# In Vivo Preclinical Characterization of a Novel FGFR2 Selective Inhibitor with Potency Against FGFR Activating Mutations

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## Background

- Fibroblast growth factor receptors (FGFRs) are a family of transmembrane receptors consisting of isoforms FGFR1-FGFR4[1]
  - FGFR signaling impacts key cellular processes (**Fig. 1**)
  - Binding of a ligand to the inactive FGFR monomer leads to receptor dimerization, phosphorylation, and downstream signaling
  - Key processes include cell survival, proliferation, migration and differentiation
- FGFR2/3 alterations are well-established oncogenic drivers in multiple indications[2]
- 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 endometroid tumors (**Fig. 2**)

**Figure 1. Fibroblast Growth Factor Receptors (FGFRs)**

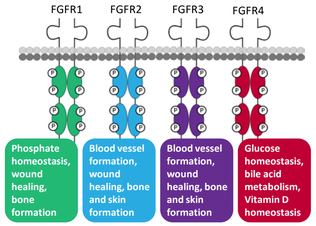



**Figure 2. FGFR2 Alteration Frequency by Tumor Types[2]**

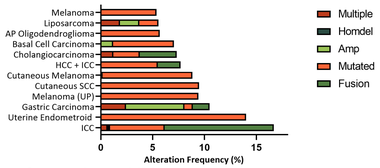



**Table 1. Clinical Features and Clinical Coverage of Pan-FGFR Inhibitors**

| Clinical Compound | Clinical Features | | | | Clinical Coverage | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Indication | | | FGFR alteration | | |
| | Dose Schedule | ORR | Hyperphos | Stomatitis | Adv/met ICC | Adv/met UC | Indications outside of ICC/UC | FGFR2 fusions | FGFR2 activating mutations | FGFR2 resistance mutations |
| **Pemigatinib**[3,5] | 2 wk on/ 1 wk off | 36% ICC | 92% | 35% | | | | | | |
| **Infigratinib**[6,7] | 3 wk on/ 1 wk off | 23% ICC | 82% | 56% | | | | | | |
| **Futibatinib**[8,9] | Monitor tolerability | 42% ICC | 85% | 30% | | | | | | |

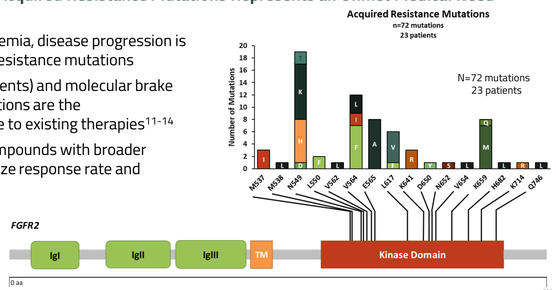
UC, Urothelial Carcinoma; ICC, Intrahepatic Cholangiocarcinoma; KD, Kinase Domain

Not Approved: Approved:

- 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[3,4]
- There remains an unmet need for a potent FGFR2 inhibitor with broad mutational coverage and which avoids FGFR1 to enable increased response rates with longer durability (current drugs 5-9 months)[3, 10] and better tolerability than existing agents

**Figure 3. Treatment of FGFR2 Acquired Resistance Mutations Represents an Unmet Medical Need[11-14]**

- Despite clinical hyperphosphatemia, disease progression is frequently driven by acquired resistance mutations
- Gatekeeper V564X (43% of patients) and molecular brake N549K (48% of patients) mutations are the main mechanisms of resistance to existing therapies[11-14]
- This highlights the need for compounds with broader mutational coverage to maximize response rate and increase duration of response



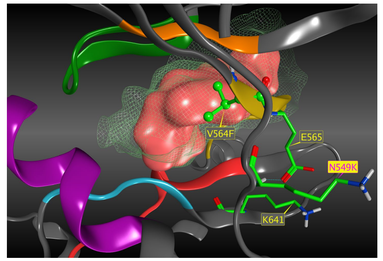

## Results

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

| | Anti-Target (nM) | FGFR2 (nM) | | | | |
|---|---|---|---|---|---|---|
| | FGFR1 | WT | V564F | V564L | V564I | N549K |
| CGT1672 | 346 | 15 | 9 | 7 | 14 | 18 |
| RLY4008 | 2063 | 8 | 1 | 5 | 88 | 28 |
| Pemigatinib | 10 | 2 | >1000 | 819 | 58 | 81 |
| Futibatinib | 4 | 2 | 147 | 30 | 2 | 1 |

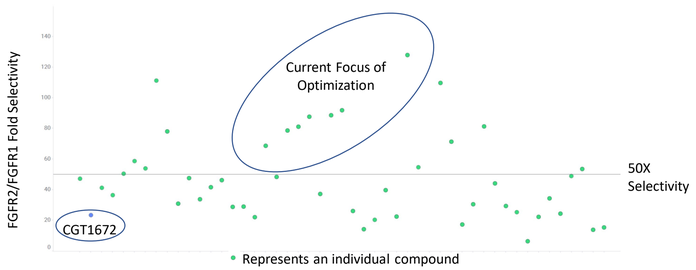
- Table 2 shows mechanistic cellular $IC_{50}$'s of FGFR1, FGFR2WT and the FGFR2 gatekeeper and molecular brake mutants
- Optimization of CGT0292 (AACR 2022 Abs 167) led to CGT1672 with improved potency vs. point mutation
- **Only CGT1672 is selective over FGFR1 and maintains potency across the acquired resistance mutations**
- Known clinical and commercial stage FGFR2 inhibitors have FGFR1 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 4. Crystal Structure of CGT1672 Bound to FGFR2 N549K Supported Structure Based Drug Design**



