A Real-World Study of the Effectiveness and Safety of Trastuzumab Deruxtecan (T-DXd) in HER2-Low Metastatic Breast Cancer (mBC) among Racial and Ethnic Minorities and Older Populations in the United States: Trial in Progress (TiP)

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Plain Language Summary

Why are we performing this research?

- Trastuzumab deruxtecan is the only drug approved for a specific type of breast cancer known as 'HER2-low' breast cancer
- We need to study how this drug works in groups of people who are often under-represented in research, such as those from different racial/ethnic and age groups

How are we performing this research?

- We will look at the health records of patients with HER2-low metastatic breast cancer who used trastuzumab deruxtecan between August 5, 2022 - December 31, 2026
- We will evaluate how well trastuzumab deruxtecan works by estimating how long patients of different races/ethnicities and ages live without their cancer getting worse after taking the drug
- We will also evaluate how safe trastuzumab deruxtecan is by looking at these patients' health records to see if they had any adverse events

What is the current status of this research?

- This study is in progress. We will continue to collect patient information through the end of 2026
- The final study results are expected in late-2027

Background

Breast Cancer (BC) Epidemiology

- **Most common cancer among women** in the U.S. (excluding skin cancer), with an estimated 310,720 new cases in the U.S. in 2024[1]
- Significant public health issue; approximately **13.1% of U.S. women will be diagnosed with BC in their lifetime**[1]

Human Epidermal Growth Factor-2 (HER2) Low BC

- HER2 status and HER2-low BC definitions by immunohistochemistry (IHC) and *in situ* hybridization (ISH) testing results are outlined below in **Table 1**
- **HER2-low BC accounts for 45 – 55% of all primary BC cases**[2,3]

Table 1. HER2 Status Definitions

HER2 Status	Definition
HER2-Ultra Low	IHC 0 with membrane staining
HER2-Low	IHC 1+ or IHC 2+/ISH-
HER2-Positive	IHC 2+/ISH+ or IHC 3+

HER2, human epidermal growth factor receptor-2; IHC, Immunohistochemistry; ISH, In situ hybridization

Trastuzumab Deruxtecan (T-DXd) in HER2-Low BC

- T-DXd is an antibody drug conjugate (ADC) composed of an anti-HER2 antibody (trastuzumab) linked to a topoisomerase I inhibitor (DXd)
- **T-DXd is the only drug approved for HER2-low metastatic BC (mBC)** in the U.S. based on the results of the DESTINY-Breast04 study[4]

Health Disparities in BC

- Black/African American patients with BC have a 40% higher mortality rate than white patients in the U.S.[5]
- BC incidence and mortality rates increase dramatically with age, and older patients (≥65 years) often have comorbidities and concomitant medications that can affect treatment decisions and outcomes[6]

Study Rationale

- In the DESTINY-Breast04 global study, median age of patients who received T-DXd was 57 years and 47.2% were white, while 40.5% were Asian and 1.9% were Black[7]
- It is important to **further evaluate the effectiveness and safety of T-DXd among older patients and among racial/ethnic minorities** that had limited representation in the DESTINY-Breast04 study

Objectives

Primary Objective	• Assess the **effectiveness of T-DXd by real-world progression free survival (rwPFS)** among HER2-low mBC patients treated with T-DXd by race/ethnicity and age
Secondary Objectives	• Assess **the safety profile of T-DXd** by targeted adverse events (TAEs) among HER2-low mBC patients treated with T-DXd by race/ethnicity and age • Describe the **demographic and clinical characteristics and systemic anticancer treatments** among HER2-low mBC patients by race/ethnicity, age, and hormone receptor status
Exploratory Objective	• Assess the **effectiveness of T-DXd by real-world overall survival (rwOS), time to next treatment (rwTTNT), time to treatment discontinuation (rwTTD), and number of cycles of T-DXd** administered before discontinuation among HER2-low mBC patients treated with T-DXd by race/ ethnicity and age

Study Design and Population

Study Design

- **Non-interventional, retrospective cohort study** (Figure 1)

Data Source

- **Guardian Research Network (GRN)** is the data source for this study
- GRN is a **de-identified oncology focused electronic medical record (EMR) database** sourced from a community hospital consortium spanning the eastern and central U.S.
- GRN includes ~40 million patients (3.5 million oncology patients) and captures longitudinal patient data covering cancer and non-cancer care
- Most variables have excellent completeness, ranging from **85-100%**

Planned Sample Size

- We estimate a **total of 449 eligible T-DXd treated HER2-low patients** by the end of the study period
- Of these patients, an estimated 359 will be evaluable for rwPFS (assuming a 50% increase in T-DXd uptake during the study)

Statistical Methods

- All **analyses will be descriptive;** no hypothesis testing is planned
- *Source Population* will be used to describe patient demographics, clinical characteristics, and treatment patterns
- *T-DXd Treated Cohort* will be used to evaluate effectiveness and safety endpoints

