**Discovery and Characterization of the Potent, Allosteric SHP2 inhibitor GDC-1971 for the Treatment of RTK/RAS Driven Tumors**

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**Introduction**

The non-receptor tyrosine phosphatase SHP2 (PTPN11) plays an important role in the regulation of RTK/RAS signaling transduction downstream of growth factor receptor activation. GDC-1971 (formerly RLY-1971), is a highly potent, selective, and orally bioavailable small-molecule SHP2 inhibitor that stabilizes SHP2 in a closed, auto-inhibited conformation. GDC-1971 inhibits both wild-type SHP2 (IC50 = 1.7 nM) and the ERK activating mutant (IC50 = 230 nM) in biochemical assays. In standard 2-dimensional and anchorage-independent growth conditions, GDC-1971 inhibits cellular proliferation in models harboring receptor tyrosine kinase (RTK), SHP2, or KRAS mutations in a dose-dependent manner. GDC-1971 potently inhibits the proliferation of cell lines harboring KRAS G12C or G12V mutations (median IC50 = 85 nM) compared to models harboring other KRAS G12, G13 Q61 mutations (median IC50 = 1.4 μM), indicating a link between KRAS GTP hydrolysis and SHP2 dependency. In vivo, GDC-1971 demonstrates dose-dependent RAS/MAPK pathway inhibition and induces significant tumor-growth inhibition in human xenograft models harboring ERK and KRAS alterations at continuous daily doses that are well tolerated. GDC-1971 also displays significant synergy in combination with other targeted therapies in cell line models. GDC-1971 in combination with the KRAS G12C inhibitor GDC-6036 resulted in significant tumor regression in a KRAS G12C mutant NSCLC xenograft model at doses where single agent treatment showed only modest tumor growth inhibition. In rodent and dog toxicology studies, GDC-1971 is well tolerated at exposures above those required to induce regression in xenograft models. Continuous daily dosing of GDC-1971 is being studied in combination with GDC-6036 in the clinic (NCT04448874).

**GDC-1971 Pharmacokinetic Properties**

<table>
<thead>
<tr>
<th>PK</th>
<th>Mouse</th>
<th>Rat</th>
<th>Dog</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (ml/kg/min)</td>
<td>18 (1.01)</td>
<td>18 (1.07)</td>
<td>7 (0.59)</td>
</tr>
<tr>
<td>Vd (l/kg)</td>
<td>1.8</td>
<td>3.9</td>
<td>6.8</td>
</tr>
<tr>
<td>t1/2</td>
<td>3.2 hours</td>
<td>1.1 hours</td>
<td>1.1 hours</td>
</tr>
<tr>
<td>F (%) (oral)</td>
<td>20</td>
<td>37</td>
<td>80</td>
</tr>
<tr>
<td>PNL (%) (unbound)</td>
<td>2.8</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>14 (ng/ml • h) + 1</td>
<td>3</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Mean residence time (h)</td>
<td>2</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>% renal clearance</td>
<td>1.6</td>
<td>0.75</td>
<td>0.8</td>
</tr>
</tbody>
</table>

**Results**

**1. GDC-1971 is a potent SHP2 inhibitor**

A. **In vitro inhibition of WT and G12C SHP2**

B. **GDC-1971 inhibits MAPK signaling in cells**

**2. GDC-1971 inhibits the proliferation of tumor cell lines in vitro**

A. Treatment with GDC-1971 inhibits growth of an EGF-amplified model

B. GDC-1971 is active in KRAS G12A/C and a subset of KRAS WT cell line models

**3. GDC-1971 inhibits the growth of RTK and KRAS mutant tumor models in vivo**

A. **KYE5320** EGF-amplified Esophageal

B. **NGI-5358** KRAS G12C NSCLC

C. **In vivo PK/PD Relationship**

D. **In vivo PK/PD Relationship**

**4. GDC-1971 combines with ALK targeted therapies and can reverse resistance in vivo**

A. **Alexinostatin-resistant ALK-driven cell line model**

B. **GDC-1971 Potency is Similar in Alexinostatin-Resistant Model**

C. **Synergy between GDC-1971 and Alexinostatin**

**5. GDC-1971 shows potent synergy in combination with the KRAS G12C inhibitor GDC-6036 in vitro and in vivo**

A. **GDC-1971 and GDC-6036 are Synergistic in KRAS G12C Mutant Models**

B. **Combination Assay Plot of GDC-1971 and GDC-6036 in NCI-H2122**

C. **MAPK-pathway signaling is suppressed in GDC-1971/GDC-6036 Treated NCI-H2122 Cells**

**D. Sustained Pathway Inhibition is Observed with in vivo Treatment of GDC-1971 and GDC-6036**

E. **The Combination of GDC-1971 and GDC-6036 Results in Tumor Regressions in vivo in NCI-H2122 Xenografts**

**Conclusions**

- GDC-1971 is a potent, allosteric SHP2 inhibitor
- GDC-1971 demonstrates inhibition of the MAPK pathway in cells, resulting in an anti-proliferative effect
- GDC-1971 achieves significant anti-tumor growth effect as a single-agent in tumor xenograft models and continuous daily dosing is well tolerated
- The combination of GDC-1971 with Alexinostatin in cells that have acquired resistance to the ALK inhibitor Crizotinib and Alexinostatin results in a synergistic anti-proliferative response
- The combination of GDC-1971 with the KRAS G12C inhibitor GDC-6036 results in synergistic effects on cell line viability in KRAS G12C mutant cell line models and drives potent tumor regressions in vivo in the KRAS G12C model NCI-H2122
- The combination trial of GDC-1971 and GDC-6036 is ongoing to assess clinical benefit in KRAS G12C mutant tumors

**References**


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