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# HERTHENA-Breast01: A Phase 1b/2, Multicenter, Open-Label, Dose-Finding Study to Evaluate the Safety and Antitumor Activity of Patritumab Deruxtecan (HER3-DXd) in Human Epidermal Growth Factor Receptor 2–Positive Unresectable Locally Advanced or Metastatic Breast Cancer

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## Background

- Human epidermal growth factor receptor 2 (HER2)–targeted antibody-drug conjugates (ADCs) have improved outcomes in HER2-positive (HER2+) advanced and metastatic breast cancer; however, safe and effective later-line therapies are needed for patients who have disease progression following treatment with trastuzumab deruxtecan (T-DXd)[1,2]
- Human epidermal growth factor receptor 3 (HER3) is overexpressed in 50%–70% of breast cancers,[3] including in HER2+ subtypes.[4] HER3 overexpression is associated with poor prognosis and may have a role in the development of drug resistance, including to HER2-targeted therapy[3]
- Patritumab deruxtecan (HER3-DXd), a novel ADC that selectively binds HER3, is composed of a fully human anti-HER3 IgG1 antibody linked to a cytotoxic topoisomerase I inhibitor via a stable tetrapeptide-based linker that is selectively cleaved within tumor cells
  - HER3-DXd has a drug-to-antibody ratio of ~8
- In a phase 1/2 study, HER3-DXd monotherapy showed durable antitumor activity and a manageable safety profile in heavily pretreated participants across breast cancer subtypes, including those with HER2+, HER3-expressing metastatic breast cancer[5]
  - In the 14 participants with HER2+, HER3-expressing breast cancer, the objective response rate (ORR) was 43% (95% CI, 18%–71%), median progression-free survival (PFS) was 11.0 (95% CI, 4.4–16.4) months, and median overall survival (OS) was 19.5 months (95% CI, 12.2 months to not evaluable)
- HERTHENA-Breast01 (NCT06686394) is a phase 1b/2 study evaluating the safety, pharmacokinetic parameters, and preliminary antitumor activity of HER3-DXd in combination with anti-HER2 agents in participants with HER2+ unresectable locally advanced or metastatic breast cancer

## Objectives

### Primary

- Evaluate the safety of HER3-DXd in combination with anti-HER2 agent(s) for each treatment arm, including
  - Dose-limiting toxicities (DLTs)
  - Adverse events (AEs)
  - Treatment discontinuation due to AEs

### Secondary

- Evaluate the pharmacokinetic parameters of HER3-DXd in combination with anti-HER2 agent(s) for each treatment arm, including
  - $C_{max}$, $C_{trough}$, and area under the concentration-time curve (where feasible) of HER3-DXd
  - Total HER3-DXd antidrug antibodies
  - Free DXd payload

