TPS1149

HERTHENA-Breast04: A Phase 3, Randomized, Open-Label Study Evaluating the Efficacy and Safety of Patritumab Deruxtecan (HER3-DXd) versus Treatment of Physician's Choice in Hormone Receptor–Positive/ Human Epidermal Growth Factor Receptor 2–Negative Unresectable Locally Advanced or Metastatic Breast Cancer

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Background

- First-line standard-of-care treatment for patients with hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2−) advanced breast cancer is endocrine therapy (ET) in combination with a cyclin-dependent kinase (CDK) 4/6 inhibitor[1]
- After disease progression or recurrence on first-line therapy, the main treatment options for patients who are not considered suitable for additional endocrine-based therapy or targeted therapies are chemotherapy and antibody-drug conjugates (ADCs)[1]
  - There is potential to develop novel ADCs that expand the set of targetable antigens and improve safety in this patient population
- Human epidermal growth factor receptor 3 (HER3) is overexpressed in 50%–70% of breast cancers,[2] with the highest expression in HR+/HER2− breast cancer.[3] Its overexpression is associated with poor prognosis and drug resistance[2]
- Patritumab deruxtecan (HER3-DXd), a novel ADC directed against HER3, is composed of a fully human anti-HER3 immunoglobulin G1 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 the phase 2 ICARUS-Breast01 study, HER3-DXd showed clinically meaningful antitumor activity and manageable safety in participants with HR+/HER2− advanced breast cancer who had disease progression on CDK4/6 inhibitor treatment and one line of chemotherapy[4]
  - Objective response rate (ORR) was 53.5% (90% CI, 44.8%–62.1%)
  - Median progression-free survival (PFS) was 9.2 (95% CI, 8.0–12.8) months
  - There was preliminary evidence of an association between HER3 expression and efficacy outcomes with HER3-DXd treatment
- HERTHENA-Breast04 (NCT07060807) is a phase 3, multicenter, open-label, randomized study evaluating the efficacy and safety of HER3-DXd monotherapy vs treatment of physician's choice (TPC) in participants with HR+/HER2− unresectable locally advanced or metastatic breast cancer after progression or recurrence on one line of ET plus CDK4/6 inhibitor treatment

Objectives

Primary

- Compare the effect of HER3-DXd monotherapy vs TPC on
  - PFS per RECIST version 1.1 by blinded independent central review (BICR)
  - Overall survival (OS)

