HER2CLIMB-04: PHASE 2 TRIAL OF TUCATINIB + TRASTUZUMAB DERUXTECAN IN PATIENTS WITH HER2+ LOCALLY ADVANCED OR METASTATIC BREAST CANCER WITH AND WITHOUT BRAIN METASTASES (ONGOING CLINICAL TRIAL)

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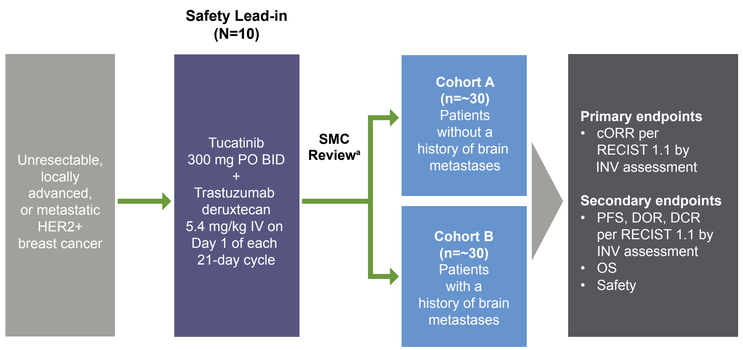
Background and Rationale

- Breast cancer is the most common cancer in women and the second-most common cause of cancer-related death with 43,600 deaths estimated in the US in 2021.[1]
- Approximately 15%–20% of breast cancers overexpress HER2.[2,3]
- HER2+ MBC remains incurable and patients will ultimately progress on currently available therapies.[4–6]
- Up to 50% of patients with HER2+ MBC will develop brain metastases over their disease course.[7]
- Tucatinib is an oral TKI highly selective for HER2 with minimal inhibition of EGFR.[8]
- Tucatinib is approved in the US for use in combination with trastuzumab and capecitabine in patients with HER2+ MBC, with and without brain metastases, who have received ≥1 prior anti–HER2-based regimens in the metastatic setting.[9]
- Tucatinib in combination with trastuzumab and capecitabine is the first treatment regimen to demonstrate a statistically significant and clinically meaningful improvement in PFS and OS in patients with HER2+ MBC, with or without brain metastases and who have received prior trastuzumab, pertuzumab, and trastuzumab emtansine.[10,11]
- Trastuzumab deruxtecan, an ADC comprising a HER2-directed monoclonal antibody conjugated to a topoisomerase I inhibitor payload, is approved in the US for patients with HER2+ MBC who have received ≥2 prior anti–HER2-based regimens in the metastatic setting.[12]
- Trastuzumab deruxtecan showed durable antitumor activity in patients with HER2+ MBC previously treated with trastuzumab emtansine.[13]
- In HER2+ breast cancer xenograft models, tucatinib increased the antitumor activity of a HER2-directed ADC comprising a HER2-directed monoclonal antibody conjugated with 8 exatecan moieties (T-Ex) when compared to T-Ex alone.[14]
- Clinical data suggest there are no major overlapping toxicities between each of the regimens.[10,11,13]
- Combining tucatinib with trastuzumab deruxtecan may result in further improvement on the efficacy seen with both agents individually.

Study Design

- HER2CLIMB-04 (NCT04539938) is a single-arm, open-label, multicenter, phase 2 study evaluating the efficacy and safety of tucatinib in combination with trastuzumab deruxtecan in patients with unresectable, locally advanced, or metastatic HER2+ breast cancer, with or without brain metastases, who have received ≥2 HER2-based regimens in the metastatic setting (**Figure 1**).

Figure 1: HER2CLIMB-04 Study Design



[a]If there are no safety signals in the safety lead-in (≥1 cycle), 50 additional patients will be enrolled in the study.

Eligibility

Table 1: Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Histologically confirmed HER2+ LA or MBC[a] • Received ≥2 prior anti–HER2-based regimens in the metastatic setting • Progression of unresectable LA or MBC after last systemic therapy, or intolerant of last systemic therapy • Measurable disease per RECIST 1.1 • ≥18 years • Adequate baseline hematologic, hepatic, and cardiac function • ECOG performance status of 0 or 1 • Life expectancy of ≥6 months	• Previously had: ◦ Lapatinib or neratinib within 12 months of starting study treatment[b] ◦ Tucatinib (or enrolled on a tucatinib clinical trial) ◦ Any investigational HER2/EGFR or HER2 TKI ◦ Trastuzumab deruxtecan or another ADC consisting of an exatecan derivative ◦ Any systemic anticancer therapy or experimental agent ≤21 days after first dose of study treatment or are currently participating in another interventional clinical trial[c] ◦ Non-CNS radiation ≤7 days prior to first dose of study treatment ◦ Major surgery <28 days from first dose of study treatment • Clinically significant cardiopulmonary disease ◦ Current ILD/pneumonitis ◦ History of ILD/pneumonitis that required systemic corticosteroids ◦ Suspected ILD/pneumonitis which cannot be ruled out at screening

