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

Erika Hamilton[1], Jorge Ramos[2], Wentao Feng[2], Ian Krop[3]

[1]Sarah Cannon Research Institute/Tennessee Oncology PLLC, Nashville, TN, USA; [2]Seagen Inc., Seattle, WA, USA; [3]Dana-Farber Cancer Institute, Boston, MA, USA

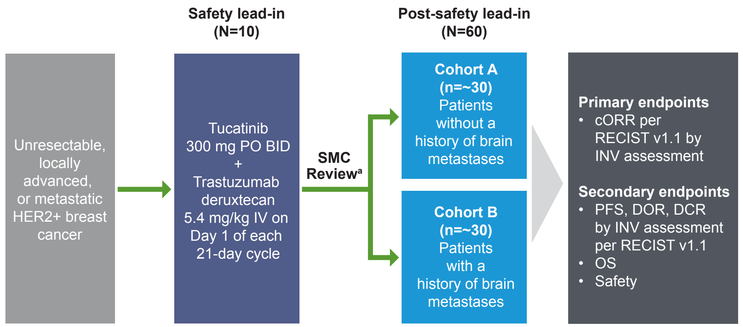
Background and Rationale

- Breast cancer is the most commonly occurring cancer in women, and the second-most common cancer overall with more than 2 million new cases globally in 2018.[1]
- Approximately 15–20% of breast cancers overexpress HER2.[2,3]
- MBC remains incurable, and third-line patients generally experience disease progression within 1 year of therapy.[4–6]
- Up to 50% of patients with HER2+ MBC will develop brain metastases over their disease course.[7,8]
- Tucatinib is an oral TKI highly selective for HER2 with minimal inhibition of EGFR.[9]
- Tucatinib in combination with trastuzumab and capecitabine is approved for the treatment of patients with HER2+ MBC, including those with brain metastases, who have received prior anti-HER2 therapy.[10,11]
- Tucatinib in combination with trastuzumab and capecitabine is the first treatment regimen to demonstrate a statistically significant and clinically meaningful improvement in OS and PFS in patients with HER2+ MBC, with and without brain metastases, who have received prior trastuzumab, pertuzumab, and T-DM1.[12]
- Trastuzumab deruxtecan is an ADC composed of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor.[13]
- In the DESTINY-Breast01 study of patients with HER2+ MBC previously treated with trastuzumab emtansine, trastuzumab deruxtecan showed durable antitumour activity.[13]
- Tucatinib increased the antitumour activity of a HER2-directed ADC comprised of trastuzumab conjugated with exatecan moieties, similar to trastuzumab deruxtecan, in preclinical models of HER2+ breast cancer.[14]
- Clinical data suggest no major overlapping toxicities observed with tucatinib in combination with trastuzumab and capecitabine, and trastuzumab deruxtecan monotherapy.[12,13]
- 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, multicentre, phase 2 study designed to evaluate 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-directed regimens in the metastatic setting.

Figure 1: HER2CLIMB-04 Study Design



[a]If there are no safety signals in the safety lead-in, 50 additional patients will be enrolled in the post-safety lead-in.

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 v1.1 • ≥18 years • Adequate baseline haematologic, hepatic, and cardiac function • ECOG performance status of 0 or 1 • Life expectancy of ≥6 months	• Previously treated with: ◦ 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 of 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 ◦ History of interstitial lung disease/pneumonitis

[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 may 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 for this study may be eligible to enrol 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 at a total daily dose of >2 mg dexamethasone or equivalent ◦ Known or suspected leptomeningeal disease ◦ Poorly controlled generalised 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 enrolment is given.

Assessments

Efficacy[a]
- Primary and secondary efficacy assessments will be made by the INV according to RECIST v1.1
- Exploratory efficacy assessments will be made by ICR according to RECIST v1.1
- 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 v1.1 by INV assessment

Secondary
- PFS, DOR, and DCR per RECIST v1.1 by INV assessment
- OS
- Safety

Exploratory
- cORR, PFS, DOR, and DCR per RECIST v1.1 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 tumour-samples

Summary

- Tucatinib in combination with trastuzumab and capecitabine is approved for the treatment of patients with HER2+ MBC, including those with brain metastases, who have received prior anti-HER2 therapy.[10,11]
- The HER2CLIMB-04 trial is assessing the efficacy and safety of tucatinib in combination with trastuzumab deruxtecan in patients with HER2+ MBC, with or without brain metastases, who have received ≥2 HER2-directed regimens in the metastatic setting.
- Enrolment is underway in the USA.
- Total number of planned sites: ~30.

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; HER2, human epidermal growth factor receptor 2; ICR, independent central review; INV, investigator; IV; intravenous; LA, locally advanced; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PO; orally; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SMC, Safety Monitoring Committee; T-DM1, trastuzumab emtansine; TKI, tyrosine kinase inhibitor.

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