

A First-in-Human Study of CGT4255 in Patients who have Advanced Solid Tumors with ERBB2 Alterations or HER2 Overexpression

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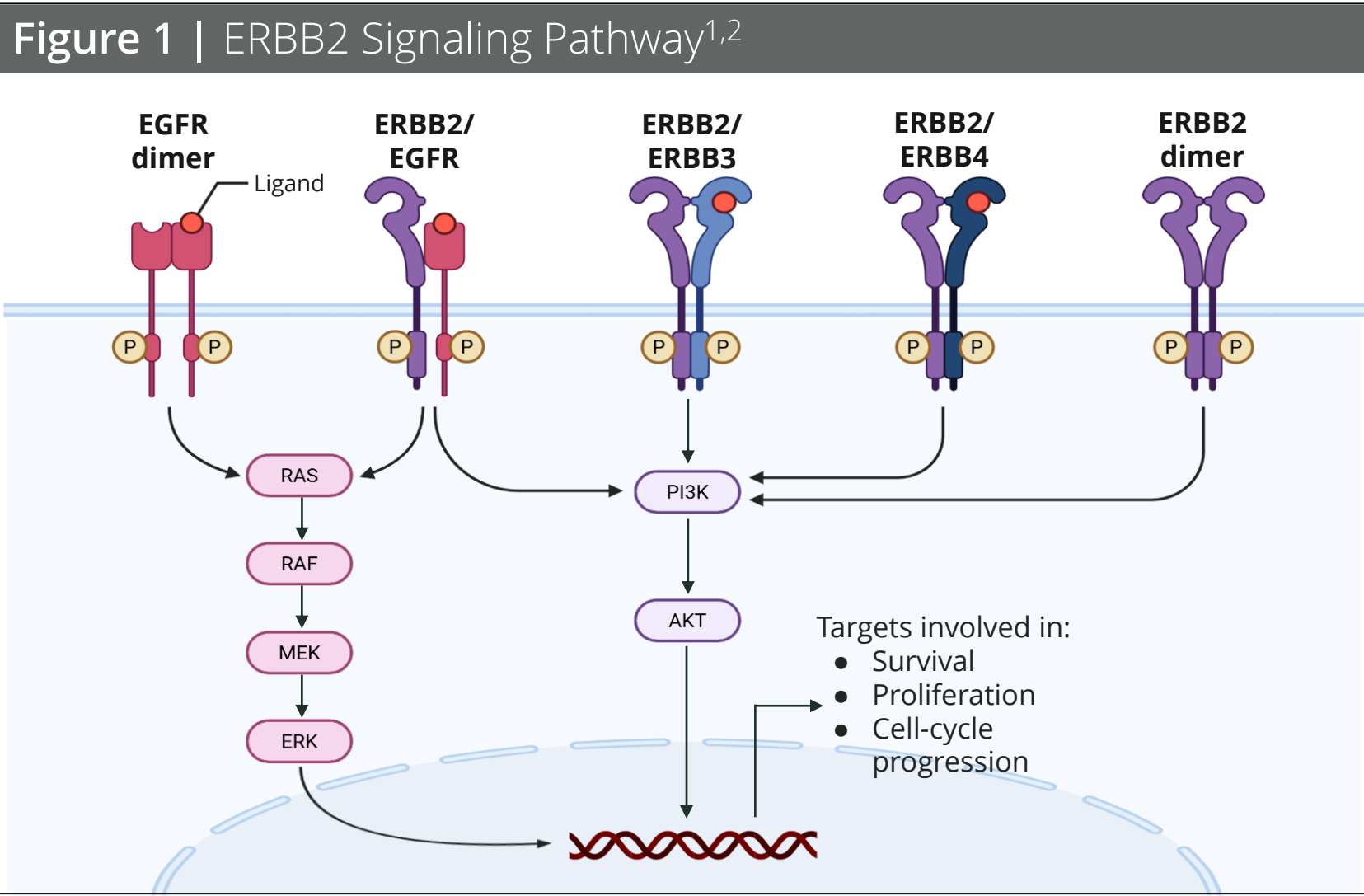
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Background