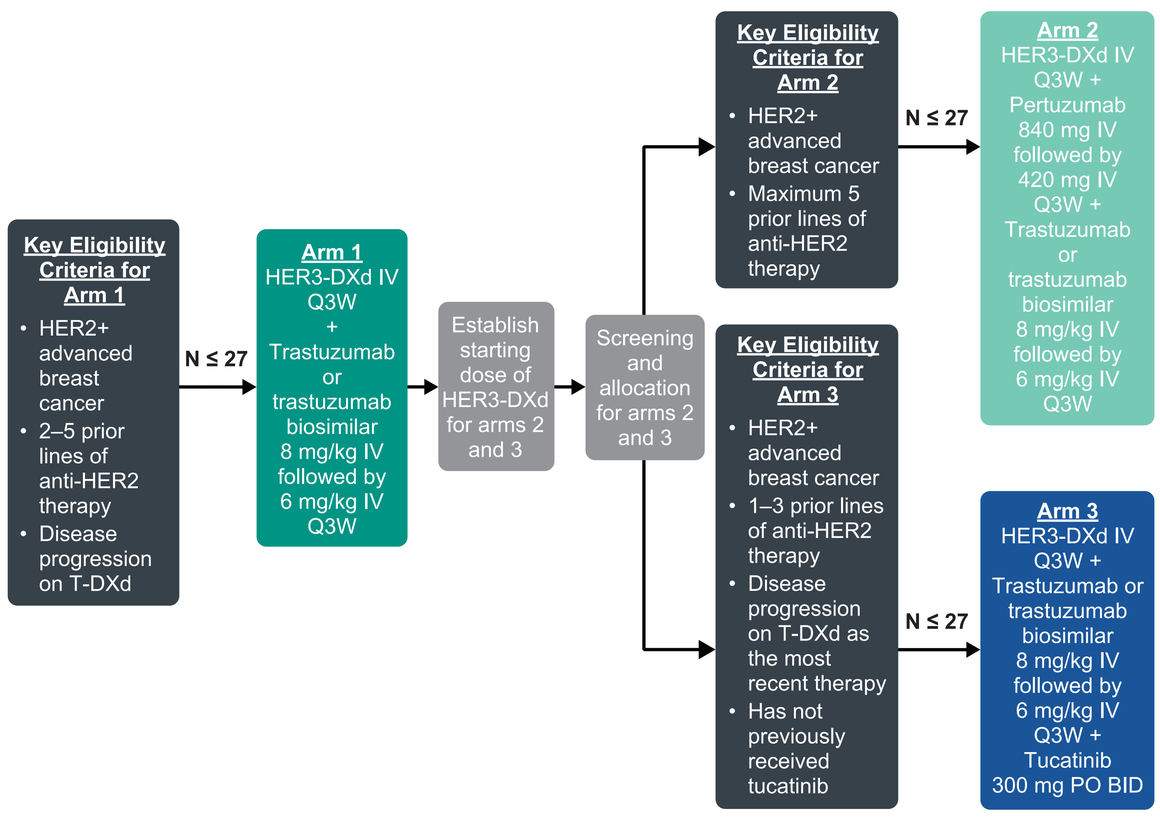
### Exploratory

- Evaluate the efficacy of HER3-DXd in combination with anti-HER2 agent(s) for each treatment arm

## Methods

### Study design, participants, and treatment

**Figure. Study design of HERTHENA-Breast01 (NCT06686394)**




BID, twice daily; IV, intravenously; PO, orally; Q3W, every 3 weeks.

### Assessments

- AEs are monitored from the time of treatment allocation until 30 days after the last dose of study treatment and are graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0
- Blood samples for pharmacokinetic measurements are collected at prespecified times during cycles 1–4, every 2 cycles until cycle 8, and at end of treatment
- Tumor imaging is performed at baseline, every 6 weeks from day 1 of cycle 1 through week 24, and every 12 weeks thereafter

### Analyses

- Safety will be assessed in all participants who receive ≥1 dose of study treatment and analyzed according to the treatment received (all-participants-as-treated population)
- DLTs will be assessed in all-participants-as-treated who meet the criteria for DLT evaluability
- Pharmacokinetic parameters will be assessed in all participants who receive ≥1 dose of study treatment and have available pharmacokinetic measurements
- Efficacy will be assessed in all participants who receive ≥1 dose of study treatment and have measurable disease at baseline
- Dose level decisions (ie, escalation and de-escalation) will be performed based on the Bayesian Optimal Interval design in all 3 arms
  - On completion of dose finding in arm 1, the dose levels in arms 2 and 3 will be selected from the prespecified dose levels tested in arm 1, based on the totality of data from arm 1