Effectiveness Endpoints

- Primary endpoint (rwPFS) and exploratory endpoints (rwOS, rwTTNT, rwTTD) will be analysed using a **time-to-event approach (Kaplan-Meier estimator)**
- Proportion of patients still on T-DXd therapy at 3-, 6- and 12- months, as well as 2- and 3- years will be reported
- Number of T-DXd cycles administered before discontinuation will be reported as mean, standard deviation, range and interquartile range

Safety Endpoints

- For each TAE**, the proportion of patients with occurrence of the event will be described**
- Among patients with multiple occurrences of the TAE, the number and duration of episodes will be summarized
- Severity of neutropenia/febrile neutropenia will be assessed based on laboratory values
- Severity of other TAEs will not be assessed in this study

Racial/Ethnic and Age Subgroups

- Providing adequate data, racial subgroups will be evaluated using the categories reported in the U.S. Census (see **Table 2**), otherwise subgroups will be combined in a scientifically and clinically appropriate manner

Study Timeline

- The study period will end on 31 Dec 2026
- Final analysis results from this study are expected in late-2027

Key Inclusion and Exclusion Criteria

Source Population:

- **Adult patients (≥18 years) with HER2-low mBC** diagnosed between 05 Aug 2017 and 31 Dec 2026
- ≥1 clinical encounter (e.g. doctor visit, hospital admission) recorded in the EMR before and after the date of the first mBC diagnosis
- Exclusion criteria: other non-BC primary cancer, prior HER2-positive disease, no race/ethnicity data

T-DXd Treated Cohort:

- Patients in the *Source Population* who first **received T-DXd** within 30 days prior to or any time after the date of the first mBC diagnosis
- **Index Date** is defined as the earliest date of T-DXd administration

Key Study Endpoints

1° Primary Effectiveness Endpoint

rwPFS	Time from Index Date to date of first documentation of disease progression or death due to any cause

2° Secondary Safety Endpoint

TAEs	TAEs include interstitial lung disease/pneumonitis, left ventricular dysfunction, neutropenia/febrile neutropenia, nausea/vomiting

Exploratory Effectiveness Endpoints

rwOS	Time from Index Date to date of death due to any cause
rwTTNT	Time from Index Date to date patient initiates a subsequent systemic anticancer therapy
rwTTD	Time from Index Date to T-DXd treatment discontinuation date
# of T-DXd cycles	Number of T-DXd cycles administered from Index Date to date of discontinuation

Table 2. Proposed Racial/Ethnic and Age Subgroups to be Evaluated

Variable	Proposed Subgroups
Race	• American Indian or Alaska Native • Asian • Black or African American • Native Hawaiian or Other Pacific Islander • White • Other
Ethnicity	• Hispanic • Non-Hispanic
Age Group	• ≤65 years • >65 years • >75 years

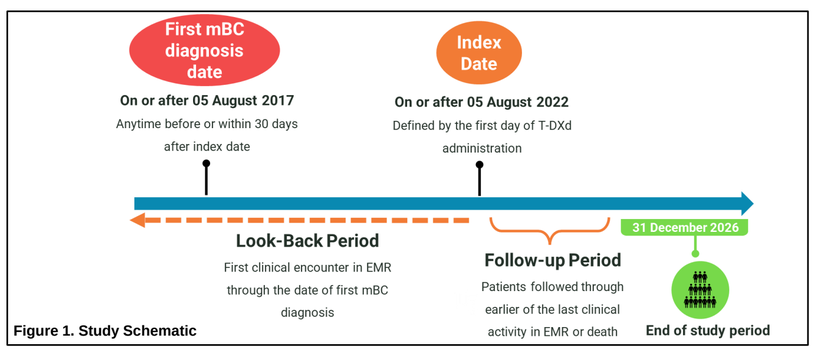

Figure 1. Study Schematic

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Disclosures

Authors AAG, MH, DA, SA, and COA are employees of Daiichi Sankyo, Inc., the sponsor of this study. Authors AAG, MH, DA, SA, and COA own stock in Daiichi Sankyo, Inc. Authors CD and RC are contracted to work for Daiichi Sankyo, Inc. Author DP is an employee of IQVIA, Inc and owns stock in AstraZeneca and IQVIA, Inc. Authors VGM, GP, and KR are employees of AstraZeneca and own stock in AstraZeneca.

Abbreviations

ADC, antibody-drug conjugate; BC, breast cancer; EMR, electronic medical records; GRN, Guardian Research Network; HER2, human epidermal growth factor receptor-2; IHC, immunohistochemistry; ISH, In situ hybridization; mBC, metastatic breast cancer; rwPFS, real-world progression free survival; rwOS, real-world overall survival; rwTTD, real-world time to treatment discontinuation; rwTTNT, real-world time to next treatment; TAE, targeted adverse event; T-DXd, trastuzumab deruxtecan; TiP, trial in progress; U.S., United States

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