Induction of Resistances to Crizotinib in NSCLC Patient-Derived Xenograft Models Upon Treatment

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Abstract

We recently established a large collection of lung cancer patient-derived xenografts (~350 PDXs), and we screened some of them for the presence of ALK gene fusion (by RT-PCR and RNaseq). The ALK fusion-positive models were tested for sensitivity to crizotinib. We kept these PDXs under crizotinib treatment pressure in vivo in order to induce acquired resistance, as seen in the clinic. The resistant models were genomically profiled to identify the changes that could potentially be responsible for the emergence of crizotinib resistance.

We identified the NSCLC-ADC LU1656 model as a candidate for our study since it displays EML4-ALK fusion and elevated ALK expression (type-1). This model initially responds well to crizotinib treatment. Eventually leads to the development of resistance in the LU1656 model; the molecular mechanism underlying the observed resistance is still to be identified.

Table 1: Summary of patient and PDX model information

<table>
<thead>
<tr>
<th>ID</th>
<th>Ethnicity</th>
<th>Gender</th>
<th>Hospital pathology</th>
<th>Pathology QC</th>
</tr>
</thead>
<tbody>
<tr>
<td>LU1656</td>
<td>Asian</td>
<td>Female</td>
<td>NSCLC-Carcinosarcoma</td>
<td>Moderately differentiated squamous cell carcinoma (PS).</td>
</tr>
<tr>
<td>LU2445</td>
<td>Asian</td>
<td>Female</td>
<td>Carcinosarcoma</td>
<td>Poorly differentiated tumor; giant cells; spindle cells and clear cells observed.</td>
</tr>
</tbody>
</table>

Results

Figure 1: The LU1656 NSCLC PDX model is sensitive to crizotinib but not to MET inhibitors

Figure 2: Generation of crizotinib resistant model LU2445 by repetitive exposure of LU1656 sensitive model

Figure 3: H&E Stain of LU1656

Figure 4: H&E Stain of LU2445

Figure 5: EML4-ALK fusion in LU1656

Figure 6: EML4-ALK fusion in LU2445

Figure 7: ALK, MET and EGFR expression in LU1656 vs. LU2445

Figure 8. EML4-ALK fusion in LU1656

Conclusions

1. The NSCLC PDX model LU1656 carries a EML4-ALK fusion;
2. LU1656 is sensitive to crizotinib;
3. LU1656 has no c-MET activation, mutation or amplification, and is insensitive to c-MET inhibitors;
4. LU1656 partially responds to EGFR inhibitors (Erlotinib®);
5. Prolonged exposure to crizotinib in vivo causes development of resistance in the LU1656 model;
6. No further ALK mutations or change in the level of expression were identified in the resistant model. The molecular mechanism underlying the observed resistance is still to be identified.

References