An Open-Label, Interventional, Multicenter Study of Trastuzumab Deruxtecan Monotherapy in Patients With Unresectable and/or Metastatic HER2-low or HER2 Immunohistochemistry 0 Breast Cancer: DESTINY-Breast15

DESTINY-Breast15

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https://clinicaltrials.gov/study/NCT05950945

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Plain Language Summary

Why are we performing this research?

Breast cancer can be categorized by the amount of a protein called human epidermal growth factor receptor 2 (HER2) expressed on the surface of tumor cells.[1] Breast cancer can also be categorized by hormone receptor–positive (HR+) and hormone receptor–negative (HR–) tumors that can confer variation in terms of prognosis and sensitivity to treatments.[2] Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody-drug conjugate (ADC) designed to target and kill tumor cells that express HER2. T-DXd can also kill neighboring tumor cells that do not necessarily express HER2.[1,3,4] In the previous DESTINY-Breast04 clinical trial, T-DXd treatment resulted in better outcomes than physician's choice of chemotherapy for patients with HER2-low (defined as immunohistochemistry [IHC] 1+ or IHC 2+/in situ hybridization negative[a]) metastatic breast cancer.[5] This trial led to the approval of T-DXd for the treatment of HER2-low breast cancer.[7] DESTINY-Breast04 only included a small number of patients who were HR–, and patients with HER2 IHC 0 (defined as no staining observed or membrane staining that is incomplete and is faint or barely perceptible and within ≤10% of tumor cells[b]) status were not enrolled.[6] Furthermore, only a small number of patients treated with T-DXd who had disease progression within 6 months of concluding a prior course of chemotherapy in early breast cancer were enrolled in DESTINY-Breast04. Therefore, this DESTINY-Breast15 study will be conducted to assess T-DXd in patients with HR+ or HR– metastatic breast cancer with low or no measurable tumor HER2 expression, including patients with rapidly progressing disease, treatment of which is a high unmet need in patients with metastatic breast cancer.

How are we performing this research?

Tumor tissue samples will be collected to determine patient eligibility for the trial. Patients must have unresectable and/or metastatic breast cancer that has been assessed as having HER2-low expression or HER2 IHC 0 expression. Eligible patients will receive 5.4 mg/kg T-DXd on day 1 of each 21-day cycle. Before starting and during treatment, tumor tissue and blood samples will be collected. Samples will be used for exploratory biomarker assessments of genetic changes, gene expression patterns, and/or protein expression patterns that may help identify patients likely to derive clinical benefit or identify mechanisms of action/resistance. Assessment of the utility of an in-house digital pathology tool will also be an exploratory objective. Patients will continue to receive T-DXd until the investigator assesses disease progression, unacceptable toxicity occurs, other discontinuation criteria are met, or 2 years after first dose of study treatment. The primary endpoint of interest in this study is "time to next treatment," a measure of how long T-DXd allows patients to gain clinical benefit from the drug.

Where can I access more information?

For more information, about DESTINY-Breast15, please visit https://clinicaltrials.gov/study/NCT05950945.
You may also speak to your doctor about clinical studies.

References

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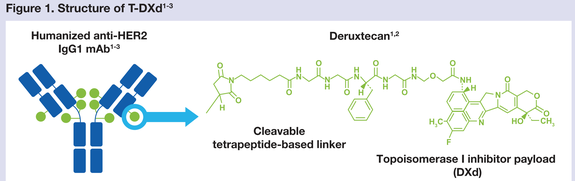
Background

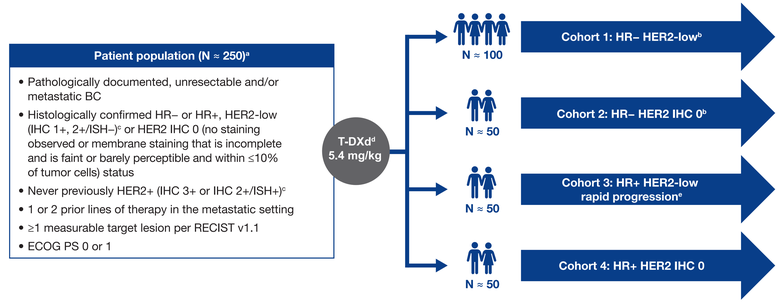
Figure 1. Structure of T-DXd[1-3]



