Response to Crizotinib Re-administration After Progression on Lorlatinib in a Patient With ALK-rearranged Non–small-cell Lung Cancer

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Clinical Practice Points

- Non–small-cell lung cancer (NSCLC) with anaplastic lymphoma kinase (ALK) gene rearrangement is sensitive to ALK-tyrosine kinase inhibitors (TKIs). First- and second-generation ALK-TKIs are effective for ALK-rearranged NSCLC; however, resistance to ALK-TKI treatment arises.
- Lorlatinib is a third-generation ALK-TKI and shows clinical activity for patients who have undergone previous ALK-TKI treatment. Although the response to lorlatinib was observed, eventually, acquired resistance to lorlatinib occurs, and post-lorlatinib treatment has not been determined.
- We present a case of ALK-rearranged NSCLC in a patient who responded to crizotinib re-administration after progression on lorlatinib. Although tumor heterogeneity, exposure of several therapies, and the limited small tissue samples can impact measurements of MET expression, phospho-MET was up-regulated focally in post-lorlatinib tissue compared with pre-lorlatinib tissue, suggesting that resistance to lorlatinib and the subsequent response to re-administration of crizotinib after progression on lorlatinib might be partly related to MET pathway activation.
- Re-administration of crizotinib following lorlatinib might enhance the better prognosis of patients with ALK-rearranged NSCLC.

Introduction

Chromosomal rearrangements of the anaplastic lymphoma kinase (ALK) gene are detected in approximately 5% of non–small-cell lung cancers (NSCLCs) and function as oncogenic driver genes.1 First- and second-generation ALK-tyrosine kinase inhibitors (TKIs) were developed and showed clinical response for ALK-rearranged NSCLC.2-4 However, resistance to those ALK-TKIs almost develops, resulting in clinical relapse.5,6 Lorlatinib is a third-generation ALK-TKI and has demonstrated significant antitumor activity against ALK-rearranged NSCLC with previous ALK-TKI resistance.7,8 Although lorlatinib response was observed, relapse on lorlatinib ultimately developed.9-11 Mechanisms of lorlatinib resistance were reported9-11 but remained unknown. Moreover, post-lorlatinib treatment has not been determined.
Here, we present a case of a patient who prolonged survival by sequential ALK-TKI treatment and responded to crizotinib re-administration after progression on lorlatinib.

**Case Report**

A 40-year-old woman was diagnosed with primary adenocarcinoma of the lung (cT1bN2M1c, cStage IVB, 8th edition of the International Union against Cancer/American Joint Committee on Cancer TNM staging system) in October 2012. Figure 1 shows a summary of the treatment. A magnetic resonance image of her brain showed multiple metastases, and subsequently, a large tumor in the right temporal lobe was resected. Adenocarcinoma with ALK rearrangement was detected in the resected brain tumor. After receiving whole brain radiotherapy, she underwent first-line therapy with crizotinib (250 mg twice daily) in December 2012 with a partial response (PR) for 8 months. After disease progression was observed in August 2013, she was treated with chemotherapy containing carboplatin (AUC = 6) and pemetrexed (500 mg/m²) for 6 cycles,

![Figure 1](image)

**Figure 1 Summary of Patient Treatments**

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Summary of treatment

<table>
<thead>
<tr>
<th>Brain tumor resection</th>
<th>First-line crizotinib before lorlatinib</th>
<th>crizotinib re-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole brain radiotherapy</td>
<td>carboplatin/pemetrexed</td>
<td>lorlatinib</td>
</tr>
<tr>
<td>Pre-lorlatinib biopsy</td>
<td>docetaxel</td>
<td>Post-lorlatinib biopsy</td>
</tr>
</tbody>
</table>

| December 2012 | August 2013 | December 2014 | October 2015 | June 2016 | October 2017 |
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![Figure 2](image)


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A. **Before lorlatinib**

- June 2016
- July 2016
- August 2016
- February 2017

**Response to lorlatinib**

- March 2017
- June 2017
- October 2017
- October 2017

**Resistance to lorlatinib**

- April 2018
- December 2018

B. **Before crizotinib re-administration**

- June 2017
- October 2017

**Response to crizotinib re-administration**

- April 2018
- December 2018

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followed by maintenance pemetrexed for 11 cycles with PR. Sixteen months later, she experienced disease progression and was administered alectinib (600 mg once daily) in December 2014 with PR, which lasted 10 months. After the failure of alectinib and subsequent docetaxel treatment failed, crizotinib was administered. However, she experienced further disease progression with both sides of her supraclavicular lymph nodes, multiple mediastinal lymph nodes, and right adrenal gland and new brain metastasis in the right frontal lobe (Figure 2A). She enrolled in a phase II clinical trial of lorlatinib in June 2016, and metastases in the #2R lymph node and right adrenal gland were evaluated as target lesions for Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. She experienced significant response in all the metastatic lesions that lasted 9 months. When isolated progression occurred in #2R lymph node in March 2017, the sum of the diameters had increased 25% from their nadir, and progressive disease was confirmed.

