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HERTHENA-Breast03: A Phase 2, Randomized, Open-Label Study Evaluating Neoadjuvant Patritumab Deruxtecan (HER3-DXd) Plus Pembrolizumab Before or After Pembrolizumab Plus Chemotherapy for Early-Stage Triple-Negative Breast Cancer (TNBC) or Hormone Receptor–Low Positive (HR-low+)/Human Epidermal Growth Factor Receptor 2–Negative (HER2−) Breast Cancer

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Background

- Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab is a standard of care (SOC) for patients with high-risk, early-stage TNBC[1,2]
  - Due to the biological and clinical similarities between TNBC and HR-low+/HER2− breast cancer, guidelines suggest the latter may also be treated with a TNBC treatment regimen
- Despite recent advances, there remains an unmet medical need for patients who do not achieve a pathologic complete response (pCR) after neoadjuvant therapy who have a high risk of recurrence[3]
- Cyclophosphamide and anthracyclines are associated with long-term toxicities[4]
- New approaches are warranted to improve the efficacy of neoadjuvant therapy to increase the rate of pCR and reduce long-term toxicities
- HER3, which is frequently expressed in breast cancer, has been implicated in disease progression and resistance to different types of cancer therapies[5,6]
- Patritumab deruxtecan (HER3-DXd) is an antibody-drug conjugate (ADC) composed of a fully human anti-HER3 IgG1 monoclonal antibody linked to a topoisomerase I inhibitor via a stable tetrapeptide-based linker that is selectively cleaved within tumor cells[6]
- HERTHENA-Breast03 (NCT06797635) is an open-label, randomized, phase 2 study evaluating neoadjuvant HER3-DXd plus pembrolizumab before or after carboplatin plus paclitaxel plus pembrolizumab for early-stage TNBC or HR-low+/HER2− breast cancer
- Part 1 is a single-arm safety run-in and part 2 is the randomized, 3-arm, phase 2 study

Objectives

Part 1

Primary objective:

- Evaluate safety and tolerability by analyzing the incidence of adverse events (AEs), dose-limiting toxicities (DLTs), and AEs leading to discontinuation

Part 2

Primary objective:

- Evaluate pCR (ypT0/Tis ypN0; defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the completely resected breast specimen and all sampled regional lymph nodes after completion of neoadjuvant systemic therapy) at the time of definitive surgery assessed by local pathologist
- Evaluate safety and tolerability by analyzing the incidence of AEs and AEs leading to discontinuation

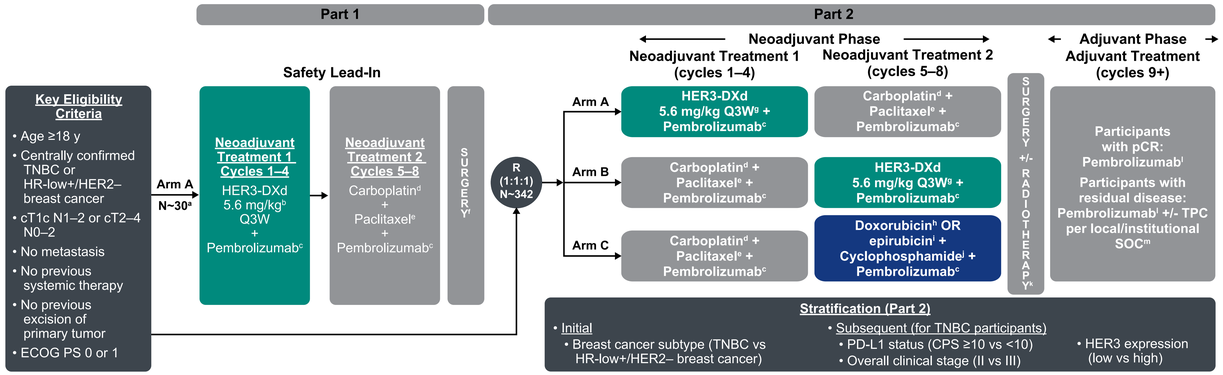
Secondary objectives:

- Evaluate pCR-no ductal carcinoma in situ (pCR-no DCIS; ypT0 ypN0; defined as the absence of residual invasive and in situ cancer on hematoxylin and eosin evaluation of the completely resected breast specimen and all sampled regional lymph nodes after completion of neoadjuvant systemic therapy) at the time of definitive surgery assessed by local pathologist
- Evaluate event-free survival (EFS; defined as the time from randomization to progression of disease that precludes surgery, local or distant recurrence, or death due to any cause, whichever occurs first) assessed by investigator
- Evaluate overall survival (OS; defined as the time from randomization to date of death due to any cause)
- Evaluate distant progression– or distant recurrence–free survival (DPDRFS; defined as the time from randomization to first distant progression or distant recurrence event, or death due to any cause, whichever occurs first) assessed by investigator
- Evaluate residual cancer burden (RCB; defined as residual disease in either the breast or lymph nodes) at the time of definitive surgery assessed by local pathologist

Methods

Study design, participants, and treatment

Figure. HERTHENA-Breast03 study design (NCT06797635)