- T-DXd has been approved in more than 40 countries worldwide for the treatment of adult patients with unresectable or metastatic HER2-low breast cancer (BC; IHC 1+ or IHC 2+/ISH–), regardless of HR status, who have received prior chemotherapy in the metastatic setting or who have developed disease recurrence during or within 6 months of completing adjuvant chemotherapy[4,5]
- Approval was based on the DESTINY-Breast04 trial, in which T-DXd showed clinically meaningful and statistically significant prolonged progression-free survival and overall survival benefit compared with physicians' choice of chemotherapy in patients with HER2-low unresectable and/or metastatic BC.[6] Sustained overall survival benefit was observed in long-term follow-up (median, 32 months)[7]
  - DESTINY-Breast04 included only 63 patients who were HR–, and patients with HER2 IHC 0 status were not enrolled. Furthermore, a limited number of patients who experienced rapid progression (defined as disease progression within 6 months of concluding a prior course of chemotherapy in early breast cancer) were enrolled (n = 14 in the T-DXd group)[8]
- Preliminary evidence of T-DXd efficacy in patients with HER2 IHC 0 metastatic BC was reported in the DAISY trial[9]
- There are few targeted agents available for patients with HR– HER2 IHC 0 metastatic BC, particularly those without pathogenic BC gene mutations or programmed death ligand 1 expression.[10] Therefore, there is an unmet need for treatments with a better benefit/risk profile for patients with HER2 IHC 0 (HR+ and HR–) metastatic BC, which represent up to 40% of BCs[11,12]
- DESTINY-Breast15 is a multicenter, open-label, single-arm, phase 3b trial being conducted to evaluate the efficacy, safety, and tolerability of T-DXd in patients with HR+ or HR– unresectable or metastatic HER2-low (defined as IHC 1+ or IHC 2+/ISH–) or HER2 IHC 0 (defined as no staining observed or membrane staining that is incomplete and is faint or barely perceptible and within ≤10% of tumor cells[13]) BC who had received up to 2 lines of prior therapy in the metastatic setting
  - The study aims to address the high unmet treatment need for these patients, including those with rapidly progressing HR+ HER2-low and HER2 IHC0 (HR+ and HR-) metastatic BC, who have exhausted current standard of care and have diminished benefit from current subsequent treatment options

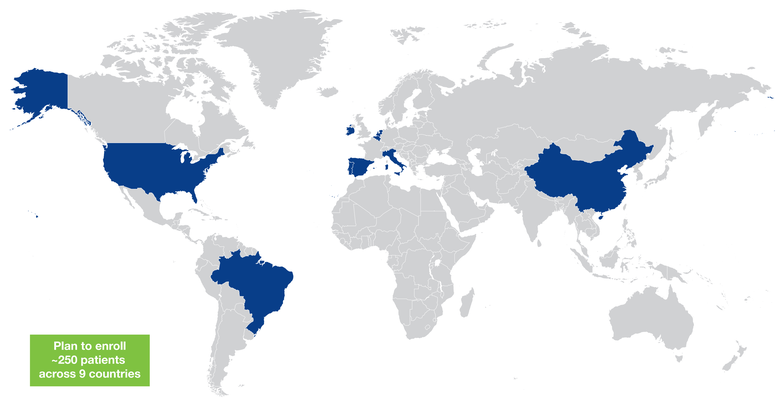
Study Design and Population

Figure 2. DESTINY-Breast15: An Open-Label Phase 3b Study of T-DXd Monotherapy in Patients With HR+ or HR– Unresectable or Metastatic HER2-low or HER2 IHC 0 Breast Cancer (NCT05950945; https://clinicaltrials.gov/study/NCT05950945)



[a]Sample size calculation is based on the primary endpoint TTNT, a 24-month accrual period, and 24-month follow-up time. Survival data were simulated using the Weibull distribution with parameters based on TTNT data from the HR+ and HR– cohorts of DESTINY-Breast04. These samples are designed with the intent to increase confidence in the clinical use of T-DXd in the HR– HER2-low population and to investigate the efficacy and safety of T-DXd in HER2 IHC 0 patients and HR+ HER2-low patients with rapid progression.
[b]Enrollment of patients with HR– BC (cohorts 1 and 2) previously treated with sacituzumab govitecan will be capped at 25% for each cohort.
[c]Per ASCO CAP 2018 guidelines.
[d]T-DXd will be administered at a dose of 5.4 mg/kg intravenously once every 3 weeks until disease progression, unacceptable toxicity, or 2 years after the first dose of T-DXd.
[e]Cohort 3 will specifically recruit patients with rapid disease progression, defined as recurrent disease for <2 years from the initiation of adjuvant endocrine therapy, or disease progression on CDK4/6i-based regimen within 12 months of completion of adjuvant therapy with a CDK4/6i, or disease progression within the first 12 months of CDK4/6i in the first-line metastatic setting.

Figure 3. Estimated Study Start: October 2023; Not Yet Recruiting Patients



Nine countries with 80 participating study sites, which include Belgium, Brazil, China, Ireland, Italy, the Netherlands, Portugal, Spain, and the United States of America.