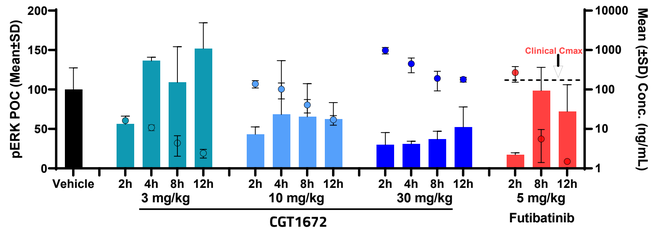

- 2.1Å Crystal structure of CGT1672 (shown as pink surface) bound to FGFR2 N549K mutant reinforces understanding for potency and selectivity
- CGT1672 has optimized binding in the ATP pocket and maintains potency for all of the prevalent FGFR2 mutations which are common modes of resistance to current drugs
- Structure based drug design has also been used to further optimize the inhibitors for selectivity over the general kinome, FGFR1, and FGFR4

**Figure 5. Ongoing Optimization of CGT1672 has Led to Enhanced FGFR2/FGFR1 Selectivity**



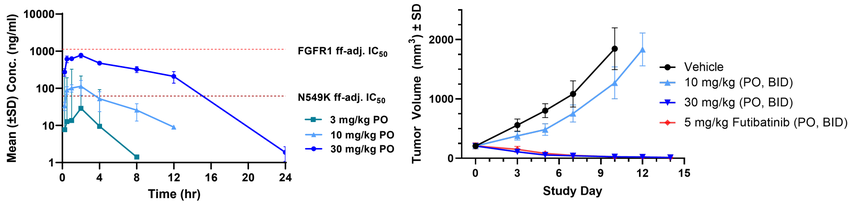

- CGT1672 was selected as a tool compound to be used to complete validation of our in vivo models
- Optimization of CGT1672 has led to a set of analogs that retain high potency across all FGFR2 mutants, 30% of which are >50X selective for FGFR2 vs. FGFR1

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




- CGT1672 shows a dose dependent inhibition of pERK in the AN3 CA PK/PD model
- Futibatinib was used as the control compound for both the PD(**Fig. 6**) and TGI(**Fig. 7**) AN3 CA mouse tumor models but has limited clinical utility due to hyperphosphatemia

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




- CGT1672 dose response PK shows $IC_{50}$ target coverage of N549K mutant FGFR2 with a selectivity window for FGFR1 at 30 mg/kg
- CGT1672 at 30 mg/kg and futibatinib at 5 mg/kg gave regression with BID PO dosing
- Futibatinib is clinically limited due to inhibition of FGFR1, preventing treatment of the N549K molecular brake mutation

## Conclusions

- FGFR2 alterations are well established oncogenic drivers in multiple indications
- Approved FGFR pan-inhibitors fail to capture the full landscape of FGFR2 altered tumor types
- **Gatekeeper (V564X) and molecular brake (N549K) mutations are untreated in the primary setting and have been identified as a common mechanisms of resistance to current therapies, 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 that are >50x selective for FGFR2 over FGFR1
- Dose Response PK/PD is shown with CGT1672 in the AN3 CA (K310R/N549K) model
- CTGT1672 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 mutantion
- Further optimization of this series has led to compounds which are at least 50X selective versus FGFR1

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**References.** 1. Helsten T, et al. *Clin Cancer Res.* 2016;22(1):259–267; 2. AACR Project GENIE Consortium. *Cancer Discov.* 2017;7(8):818-831; 3. Abou-Alfa GK, et al. *Lancet Oncol.* 2020;21(5):671-684; 4. Siefker-Radtke et al. *Lancet Oncol.* 2022;23(2):248-258; 5. PEMAZYRE (pemigatinib; prescribing information). Wilmington, DE: Inctye; Corporation; 2021; 6. Javle M, et al. *J Clin Oncol.* 2018;36(3):276-282. *2018;* 7. TRUSELTIQ (infigratinib; prescribing information). Brisbane, CA: QED Therapeutics: 2021; 8. Goyal L, et al. *Cancer Discov.* 2017; 7(3): 252–263; 9. LYTGOBI (futibatinib, prescribing information). Princeton, NJ: Taiho Pharmaceutical Co., Ltd.; 2022; 10. Goyal L, et al. *Cancer Research.* 2021;81(13_Suppl) Abstract CT010; 11. Goyal L, et al. *Cancer Discov.* 2017; 7(3): 252–263; 12. Goyal L, et al. *Cancer Discov.* 2019;9(8):1064-1079; 13. Varghese AM, et al. *JCO Precis Oncol.* 2021;5:PO.20.00178; 14. Silverman IM, et al. *Cancer Discov.* 2021;11(2):326-339. **Disclosures.** All authors are employees of Cogent Biosciences