CGT4255 is an EGFR Sparing, Pan-Mutant HER2 Clinical Development Candidate with Potential Best-In-Class Brain Penetration

John I. Trujillo, Jennifer Fulton, Tanna Bettendorf, Abiezer Blandon, Karyn Bouhana, Richard K. Brizendine, LouAnn Cable, Mark J. Chicarelli, Michelle Crow, Brad Fell, John Fischer, Anna Guarnieri, Leyla Haygood, Madison Hillman, Ravi Jalluri, Vijay Kumar, Cori A. Malinky, Maralee McVean, Brad Newhouse, Rob Rieger, John Robinson, Lee Stunkard, Francis Sullivan, Logan E. Vine, Shannon Winski, and Yeyun Zhou

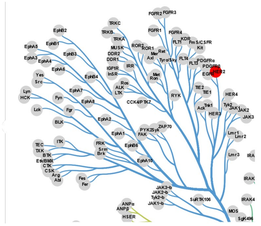
Cogent Biosciences, Waltham, MA and Boulder, CO

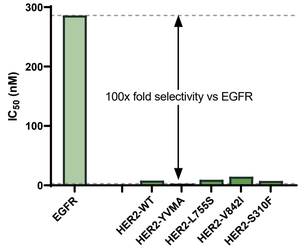
Poster #1
Abstract #5623

Cogent HER2 Inhibitor Opportunity Target Product Profile

EGFR Sparing	Potential to avoid EGFR related toxicities
Potent on Mutations	Retains high potency against prevalent HER2 mutations
Covalent	Provides a prolonged pharmacodynamic effect for maximum efficacy
Brain Penetrant	Provides coverage in the CNS to treat brain metastases
Selective	Selective for HER2 across the kinome, receptors, channels, and hERG
Combinable	Low DDI risk based on in vitro data, potential to combine with ADCs and other agents

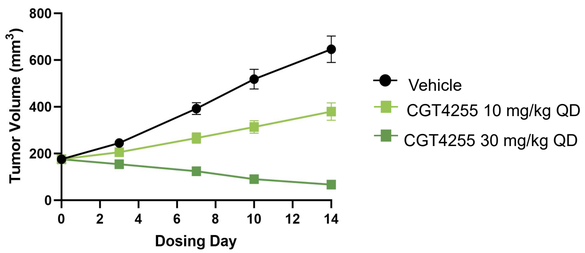
Selective Across the Kinome and 100x Selective Over EGFR





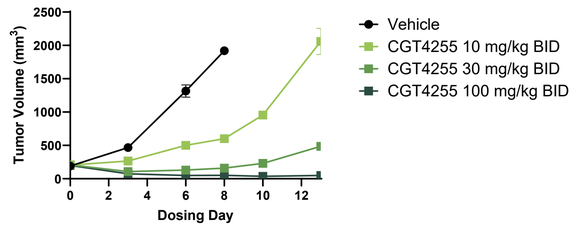
- CGT4255 was profiled at 10x the enzyme IC_{50} for WT HER2 against a panel of 396 kinases, HER2 was the only kinase that showed >30% target inhibition.
- Mechanistic cellular assays show CGT4255 is 100-fold selective for HER2 YVMA over WT-EGFR.
- CGT4255 covers HER2 mutations tested, including L755S and YVMA.[1]

Regressions in HER2+ Subcutaneous TGI Model



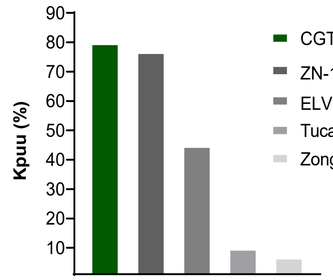
- CGT4255 was orally administered at 10 or 30 mg/kg QD in a subcutaneous BT-474 TGI model.
- CGT4255 demonstrated dose responsive TGI with tumor regression observed at 30 mg/kg.

Regressions in Mutant HER2-L755S Subcutaneous TGI Model

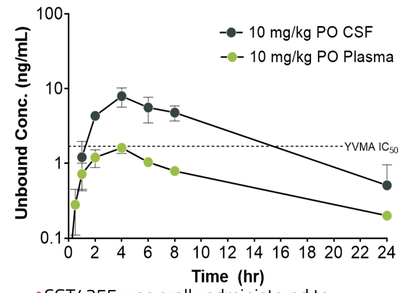


- CGT4255 was orally administered at 10, 30, and 100 mg/kg BID in a NIH3T3-HER2-L755S TGI model.
- CGT4255 demonstrated dose responsive TGI with complete responses observed at 100 mg/kg.

