Pre-Clinical Characterization of a Novel EGFR Sparing ErbB2 Inhibitor with Activity Against Oncogenic ErbB2 Mutations

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Background

- ErbB2 is a receptor tyrosine kinase that belongs to a family of four receptors EGFR, ErbB2, ErbB3, and ErbB4, also known as HER1, 2, 3, 4.[1]
- Receptor activation induces rapid dimerization with a marked preference for ErbB2 as a partner.[2]
- Phosphorylation of the ErbB2 kinase domain activates PI3K/Akt and the Ras/Raf pathways which regulate cell growth, survival and differentiation.[3]

Figure 1. HER Receptor Signaling Pathway

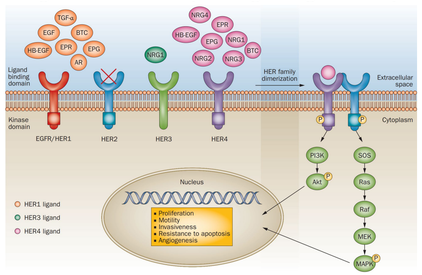


Table 1. ErbB2 Mutational Frequency in Solid Tumors[4, 5]

Cancer Type	Yearly US Patients	ErbB2 Mutational Frequency	Patients With ErbB2 Mutations	Commonly Occurring Mutation
Bladder Cancer	83,000	11.6%	9,600	S310F/Y
Endometrial Cancer	66,000	5.9%	3,900	V842I
Colorectal Carcinoma	153,000	4.8%	7,340	V842I
Melanoma	98,000	4.6%	4,510	S310F
Breast	284,000	3.2%	9,000	L755S
Non-Small Cell Lung Cancer	195,000	3.5%	6,800	YVMA ins

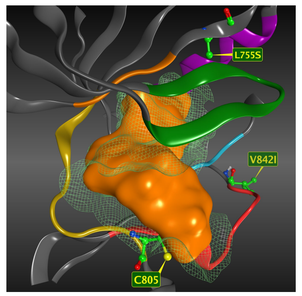
- ErbB2 amplifications and mutations are mutually exclusive in 80-90% of cases and represent independent drivers of human cancer pathogenesis
- Activating mutations in the ErbB2 gene demonstrate a tumorigenic role in multiple cancers similar to that of ErbB2 amplification
- Emerging mutations result in both acquired and cross resistance
- The non-selective dual EGFR/ErbB2 inhibitors are active against ErbB2 point mutations, however, inhibition of EGFR leads to dose limiting toxicities that include severe rash, diarrhea and mucositis
- Tucatinib, the first-generation selective EGFR sparing ErbB2 inhibitor, does not reach clinical plasma concentrations to cover the IC_{90} efficacious concentration for prevalent ErbB2 mutations

Goal

Identify a potent, brain penetrant, mutant active, WT-EGFR sparing, ErbB2 inhibitor for the treatment of patients with ErbB2 alterations and emerging ErbB2 resistance mutations.

Results

Figure 2. Co-Crystal Structure of ErbB2(V842I)-CGT1786 Enabled Structure-Based Drug Design



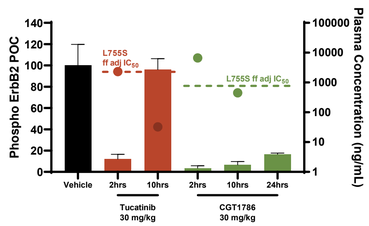
- 2.3 Å Resolution crystal structure of mutant ErbB2 V842I with the ErbB2 inhibitor CGT1786 bound.
- Covalent bond from inhibitor to Cys805 is highlighted, the remainder of the compound is masked as an orange surface.
- Proprietary crystal structures of ErbB2 were used to optimize inhibitors for potency and selectivity.

Table 2. EGFR Sparing ErbB2 Inhibitors with Cellular Activity Against Oncogenic Mutations

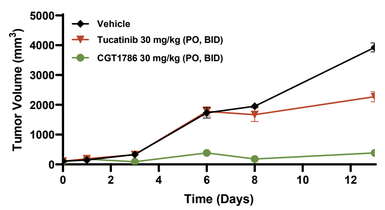
Free Fraction Adjusted pErbB2 Inhibition IC_{50} (nM) in Engineered Cell Lines				
Target	**Tucatinib**	**CGT1786**	**CGT2724**	**CGT4069**
WT-ErbB2	6	8	4	2
S310F (Urothelial)	8	6	4	2
V842I (Uterine)	24	14	6	3
L755S (Breast)	53	12	4	3
YVMA (Breast)	28	2	2	1
WT-EGFR/YVMA Selectivity	46x	220x	52x	>1350x
Chemotype	--	*A*	*A*	*B*

- CGT1786 has low nM potency on WT-ErbB2 and prevalent mutations including L755S and YVMA.
- CGT1786 is 220-fold selective for ErbB2 YVMA over WT-EGFR.
- Next generation compounds CGT2724 and CGT4069, optimized from CGT1786, showed similar selectivity and activity profiles and significantly improved free brain to plasma ratios (Table 3).
- CGT compounds are more potent on ErbB2 mutations and more selective over WT-EGFR than tucatinib.

