ESMO Breast Cancer 2024 (15-17 May), Berlin, Germany

PROVIDENCE: A prospective, non-interventional study examining real-world clinical and patient-reported outcome (PRO) data in patients (pts) with HER2-positive or HER2-low unresectable or metastatic breast cancer (mBC) treated with trastuzumab deruxtecan (T-DXd)

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Plain Language Summary

Why are we performing this research?
Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate (ADC) designed to treat cancer cells that express HER2. Depending on the expression level of HER2, tumors used to be classified as HER2-positive (HER2+) or HER2-negative (HER2-). The majority of HER2- tumors express low levels of HER2 and recently it was shown that these so-called HER2-low tumors also respond to new anti-HER2-directed agents. T-DXd has demonstrated superior efficacy compared to the ADC T-DM1 in patients with HER2+ metastatic breast cancer (mBC) treated in second line (2L) (DESTINY-Breast03[1]) and has therefore replaced T-DM1 as the new standard for 2L treatment. Moreover, superior efficacy of T-DXd compared to chemotherapy was demonstrated in patients with HER2-low mBC (DESTINY-Breast04[2]). In this non-interventional study, we evaluate effectiveness, quality of life and safety of T-DXd in patients with HER2+ (treated in 2L) and HER2-low mBC in a real-world setting.

How are we performing this research?
The non-interventional PROVIDENCE study started in Q3 2023 and is observing patients with HER2+ and HER2-low mBC treated with T-DXd in a clinical routine setting. We will primarily look at how long it will take until the patients receive their next systemic treatment (this is called time to next treatment or TTNT1) and at their quality of life during the first 6 months of T-DXd treatment.

Who will participate in this study?
Patients in Germany with HER2+ mBC must have received one prior anti-HER2-based regimen, i.e., they can participate in this study if they are receiving T-DXd in 2L. Patients with HER2-low mBC must have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy according to label.

Where can I access more information?
This study is expected to end in Q4 2030. For more information about PROVIDENCE, please visit https://clinicaltrials.gov/study/NCT05573893. You may also speak to your doctor about non-interventional studies.

1. Cortés J et al. NEJM 2022; 386: 1143–1154. 2. Modi S et al. NEJM 2022; 387: 9–20.

Background

The treatment of HER2-positive (HER2+) tumors is continuously improving through the development of new anti-HER2-directed agents. Approximately 20% of breast cancers (BC) are HER2+ based on protein overexpression by immunohistochemistry (IHC3+) or gene amplification by in situ hybridization (ISH+). In addition, low levels of HER2 (IHC1+ or IHC2+/ISH-) can be detected in about 60% of BC that used to be defined as HER2-negative and are now categorized as HER2-low BC.[1] HER2-low tumors can be hormone receptor positive (HR+) or hormone receptor negative (HR-).

T-DXd: Superior second-line option for HER2-positive metastatic breast cancer

While dual anti-HER2 blockade with the monoclonal antibodies trastuzumab and pertuzumab in combination with a taxane remains the preferred first-line (1L) therapy, the antibody-drug conjugate (ADC) trastuzumab deruxtecan (T-DXd), which consists of trastuzumab and a topoisomerase-I inhibitor, is the new standard for 2L HER2+ mBC.
T-DXd was first authorized in the EU by the European Commission in 01/2021 for HER2+ mBC in the 3L setting and approval was extended to 2L treatment in 07/2022 based on the DESTINY-Breast03 study.[2,3] Among patients with HER2+ mBC previously treated with trastuzumab and a taxane, T-DXd significantly improved overall survival (OS) versus T-DM1, reducing the risk of death by approx. 36%. Benefits in median progression-free survival (PFS) (28.8 vs 6.8 months; HR 0.33; nominal P < 0.000001) were highly significant and the enhanced objective response rate (ORR) (79% vs 35%; nominal P < 0.0001) were also clinically meaningful.[4,5]

Targeting HER2-low with T-DXd in metastatic breast cancer

The clinical relevance of the HER2-low patient population was demonstrated in the DESTINY-Breast04 study and T-DXd was approved in 01/2023 for the treatment of patients with HER2-low mBC who have received prior chemotherapy.[2] In this patient population, T-DXd significantly improved median PFS (HR+ cohort: 10.1 vs 5.4 months; HR 0.51; P < 0.001; all patients: 9.9 vs. 5.1 months; HR 0.50; P < 0.001) and OS (HR+ cohort: 23.9 vs 17.5 months; HR 0.64; P = 0.003; all patients: 23.4 vs. 16.8 months ; HR 0.64; P = 0.001) compared to chemotherapy.[6] Updated results from the extended follow-up of 32 months confirmed the sustained clinically meaningful improvement with T-DXd versus chemotherapy showing a 31% reduction in the risk of death regardless of HR status.[7]

Using electronic health tools to improve the clinical management of therapies for metastatic breast cancer