AUC, area under the concentration-time curve; ECOG PS, Eastern Cooperative Oncology Group performance status; TPC, treatment of physician's choice.
[a]N ≥10 and ≤30.
[b]HER3-DXd may be evaluated at a lower dose level if dose de-escalation is warranted as guided by the BOIN design.
[c]200 mg Q3W.
[d]AUC 1.5 mg/mL/min QW.
[e]80 mg/m² QW.
[f]Surgery should occur approximately 3-6 weeks after the last dose of neoadjuvant treatment. Further therapy may include radiation and systemic adjuvant therapy off-study as clinically indicated.
[g]HER3-DXd may be evaluated at reduced dose level if dose de-escalation is warranted as guided by BOIN design in Part 1.
[h]60 mg/m² Q3W.
[i]90 mg/m² Q3W.
[j]600 mg/m² Q3W.
[k]Postoperative radiotherapy, if clinically indicated, will be administered concurrently with or before initiation of adjuvant pembrolizumab.
[l]400 mg Q6W for 5 cycles.
[m]Additional TPC options depend on the study arm and germline *BRCA* mutation status. Options include capecitabine (all arms), doxorubicin or epirubicin (physician's choice) and cyclophosphamide (arms A and B), or olaparib (all arms; for participants with known deleterious or suspected deleterious germline *BRCA* mutations where olaparib is approved and available).

Assessments

Part 1

- HER3-DXd may be evaluated in up to 3 dose levels (5.6, 4.8 and 3.2 mg/kg)
- AEs will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0
- Safety lead-in assessment of DLTs will be performed during the 21 days after the first dose (cycle 1) in up to 30 participants (up to 10 participants per dose level)
- The Bayesian optimal interval design (BOIN) with a target DLT rate of 30% will be used to determine an acceptable dose level for Part 2

Part 2

- Assessments include pCR (by local pathologist), EFS (by investigator), OS, RCB (by local pathologist), and DPDRFS (by investigator)
- AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0

Analyses

Part 1

- Safety will be assessed in the all-participants-as-treated population (i.e. all allocated participants who receive ≥1 dose of study intervention) and analyzed by dose level
- The DLT-evaluable population includes participants in the all-participants-as-treated population who completed cycle 1 days 1–21 of neoadjuvant treatment 1 without a DLT or who experienced a DLT during cycle 1 days 1–21

Part 2

- Safety will be assessed (separately from Part 1) in all-participants-as-treated (all randomized participants who receive ≥1 dose of study intervention) and analyzed according to treatment received
- Efficacy will be evaluated in the intention-to-treat population, which will include all randomized participants
- For pCR (ypT0/Tis ypN0), differences between groups and corresponding 95% CIs will be analyzed using the stratified Miettinen and Nurminen method; point estimates and exact Clopper-Pearson 95% CIs will be provided
  - pCR-no DCIS will be analyzed similarly
- Hypothesis testing will only be performed for pCR (ypT0/Tis ypN0)
- For EFS, OS, and DPDRFS, the survival time will be estimated by the nonparametric Kaplan-Meier method; hazard ratios and 95% CIs will be estimated using an unstratified Cox proportional hazard model with the Efron method of tie handling
- Descriptive statistics will be provided for RCB

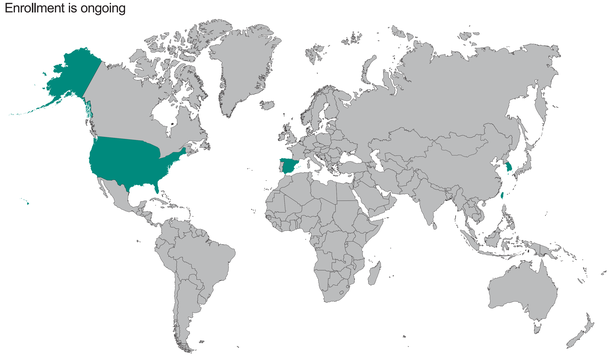
Table. Key eligibility criteria

Inclusion criteria	Exclusion criteria
• Age ≥18 y • Locally advanced nonmetastatic (AJCC stage cT1c, N1–N2 or cT2–cT4, N0–N2) TNBC[a] or HR-low+/HER2–[b] breast cancer • Provision of tumor tissue from core needle biopsy of primary breast tumor for central assessment of histology, ER, PgR, HER2, HER3, and PD-L1 status at screening • ECOG PS of 0 or 1 within 28 d before first dose of study treatment • Adequate organ function	• Receipt of prior radiation therapy, systemic therapy, or definitive surgery for currently diagnosed breast cancer • Prior therapy with an anti–PD-1, anti–PD-L1, or anti–PD-L2 treatment or an agent directed to another stimulatory T-cell receptor • Receipt of systemic anticancer therapy including investigational agents ≤4 wk before randomization • Receipt of prior treatment with an anti-HER3 antibody or an ADC that contains an exatecan derivative that is a topoisomerase I inhibitor

AJCC, American Joint Committee on Cancer; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; ER, estrogen receptor; PgR, progesterone receptor.
[a]Defined as <1% of ER and PgR expression on cells and HER2− per ASCO/CAP guidelines.
[b]Defined as 1%–10% of ER expression and HER2− per ASCO/CAP guidelines; any level of PgR expression allowed for HR-low+/HER2− breast cancer.

Current Status

- Enrollment is ongoing



References

1. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Breast Cancer. Version 6.2024. www.nccn.org/patients.
2. Keytruda (pembrolizumab). Full Prescribing Information, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, 2024.
3. Schmid P, et al. *N Engl J Med*. 2020;382(9):810-821.
4. Guarneri V and de Azambuja E. *ESMO Open*. 2022;7(3):100461.
5. Gandullo-Sanchez L, et al. *J Exp Clin Cancer Res*. 2022;41(1):310.
6. Uliano J, et al. *ESMO Open*. 2023;8(1):100790.

Poster presented
https://bit.ly/4hqWxHc

Plain language summary
https://bit.ly/4opa4Sb

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