[a]As defined by the current American Society of Clinical Oncology – College of American Pathologists guidelines, previously determined at a Clinical Laboratory Improvements Amendments-certified or International Organization for Standardization-accredited laboratory.
[b]Except in cases where lapatinib or neratinib was given for ≤21 days and was discontinued for reasons other than disease progression or severe toxicity.
[c]An exception for the washout of hormonal therapies is gonadotropin-releasing hormone agonists used for ovarian suppression in premenopausal women, which are permitted concomitant medications.

Table 2: CNS Eligibility Criteria[a]

Key CNS Inclusion Criteria	Key CNS Exclusion Criteria
• Patients with a history of brain metastases must have 1 of the following: ◦ Untreated brain metastases not needing immediate local therapy ◦ Previously treated brain metastases ▪ Brain metastases previously treated with local therapy may either be stable or have progressed since prior local CNS therapy ▪ Patients treated with CNS local therapy for newly identified or previously treated progressing lesions found on contrast brain MRI performed during screening may be eligible to enroll if all the predefined criteria are met	• Based on medical history and screening contrast brain MRI, patients must not have any of the following: ◦ Brain metastases requiring immediate local therapy ◦ Untreated brain lesions >2.0 cm in size[b] ◦ Ongoing treatment with corticosteroids for control of symptoms of brain metastases at a total daily dose of >2 mg dexamethasone or equivalent ◦ Known or suspected leptomeningeal disease ◦ Poorly controlled generalized or complex partial seizures or manifest neurological progression due to brain metastases

[a]A full list of brain metastases inclusion and exclusion criteria can be found at: https://www.clinicaltrials.gov/ct2/show/NCT04539938.
[b]Unless discussed with medical monitor and approval for enrollment is given.

Assessments

Efficacy[a]

- Primary and secondary efficacy assessments will be made by the INV according to RECIST 1.1.
- Exploratory efficacy assessments will be made by ICR according to RECIST 1.1.
- Contrast MRI scan of the brain will be performed for all patients at screening or baseline.

PK

- Plasma and serum PK samples for analysis of tucatinib will be performed from baseline through Cycle 6.

Safety and Tolerability

- Adverse events will be recorded and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 criteria.

Patient-Reported Outcomes

- The EQ-5D-5L instrument will be used.[b]

[a]Assessments every 6 weeks through Week 24, then every 9 weeks through end of treatment.
[b]To be completed prior to evaluation by study personnel and administration of study treatment on treatment days.

Endpoints

Table 3: Endpoints

Primary

- cORR per RECIST 1.1 by INV assessment

Secondary

- PFS, DOR, and DCR per RECIST 1.1 by INV assessment
- OS
- Safety

Exploratory

- cORR, PFS, DOR, and DCR per RECIST 1.1 by ICR assessment
- PK
- Change from baseline in patient-reported outcomes by EQ-5D-5L
- Biomarkers of response, resistance, or toxicity from blood-based or tumor samples

Statistical Analysis

- Efficacy and safety will be summarized using descriptive statistics.
- The response rate will be estimated and reported with 2-sided 95% exact confidence intervals using the Clopper-Pearson method.

Summary

- The HER2CLIMB-04 trial is investigating the efficacy and safety of tucatinib in combination with trastuzumab deruxtecan in patients with unresectable, locally advanced, or metastatic HER2+ breast cancer, with or without brain metastases and who have received ≥2 HER2-based regimens in the metastatic setting.
- Combining tucatinib with trastuzumab deruxtecan, which targets HER2 through different mechanisms of action, may result in further improvement on the efficacy seen with either agent individually.
- Enrollment began in late 2020 at ~30 study sites in the US.

Abbreviations

ADC, antibody–drug conjugate; BID, twice weekly; CNS, central nervous system; cORR, confirmed overall response rate; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EQ-5D-5L, EuroQol-5 dimension-5 level; HER2, human epidermal growth factor receptor 2; ICR, independent central review; ILD, interstitial lung disease; INV, investigator; IV, intravenous; LA, locally advanced; MBC, metastatic breast cancer; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PO, orally; RECIST, Response Evaluation Criteria in Solid Tumors; SMC, Safety Monitoring Committee; TKI, tyrosine kinase inhibitor.

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