ERBB2 is an Oncogenic Driver in Lung Cancer

- The human epidermal growth factor receptor (HER) family of tyrosine kinases consists of epidermal growth factor receptor (EGFR/ERBB1), HER2 (ERBB2), HER3 (ERBB3), and HER4 (ERBB4)¹
 - These transmembrane receptors activate downstream signaling via pathways (i.e., PI3K/AKT, RAS/RAF/MEK)¹ (Figure 1)
- ERBB2-activating alterations and HER2 overexpression are present in a wide range of cancers, including non-small cell lung cancer (NSCLC)¹⁻³
- ERBB2 alterations include gene mutations (~4% of NSCLC cases) and protein overexpression⁴
- The central nervous system (CNS) is an important and common site of metastases for many solid tumors⁵⁻⁶, particularly for lung cancer
 - Brain metastases (BM) are found in ~7-20% of NSCLC patients at diagnosis and develop in 25–30% NSCLC patients during the course of their disease^{7,8}
 - Incidence of BMs is ~50% in patients with HER2-mutated NSCLC⁹
 - Higher rates of BM have been documented in different ERBB2-altered solid tumors compared to the same tumor types with other molecular drivers¹⁰⁻¹²



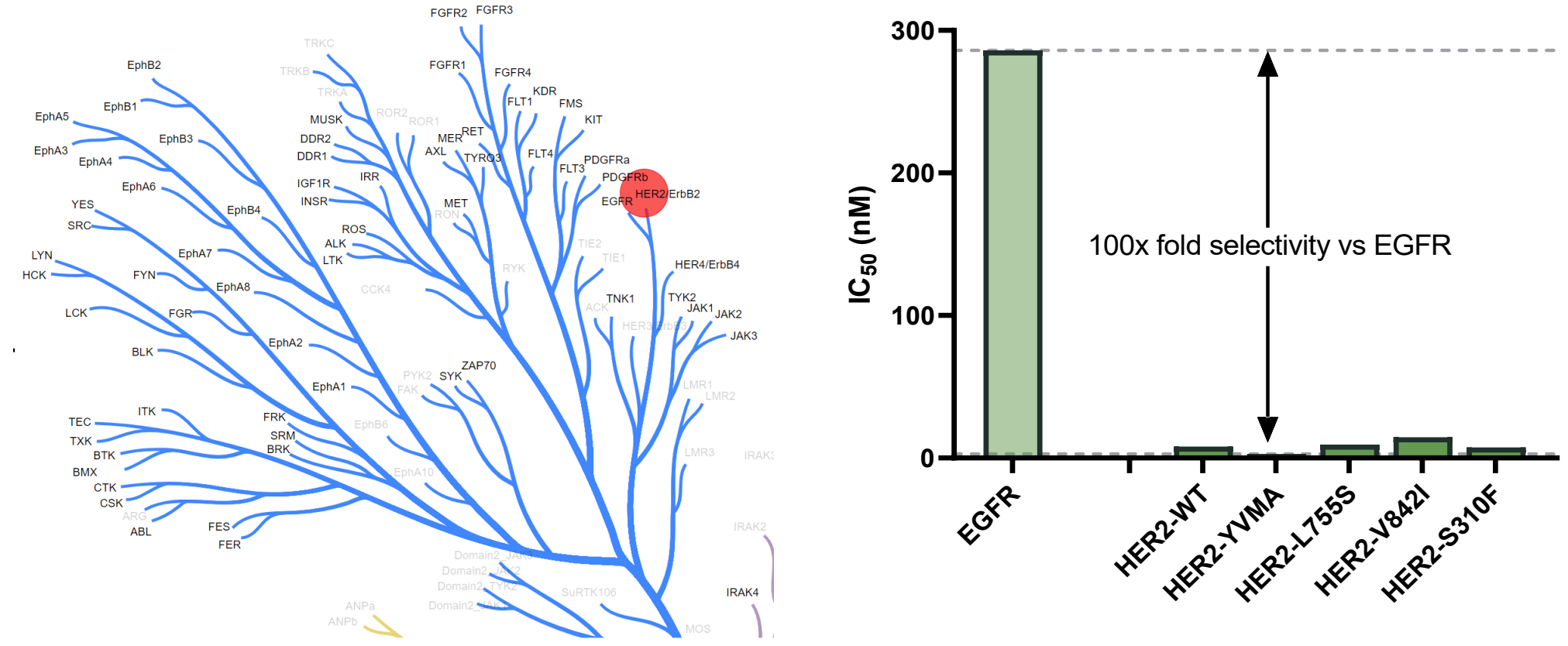
Unmet Need with Current ERBB2 Inhibitors