**Table. Key eligibility criteria**

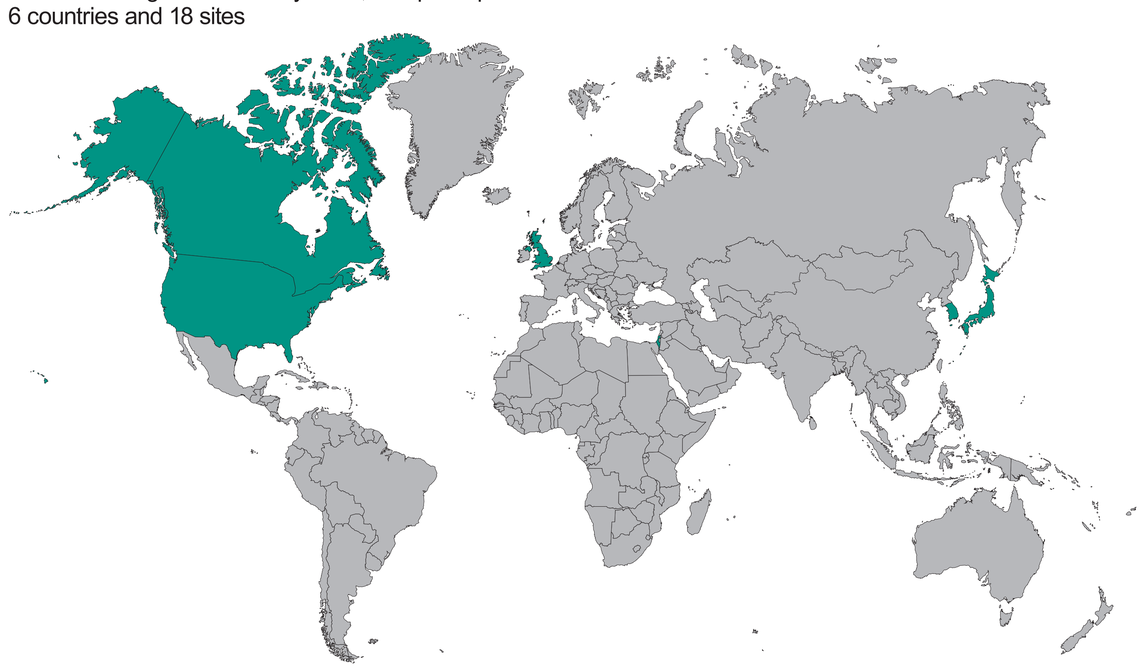
| Inclusion criteria | Exclusion criteria |
|---|---|
| Aged ≥18 y | Prior treatment with an ADC that comprises an exatecan derivative other than T-DXd.<br>Prior trastuzumab emtansine treatment is permitted |
| Histologically confirmed HER2+[a] unresectable locally advanced or metastatic breast cancer | Arm 3 only: prior treatment with tucatinib, lapatinib, neratinib, or any investigational HER2-targeted tyrosine kinase inhibitor in the locally advanced or metastatic setting |
| Has received the following previous treatments: | Prior systemic anticancer therapy, including investigational agents, within 4 wk or 5 half-lives (whichever is shorter) before treatment allocation |
| Arm 1:<br>• 2–5 prior lines of anti-HER2 therapy in the locally advanced or metastatic setting<br>• Has had disease progression on or after any previous T-DXd treatment | Received ICI therapy <21 d before allocation or other monoclonal antibodies (eg, bevacizumab and cetuximab) <28 d before allocation |
| Arm 2:<br>• No more than 5 prior lines of anti-HER2 therapy in the locally advanced or metastatic setting | Received chloroquine or hydroxychloroquine ≤14 d before allocation |
| Arm 3:<br>• Has had disease progression on or after T-DXd treatment in any setting<br>• Maximum of 3 prior lines of anti-HER2 therapy in the locally advanced or metastatic setting<br>• T-DXd must be the most recent therapy received before enrollment | Received endocrine therapy <14 d before allocation |
| Recent or new tumor tissue sample from a nonirradiated metastatic lesion collected on or after the most recent systemic anticancer therapy. Local HER2+, estrogen receptor, and progesterone receptor status must be collected | Is receiving chronic systemic corticosteroids at a dose of prednisone 10 mg equivalent or any form of immunosuppressive therapy before allocation[b] |
| Measurable disease per RECIST version 1.1[c] | Evidence of spinal cord compression or brain metastases, defined as clinically active and symptomatic, or requiring corticosteroid or anticonvulsant treatment to control symptoms[d] |
| ECOG PS of 0 or 1 | Received whole-brain radiotherapy <28 d or stereotactic brain radiotherapy <7 d before allocation |
| Adequate organ function | Received radiotherapy to >30% of the bone marrow or wide field radiation <28 d or palliative radiotherapy <7 d before allocation |

ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitors; IHC, immunohistochemistry; ISH, in situ hybridization.

[a]IHC 3+, IHC2+/ISH+, or IHC undetermined/ISH+ based on local assessment per most recent ASCO/CAP guidelines. The local HER2 results must be from a pretreatment tumor biopsy from a lesion not previously irradiated.
[b]Participants who require use of bronchodilators, inhaled or topical steroids, or local steroid injections may be included in the study.
[c]Lesions in a previously irradiated area are considered measurable if progression has been shown in such lesions.
[d]Participants with clinically inactive or treated brain metastases who are asymptomatic may be included in the study if they have a stable neurological status for ≥4 weeks before day 1 of cycle 1. Prophylactic treatment with anticonvulsants is permitted.

## Current status

- Enrollment began in February 2025, and participants continue to be enrolled across 6 countries and 18 sites



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**Poster presented**

https://bit.ly/4mFWnfO

**Poster slides**

https://bit.ly/3VFzqP9

**PLS presented**

https://bit.ly/4nFa0NC

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