimertinib (69-gene panel) | *EGFR* | p. L858R | 86.75% |
| | *MRPL13-ALK* | Fusion | 5.73% |
| | *PPP1CB-ALK* | Fusion | 12.80% |
| | *EGFR* | Amplification | 5.28 |
| | *RET* | Amplification | 9.79 |
| | *CDKNA* | Copy number loss | 0.49 |

ctDNA, circulating tumor DNA; NGS, next-generation sequencing.

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