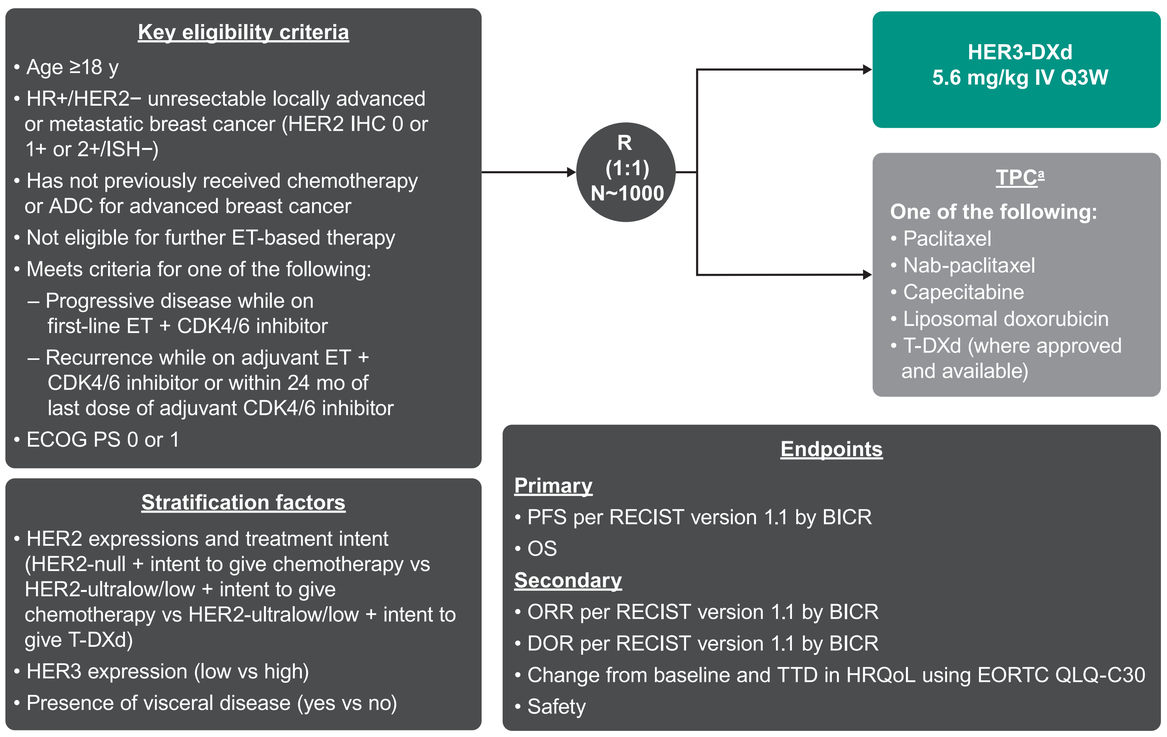
Secondary

- Evaluate the effect of HER3-DXd monotherapy and TPC on
  - ORR per RECIST version 1.1 by BICR
  - Duration of response (DOR) per RECIST version 1.1 by BICR
  - Change from baseline and time to first deterioration (TTD) in health-related quality of life (HRQoL) using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30)
  - Safety

Methods

Study design, participants, and treatment

Figure. Study design of HERTHENA-Breast04 (NCT07060807)



ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenous; Q3W, every 3 weeks; Q4W, every 4 weeks; R, randomization; T-DXd, trastuzumab deruxtecan.
[a]One of the following: (1) paclitaxel 80 mg/m² IV on days 1, 8, 15, and 22 Q4W; (2) paclitaxel 90 mg/m² IV on days 1, 8, and 15 Q4W; (3) nab-paclitaxel 100 mg/m² IV on days 1, 8, and 15 Q4W; (4) capecitabine 1000 mg/m² orally twice daily on days 1 to 14 Q3W; (5) liposomal doxorubicin 50 mg/m² IV on day 1 Q4W; or (6) T-DXd 5.4 mg/kg IV on day 1 Q3W (where approved and available).

Table. Key eligibility criteria

Inclusion criteria	Exclusion criteria
Aged ≥18 y	Breast cancer amenable to treatment with curative intent
HR+/HER2− invasive breast carcinoma that is locally advanced and not amenable to resection with curative intent or metastatic and not treatable with curative intent	Eligible to receive additional endocrine-based treatment in the advanced setting as determined by the investigator
Centrally confirmed HR+,[a] HER2−,[b] and HER3 evaluable results from biopsy of distant metastatic site on or after the most recent line of therapy[c]	Known germline *BRCA* mutation (deleterious or suspected deleterious) where PARP inhibitor(s) is a potential treatment option (ie, available and not medically contraindicated)
Disease progression or recurrence on or after prior ET + CDK4/6 inhibitor with one of the following: • Radiographic disease progression, as assessed by the investigator, on first-line ET + CDK4/6 inhibitor for advanced HR+/HER2− breast cancer.[d] ET + CDK4/6 inhibitor must be the only line of therapy in the advanced setting • Disease recurrence, either radiographic and/or confirmed histologically via biopsy as assessed by the investigator, while on adjuvant ET + CDK4/6 inhibitor or within 24 mo from the last dose of adjuvant CDK4/6 inhibitor[e]	Prior chemotherapy for unresectable locally advanced or metastatic breast cancer
Candidate for at least one TPC option	Prior treatment with an anti-HER3 antibody and/or ADC that consists of a topoisomerase I inhibitor (eg, T-DXd) or any other topoisomerase I inhibitor therapy
Measurable disease per RECIST version 1.1[f]	Prior systemic anticancer therapy within 4 wk or 5 half-lives, whichever is shorter, before randomization[g]
ECOG PS of 0 or 1	Prior radiotherapy for non-CNS disease, or required corticosteroids for radiation-related toxicities, within 14 d of first dose of study treatment
Adequate organ function	Current visceral crisis or at risk for impending visceral crisis that has or may cause imminent organ compromise and/or other life-threatening complications