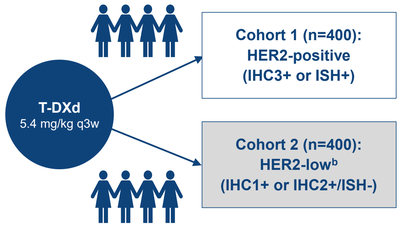
Since metastatic BC patients are usually not treated with a curative intention, maintaining health-related quality of life (HRQoL) is important. Mindful dealing with symptoms can be supported by eHealth tools to improve the clinical management of and the adherence to the treatment, thereby improving HRQoL.[8] In Germany, physicians can prescribe digital health applications (Digitale Gesundheitsanwendungen, DiGA) that are classified as class I or class IIa medical devices and that are approved for the respective illness.[9]

Study Design and Population

- PROVIDENCE is a German multicenter, prospective, non-interventional study (NIS) to evaluate real-world effectiveness, HRQoL, treatment patterns, and safety in patients with HER2+ and HER2-low mBC treated with T-DXd.
- Patients with HER2+ mBC must have received one prior anti-HER2-based regimen, i.e., they are eligible if they receive T-DXd in 2L.
- Patients with HER2-low mBC must have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy according to label.
- Informing the patients about DiGAs is a prerequisite.
- Patients are stratified according to HER2 status, i.e., HER2+ and HER2-low.
- It is planned to include 400 patients per cohort from up to 150 sites.
- Patients are followed up for up to 5 years.
- First-patient-in (FPI) was on 12 Sept 2023. Primary completion date (LPLV) is estimated for Q4 2030.

Patient population (N=800)

- HER2-positive or HER2-low unresectable or metastatic breast cancer
  - HER2-positive: one prior anti-HER2-based regimen
  - HER2-low: prior CT in the metastatic setting or disease recurrence during or within 6 months of completing adjuvant CT
- Informed about digital health applications (DiGAs)[a]



Key Endpoints

- TTNT1
- HRQoL
- ORR
- PFS
- OS
- TTD
- TTNT2, PFS2, TTD2
- Safety

Use of DiGAs (optional)[a]

[a] DiGAs are approved by the relevant health supervisory authority and are hence reimbursable in Germany. They are eHealth tools that have been shown to be effective in a clinical trial; e.g., DiGAs have been shown to improve illness-related mental stress and HRQoL.
[b] Recruitment of at least 10% of patients with a hormone receptor negative (HR-) tumor is planned. Therefore, recruitment of patients with a HER2-low/HR+ tumor will be stopped if 360 patients with a HR+ tumor have been recruited.

Inclusion Criteria

- Age ≥ 18 years
- Patients (irrespective of sex and gender) with pathologically documented breast cancer that:
  - is unresectable or metastatic
  - has confirmed HER2+ or HER2-low tumor status by local pathology
  - if HER2+: was previously treated with one anti-HER2-based regimen or
  - if HER2-low: was previously treated with prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy
- Radiologic progression
- Eligibility for T-DXd treatment in line with the specifications mentioned in the Enhertu® SmPC and scheduled for T-DXd as 2L treatment if the tumor is HER2+ or scheduled for T-DXd treatment if the tumor is HER2-low*
- Able to read and understand German or English
- Signed written informed consent

* The prescription of the medicinal product is clearly separated from the decision to include the patient in this NIS.

Exclusion Criteria

- Hypersensitivity to T-DXd or any excipients of the drug
- Pregnancy or breast feeding
- Current or planned participation in an interventional clinical trial
- Current or planned treatment of any tumor other than unresectable or metastatic BC

Study Endpoints

1° Primary endpoint
- Time to next treatment 1 (TTNT1)

2° Secondary endpoints
- Changes in health-related quality of life (HRQoL)[a] at 6 months based on:
  - the Functional Assessment of Cancer Therapy–Breast (FACT-B) questionnaire
  - the Functional Assessment of Cancer Therapy–General (FACT-G) questionnaire

Selected exploratory endpoints
- Changes in HRQoL[a] over time based on FACT-B and EQ-5D
- Overall response rate (ORR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Time to treatment discontinuation (TTD)
- Post-progression outcomes (TTNT2, PFS2, TTD2)
- Safety
- Description of DiGA users and non-users

[a] During the T-DXd treatment phase, patients are asked to complete HRQoL questionnaires at treatment initiation, at each cycle during the first 6 months, thereafter 3-monthly during the first 3 years and 6-monthly in year 4 and 5, and at the end of treatment.

All endpoints will be analyzed separately for the HER2+ and the HER2-low cohort. Both cohorts may be combined for the analysis of certain endpoints (e.g., safety, description of DiGA users and non-users).

Please scan this quick response (QR) code with your smartphone camera or app to receive further information.

Alternatively, please click on the link: https://clinicaltrials.gov/study/NCT05573893

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Disclosures

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Abbreviations

ADC, antibody-drug conjugate; BC, breast cancer; DiGA, digital health application (Digitale Gesundheitsanwendung); HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HR+, hormone receptor positive; HR-, hormone receptor negative; HRQoL, health-related quality of life; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PFS2, second progression or death; q3w, every 3 weeks; T-DXd, trastuzumab deruxtecan; TTD, time to treatment discontinuation; TTD2, time to subsequent treatment discontinuation; TTNT1, time to next treatment; TTNT2, time to second next treatment

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