Abstract #352 57P: Acquired Concurrent EGFR T790M and Driver Gene resistance from EGFR-TKIs hampered osimertinib efficacy in Advanced Lung Adenocarcinoma

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Background

• The resistance mechanisms to EGFR-TKIs are inevitable and heterogeneous.
• Secondary T790M mutation was the most frequent acquired resistance mechanism to early-generation EGFR-TKIs and osimertinib was the standard second-line therapy.
• Driver gene alterations like ALK, ROS1, and RET were increasingly observed in resistance mechanisms.
• Additionally, driver gene resistance overlaps with EGFR T790M accounted for 4%-8% in patients resistant to prior early-generation EGFR-TKIs. However, no good consensus was formulated in such circumstances.

Methods

• We searched the lung cancer database of the Second Xiangya Hospital and screened for EGFR-mutant NSCLC patients who developed secondary T790M positive after early-generation EGFR-TKI.
• Further, Patients who had acquired T790M cooperating with driver gene resistance, such as alterations of ALK, ROS1, MET, HER2, RET, KRAS were included.
• Meanwhile, extensive literature reviews in PubMed were conducted to identify characteristics of concurrent EGFR T790M and driver gene resistance. The efficacy and prognosis were evaluated based on the RECIST v1.1.

Results

• 216 EGFR-mutant NSCLC patients who received early-generation EGFR-TKI were identified in the database and 105 patients had detailed gene testing after disease progression.
• 57.1% (65/105) patients developed into secondary EGFR T790M mutation and 61.5% (40/65) patients were identified by the next-generation sequencing.
• Two (2.0%) patients cooperated with MET amplification and ALK fusion. One patient had acquired EGFR T790M, STRN-ALK fusion, and EGFR amplification after gefitinib progression and was strongly resistant to osimertinib with MET amplification.
• The other patient developed to acquire EGFR T790M and MET amplification post-docetaxel and acquired CDCDC6-RET fusion after 4-month osimertinib treatment.
• Five published cases of co-existence of EGFR T790M and HER2 amplification or KRAS G12X were identified (Table 1).
• The presented 7 cases showed median progression-free survival (PFS) of 3 months and did not benefit from osimertinib monotherapy.

Conclusions

• Patients with concurrent alterations of EGFR T790M and driver gene resistance had poor outcomes from osimertinib.
• Additionally, subsequent new bypass activations were possible resistance mechanisms to second-line osimertinib.
• The T790M accompanying driver gene resistance will be a new subtype after EGFR-TKIs progression and needs effective treatment options.

Table 1. Clinicopathological characteristics of concurrent EGFR-T790M and driver gene resistance NSCLC patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Smoking history</th>
<th>Pathology</th>
<th>staging</th>
<th>Baseline driver gene</th>
<th>First-line therapy</th>
<th>Resistance mechanisms</th>
<th>Second-line therapy</th>
<th>Best response</th>
<th>PFS (mo)</th>
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<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>M</td>
<td>Never</td>
<td>ADC</td>
<td>IV</td>
<td>EGFR L858R, HER2 amp</td>
<td>Gefitinib</td>
<td>EGFR T790M, HER2</td>
<td>Osimertinib and trastuzumab</td>
<td>SD</td>
<td>4</td>
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<tr>
<td>2</td>
<td>57</td>
<td>M</td>
<td>Never</td>
<td>ADC</td>
<td>IV</td>
<td>EGFR L858R</td>
<td>Icotinib</td>
<td>EGFR T790M, HER2</td>
<td>Osimertinib</td>
<td>PD</td>
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</tr>
<tr>
<td>3</td>
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<td>M</td>
<td>Never</td>
<td>ADC</td>
<td>IV</td>
<td>EGFR L858R, HER2 amp</td>
<td>Gefitinib</td>
<td>V77L mutation, HER2 amp</td>
<td>Osimertinib</td>
<td>SD</td>
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<tr>
<td>4</td>
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<td>ADC</td>
<td>IV</td>
<td>EGFR L858R</td>
<td>Gefitinib</td>
<td>EGFR T790M, KRAS G12V</td>
<td>Chemotherapy</td>
<td>PD</td>
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<td>ADC</td>
<td>IV</td>
<td>EGFR 19del</td>
<td>Gefitinib</td>
<td>EGFR T790M, KRAS G12V</td>
<td>Osimertinib</td>
<td>PD</td>
<td>3</td>
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<tr>
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<td>76</td>
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<td>IV</td>
<td>EGFR 19del</td>
<td>Gefitinib</td>
<td>EGFR T790M, MET, MET</td>
<td>Osimertinib</td>
<td>SD</td>
<td>3</td>
</tr>
</tbody>
</table>

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