ERAS-007 is a selective ERK1/2 inhibitor with preclinical activity across RAS/MAPK pathway-driven CRC models

Abstract

Colorectal cancer (CRC) remains an unmet medical need where more than 90% of patients harbor RAS mutations or are resistant to anti-EGFR therapy. Additional treatment options for patients with RASmut CRC are a priority. ERAS-007 is a selective ERK1/2 inhibitor targeting the terminal node of the RAS/MAPK signaling pathway, downstream of RAF and BRAF. Preclinical activity in cell-based assays as well as the superior combination efficacy relative to other ERK inhibitors determined in combination with MEK inhibitors in preclinical models. ERAS-007 demonstrates promising preclinical activity across a wide range of RAS/MAPK pathway-driven CRC models both as a monotherapy and in combination that supports further exploration in the clinic.

Introduction

Key biological driver of CRC cell cycle progression is activation of the RAS/MAPK pathway, which includes mutations in RAS, BRAF and MEK, or loss of p16 function (Montague, 2009). ERK is the most distal node of the RAS/MAPK signaling pathway downstream of BRAF and RAF. Preclinical models in BRAFmut CRC cells expressing emergence resistance mutations in the RAS/MAPK pathway suggest that the triple blockade of RAF, ERK and MEK would be the most effective in reducing tumor volume and preventing the emergence of resistance clones (Hazar Rethinam, 2018). Moreover, ERK activity and the cell cycle machinery, ERAS-007 and palbociclib demonstrate combination activity in vitro across multiple RASmut CRC models.

Results

Figure 2. ERAS-007 exhibits both long biophysical target residence time and sustained RAS/MAPK pathway inhibition relative to other ERK and MEK inhibitors

<table>
<thead>
<tr>
<th>Compound</th>
<th>ERK2 residence time (τ) (min)</th>
<th>pRSK IC50 in RKO</th>
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<tbody>
<tr>
<td>ERAS-007</td>
<td>550</td>
<td>7.0</td>
</tr>
<tr>
<td>ulixertinib</td>
<td>16</td>
<td>116.6</td>
</tr>
<tr>
<td>trametinib</td>
<td>&lt;0.03</td>
<td>1.3</td>
</tr>
<tr>
<td>binimetinib</td>
<td>&lt;0.03</td>
<td>8.3</td>
</tr>
</tbody>
</table>

Figure 3. ERAS-007 inhibits cellular proliferation and exhibits combination activity with encorafenib in BRAFmut CRC cell lines

ERAS-007 exhibits monotherapy and combination activity in BRAFmut CRC cell lines in 3D cell viability assays. (A) ERAS-007 inhibited cellular proliferation and viability in BRAFmut CRC cell line. (B) ERAS-007 and encorafenib exhibit synergy in the RKO cell line.

Figure 4. ERAS-007 in combination with encorafenib ± cetuximab (EC) demonstrates efficacy in BRAFmut CRC CDX and PDX models

Figure 5. ERAS-007 and palbociclib demonstrate combination benefit in vitro across multiple RASmut CRC models

Conclusions

- ERAS-007 is a potent ERK1/2 small molecule inhibitor with durable target residence time and promotes sustained RAS/MAPK pathway inhibition
- ERAS-007 demonstrates promising preclinical activity across a wide range of RAS/MAPK pathway-driven CRC models both as a monotherapy and in combinations that support further exploration in the clinic.
- Accordingly, ERAS-007 in combination with encorafenib + cetuximab or palbociclib in BRAFmut CRC or KRASmut CRC, respectively, is currently being evaluated in the HERKULES-3 phase 1b/2 clinical trial.