Preclinical Characterization of CGT4255, an EGFR Sparing, Pan-mutant HER2 Clinical Development Candidate with Potential Best-in-class Brain Penetration

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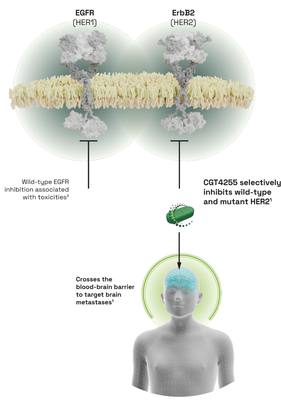
Poster #5869

CGT4255 - Brain Penetrant Selective HER2 Clinical Candidate

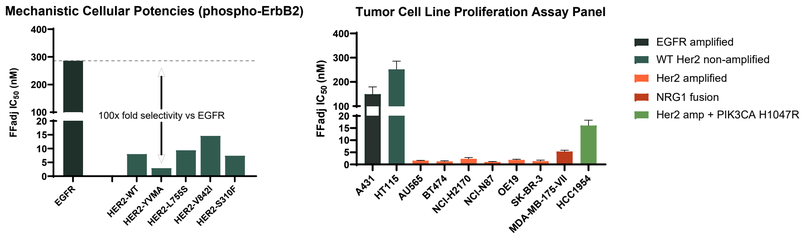


50% of HER2⁺ breast cancer patients and

47% of mutant HER2 NSCLC patients develop brain metastases[2, 3]

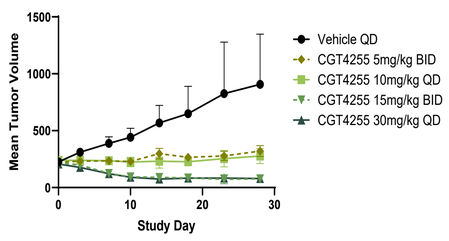
- HER2 overexpression or activating mutations are well known oncogenic drivers of tumor growth and especially prevalent in breast cancer via amplification/overexpression and in NSCLC via mutation[1]
- HER2-altered cancers frequently spread to the CNS, a sanctuary site where the blood-brain barrier shields them from most HER2 inhibitors[2,3]
- Inhibitors that target the closely related EGFR receptor tyrosine kinase are associated with gastrointestinal and skin toxicities which can affect quality of life and lead to treatment adjustments[4]
- There is an unmet need for potent HER2 inhibitors that target prevalent mutations, are selective for HER2 over EGFR, and can penetrate the blood-brain barrier
- Her2 targeted ADCs, like T-DXd, have recently been approved in Her2-altered cancers, although durability can be limited by mechanisms of resistance leading to progression[5]. Preclinical data herein shows that concurrent treatment of **CGT4255** and T-DXd enhances receptor internalization and cancer cell apoptosis, suggesting the potential for a synergistic combination that could improve patient outcomes.

CGT4255 is HER2 Selective and Potent in HER2-Amp and HER2 Mut Lines



- Mechanistic assays in 3T3-HER2 engineered cells show nM IC_{50}s in mutant lines and 100x selectivity for HER2 YVMA over EGFR
- Similar potency and selectivity for HER2 over EGFR dependent cancer cells were observed in a functional assay measuring cell proliferation

CGT4255 Efficacy is Independent of Schedule and Driven by Exposure

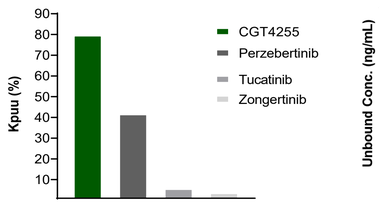


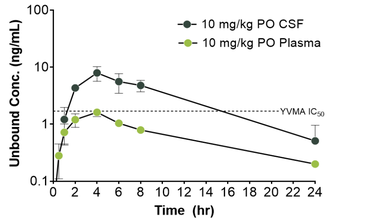
Treatment	C_{max} (ng/mL)	AUC_{0-24} (ng·hr/mL)
Vehicle (PO, QD x 28 days)	N/A	N/A
5 mg/kg CGT4255 (PO, BID x 28 days)	1617	15,800*
10 mg/kg CGT4255 (PO, QD x 28 days)	3527	19,800
15 mg/kg CGT4255 (PO, BID x 28 days)	3783	39,800*
30 mg/kg CGT4255 (PO, QD x 28 days)	8297	44,800

*BID adjusted

- CGT4255 was orally administered at 10 or 30 mg/kg QD versus 5 or 15 mg/kg BID in a subcutaneous NCI-N87 TGI mouse model
- CGT4255 demonstrated overlapping TGI when same daily dose was administered QD or BID

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

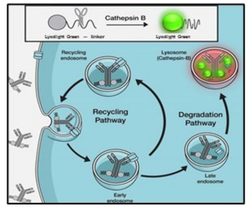


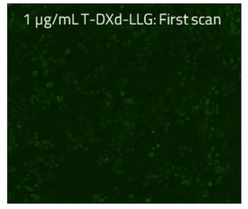


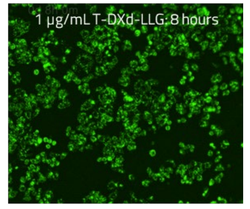
- CGT4255 with 80% unbound brain to plasma partition coefficient (Kpuu) is considered fully brain penetrant[6]
- Shows ~2-fold higher Kpuu than the Zion/Roche HER2 inhibitor perzebertinib
- Shows 13-40x higher Kpuu compared to the approved agents tucatinib and zongertinib
- All comparative data were generated in-house using CD-1 mice CNS PK study
- CGT4255 was administered orally 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[7,8]