Figure 3. CGT1786 Demonstrated Robust Inhibition of pErbB2 Levels and Superior Tumor Growth Inhibition Compared to Tucatinib in 3T3 L755S Models

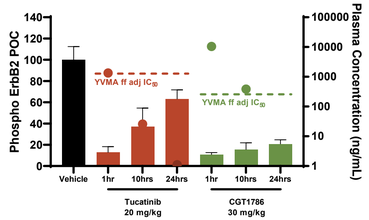


- Tucatinib showed 85% inhibition of pErbB2 at 2 hrs with plasma concentrations 6x higher than clinical Cmax[6] and no inhibition at 10 hrs.
- **CGT1786 showed improved inhibition of pErbB2 vs. tucatinib over the complete duration of the study.**



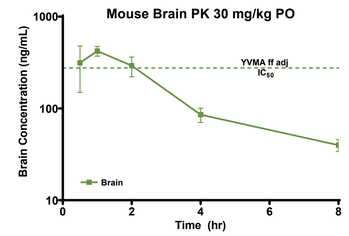
- Tucatinib had minimal TGI (42%) at 30 mg/kg PO BID.
- **CGT1786 dosed PO BID at 30 mg/kg resulted in >90% TGI in a 13-day study.**

Figure 4. CGT1786 Demonstrated Prolonged Inhibition of pErbB2 Levels in 3T3 YVMA Model



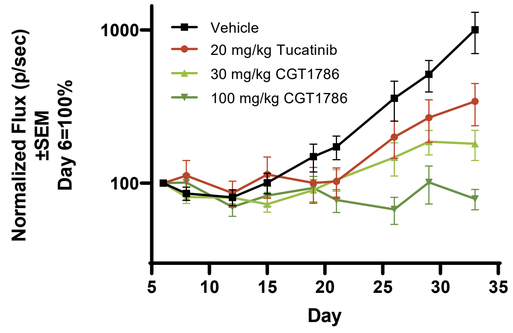
- At 1 hr tucatinib showed 90% inhibition of pErbB2 at plasma concentrations that are 3x above clinical Cmax, with significant loss of inhibition at 10 and 24 hrs.
- **CGT1786 showed >90% inhibition at 1 hr and has a prolonged pharmacodynamic effect with >80% inhibition out to 24 hrs.**

Figure 5. CGT1786 Is Brain Penetrant with CNS-YVMA Coverage in Mice



- CGT1786 dosed at 30 mg/kg PO had 2 hr YVMA coverage in the brain.
- Free brain to plasma ratio for CGT1786 was 22%.

Figure 6. CGT1786 Showed Superior Efficacy Compared to Tucatinib in a BT474/Luciferase (WT-ErbB2) Intracranial Model



- CGT1786, dosed PO BID at 30 and 100 mg/kg, was compared to tucatinib, dosed PO BID at 20 mg/kg, in an intracranial BT474 WT-ErbB2 model tagged with luciferase.
- Dosing was initiated on day 7 post-implantation and continued until day 33.
- Tumor size is approximated as flux (photons/sec) normalized to vehicle control using the IVIS imaging system.
- Tucatinib showed insignificant reduction in normalized flux .
- CGT1786 showed dose response characteristics between the 30 and 100 mg/kg doses.
- Significant reduction in tumor flux was observed with both doses.

Table 3. Focused Optimization: Improving Brain Penetrance and Whole Blood Stability

Assay	CGT1786	CGT2724	CGT4069
Free Brain to Plasma Ratio (1hr)	22%	**36%**	**40%**
Human Whole Blood $t_{1/2}$	612 min	318 min	**1410 min**

- CGT1786 exhibited a 22% brain to plasma ratio following single dose PK assessment in mice at the 1 hr timepoint (Figure 5).
- **Increasing CNS exposure:** Recent analogs, including CGT2724 and CGT4069, have measured brain to plasma ratios in mice, dosed PO at 30 mg/kg, of 36% and 40% respectively (1-hour time point).
- Structural changes to CGT1786 have led to next generation inhibitors with improved whole blood stability in the range of approved covalent drugs.[7]

Conclusions

- Co-crystal structures of ErbB2(V842I) with CGT1786 enabled the design of potent selective inhibitors.
- CGT1786 – early lead compound
  - >200-Fold selectivity for WT-EGFR , potent on prevalent point mutations, and the exon 20 insertion YVMA mutation
  - Robust PK/PD in a L755S model led to superior tumor growth inhibition compared to tucatinib
  - Prolonged inhibition of pErbB2 observed in a 3T3 YVMA mouse model
  - After dosing at 30 mg/kg PO, CGT1786 gave 22% free brain to plasma ratio and coverage of YVMA IC_{50} in the brain
  - In an intracranial model, CGT1786 demonstrated dose response characteristics with significant reduction in tumor flux compared to tucatinib
- Next Gen Cogent compounds, such as CGT2724 and CGT4069, maintain mutant potency, demonstrate superior brain penetrance, and show whole blood stability in the range of approved drugs.
- Work continues to identify a clinical candidate

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DISCLOSURES: All authors are employees of Cogent Biosciences

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