

# CGT4255 Brain Penetrant HER2 Selective Clinical Development Candidate

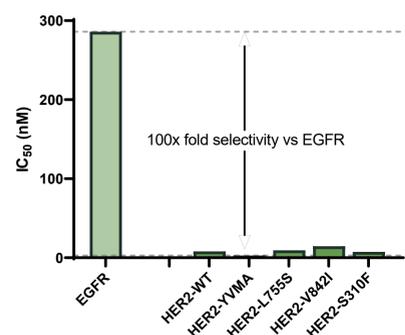
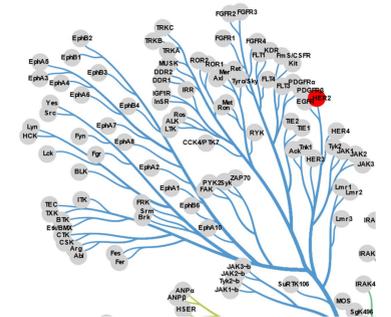


## CGT4255 is a Brain Penetrant, HER2 Selective Clinical Development Candidate With Activity in CNS and Subcutaneous Tumors

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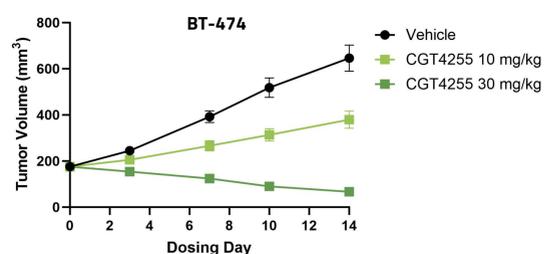
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### Selective Across the Kinome and 100X Selective Over EGFR

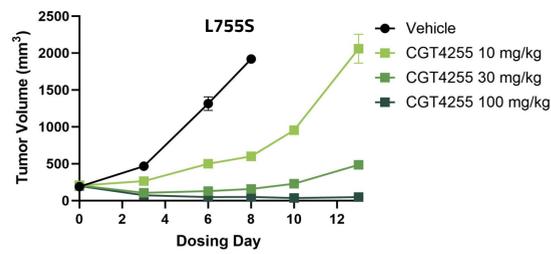


- CGT4255 was profiled at 10x the enzyme IC<sub>50</sub> for WT HER2 against a panel of 396 kinases, HER2 was the only kinase that showed >30% target inhibition
- Mechanistic cellular assays show CGT4255 is 100-fold selective for HER2 YVMA over WT-EGFR
- CGT4255 covers all HER2 mutations tested, including L755S, a prevalent activating mutation in breast cancer<sup>1</sup>

### Regressions Observed in HER2+ and Mutant HER2-L755S Models

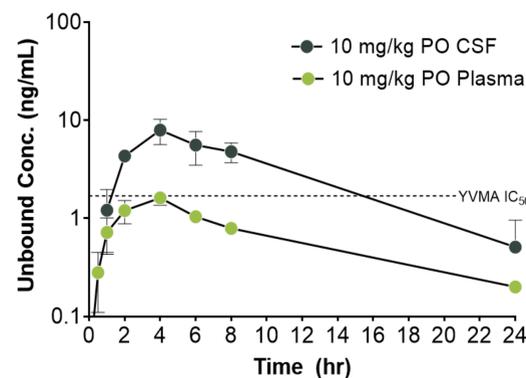
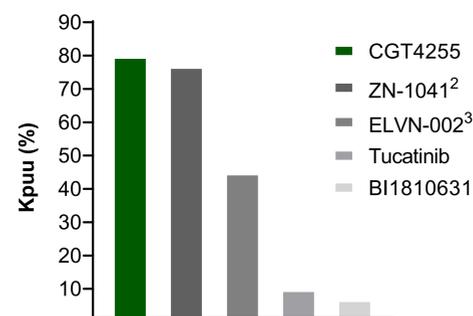


- CGT4255 was orally administered at 10 or 30 mg/kg QD in a subcutaneous BT-474 TGI model
- CGT4255 demonstrated dose responsive TGI with tumor regression observed at 30 mg/kg



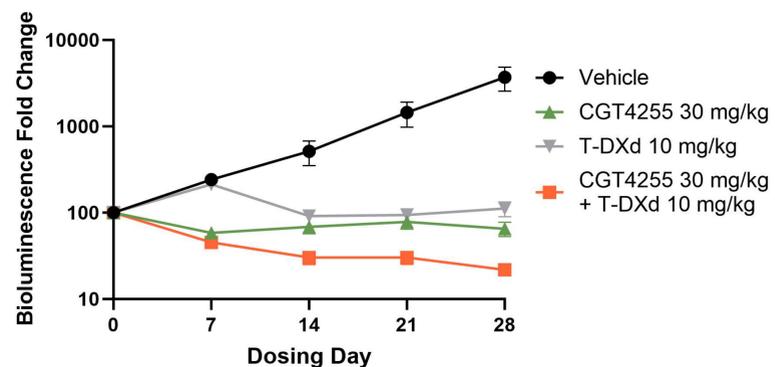
- CGT4255 was orally administered at 10, 30 or 100 mg/kg BID in a NIH3T3-Her2-L755S TGI model
- CGT4255 demonstrated dose responsive TGI with complete responses observed at 100 mg/kg

### 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<sup>4</sup>
- Equivalent to reported Kpuu of Zion/Roche ZN-1041
- Two-fold higher Kpuu than ELVN-002 reported values
- Eight to ten times higher brain to plasma ratio compared to tucatinib and BI1810631
- CGT4255 was orally administered to cynomolgus monkeys at 10 mg/kg and drug concentrations were measured in both plasma and cerebral spinal fluid (CSF)
- CSF/Plasma ratio of 4.8 confirms full brain penetration; literature precedence of similar data correlates with high brain levels in human<sup>5</sup>

### Added Efficacy in Combination with T-DXd in an 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

### CGT4255 Profile

- 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
- Well-tolerated at efficacious doses in TGI models
- Low DDI risk based on in vitro safety panel
- Low nM potency across HER2 mutations
- >100-fold selectivity over EGFR

**CGT4255 is currently in IND-enabling studies with clinical trials planned in 2025**

### In Vitro Safety Assessment Predicts Low DDI Risk

Assay	CGT4255
Kinome Screen	Clean
Safety Receptor Panel	Clean
Ion Channel Panel	Clean
P-gp Efflux Transporter Substrate	No
BCRP Efflux Transporter Substrate	No
CYP Inhibition	Favorable CYP inhibition profile
CYP450 TDI	Clean
CYP Induction	3A4 – Moderate Risk
Transporter Inhibition	Low Risk
Non GLP AMES	Negative
hERG	No Risk

- High kinome selectivity for HER2, no inhibition >30% of 396 kinases tested
- Clean on safety receptor and ion channel panels
- Not a P-gp or BCRP efflux transporter substrate, efflux ratio < 1.5 for both transporters
- Favorable CYP inhibition profile, IC<sub>50</sub> > 20 μM across CYPs
- No CYP450 time-dependent inhibition risk
- Moderate risk for CYP 3A4 induction, no induction risk for 1A2 and 2B6
- Low risk for OATP1B1 inhibition
- > 400X safety window on hERG

