Characterization of a Novel, EGFR Sparing, ErbB2 Inhibitor with Activity Across Activating Mutations in Systemic and CNS Tumors

Jennifer Fulton, Tanna Bettendorf, Abiezer Blandon, Karyn Bouhana, Richard K. Brizendine, LouAnn Cable, Mark J Chicarelli, Michelle Crow, Brad Fell, John Fischer, Anna Guarnieri, Madison Hillman, Ravi Jalluri, Amber Johnson, Hailey Knox, Keith A. Koch, Vijay Kumar, Cori A. Malinky, Rob Rieger, John Robinson, Lee M Stunkard, Francis Sullivan, John I Trujillo, Logan E Vine, Shannon Winski, and Yeyun Zhou;
Cogent Biosciences, Inc., Boulder, CO and Waltham, MA

Abstract Presentation Number: 4486

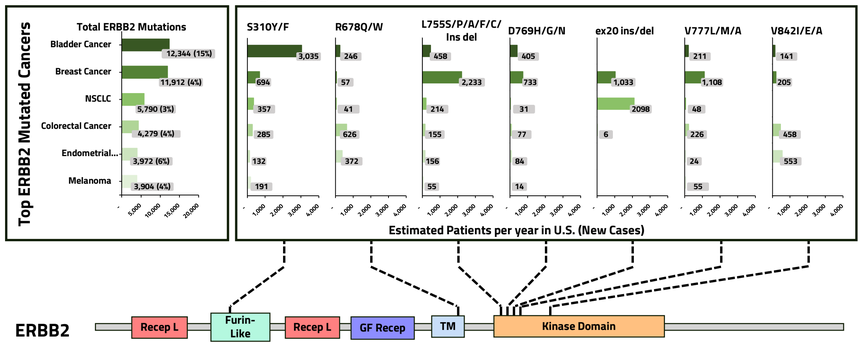
Cogent ErbB2 Inhibitor Opportunity

Target Product Profile

EGFR Sparing	Avoids EGFR related toxicities
Potent on Mutations	Retains high potency against prevalent ErbB2 mutations
Covalent	Provides a prolonged pharmacodynamic effect for maximum efficacy
Brain Penetrant	Best in class coverage in the CNS to treat brain metastases
Selective	Selective for ErbB2 across the kinome, receptors, channels, and hERG
Combinable	Low DDI risk based on in vitro data, potential to combine with other agents

Background

Figure 1. Prevalence of Oncogenic Mutations of ErbB2[1,2]



- ErbB2 drives breast cancer growth through amplification or genetic mutations leading to constitutive activation and increased downstream signaling
- Sequencing of tumors that have progressed post front-line breast cancer treatments have revealed ErbB2 mutations as mechanisms of resistance in metastatic breast cancer
- These mutations occur primarily in the furin-like and kinase domains of the protein

Results

Figure 2. Co-Crystal Structure of ErbB2(V842I)-CGT4255 Enabled Structure-Based Drug Design

- 2.3 Å Resolution crystal structure of mutant ErbB2(V842I) with the ErbB2 inhibitor CGT4255 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

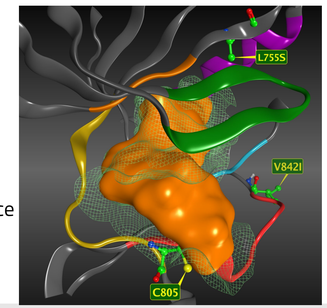


Table 1. EGFR Sparing ErbB2 Inhibitors with Cellular Activity Against Oncogenic Mutations

	ErbB2 Cellular IC_{50} Inhibition of pErbB2					
	ErbB2 WT	L755S	YVMA	S310F	V842I	EGFR WT (Shift vs YVMA)
CGT4255	8 nM	9 nM	3 nM	7 nM	15 nM	300 nM (100x)

- Mechanistic cell assay in engineered lines measuring inhibition of pErbB2
- CGT4255 Shows similar low nM potency across WT and mutant cell lines with 100x window over EGFR compared to ErbB2 YVMA

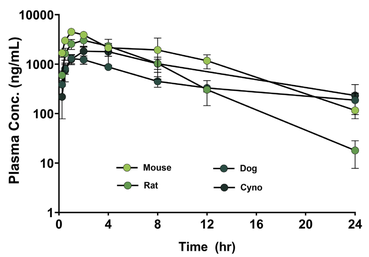
Table 2. CGT4255 has Long Half-Life in Whole Blood and Human Liver Cytosol Stability Assays

	Mouse	Rat	Dog	Cyno	Human
Whole Blood Stability, t1/2 min	637	903	1120	669	1089

	Poziotinib	Pyrotinib	ELVN-002[3]	CGT4255
Human Liver Cytosol Stability, t1/2 min	269	56	101	577

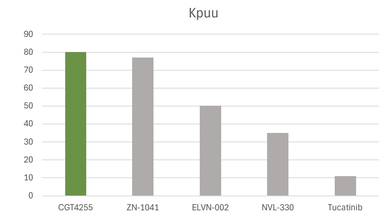
- CGT4255 shows greater than 600 min half-life across species in the whole blood stability assay, highlighting 18h half-life in human whole blood
- Compared to other covalent ErbB2i, CGT4255 has superior stability in a liver cytosol stability assay

