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)

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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 4–6 months of therapy.4,5
- Up to 50% of patients with HER2+ MBC will develop brain metastases over their disease course.1,3
- Tucatinib is an oral TKI highly selective for HER2 with minimal inhibition of EGFR.6,7
- 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.1,7
- 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 TDM4,7
- Trastuzumab deruxtecan is an ADC composed of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor.8,9
- In the DESTINY-Breast01 study of patients with HER2+ MBC previously treated with trastuzumab emtansine, trastuzumab deruxtecan showed durable antitumour activity.8,9
- 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.8
- Clinical data suggest no major overlapping toxicities observed with tucatinib in combination with trastuzumab and capecitabine, and trastuzumab deruxtecan monotherapy.10,11
- 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 to evaluate the efficacy and safety of tucatinib in combination with trastuzumab deruxtecan in patients with unrespectable, locally advanced, or metastatic HER2+ breast cancer, with or without brain metastases, who have received 2 HER2-directed regimens in the metastatic setting.

Table 1: Eligibility Criteria

<table>
<thead>
<tr>
<th>Key Inclusion Criteria</th>
<th>Key Exclusion Criteria</th>
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</thead>
<tbody>
<tr>
<td>- Histologically confirmed HER2+ LA or MBC</td>
<td>- Previously treated with:</td>
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<tr>
<td>- Received ≥2 prior anti-HER2-based regimens in the metastatic setting</td>
<td>- Locally recurrent or within 12 months of starting study treatment</td>
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<td>- Progression of unresectable LA or MBC after last prior systemic therapy</td>
<td>- Tucatinib (or enrolled on a tucatinib clinical trial)</td>
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<tr>
<td>- Unresectable disease per RECIST v1.1</td>
<td>- Any investigational HER2/EGFR or TKI</td>
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| - ≥18 baseline haematologic, hepatic, and renal function per study requirements | - Trastuzumab deruxtecan or another ADC consisting of an
| - Life expectancy of ≥6 months | - Any systemic anti-cancer or experimental agent that is currently being considered or has been used within 8 weeks of starting study treatment |

Table 2: CNS Eligibility Criteria

<table>
<thead>
<tr>
<th>Key CNS Inclusion Criteria</th>
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</tr>
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<tbody>
<tr>
<td>- Patients with a history of brain metastases must have ≥1 ≥6-months</td>
<td>- Patients must have not had any of the following:</td>
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<tr>
<td>- Unresected brain metastases not meeting immediate local therapy</td>
<td>- Brain metastases resected with local therapy may either be stable or may have progressed since prior CNS local therapy</td>
</tr>
<tr>
<td>- Previously treated with local therapy</td>
<td>- Brain metastases previously treated with local therapy may either be stable or may have progressed since prior CNS local therapy</td>
</tr>
<tr>
<td>- Brain metastases previously treated with local therapy may either</td>
<td>- Brain metastases resected ≥2 cm in size at study entry</td>
</tr>
<tr>
<td>be stable or may have progressed since prior CNS local therapy</td>
<td>- Comparable tumour burden across 5 cm or more daily dose of ≥2 mg dexrazoxane or equivalent</td>
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<tr>
<td>- Patients treated with CNS local therapy for newly</td>
<td>- Poorly controlled generalised or multiple extracranial, or uncontrolled neurological progression due to brain metastases</td>
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<tr>
<td>identified or previously treated progressing lesions</td>
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Figure 1: HER2CLIMB-04 Study Design

Table 3: Endpoints

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Secondary endpoints</th>
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<tbody>
<tr>
<td>cORR per RECIST v1.1 by INV assessment</td>
<td>PFS, DOR, and DCR per RECIST v1.1 by INV assessment</td>
</tr>
<tr>
<td>OS</td>
<td>Safety</td>
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Exploratory endpoints
- ORR, 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-borne 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.1,7
- 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; LA, locally advanced; CNS, central nervous system; ORR, overall response rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; LHR, life expectancy of ≥6 months; MBC, metastatic breast cancer; PFS, progression-free survival; DCR, durable complete response; CR, complete response; RR, response rate; OS, overall survival; INV, investigator; ICR, independent central review; RECIST, Response Evaluation Criteria in Solid Tumors; cORR, confirmed overall response rate; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; SOR, standard overall response rate; EMA, European Medicines Agency; CNS, central nervous system; TKI, tyrosine kinase inhibitor.

Assessments
- Efficacy
  - 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
- 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 health questionnaire may be used.
- Assessments may be performed every 4 weeks throughout the study, or every 6 weeks through end of treatment

References