CGT4255 is a Potential Best-in-Class Fully Brain Penetrant HER2 Inhibitor

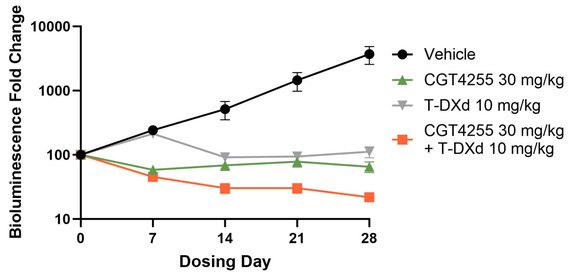


- CGT4255 has a high unbound brain to plasma partition coefficient (Kpuu) and is considered fully brain penetrant.[4]



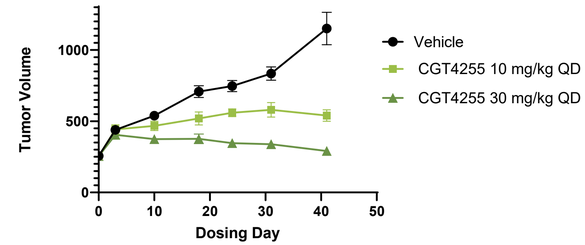
- CGT4255 was orally administered to cynomolgus monkeys at 10 mg/kg.
- CSF/Plasma ratio of 4.8 confirms full brain penetration; literature precedence of similar data correlates with high brain levels in human.[5]

Added Efficacy in Combination with T-DXd in an NCI-N87 Intracranial Model



- CGT4255 was orally administered at 30 mg/kg QD in an NCI-N87-luc intracranial model as a single agent and in combination with T-DXd at 10 mg/kg IV, Q3W.
- CGT4255 and T-DXd demonstrate stable disease as monotherapies.
- Added efficacy was observed in combination with T-DXd with decreased luminescence indicative of tumor regression.
- All regimens were well tolerated with no body weight decreases or other safety signals observed.

Robust TGI in a HER2-YVMA Subcutaneous PDX Model



- CGT4255 was orally administered at 10 or 30 mg/kg once daily in a lung PDX model with a HER2-YVMA insertion.
- Robust tumor growth inhibition was observed with 30 mg/kg CGT4255
- These data support the clinical investigation of CGT4255 in HER2-YVMA lung cancer

In Vitro Safety and ADME Assessments

Assay	Result
Kinome Screen	No inhibition >30%, 396 kinases tested
Safety Receptor/ Ion Channel Panel	1 target IC50 <1 uM, 87 targets tested
hERG	>400x window
Non GLP Ames	Negative

Assay	Result
P-gp Efflux/BCRP Efflux Transporter Substrate	Not a substrate
Transporter Inhibition	Low risk for OATP1B1
CYP Inhibition	IC_{50} >20 μM

CGT4255 Highlights

- Fully brain penetrant in mouse and monkey; high brain concentrations predicted for human
- Added efficacy in an intracranial model in combination with T-DXd
- Regressions in HER2-overexpressed subcutaneous mouse tumor model
- Complete regressions in mutant HER2 L755S subcutaneous mouse TGI
- Robust tumor growth inhibition in mutant HER2-YVMA subcutaneous PDX
- Well-tolerated at efficacious doses in TGI models
- >100-fold selectivity over EGFR

Cogent plans to submit an IND application for CGT4255 in 2025

American Association for Cancer Research (AACR) annual meeting | April 29, 2025 Chicago, Illinois

REFERENCES: 1. (a) American Cancer Society. Cancer Facts & Figures 2021. Atlanta: American Cancer Society; 2021. (b) The AACR Project GENIE Consortium. AACR Project GENIE: Powering Precision Medicine Through An International Consortium, Cancer Discovery 2017. 2. Fei Ma et al. ASCO 2023 Poster#1040. 3. (a) Monette Aujay et al. AACR 2023 Poster # 4019. (b) Andrews et al. EORTC 2022, Poster #212. 4. Irena Lorvan et al. Pharmaceutical Research (2022) 39:1321-1341. 5. (a) J. Med Chem (2013), 56, 2-12. (b) The AAPS Journal (2021) 23:81, 1-12. (c) Zhang et al. Breast Cancer Research (2023), 25:81, 1-14.

Acknowledgments/Disclosures This study was funded by Cogent Biosciences. All authors are employees of Cogent Biosciences.