Introduction

- Osimertinib, a third generation EGFR inhibitor, is a front-line therapy for EGFR mutated non-small lung cancer (NSCLC). The long-term effectiveness of osimertinib is limited by acquired resistance.
- Clinically identified resistance mechanisms include EGFR-dependent mechanisms such as mutations on EGFR that preclude drug binding (e.g., EGFR C797S), and EGFR-independent activation of the MAPK pathway (e.g., activation of alternate RTKs)1. It has also been noted that frequently a tumor from a single patient harbors more than one resistance mechanism (e.g., RTK bypass), IACS 13909 suppresses proliferation of NSCLC PDx harboring EGFR on-target resistance mutation ex vivo

IACS-13909 suppresses proliferation of NSCLC PDx harboring EGFR on-target resistance mutation ex vivo

PDX LD-0002-200717 (EGFR \textit{Ex}{19del} T790M \textit{C787S})

<table>
<thead>
<tr>
<th>Osimertinib</th>
<th>IACS-13909</th>
<th>OsiR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC50 (nM)</td>
<td>IC50 (nM)</td>
<td>IC50 (nM)</td>
</tr>
<tr>
<td>139000</td>
<td>165000</td>
<td>70000</td>
</tr>
<tr>
<td>139003</td>
<td>178000</td>
<td>90000</td>
</tr>
</tbody>
</table>

**RTK-driven cell lines are sensitive to SHP2 inhibition by IACS-13909.**

- Src homology 2-domain-containing phosphatase (SHP2) is a phosphatase that mediates the signaling of multiple RTKs and is required for full activation of the MAPK pathway1,2.
- Since SHP2 is required for full activation of the MAPK pathway downstream of multiple RTKs, we hypothesize that a SHP2 inhibitor may target both EGFR-dependent and EGFR-independent mechanisms for osimertinib resistance in EGFRmut NSCLC.

**IACS-13909 is a potent allosteric inhibitor of SHP2.**

IACS-13909

- In enzymatic assays, IACS-13909 suppresses activity of the full-length SHP2, but not the truncated phosphatase domain.
- In vitro anti-proliferative effect of IACS-13909 across a panel of human cancer cell lines

**In vitro anti-proliferative effect of IACS-13909 across a panel of human cancer cell lines**

<table>
<thead>
<tr>
<th>RTK-altered/added cell lines</th>
<th>In vitro assay</th>
<th>IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akt</td>
<td>13909</td>
<td>7000</td>
</tr>
<tr>
<td>MAPK</td>
<td>13909</td>
<td>90000</td>
</tr>
</tbody>
</table>

**IACS-13909 potently suppresses the proliferation of cell lines driven by SHP2-driven MAPK signaling.**

- In vivo anti-tumor efficacy of IACS-13909+osimertinib in osimertinib-sensitive and -resistant models

**In vivo anti-tumor efficacy of IACS-13909+osimertinib in osimertinib-sensitive and -resistant models**

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Clevactin</th>
<th>IACS-13909+osimertinib</th>
<th>OsiR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC4006</td>
<td>25%</td>
<td>90%</td>
<td>100%</td>
</tr>
<tr>
<td>HCC4006-OsIR</td>
<td>10%</td>
<td>90%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**SHP2-ER tumors that progress on osimertinib treatment remain sensitive to combination treatment**

- MD Anderson and Navire pharma have developed IACS-13909, a potent and selective allosteric inhibitor of SHP2.
- IACS-13909 potently suppresses the proliferation of cell lines driven by a broad range of RTKs.
- IACS-13909 inhibits both EGFR-dependent and EGFR-independent resistance mechanisms towards osimertinib.
- Navigen is currently taking its clinical candidate SHP2 inhibitor through IND-enabling studies.

**Summary**

- MD Anderson and Navire Pharma have developed IACS-13909, a potent and selective allosteric inhibitor of SHP2.
- IACS-13909 potently suppresses the proliferation of cell lines driven by a broad range of RTKs.
- IACS-13909 inhibits both EGFR-dependent and EGFR-independent resistance mechanisms towards osimertinib.
- Navigen is currently taking its clinical candidate SHP2 inhibitor through IND-enabling studies.

**References**


A copy of the poster can be found at: www.navirepharma.com