- Currently available ERBB2-directed therapies include monoclonal antibodies, antibody-drug conjugates, and tyrosine kinase inhibitors (TKIs), which are well established for the treatment of NSCLC^{13,14}
 - These therapies have variable CNS penetration⁸
- Many current TKIs also inhibit EGFR, causing EGFR-mediated toxicities such as rash, mucositis, and paronychia¹⁵
- Thus, there is an unmet medical need for a selective, CNS-penetrant ERBB2 inhibitor that covers wild-type and mutant ERBB2, which may benefit patients who have ERBB2-mutated NSCLC⁹ with BM^{5,6}

CGT4255 is an Investigational, Oral, EGFR-Sparing, CNS-Penetrant, ERBB2 Inhibitor

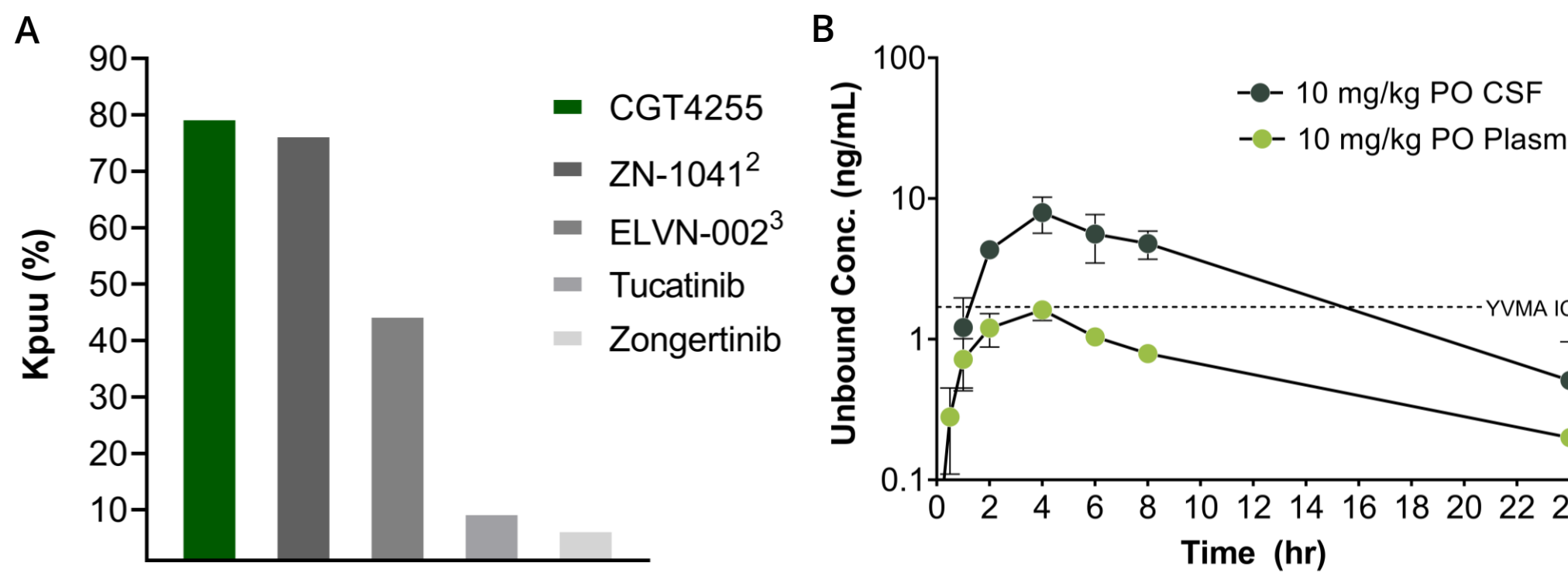
- CGT4255 exhibits selectivity across a broad panel of 396 kinases, with 100-fold selectivity for ERBB2 over wild-type EGFR and no other kinases showing >30% target inhibition (Figure 2)¹⁶
 - Sparing wild-type EGFR may reduce the risk of EGFR-mediated toxicities
 - Also found to be highly selective in a broad panel of receptors, channels, and transporters, which may carry low potential for off-target activity
 - Demonstrates potency against both wild-type and clinically relevant mutant forms of ERBB2

