Preclinical characterization of LY3537982, a novel, highly selective and potent KRAS-G12C inhibitor

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**Background**

- G12C mutations in KRAS are recurrent oncogenic events in patients with NSCLC, CRC, and other cancer types.  
- While adagrasib and sotorasib have demonstrated activity in these patients, overall efficacy may be partially limited by incomplete target occupancy.

Here, we report the identification of LY3537982, a novel, highly selective and potent inhibitor of the KRAS G12C oncoprotein discovered using structure-based design, with the potential to deliver >90% target occupancy in patients.

4-day cell growth assays were performed in cell lines with KRAS G12C or KRAS non-G12C mutations, and KRAS WT using 0 – 10,000 nM of LY3537982. The IC50 values were determined by fitting the relative cell viability data at each drug concentration using a sigmoidal dose-response (variable slope) equation (n=6).

**Table 1. LY3537982 selectively inhibits growth of KRAS G12C mutant cells**

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>KRAS Mutation</th>
<th>IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H23</td>
<td>G12C</td>
<td>1.04</td>
</tr>
<tr>
<td>H358</td>
<td>G12C</td>
<td>1.16</td>
</tr>
<tr>
<td>H2122</td>
<td>G12C</td>
<td>11.38</td>
</tr>
<tr>
<td>Calu-1</td>
<td>G12C</td>
<td>59.56</td>
</tr>
<tr>
<td>H1734</td>
<td>G13C</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>A549</td>
<td>G12S</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>SK-LU-1</td>
<td>G12D</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>HCC827</td>
<td>WT</td>
<td>&gt;10,000</td>
</tr>
</tbody>
</table>

LY3537982 inhibits the growth of subcutaneous EL3187 NSCLC PDX tumors in nude mice (n=5) in a dose dependent manner. The red line under the X axis indicates the compound treatment period; Tx = Treatment Duration (day 21-49). Data are mean ± SEM.

Fig 1. LY3537982 selectively inhibits RAS activity/ERK phosphorylation in KRAS G12C cell lines

Fig 2. H358 proteome cysteine selectivity with 10 nM LY3537982 (4h treatment)

LY3537982 selectivity for proteome-wide cysteine residues was evaluated using competitive chemical proteomics. Among 8866 peptides, only one – KRAS G12C (LVVVGACCVGK) – showed a statistically significant reduction in LY3537982/DMSO ratio with 10 nM – 100 nM LY3537982 treatment for 4 h.

**Conclusions**

- LY3537982:  
  - Is a potent, highly selective covalent inhibitor of KRAS G12C with cellular IC50 of 3.35 nM.
  - Demonstrates robust tumor growth inhibition as single agent in KRAS G12C in vivo models.
  - Demonstrates robust tumor regression in combination with other agents in KRAS G12C in vivo models.
  - Is a promising KRAS G12C inhibitor predicted to deliver >90% KRAS G12C target occupancy in the clinic.

A first-in-human trial is planned for 2021.

**References**