CGT4255 Enhancement of HER2-Targeted ADC Internalization Provides Mechanistic Rationale for Combinatorial Activity

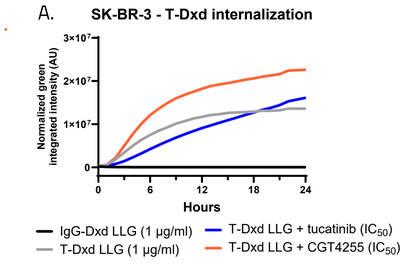
Lysolight Green (LLG)-conjugated T-DXd for tracking of Her2 internalization

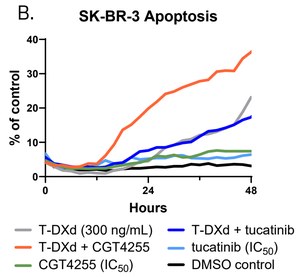






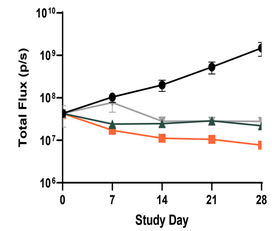
- The Incucyte Live Cell Analysis system was used to track and quantify apoptosis and HER2 internalization in the SK-BR-3 HER2-positive breast cancer cell line

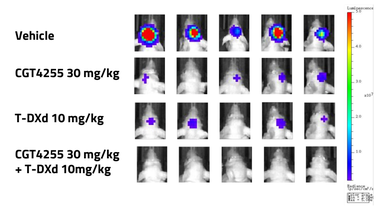




- Consistent with published reports on covalent HER2 inhibitors[9], combination of T-DXd-LLG with CGT4255 leads to enhanced HER2 internalization and lysosomal accumulation. Tucatinib, a reversible HER2-selective inhibitor, causes a delay in internalization (Fig. A)
- Enhancement of T-DXd internalization and payload delivery leads to accelerated and augmented induction of apoptosis in the CGT4255 + T-DXd combo vs T-DXd single agent. In contrast, tucatinib showed delayed internalization and no increase in apoptosis was observed in the tucatinib + T-DXd combo vs T-DXd single agent (Fig. B)

CGT4255 T-DXd Combination Induces Regression in an Intracranial Model of HER2-Amplification

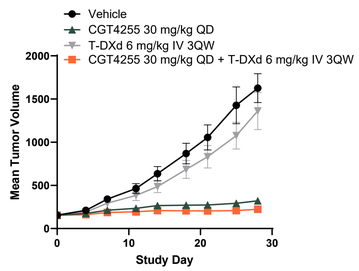




- CGT4255 was orally administered at 30 mg/kg QD in an NCI-N87-luc intracranial mouse model as a single agent and in combination with T-DXd at 10 mg/kg IV, Q3W
- CGT4255 and T-DXd demonstrate stable disease as monotherapies
- Added efficacy was observed in combination with T-DXd with decreased luminescence consistent with tumor regression

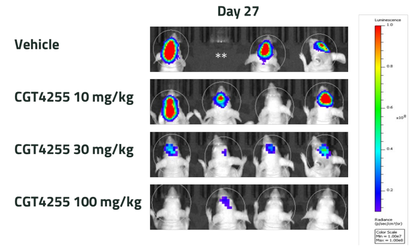
CGT4255 Retains Activity in Models of ADC-Resistance and ER-Independence

A. Enhertu-Resistant NCI-N87



- NCI-N87-Enhertu-R tumors were rendered resistant by chronic *in vitro* T-DXd administration
- CGT4255 administered at 30 mg/kg demonstrated stable disease as a monotherapy or in combination with T-DXd
- All regimens were well tolerated with no body weight decreases or other safety signals observed

B. HER2-YVMA Acquired Resistance in ER+ BRCA



- MCF-7s are an ER+/PI3Kmut breast cancer line dependent on estrogen for in vivo growth. CRISPR with YVMA engendered estrogen independent intracranial growth
- Bi-directional molecular crosstalk between the ER and HER2 signaling pathways promotes tumor growth and progression. Targeting both pathways may produce enhanced antitumor activity and overcome estrogen therapy resistance[10].
- CGT4255 retains activity in the intracranial setting and confirms cross-talk between intrinsic resistance to ER and activated HER2

CGT4255 Key Findings

- >100-fold selectivity over EGFR and potent on HER2 amp and mutant lines
- Nonclinical models predict high brain concentrations in human
- Activity independent of schedule in nonclinical models
- Strong activity observed in HER2-amplification models and HER2-YVMA intracranial tumors as monotherapy or in combination with T-DXd
- Mechanistic studies suggest CGT4255 in combo with T-DXd improved ADC internalization and subsequent apoptosis
- Demonstrates activity in models of ADC-resistance and HER2-mutant acquired resistance to endocrine therapy in ER+ positive breast cancer

CGT4255 Phase I is Ongoing (NCT07361562)

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