Because treatment of beyond progressive disease was allowed in this clinical trial, but not local therapy, and the growth of #2R lymph node metastasis was slow without accompanying disease progression of the other metastases, lorlatinib treatment was continued for another 7 months (Figure 2A). Although local therapy might be proposed after discontinuation of lorlatinib treatment, the potential

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Brain Tumor Resection</th>
<th>Pre-lorlatinib Biopsy</th>
<th>Post-lorlatinib Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>Fusion</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
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<tr>
<td>PIK3CA</td>
<td>SNV</td>
<td>p.Glu542Lys 7.3%</td>
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<tr>
<td>BRAF</td>
<td>SNV</td>
<td>p.Asp594Asn 3.7%</td>
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<tr>
<td>ERBB2</td>
<td>SNV</td>
<td>p.Ser310Phs 5.0%</td>
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<td>—</td>
</tr>
<tr>
<td>ALK</td>
<td>SNV</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ALK</td>
<td>CNV</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>MET</td>
<td>CNV</td>
<td>2.22</td>
<td>1.50&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.85/2.61&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: ALK = anaplastic lymphoma kinase; CNV = copy number variation; SNV = single nucleotide variant.

<sup>a</sup> SCRAM-JAPAN (Cancer Genome Screening Project for Individualized Medicine in Japan) data.

<sup>b</sup>Data with low quality control.
regrowth of the multiple systemic metastases was a concern during the local therapy. Then we chose a systemic therapy. Cytotoxic chemotherapy was one of the important therapeutic options; however, the patient did not want to undergo chemotherapy because she experienced severe appetite loss and fatigue during the previous chemotherapy. Moreover, the previous chemotherapy was delayed owing to prolonged myelosuppression. Because only manageable mild diarrhea was observed during the previous crizotinib treatment and there was a report about crizotinib re-administration after lorlatinib resistance,10 crizotinib administration was resumed in October 2017. Serial computed tomography showed significant radiologic response in #2R lymph node (Figure 2B). She is currently at 14 months of crizotinib administration with PR and without signs of disease progression.

To identify the mechanisms of lorlatinib resistance and response to crizotinib re-administration after progression on lorlatinib, we repeated the biopsy of #2R lymph nodes in pre-lorlatinib and post-lorlatinib treatment (Figure 1). Morphology was not changed (Figure 3A), and ALK rearrangement was detected in immunohistochemistry in brain tumor resection samples before first-line crizotinib treatment, pre-lorlatinib, and post-lorlatinib samples. MET was highly expressed in all samples (Figure 3A). Phospho-MET was observed in brain tumor resection before first-line crizotinib. In #2R lymph nodes, phospho-MET was not found in pre-lorlatinib samples and was up-regulated focally in post-lorlatinib samples (Figure 3A). We performed next generation sequencing (NGS) on formalin-fixed paraffin-embedded samples from the brain tumor resection, pre-lorlatinib samples, and post-lorlatinib samples using Oncomine Dx Target Test (Table 1), in which enchinoderm resection, pre-lorlatinib samples, and post-lorlatinib samples using Oncomine comprehensive assay ver. 3 showed no sensitive mutations to crizotinib, but G1269A, which was predicted to be sensitive to lorlatinib and resistant to crizotinib based on IC50 values.6 Yoda et al reported that one of the mechanisms of lorlatinib resistance was caused by multiple ALK compound mutations, but not single mutations, which were selected during the sequential ALK-TKI treatment.7 They also reported that ALK G1269A was detected as single mutation in one case in a post-lorlatinib sample. However, ALK in cell lines established from this case was inhibited by lorlatinib, indicating that ALK-independent mechanisms were related to the lorlatinib resistance. Based on these reports, G1269A single mutation in our post-lorlatinib sample is not likely to induce lorlatinib resistance and crizotinib resensitization.

Low ALK CNG was observed in post-lorlatinib samples. Because high levels of ALK gene amplification or ALK CNG were reported as a resistance mechanism against crizotinib,14,15 and ALK amplification has not been reported in the resistance of lorlatinib, low ALK CNG in our case is not the main resistant mechanism against lorlatinib; however, it might contribute to induction of lorlatinib resistance in part.

MET activation might explain the resistance to lorlatinib and response to re-administration of crizotinib after progression on lorlatinib. Crizotinib inhibits MET, ROS1, and RON kinase activity and has weak inhibitory activity against other receptor tyrosine kinases.20-22 In our case, the mechanism of resistance to lorlatinib might be related to the induction of a bypass pathway, including MET, which can be inhibited by crizotinib.

Although indication of the resistance mechanisms of lorlatinib and resensitization of crizotinib after relapse on lorlatinib warrants further studies, our case suggests that re-administration of crizotinib following lorlatinib might enhance the better prognosis of patients with ALK-rearranged NSCLC.
Disclosure

The authors have stated that they have no conflicts of interest.

References