AKT, protein kinase B; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; ER, estrogen receptor; PgR, progesterone receptor; PI3K, phosphatidylinositol 3-kinase.
[a]ER-positive and/or PgR-positive per most recent ASCO/CAP guidelines. Tumors will be considered HR+ if the tumor shows ≥1% expression of ER and/or PgR.
[b]Per most recent ASCO/CAP guidelines. Tumors will be considered HER2− if the tumor shows HER2 IHC 0, 1+ or IHC 2+/ISH−.
[c]If a sample from a distant (metastatic) site is not available and biopsy of a new metastatic lesion is not feasible, an archival tumor tissue sample from the primary site may be accepted in consultation with the sponsor, unless T-DXd is selected as the TPC, in which case tissue from the primary site will not be permitted. For participants who have metastatic disease with coexisting locally advanced lesions, if a newly obtained biopsy from a distant site is not feasible, a new biopsy from the local recurrence site is permitted.
[d]Participants who received single-agent CDK4/6 inhibitor therapy are not eligible. CDK4/6 inhibitor must have been given in combination with ET to be considered a line of therapy. Participants who received first-line triple therapy with a PI3K inhibitor or AKT inhibitor in combination with ET plus CDK4/6 inhibitor are eligible.
[e]Participants who subsequently received or plan to receive 1 line of endocrine-based therapy in the metastatic setting are not eligible.
[f]Lesions in a previously irradiated area are considered measurable if progression has been shown in such lesions.
[g]Participants previously treated with ET plus a CDK4/6 inhibitor may participate if ≥2 wk have elapsed since the last dose of therapy.

Assessments

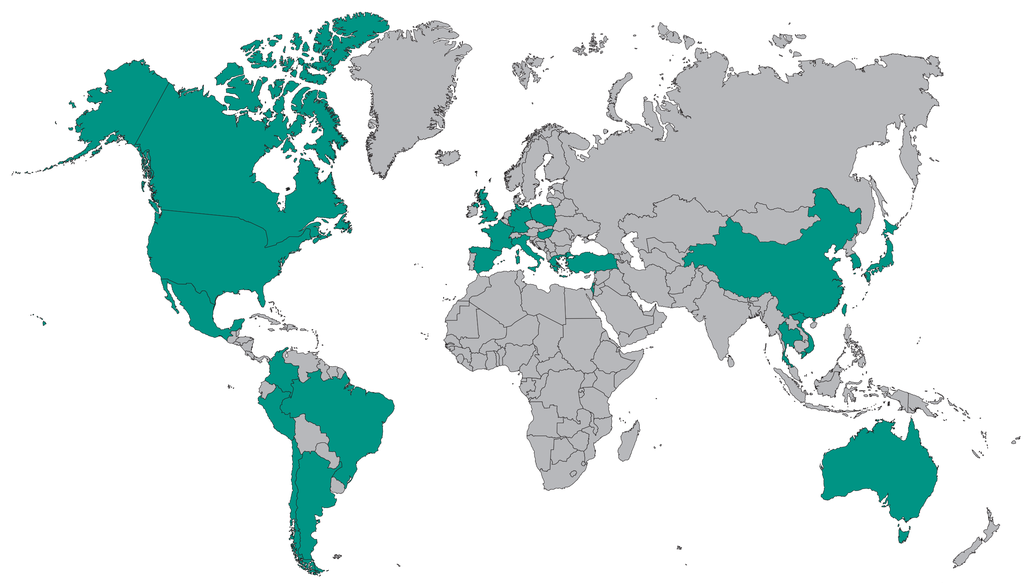
- Tumor imaging is performed at baseline, every 6 weeks from the date of randomization through week 60, and every 12 weeks thereafter
- Adverse events are monitored from randomization until 30 days after the last dose of study treatment and are graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0
- Patient-reported outcome (PRO) questionnaires are administered on day 1 of weeks 1, 4, 7, and 10 of each 12-week cycle for cycles 1–4, then every 12 weeks thereafter

Analyses

- Efficacy will be assessed in all randomized participants (intention-to-treat population)
- Safety will be assessed in all randomized participants who receive ≥1 dose of study treatment (all-participants-as-treated population)
- PROs will be assessed in all randomized participants who have ≥1 PRO assessment for the specific endpoint and have received ≥1 dose of study treatment

Current status

- Enrollment began in July 2025, and participants continue to be enrolled across 26 countries and 210 sites



Plain Language Summary

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Acknowledgments

The authors thank the participants and their families and all investigators and site personnel participating in this study. Funding for this study was provided by Daiichi Sankyo Co., Ltd., and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD). Medical writing support was provided by Tina Nie, PhD, of ICON plc (Blue Bell, PA, USA), and was funded by Daiichi Sankyo Co., Ltd., and MSD. Editorial support was provided in accordance with Good Publication Practice guidelines (https://ismpp.org/gpp-2022).

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https://bit.ly/4cZBKbL

Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; Chicago, IL, USA and online; May 29–June 2, 2026.