Figure 2 | CGT4255 is Selective Across the Kinome and 100x Selective over EGFR¹⁶



- Preclinical studies have demonstrated high CNS penetration of CGT4255, with brain penetration predictive of effective exposure in the clinical setting¹⁶
 - High unbound brain to plasma partition coefficient (Kpuu) (Figure 3A)
 - CSF/Plasma ratio of 4.8 (Figure 3B)
- CGT4255 has also demonstrated well-tolerated antitumor activity in a range of ERBB2-altered mouse models^{16, 17}
- Nonclinical data collectively support initiation of the first-in-human study of CGT4255 in adults with advanced solid tumors harboring ERBB2-activating alterations or HER2 overexpression

Figure 3 | Nonclinical Data Demonstrate Full Brain Penetration with CGT4255¹⁶



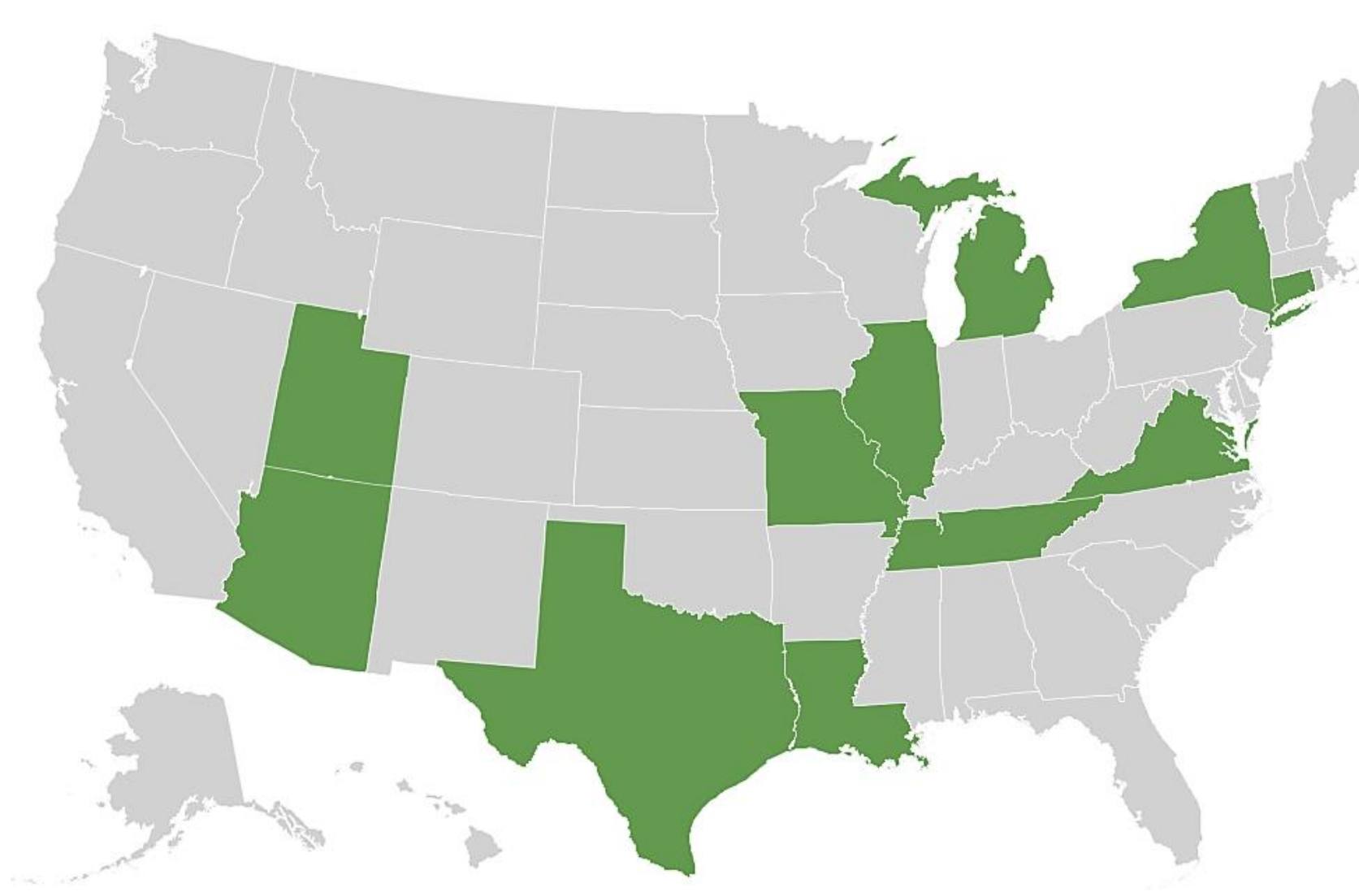
Clinical site locations & map

Table 1 | Current Active Clinical Site Locations

Site Name	City, State	Site Name	City, State
NEXT Virginia	Fairfax, VA	Washington University in St. Louis	St Louis, MO
NEXT Austin	Austin, TX	Louisiana State University	New Orleans, LA
START Midwest	Grand Rapids, MI	Northwestern University	Chicago, IL
START Mountain Region	West Valley City, UT	Yale Cancer Center	New Haven, CT
Tennessee Oncology	Nashville, TN	START New York-Long Island	Lake Success, NY
New York University Langone	New York, NY		
HonorHealth Research Institute	Scottsdale, AZ		

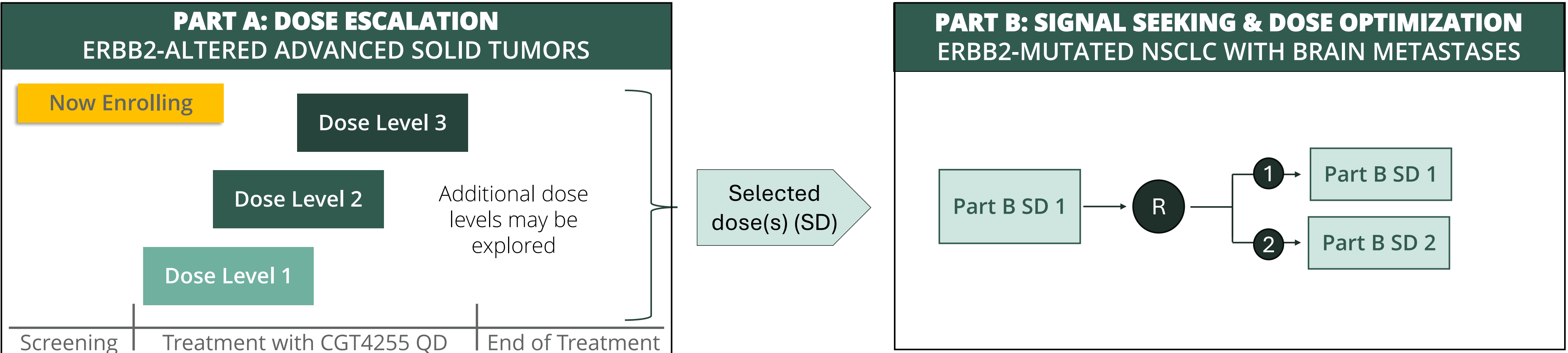
- Sites current as of August 2026; additional sites will open in the future