Key Inclusion Criteria

- Men or women aged ≥18 years
- Pathologically documented HR– or HR+, HER2-low (IHC 1+ or IHC 2+/ISH–) or HER2 IHC 0 (no staining observed or membrane staining that is incomplete and is faint or barely perceptible and within ≤10% of tumor cells) unresectable and/or mBC that was never previously HER2+ (IHC 3+ or IHC 2+/ISH+) and was never previously treated with anti-HER2 therapy in the metastatic setting
- One or 2 prior lines of therapy in the metastatic setting
- Patients with HR+ HER2-low mBC (cohort 3) must have either had recurrent disease within 2 years of initiation of adjuvant ET, disease progression on CDK4/6i-based regimen within 12 months of completion of CDK4/6i adjuvant therapy, or disease progression within 12 months of CDK4/6i therapy in the metastatic setting
- Newly obtained tumor biopsy or archival biopsy obtained within 6 weeks before enrollment screening
- Presence of at least 1 measurable lesion based on CT or MRI[a]
- ECOG PS of 0 or 1
- Patients with brain metastases are allowed in the study. The brain lesion(s) should be small (<2 cm), untreated, asymptomatic, not requiring urgent medical intervention, and be asymptomatic and clinically stable
- Minimum life expectancy of 12 weeks at screening
- Left ventricular ejection fraction ≥50% within 28 days before enrollment
- Protocol-defined adequate organ and bone marrow function

[a]Per RECIST v1.1.

Key Exclusion Criteria

- Prior treatment with an ADC that consists of an exatecan derivative that is a topoisomerase I inhibitor (other than sacituzumab govitecan)
- Cardiovascular disease including myocardial infarction within 6 months before randomization, symptomatic congestive heart failure, or clinically significant arrhythmias
- Corrected QT interval prolongation of >470 ms for females or >450 ms for males
- History of noninfectious ILD/pneumonitis that required steroids, current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening
- Spinal cord compression or clinically active CNS metastases[a]
- Lung-specific intercurrent clinically significant illness or prior complete pneumonectomy
- History of severe hypersensitivity reactions to monoclonal antibodies
- Active primary immunodeficiency, history of receiving a live, attenuated vaccine within 30 days before first exposure to study drug, or uncontrolled infection

[a]Untreated and symptomatic or requiring steroid or anticonvulsant therapy to control symptoms.

Study Endpoints[a]

Primary	• Time to next treatment (TTNT) defined as the time interval from the date of first dose of T-DXd to the initiation of the next anticancer treatment or death due to any cause	
Secondary	**Efficacy** • Real-world progression-free survival per RECIST v1.1 • Time to treatment discontinuation • Objective response rate per RECIST v1.1	**Safety** • Treatment-emergent adverse events and other safety parameters including adverse events of special interest, ECOG PS, laboratory values, vital signs, clinical laboratory results, electrocardiogram parameters, echocardiogram/multigated acquisition findings, and ophthalmologic findings
Exploratory	**Health Economics and Outcomes Research** • EORTC Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), EORTC QLQ-Breast Cancer (EORTC QLQ-BR45), EQ-5D-5L, global anchor (PGI-S, PGI-C, and PGI-TT) questionnaires, reasons for hospitalization, length of stay in hospital, and length of stay in intensive care unit	**Biomarkers and Digital Pathology** • Correlation of biomarkers with efficacy and safety • Concordance assessment between pathologist HER2 IHC+ scoring and digital pathology scoring and correlation of digital pathology scores with efficacy endpoints

[a]TTNT, rwPFS, TTD, and ORR will be evaluated separately for each cohort in the full analysis set. Time-to-event endpoints will be evaluated using Kaplan-Meier methods and presented graphically. Dichotomous endpoints will be evaluated using frequency counts, percentages, and their corresponding 2-sided 95% CIs.

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Disclosures

Dr S Modi reports consulting or advisory roles for Genentech, Daiichi Sankyo, AstraZeneca, Seattle Genetics, Gilead, and Macrogenics; honoraria from Genentech, Daiichi Sankyo, AstraZeneca, Seattle Genetics, Novartis, and Lilly; institutional financial interests from Genentech, Daiichi Sankyo, AstraZeneca, and Seattle Genetics.

Abbreviations

ADC, antibody-drug conjugate; **ASCO,** American Society of Clinical Oncology; **BC,** breast cancer; **CAP,** College of American Pathologists; **CDK4/6i,** cyclin-dependent kinase 4/6 inhibitor; **CNS,** central nervous system; **CT,** computed tomography; **ECOG PS,** Eastern Cooperative Oncology Group performance status; **EORTC**, European Organization for Research and Treatment of Cancer; **EQ-5D-5L,** EuroQol 5-dimension, 5-level (of severity); **ET,** endocrine therapy; **HER2**, human epidermal growth factor receptor 2; **HR,** hormone receptor; **IHC,** immunohistochemistry; **ILD,** interstitial lung disease; **ISH,** in situ hybridization; **mBC,** metastatic breast cancer; **MRI,** magnetic resonance imaging; **ORR**, objective response rate; **PGI-C,** patient global impression of change; **PGI-S,** patient global impression of severity; **PGI-TT,** patient global impression of treatment tolerability; **RECIST v1.1,** Response Evaluation Criteria in Solid Tumors, version 1.1; **rwPFS**, real-world progression-free survival; **T-DXd,** trastuzumab deruxtecan; **TTD**, time to discontinuation; **TTNT,** time to next treatment; **QLQ,** quality-of-life questionnaire.

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