Figure 3 . CGT4255 Has Promising Pharmacokinetics Across Species



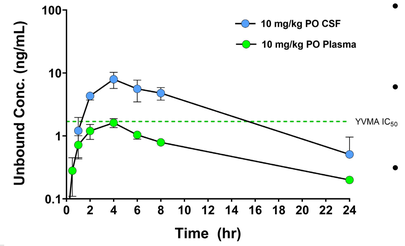
- CGT4255 was dosed PO at 10 mg/kg across a range of preclinical species
- CGT4255 has low clearance Extraction Ratio (ER) = 4-10%, across preclinical species mouse, rat, cyno, and dog
- Moderate to high oral bioavailability of 27% to 98% across species
- Based on these data, CGT4255 is expected to have high target engagement in human

Figure 4 . CGT4255 Shows Best in Class Brain Penetrance with 80% Kpuu in Mouse



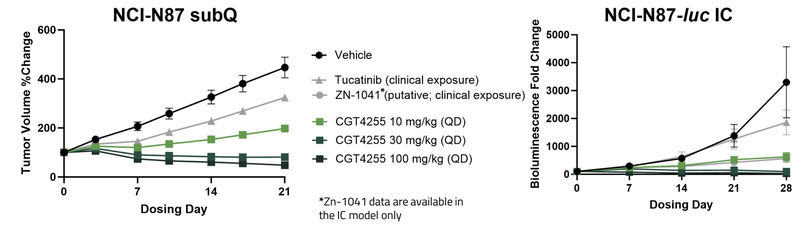
- CGT4255 Shows 80% Kpuu @ Cmax (1hr) dosed PO at 100 mg/Kg
- CGT4255 has higher free brain to plasma ratio compared to reported values for ELVN-002, NVL-330, and tucatinib[3,4]
- Similar Kpuu was seen with CGT4255 and Zion-1041[5]

Figure 5. CGT4255 Has High Exposure in Cyno CSF, High Human Brain Levels Predicted



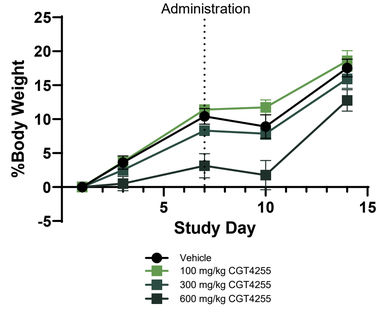
- Drug levels measured in cerebrospinal fluid are an established surrogate for drug levels found in the brain[6]
- CGT4255 was dosed in cyno at 10 mg/kg and the drug levels were measured in CSF and in plasma
- Calculated free drug concentration[7] shows levels consistent with full brain penetrance

Figure 6. CGT4255 Demonstrates Equivalent Ability to Inhibit NCI-N87 Tumors Grown Subcutaneously (subQ) or Intracranially (IC)



- CGT4255 demonstrates equivalent efficacy in subQ and IC model
- Superior performance compared to clinically relevant brain penetrant ErbB2 inhibitors when administered to match human exposure[8]
- Compound was well tolerated: ≤5% body weight loss, and showed no clinical observations across all dose groups

Figure 7. CGT4255 is Well Tolerated in Rats at High Exposure Levels



- CGT4255 was administered PO, 100-600 mg/kg for 7 consecutive days in male SD rats
- Exposure was ~10X higher than exposure resulting in mouse tumor regression
- Well-tolerated: no body weight loss, increases in LFTs or other clin chem endpoints, or findings in a neurobehavioral assessment (FOB)
- Safety profile supports dose regimens with both high systemic and CNS YVMA target coverage

CGT4255 –Advanced Lead

- **Low nM potency for ErbB2 WT and oncogenic mutations**
- **100-fold selectivity over EGFR WT**
- **Exceptional stability in human whole blood and liver cytosol fractions**
- **Moderate to high oral bioavailability and low clearance across preclinical species**
- **Best in class 80% brain penetrance in mice**
- **High exposure in monkey CSF predicts high brain exposure in human**
- **Equivalent efficacy in NCI-N87 tumors implanted either subcutaneous or intracranial**
- **Well-tolerated in rats at 10x concentration resulting in mouse tumor regressions**
- **IND-enabling studies are expected to begin mid-2024**

American Association for Cancer Research (AACR) Annual Meeting
San Diego, CA
April 9, 2024

REFERENCES: 1. American Cancer Society. Cancer Facts & Figures 2021. Atlanta: American Cancer Society; 2021. 2. The AACR Project GENIE Consortium. AACR Project GENIE: Powering Precision Medicine Through An International Consortium, Cancer Discovery 2017. 3. Aujay et al. AACR 2023 Poster # 4019. 4. Andrews et al EORTC 2022, Poster # 212. 5. Fei Ma et al ASCO 2023 Poster #1040 6. J Med Chem (2013), 56, 2-12. 7. AAPS Journal (2021) 23:81 8. Dose administration in mouse is measured and matched to be within 1-3x the mean steady state Cmax for Tucatinib administered 300 mg BID (Annals of Oncology (2020) Volume 31, Issue 9, 1231 – 1239) and Zn-1041 administered at 800 mg (approximated from Anders et al ASCO 2023 Poster #1041)

DISCLOSURES: All authors are employees of Cogent Biosciences

Scan the QR code to access a PDF copy of this poster