Trial in Progress: Open-label Single-arm Phase 2 Trial of Trastuzumab Deruxtecan in Previously Treated HER2-Immunohistochemistry (IHC) 0 Advanced Breast Cancer – HER2 PARADIGM trial

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Background:

- Trastuzumab-deruxtecan (T-DXd) showed impressive efficacy in patients whose breast cancers are either human epidermal growth factor receptor 2 (HER2) immunohistochemistry (IHC) positive or HER2-low/ultralow.[1-3]
- In a phase 2 trial, patients with HER2-IHC 0 who received T-DXd had an objective response rate of approximately 30%, revealing activity regardless of HER2-IHC status.[4]
- In this study, we will treat patients with advanced HER2 IHC 0 breast cancers with T-DXd and assess biomarkers of response and resistance to therapy.
- We will evaluate patients' breast cancer tissue with quantitative HER2 tests, including the HER2 Troplex testing[5] (Figures 1 and 2), that could help determine if T-DXd is active in patients withHER2-IHC 0 tumors regardless of HER2 quantitative expression or if there is a potentially optimal cutoff value of HER2 expression with respect to clinical outcomes.

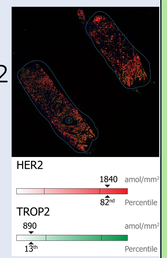


Figure 1. Report of quantitative measurements of HER2 and TROP2 by the Troplex assay [5]

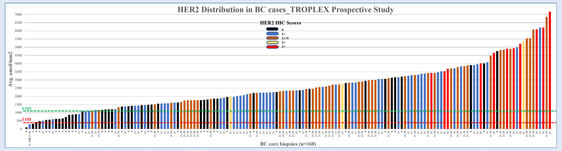


Figure 2. Troplex assay results as a histogram of 160 measurements of HER2 from breast cancer core biopsy cases sorted from lowest to highest and color coded by IHC scores. Abbreviations: LOD = Limit of Detection, LOQ = Limit of Quantification (*manuscript under review*)

Study Design: This is a non-randomized, single-arm, open-label, investigator-initiated phase 2 study to assess the efficacy and safety of T-DXd in patients whose breast cancer is HER2-IHC 0 (including 0-null and 0-ultralow) in all prior biopsies, with unresectable and/or metastatic disease regardless of hormone receptor (HR) status (**NCT06750484**).

Key eligibility criteria:

- Unresectable or metastatic HER2 IHC 0 (including 0 ultra-low and 0 null) breast cancer
- ECOG PS 0-2
- Either HR-pos or HR-neg
- Patients with HR-positive disease must have progressed or be intolerant to CDK 4/6 inhibitors plus endocrine therapy
- Patients with HR-negative disease must have received 1 line of therapy in the metastatic setting
- No limit on number of subsequent lines of therapy for study entry
- Must have adequate (<3 years-old) metastatic tissue sample

N = 40 patients →

Trastuzumab deruxtecan*

*intravenously every 3 weeks at a dose of 5.4 mg per kilogram of body weight until disease progression, limiting toxicity, withdrawal of consent, or death

References: **1.** Modi, Shanu, et al. "Trastuzumab deruxtecan in HER2-low metastatic breast cancer: long-term survival analysis of the randomized, phase 3 DESTINY-Breast04 trial." Nature Medicine (2025): 1-9.; **2.** Bardia, Aditya, et al. "Trastuzumab deruxtecan after endocrine therapy in metastatic breast cancer." New England Journal of Medicine 391.22 (2024): 2110-2122.; **3.** Cortés, Javier, et al. "Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer." New England Journal of Medicine 386.12 (2022): 1143-1154.; **4.** Mosele, Fernanda, et al. "Trastuzumab deruxtecan in metastatic breast cancer with variable HER2 expression: the phase 2 DAISY trial." Nature medicine 29.8 (2023): 2110-2120; **5.** Robbins, Charles J., et al. "Quantitative Multiplex Immunofluorescence Assay for Trophoblast Cell-Surface Antigen 2 and Human Epidermal Growth Factor Receptor 2 Expression in Breast Cancer: Toward Guiding Patient Selection for Antibody-Drug Conjugate Therapies." JCO Precision Oncology 9 (2025): e2500128.

Primary endpoint

- ORR in the total population

Secondary endpoints:

- ORR by HER2 Troplex detectable and non-detectable measurements
- Distribution of quantitative HER2 Troplex measurements across HER2 IHC 0 tumors
- PFS
- OS

Safety endpoints:

- Adverse events

Exploratory endpoints:

- HER2 phosphoprotein expression
- HER2 mRNA expression
- HER2 FISH testing
- TROP2 Troplex measurements
- Tumor-associated macrophages and cathepsins

Statistical Considerations:

- For the primary endpoint analysis, we assume the ORR under the null hypothesis to be 15% and under the alternative to be 32% overall for the entire study population.
- A sample size of 38 patients will achieve 82% power to detect a difference in ORR of 0.17 using a two-sided exact test with a target significance level of 0.1. The actual significance level achieved by the test is 0.065.
- We will reject the null hypothesis if there are at least 10 responders among the T-DXd treated subjects.
- The total sample size for this study will be 40 subjects, adding 2 patients to the estimated sample size to account for potential dropouts.
- No interim analyses are planned during this study.
- The 2-sided 95% exact confidence interval using Clopper-Pearson method will be calculated for the response rate (ORR).

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