Figure 5 | Map of Current Active Clinical Sites Locations



Open-label, Phase 1/1b study of CGT4255 in adults with advanced solid tumors harboring ERBB2-activating alterations or HER2 overexpression (NCT07361562)¹⁸

Figure 4 | CGT4255 Phase 1/1b Study Design



PART A: DOSE ESCALATION IN PATIENTS WITH ERBB2-ALTERED ADVANCED SOLID TUMORS

Key Eligibility Criteria^a

- Histologically confirmed diagnosis of locally advanced, metastatic, and/or unresectable solid tumor
- Documented ERBB2-activating alteration (i.e., gene amplifications, point mutations, insertions and short variants, or rearrangements) or NRG1 gene fusion in blood and/or tumor or HER2 overexpression in tumor

Objective & Endpoints

- Primary Objective:** Determine the maximum tolerated or evaluated dose of CGT4255
- Primary Endpoint:** Safety (Incidence and Grade of AEs)
- Secondary Endpoints:** Plasma PK, Overall ORR^b, DCR^c

PART B: SIGNAL SEEKING IN PATIENTS WITH NSCLC WITH BRAIN METASTASES

Key Eligibility Criteria^a

- Histologically confirmed diagnosis of locally advanced, metastatic, and/or unresectable NSCLC
- Documented ERBB2 mutation in blood and/or tumor
- Measurable disease per RECIST v1.1
- CNS involvement of at least 1 active BM ≥5 mm

Objective & Endpoints

- Primary Objective:** Evaluate the antitumor activity of CGT4255
- Primary Endpoint:** Overall ORR^b
- Secondary Endpoints:** DCR^c, DOR^d, PFS^e, Safety, Plasma & CSF PK, Additional Intracranial Assessments

^aOther inclusion and exclusion criteria apply.
^bConfirmed complete response + confirmed partial response of all lesions (intracranial and extracranial) based on investigator assessment using whole-body RECIST v1.1.
^cOverall confirmed complete response + confirmed partial response + stable disease based on investigator assessment using whole-body RECIST v1.1.
^dTime from first confirmed response (complete or partial) to progressive disease or death from any cause, whichever occurs earlier.
^eTime from first dose of study drug to progressive disease, based on investigator assessment using whole-body RECIST v1.1, or death from any cause, whichever occurs earlier.

Summary

- CGT4255 is an investigational, oral, highly selective, CNS-penetrant ERBB2 inhibitor with potency against wild-type and mutant ERBB2
- Nonclinical data supported initiation of the first-in-human study (NCT07361562) of CGT4255 in adults with advanced solid tumors harboring ERBB2-activating alterations or HER2 overexpression
- Part A is enrolling, and Part B is planned to initiate in patients with ERBB2-mutated NSCLC with brain metastases, at select sites in the United States

AE, adverse event; BM, brain metastases; CNS, central nervous system; CSF, cerebrospinal fluid; DCR, disease control rate; DOR, duration of response; EGFR, epidermal growth factor receptor; NRG1, neuregulin 1; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetics; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors Version 1.1; SD, selected dose; TKI, tyrosine kinase inhibitor.

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