Background • Fibroblast growth factor receptors (FGFRs) are a family of transmembrane receptors consisting of isoforms FGFR1-4. FGFR2 is highly altered in tumors, 80% of which are activating mutations.

FGFR2 alterations are well-established oncogenic drivers in multiple indications.

FGFR2/3 alterations are present in 4.1% of all cancers, 80% of which are activating mutations.

FGFR2 is highly altered in cholangiocarcinoma and uterine endometrial tumors.

FGFR1-mediated hyperphosphatemia was the most common DLT of approved pan-FGFR inhibitors.

Inhibition of FGFR2 fusions in cholangiocarcinoma and FGFR3 mutations in urothelial cancer has led to improved clinical outcomes in defined patient populations.

FGFR2 alterations are well-established oncogenic drivers in multiple indications.

Results

Table 2. CGT1672 Retains Potency Across Primary and Acquired Resistance Mutations

<table>
<thead>
<tr>
<th>FGFR2</th>
<th>WT</th>
<th>V549F</th>
<th>V549M</th>
<th>V549L</th>
<th>N549K</th>
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<td>CGT1672 346</td>
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<td>9</td>
<td>7</td>
<td>14</td>
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<td>RIFX008 2063</td>
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<td>1</td>
<td>5</td>
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<td>Futibatinib 10</td>
<td>2</td>
<td>1000</td>
<td>839</td>
<td>58</td>
<td>81</td>
</tr>
</tbody>
</table>

• Table 2 shows mechanistic IC50 of FGFR1, FGFR2W19, and the FGFR2 gatekeeper and molecular brake mutants.

Optimization of CGT1672 led to the N549K mutant FGFR2 with improved potency vs. point mutation.

Only CGT1672 is selective over FGFR1 and maintains potency across the acquired resistance mutations.

Known clinical and commercial stage FGFR2 inhibitors have FGFR2 selectivity and/or target coverage issues which prevent optimal clinical efficacy.

Inhibition of the primary and acquired resistance mutations may provide deeper and more durable clinical responses.

Figure 6. CGT1672 Shows Favorable PK/PD in the Clinically Relevant AN3 CA (K310R/N549K) Model

CGT1672 has optimized binding in the ATP-pocket and maintains potency for all of the prevalent FGFR2 mutations which are common modes of resistance to current drugs.

Structure-based drug design has also been used to further optimize the inhibitors for selectivity over the general kinome, FGFR1, and FGFR4.

Figure 7. CGT1672 Demonstrates DE Mouse PK and Regressions in the AN3 CA (K310R/N549K) TGI Model

CGT1672 was selected as a tool compound to be used to complete validation of our in vivo models.

Optimization of the tool compound CGT1672, using structure-based drug design, has led to a promising series of FGFR2 inhibitors that are >50X selective for FGFR2 over FGFR1.

Optimization of CGT1672 to the AN3 CA (K310R/N549K) model shows tumor regressions in an AN3 CA mouse xenograft model, which differentiates CGT1672 from other selective FGFR2 inhibitors that lack activity against the N549K molecular brake mutation.

Further optimization of this series has led to compounds which are at least 50X selective vs. FGFR1.

Conclusions

• FGFR2 inhibitors are well-established oncogenic drivers in multiple indications.

• Approved FGFR pan-inhibitors fail to capture the full landscape of FGFR2 altered tumors.

• Gatekeeper (V549K) and molecular brake (N549K) mutations are untreated in the primary setting and have been identified as a common mechanism of resistance to current brakes which may explain their limited durability of response.

• CGT1672 and inhibitors in this series are potent across FGFR2 primary and required resistance mutations.

• Optimization of the tool compound CGT1672, using structure-based drug design, has led to a promising series of FGFR2 inhibitors which are >50X selective for FGFR2 over FGFR1.

• CGT1672 shows tumor regressions in an AN3 CA mouse xenograft model, which differentiates CGT1672 from other selective FGFR2 inhibitors that lack activity against the N549K molecular brake mutation.

Further optimization of this series has led to compounds which are at least 50X selective vs. FGFR1.

References: