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Clinical Trial Protocol

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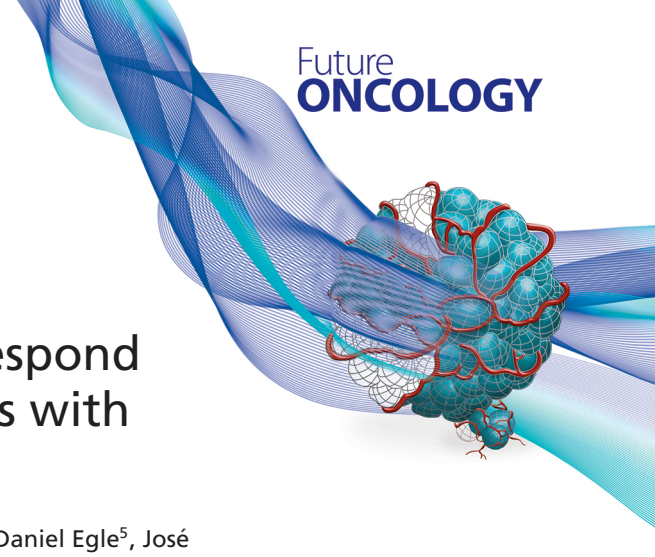

Study design for DESTINY-Breast Respond HER2-low Europe: T-DXd in patients with HER2-low advanced breast cancer

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Trastuzumab deruxtecan (T-DXd) is approved for the treatment of human epidermal growth factor receptor 2 (HER2)-low metastatic breast cancer (mBC). Results on T-DXd treatment in HER2-low mBC have so far been limited to clinical trials. DESTINY-Breast Respond HER2-low Europe (NCT05945732) is a multi-center, multi-country, observational, prospective, non-interventional study planning to enroll 1350 patients from 216 sites receiving T-DXd or conventional chemotherapy as their routine clinical care for advanced stage breast cancer in 12 European countries. This non-interventional study will provide real-world insight into T-DXd treatment for HER2-low mBC with data on effectiveness, safety and tolerability, patient-reported outcomes, treatment patterns, geriatric health status and HER2 testing. This will be beneficial for improving guidance to maximize patient treatment benefit.

Plain language summary: Trastuzumab deruxtecan (T-DXd; Enhertu®) is a medicine approved to treat cancers that produce a protein called HER2 on the surface of cancer cells. T-DXd works by targeting the HER2 protein to deliver chemotherapy directly to cancer cells. Until recently, breast cancers were classified as HER2-positive (high level of HER2 protein on cancer cells) or HER2-negative (very low level/no HER2 protein on cancer cells). T-DXd was approved for treating patients with HER2-positive advanced breast cancer in Europe in 2022. In 2023 the DESTINY-Breast04 clinical trial showed that T-DXd was more effective than current standard chemotherapies, when treating advanced breast cancer patients with low levels of the HER2 protein (historically classified as HER2-negative cancer). This trial led to the approval of T-DXd for treating advanced HER2-low breast cancer, providing a new treatment option for 50–60% of breast cancer patients. More information is needed about T-DXd treatment in the real world (for patients treated in the hospital, rather than in a clinical trial). This article describes the purpose and design of the DESTINY-Breast Respond HER2-low Europe study, which will collect and report more information about how effective T-DXd treatment is in the real world. This is a large study aiming to include 1350 eligible patients from 12 countries across Europe. Patients will report their experience of side effects (such as nausea and vomiting)

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to improve management of T-DXd treatment and maximize patient benefit. The study will also examine how elderly patients respond to T-DXd treatment, and how HER2 levels are being tested.

Clinical Trial Registration: ICH CGP: **NCT05945732**, registered on 6 July 2023 (ClinicalTrials.gov)

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Keywords: adverse events • HER2-low • metastatic breast cancer • overall survival • patient-reported outcomes • progression-free survival • trastuzumab deruxtecan

Breast cancer is the most common type of cancer diagnosed in women in Europe [1]. The median survival for metastatic breast cancer varies by breast cancer subtype, with a large real-world study reporting median overall survival (OS) of 43 months for hormone receptor positive (HR+) human epidermal growth factor receptor-2 negative (HER2)- breast cancer, 50 months for HER2+ breast cancer and 15 months for triple-negative breast cancer (TNBC) [2,3]. More than half of all breast cancers show low level expression of HER2. HER2-low is defined as immunohistochemistry (IHC) 1+ or IHC 2+/*in-situ* hybridization (ISH) negative [4,5]. The authors of the ESMO consensus statements do not consider HER2-low breast cancer to be its own subtype of breast cancer, but rather a variable group of tumors [6], and HER2-low status is more commonly found in patients with HR+ compared with HR- metastatic breast cancer (mBC) [7]. HER2-low can be a useful biomarker for selecting patients, who represent a new population eligible for treatment with trastuzumab deruxtecan (T-DXd). Based on the findings of the DESTINY-Breast04 trial, T-DXd is the first approved antibody-drug conjugate (ADC) for use in patients with HER2-low breast cancer [8] (see Box 1 for further information). However, there is a need to optimize treatment options and sequences for patients with HER2-low breast cancer.

Box 1. Approval of trastuzumab deruxtecan for HER2-low metastatic breast cancer.

Approval of T-DXd was first granted by the European Medicines Agency (EMA) in 2021 for patients with HER2+ mBC. In 2023, EMA extended the indication of T-DXd for patients with HER2-low unresectable or mBC who have received prior chemotherapy in the metastatic setting or had disease recurrence during or within 6 months of completing adjuvant therapy [9]. T-DXd is recommended at 5.4 mg/kg administered as an intravenous infusion once every 3 weeks until disease progression or unacceptable toxicity [9]. This approval was based on the results from the DESTINY-Breast04 trial [10]. In addition, the results from the DESTINY-Breast04 trial have led to the inclusion of T-DXd as a treatment for HER2-low mBC in the European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines [11].

DESTINY-Breast04 was a randomized, open-label phase III clinical trial in which 557 patients with HER2-low unresectable or mBC are treated with either T-DXd or physician's choice of chemotherapy in similar lines of therapy. In the DESTINY-Breast04 trial, T-DXd significantly improved median progression-free survival (PFS; 10.1 vs 5.4 months) and median OS (23.9 vs 17.5 months) compared with physician's choice of chemotherapy in pretreated patients with HER2-low mBC, highlighting T-DXd as beneficial for this study population [10]. In DESTINY-Breast04, the most common drug-related adverse events (AEs) in patients treated with T-DXd were nausea (73.0%) and vomiting (34.0%), fatigue (47.7%) and alopecia (37.7%). The most common drug-related AE of Grade 3 or higher was neutropenia (13.7%). Interstitial lung disease (ILD) or pneumonitis occurred in 12.1% of patients treated with T-DXd, and left ventricular dysfunction occurred in 4.6% [10].

T-DXd is understood to be so effective due to a potent and large payload per molecule, and its bystander effect, enabling it to enter and destroy HER2- tumor cells within close proximity to the HER2+ cells it targets [8]. In this way, T-DXd can be very effective in treating HER2-low tumors with very limited levels of HER2 expression. However, the importance of HER2-low testing has created challenges for pathologists with HER2 categorization [12]. HER2 testing relies on multiple methodological and analytical variables, as such, repeated tests can have low levels of concordance and categorization may vary between laboratories [12,13]. Therefore, collection of real-world data on HER2 testing practices may help to provide guidance on standardization of HER2 testing practices for pathologists, and more accurate categorization for patients. An additional challenge is the ongoing debate on the definition of HER2-low, with the American Society of Clinical Oncology – College of American Pathologists (ASCO-CAP) 'HER2 Testing in Breast Cancer – 2023 Guideline Update' choosing to reaffirm their 2018 guidelines by not supporting the use of a HER2-low interpretative category as the DESTINY-Breast04 trial did not include a

HER2 IHC 0 patient group. The ongoing DESTINY-Breast06 trial will look to address this gap and enhance our understanding of HER2-ultra low breast cancer (IHC>0 and ≤10%) by investigating T-DXd treatment in this subset of patients. Furthermore, the ongoing DESTINY-Breast15 trial of T-DXd treatment is enrolling patients with HER2-low and HER2 0 advanced breast cancer. In DESTINY-Breast Respond HER2-low Europe, the definition of HER2-low used is the same as in the DESTINY-Breast04 trial; as described in the ASCO-CAP 'HER2 Testing in Breast Cancer – 2023 Guideline Update' [5].

There are currently no real-world data on T-DXd effectiveness, safety and tolerability in patients with HER2-low unresectable and/or mBC. As patients with breast cancer primary tumors HER2-low are a broad group [14], and gathering real-world evidence of treatment outcomes with T-DXd is suitable to optimize overall patient benefit. DESTINY-Breast Respond HER2-low Europe (NCT05945732) is a multi-center, multi-country, observational, prospective, non-interventional study (NIS). The aim of the study is to provide real-world data on the effectiveness, safety and tolerability of T-DXd in patients with HER2-low unresectable and/or mBC who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months after completing adjuvant chemotherapy. Data will also be collected on patient demographic and clinical characteristics, treatment patterns, management of AEs, geriatric health status and HER2 testing. Characterizing management of AEs associated with T-DXd in the real-world is important for the aim of optimizing patient treatment to ensure maximum treatment benefit. As T-DXd is a therapy of high emetic risk there will be a focus on nausea and vomiting during T-DXd treatment and the use of antiemetics in the clinic. Use of antiemetics is recommended with T-DXd treatment, and guidance regarding this is provided in the Summary of Product Characteristics (SmPC) [9,11]. Another AE of focus will be ILD/pneumonitis, which occurred in 12.1% of patients who received T-DXd during the DESTINY-Breast 04 trial [10]. It is well established that patients with a history of lung disease or moderate to severe renal impairment are at an increased risk of developing ILD/pneumonitis [14], but this study will look to add to this by providing insight into additional physician-reported risk factors. Data will be also collected on early-identification strategies (including scan type and frequency) and their impact on ILD/pneumonitis outcomes. Guidance on ILD/pneumonitis scan frequency for patients receiving T-DXd is unclear with some studies advocating for scans every 12 weeks during treatment, or 6–9 weeks for those with respiratory symptoms [15], while the DESTINY-Breast 04 trial performed scans every 6 weeks [10]. The T-DXd SmPC does not include specific guidance on scan frequency [14] so this real-world study will help improve understanding of how ILD/pneumonitis is monitored in clinical practice.

The NIS is accompanied by a disease registry of patients treated with conventional chemotherapy (such as capecitabine, eribulin, gemcitabine, paclitaxel and nab-paclitaxel) to contextualize treatment patterns and effectiveness of T-DXd and conventional chemotherapy. The inclusion criteria for the patients receiving conventional chemotherapy will be the same as for the pool of patients receiving T-DXd. This NIS will be the first systematic collection of real-world data for T-DXd in patients with HER2-low mBC in Europe. In addition to providing details which may only be seen during treatment in the clinic, the intended pool of patients receiving T-DXd will be much larger than previous clinical trials. Without the restrictions of tight inclusion criteria of a phase III trial it will be possible to describe efficacy and adverse effects in patient populations not included in the DESTINY-Breast04 study. The results will help to determine whether patients in the real-world are being optimally managed to receive maximum benefit from T-DXd. Data on patient-reported outcomes (PROs) will be collected.

Current knowledge on the use of T-DXd in elderly patients with HER2-low mBC is very limited, with only 71 patients in DESTINY-Breast04 being 65 years or older [10]. The DESTINY-Breast Respond HER2-low Europe study will include a geriatric screening to provide data around T-DXd use specific to this group of patients. The study will also investigate reporting of HER2-low status through a survey taken by approximately 150 pathologists, detailing HER2 testing practices in different European countries. This will allow examination of potential differences in testing methodologies through data on the numbers of biopsies conducted, the date of the last biopsy collected before treatment, and test results.

This article outlines the study design and rationale for the DESTINY-Breast Respond HER2-low Europe trial.

Patients & methods

Study design

Study objectives & outcome measures

The primary objective of the DESTINY-Breast Respond HER2-low Europe study is to describe the effectiveness of T-DXd based on real-world time to next treatment (rwTTNT1) in patients with HER2-low expressing unresectable and/or mBC.

As a secondary objective, the study will describe treatment patterns, demographic characteristics and clinical characteristics for patients receiving T-DXd. Treatment patterns include treatment exposures and durations, and types of prior and subsequent treatments. Demographics and clinical characteristics will be analyzed with summary statistics or frequency tables. Another secondary objective will be to assess the safety and tolerability of T-DXd, characterizing management of physician-reported safety events of interest (SEIs) through evaluation of prophylactic and reactive treatments. SEIs will include nausea and vomiting, fatigue, alopecia, ILD or pneumonitis, and decreased left ventricular ejection fraction (LVEF). SEIs will be presented as incidences and percentages. Furthermore, patient-reported tolerability of T-DXd will be evaluated through Patient's Global Impression of Treatment Tolerability (PGI-TT), a fully linguistically validated nausea and vomiting diary, and selected items from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) library (which was validated by the EORTC Quality of Life Group). These will assess global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties. Real-world time to T-DXd treatment discontinuation (rwTTD1) will also be evaluated as a secondary objective.

The study will be accompanied by a disease registry collecting real-world data on conventional chemotherapy. All objectives, except for SEIs, drug-related treatment-emergent adverse events (TEAEs), serious drug-related TEAEs and serious adverse events (SAEs) will be evaluated for conventional chemotherapy as exploratory objectives only. Options for conventional chemotherapy include but are not limited to capecitabine, eribulin, gemcitabine, paclitaxel and nab-paclitaxel, to be chosen by the treating physician. Other exploratory objectives in DESTINY-Breast Respond HER2-low Europe include SEIs, SAEs and drug-related TEAEs for T-DXd, and OS, real-world PFS (rwPFS), rwTTNT, rwTTD, PROs, testing practices and summary statistics about hospitalization-related resource utilization for both T-DXd and conventional chemotherapy. The data on conventional chemotherapy are intended to contextualize treatment patterns and effectiveness of T-DXd. For the full list of exploratory objectives see Supplementary Table 1.

Health status of patients ≥75 years will be assessed using the Geriatric 8 screening tool. For a full list of variables collected see Supplementary Table 2. Data will be gathered from 12 European countries, including France. For France a local amendment will be prepared collecting information on T-DXd only, but not chemotherapy. In France, T-DXd is already available and recommended for patients with HER2-low mBC via the early access program, so treatment of this group with conventional chemotherapy would not be feasible. France will collect data from two T-DXd cohorts: retrospective data from patients in the early access program, as well as prospective data from newly treated patients.

Subgroup analyses will be performed for the Full Analysis Set of patients receiving T-DXd and conventional chemotherapy and presented descriptively. The purpose of these subgroup analyses is to assess whether treatment effectiveness is associated with various prognostic factors. Subgroups will include geriatric vs non-geriatric, and prior CDK4/6 inhibitor therapy (see Supplementary Table 3 for a full list of stratification factors).

See Supplementary Table 4 for full definitions of drug-related TEAE, OS, rwPFS1, rwPFS2, rwTTD1, rwTTD2, rwTTNT1, rwTTNT2, SAE and serious drug-related TEAE.

Management of SEIs & AEs

SEIs and their management will be documented according to prophylactic and reactive treatments for management of SEIs. The therapy/treatment, start/stop date, and reason(s) for treatment initiation will be recorded. Evaluation of prophylactic and reactive treatments for SEI management will be assessed by the proportion of patients given prophylactic treatment for nausea and vomiting (at the time of first dose) and the proportion of patients given reactive treatment to any SEIs. AEs that lead to dose interruption, reduction or discontinuation will also be recorded.

For the management of SEIs and AEs, patients will be treated according to the guidance in the SmPC [9]. With regard to nausea and vomiting, patients may be prescribed additional medicines to help prevent nausea and vomiting

Table 1. Approximate number of countries, sites and patients.

Country	Planned sites	Patients to receive T-DXd	Patients to receive conventional chemotherapy
First wave			
Austria	12	60	10
Switzerland	12	60	15
Second wave			
Denmark	12	60	15
Finland	10	50	10
France	60	400	0
Italy	25	120	25
Norway	8	40	10
Spain	25	120	30
Sweden	12	60	15
The Netherlands	12	60	15
Third wave			
Belgium	16	80	20
Portugal	12	60	15
Total	216	1170	180

T-DXd: Trastuzumab deruxtecan.

Table 2. Site selection criteria.

Access to patients suitable to be included in the study
Able to collect important lab values routinely
Intentionally prescribe T-DXd and conventional chemotherapy (or T-DXd only for France) as part of their routine clinical practice
Able to document the data in English
Able to document the study data in an electronic data capture system
Able to conduct the study adequately, with enough time and staff to identify eligible patients, conduct the patient consent process, participate in required trainings, enter study data and follow-up with study related activities
Agreement to follow-up patients for 2 years following site initiation, according to clinical routine

T-DXd: Trastuzumab deruxtecan.

prior to each infusion. Premedication should consist of two or three medicinal products (e.g., dexamethasone with a 5-HT3 receptor antagonist and/or an NK1 receptor antagonist) [9].

Participating sites

A total of 1350 patients (1170 treated with T-DXd and 180 with conventional chemotherapy) are planned for enrollment from 216 sites in 12 European countries, if T-DXd is available and reimbursed in that market. These countries include but are not limited to Austria, Belgium, Denmark, Finland, France, Italy, Norway, Portugal, Spain, Sweden, Switzerland and The Netherlands (Table 1). Patients will be capped at slightly above these numbers to ensure adequate patient numbers. Each site plans to enroll five to seven patients. Before the study start, each site will conduct a feasibility assessment. Site selection criteria are shown in Table 2. The study will begin in waves in different countries (Table 1). If reimbursement for T-DXd cannot be secured in any of the planned countries, the study will not be opened in that market and eligible patient numbers will be increased in other countries to compensate.

Study population & eligibility

For inclusion in the DESTINY-Breast Respond HER2-low Europe study, patients must be at least 18 years old, with unresectable and/or mBC, and documented HER2-low status (IHC1+, IHC2+/ISH-). Patients must have received at least one prior chemotherapy in the metastatic setting or experienced disease recurrence during or within 6 months of completing adjuvant chemotherapy. They must be newly initiating monotherapy of T-DXd or conventional chemotherapy according to the physician's choice. The patients recruited in the conventional arm

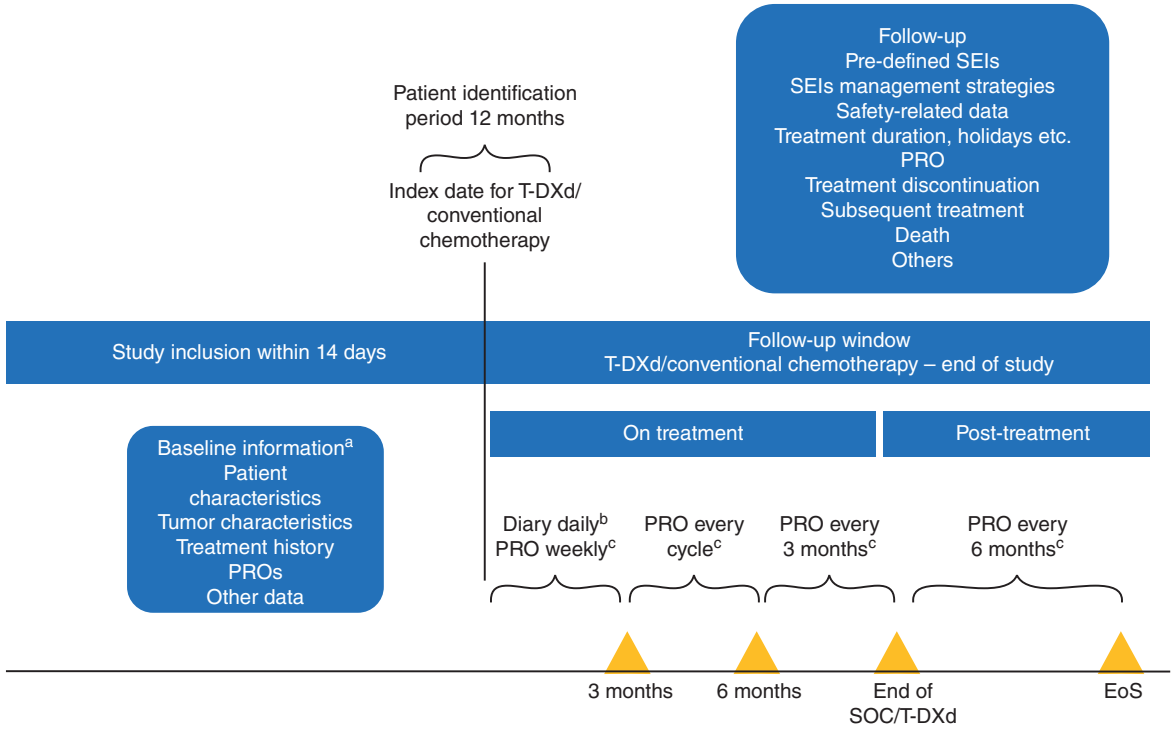

Figure 1. Study design.
[a] Documentation of some information collected at baseline (e.g., prior medication, prior SEIs, comorbidities) refers to a time period 6 months before study start date.
[b] Selected gastrointestinal toxicity of interest, including nausea and vomiting, will be assessed via daily diaries.
[c] PRO measured via validated questionnaire.
EoS: End of study; PRO: Patient-reported outcome; SEI: Safety event of interest; SOC: Standard of care; T-DXd: Trastuzumab deruxtecan.

must also be theoretically eligible for T-DXd treatment. Last, written signed and dated informed consent is required for participation in the study.

The only patients to be excluded are those pregnant or breastfeeding, and those participating in an interventional study at the time of data collection for DESTINY-Breast Respond HER2-low Europe.

Patients will be treated according to the SmPC [9].

Schedule

The study is planned to take place between Q1 2024 and Q1 2028. Individual country start dates will depend on market availability of T-DXd and approval of the study plan by the responsible Institutional Review Board and Independent Ethics Committee. Patient recruitment started in January 2024 and is estimated to last 12 months with patients ideally enrolled consecutively within 14 days, but up to 30 days prior to the first cycle of T-DXd or conventional chemotherapy. Treatment will be selected at the discretion of the treating physician, prior to, and independent of, participation in the study.

During the follow-up window, study periods will include the on-treatment period, in which patients on the index treatment are followed up, and then the post-treatment period, in which patients on the subsequent treatment are followed up (Figure 1). The total study duration is estimated to be 31 months: 12 months of recruitment, 7 months of treatment until 60% criterion is reached for primary study completion, and then 12 months of follow-up. Primary study completion date will occur when 60% of patients treated with T-DXd at the index date (date of treatment start) meet the rwTTNT1 criterion (either start to receive subsequent treatment or die). This is expected 19 months after the first dosed patient. Due to the observational nature of the study, patients may switch treatments during the 12 months follow-up period. Patients will be prospectively observed until death, voluntary discontinuation of study participation, loss to follow-up, or end of study. The end of the study is planned after 12 months of follow-up following the primary study completion (Figure 1). Based on the DESTINY-Breast04

trial, the median T-DXd treatment duration is estimated to be approximately 10 months. The median treatment duration for conventional chemotherapy is estimated to be approximately 5 months [10].

Data will be collected at time points during treatment according to medical routine and the patient-specific visit schedule. An end of study data collection point is recommended for all patients. See Table 3 for schedule of assessments. Personnel from each site will collect data via an electronic case report form which will be routinely recorded in the patient's medical records at every cycle until the end of the study.

Patients will be asked to complete PRO questionnaires and nausea and vomiting diaries during the study. Patients will have a choice between paper and electronic versions. Participating in collection of questionnaires and diaries is optional for the patients. All used questionnaires and diaries are to be fully linguistically validated. PROs, reported by EORTC QLQ-C30 and PGI-TT will be assessed once at the baseline visit, and then after every 3-week treatment cycle until 6 months after the start of treatment with T-DXd or conventional chemotherapy. Following this, PROs will be assessed every 3 months until the end of treatment, in addition to once at the end of treatment. Thereafter, PROs will be assessed every 6 months until the individual end of study. Nausea and vomiting will be assessed once at baseline visit, then daily for the first 3 months after treatment start date via nausea and vomiting diaries.

Surveys will be distributed to the pathologists selected by the treating physicians. These will provide information about HER2 testing practices used for the patients in the study, such as the type of tissue evaluated (e.g., core biopsy vs tumor excision), pre-analytics (e.g., handling, storage and fixation) and the type of testing methodology used.

Quality control

This study will be conducted according to the rules of Good Pharmacoepidemiology Practice and the Guideline on Good Pharmacovigilance Practices. Related quality control mechanisms such as data plausibility checks and monitoring of data will be performed accordingly. On-site monitoring will be performed to verify informed consent documentation and verify source data against the patients' medical records.

Sample size calculations

The sample size calculation (Table 4) is based on the primary study end point rwTTNT1, accrual over time of 12 months and primary study completion to be when 60% of patients treated with T-DXd met the rwTTNT1 criterion (have started subsequent treatment or have died, whichever occurs first). It is planned to include 1170 patients treated with T-DXd and 180 treated with conventional chemotherapy. Parameter estimates for the Weibull distribution were obtained from an extrapolation model informed by TTNT data from the DESTINY-Breast04 study [10]. The planned accrual period is 12 months, with a 7-month treatment period followed by 12 months of post-treatment follow-up. For the planned 1170 patients receiving T-DXd at the study start, the median rwTTNT1 is estimated to be 10 months (95% CI: 9.4, 10.7). The primary study will end when 60% of patients receiving T-DXd experience TTNT1. At 7 months after accrual, it is estimated that 61% of these patients will experience TTNT1. For the planned patients receiving conventional chemotherapy at the study start, the median rwTTNT1 is estimated to be 5 months (95% CI: 4.0, 5.6). At 7 months after accrual, 97% of these patients are estimated to experience TTNT1. All calculations were performed in R software (version 4.1.2).

Statistical analysis

All analyses will be descriptive and analyzed separately for the T-DXd and conventional chemotherapy groups. Any calculated p-values or inferential analyses will be interpreted in a purely explorative manner. Continuous variables will be described by the number of observations, mean, standard deviation, median, upper and lower quartiles and range. Categorical variables will be described by absolute and relative (%) frequency of non-missing data, with missing data reported separately. Means and percentages will be presented with two-sided 95% CIs. Survival distribution will be presented with Kaplan–Meier graphs with estimates at fixed time points (e.g., 3, 6, 9, 12 months) and two-sided 95% CIs. Estimated medians will be presented with 95% CIs using the Brookmeyer and Crowley method. Analysis of all end points will be performed on the Full Analysis Set, consisting of all patients with informed consent who receive at least one dose of study treatment. The overview of patients' disposition will be performed on the All-Patient Set, which includes all patients with informed consent. Subgroup analyses will be presented descriptively.

Table 3. Schedule of assessments.

Assessment	Baseline†	Routine data collection points during treatment‡	Follow-up (including routine data collection points for subsequent treatments)‡	End of study§
Patient informed consent	X			
Inclusion/exclusion criteria	X			
Baseline demographic and clinical (including documentation of relevant comorbidities)	X			
Geriatric assessment for patients ≥75 years using the G8	X			
Clinical and tumor characteristics and treatment history	X			
Number of radiations in the region of the chest in the 12 weeks prior to T-DXd initiation	X			
Effect of previous treatment	X			
ECOG PS	X	X	X	X
PRO assessments¶	X	X	X	X
Daily nausea and vomiting diary#	X	X	X	
Tumor assessment††		X	X	X
T-DXd and conventional chemotherapy treatment‡‡	X	X		
Documentation of past/concomitant medication/treatments	X	X	X	X
Imaging frequency and used type of scans to monitor ILD		X		
Latest clinical exams (heart, lung, liver, kidney): normal/abnormal; LVEF	X	X	X	X
Latest laboratory exams (blood cell count, biochemistry)	X	X	X	X
Safety parameters including physician-reported SEI§§		X	X	X
Management of SEIs for T-DXd only		X	X	X
Documentation of SAEs that lead to dose interruption, reduction, or discontinuation (for T-DXd only)		X	X	X
Documentation of serious drug-related TEAE or drug-related TEAE that lead to dose interruption, reduction or discontinuation§§ (for T-DXd only)		X	X	X
Management of serious drug-related TEAE for T-DXd only		X	X	X
Documentation of T-DXd and conventional chemotherapy discontinuation		X	X	X
Documentation of subsequent anti-cancer treatments¶¶			X	X
Documentation of subsequent anti-cancer treatments discontinuation##			X	X
Survival status†††		X	X	X
Health resource utilization		X	X	X
Documentation at study discontinuation visit/EOS‡‡‡				X

†Baseline visit will ideally be within 14 days (or up to 30 days) prior to index date.
‡The frequency of routine and follow-up visits and any associated management decisions (e.g., diagnostic and therapeutic interventions) are determined by the treating physician's preferences and current best medical practice. In line with NIS requirements, no specific visits or interventions may be performed.
§EOS is defined when the 12 months follow-up is completed, or the patient decides to withdraw from the trial.
¶Patients will be asked to answer the PRO questionnaires at varying frequencies.
7-day recall diary to be completed at baseline and daily diary (24 h recall) to be completed for first 3 months only.
††Documentation of tumor assessment includes response (y/n/not evaluated; if yes partial or complete response, stable disease, progression), and method of response evaluation. Note: to comply with NIS requirements, the modality of assessment of response is not pre-specified. Possible modalities for assessment include radiological criteria, medical criteria and other criteria.
‡‡Documentation of T-DXd and conventional chemotherapy includes start date, reason for start, initial dose, cycle scheduling, dose interruptions/reductions, and reasons for interruptions/reductions, if applicable. As the baseline visit should be within 14 days (or up to 30 days) prior to index date, the data relating to T-DXd and conventional chemotherapy initiation are to be documented as T-DXd treatment was initiated.
§§Documentation of SAEs, (serious) drug-related TEAE starts with the day of first T-DXd and conventional chemotherapy administration (index date).
¶¶Documentation at T-DXd and conventional chemotherapy discontinuation visit includes date and reason (progression, death, discontinuation due to AE, withdrawal of consent, LTFU, and other).
The treatment decision is to be taken by the treating physician according to current best medical practice. Documentation includes type of subsequent BC-related therapies and response to subsequent BC-related therapies.
†††Documentation of survival status includes date of death and reason for death, if applicable and available.
‡‡‡Documentation at EOS visit includes date and reason for discontinuation/study end (i.e., regular EOS participation [overall EOS reached death, patient's wish/withdrawal of informed consent], LTFU and other).
AE: Adverse event; BC: Breast cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EOS: End of study; G8: Geriatric 8; ILD: Interstitial lung disease; LTFU: Lost to follow-up; LVEF: Left ventricular ejection fraction; NIS: Non-interventional study; PRO: Patient-reported outcome; SAE: Serious adverse event; SEI: Safety event of interest; T-DXd: Trastuzumab deruxtecan; TEAE: Treatment-emergent adverse event.

Table 4. Sample size calculation for primary end point rwTTNT1 based on simulations.

Treatment	Sample size	Accrual period (months)	Follow-up (months)	Weibull distribution (scale; shape parameter)	Number of events n (%)	Estimated median rwTTNT1 95% CI (months)
T-DXd	1170	12	7	2.573, 0.295	714 (61)	10 (9.4, 10.7)
Conventional chemotherapy	180	12	7	1.833, 0.271	175 (97)	4.7 (4.0, 5.6)

rwTTNT1: Real-world time to next treatment; T-DXd: Trastuzumab deruxtecan.

Discussion

Based on the results from the DESTINY-Breast04 trial [10], T-DXd was authorized by EMA for use in patients with HER2-low unresectable or mBC who have received prior chemotherapy in the metastatic setting or had disease recurrence during or within 6 months of completing adjuvant therapy [9]. According to the ESMO Living Guidelines, T-DXd is now the recommended standard of care for this group of patients, after progression on a first-line chemotherapy [16]. The ESMO expert consensus statements also recommend T-DXd use for HER2-low mBC [17]. In the case of HR+ HER2-low disease, the guidelines recommend T-DXd as second- and third-line therapy followed by chemotherapy or sacituzumab govitecan (if not used before). In the case of triple-negative HER2-low disease, T-DXd is recommended as third-line therapy following sacituzumab govitecan [18,19]. Given that these ADCs have different payloads but similar mechanisms of action, there is a need for real-world data to observe the used sequences for ADC therapies, their results in terms of outcomes, to ultimately identify the best treatment sequence. The DESTINY-Breast Respond HER2-low Europe study will collect data on previous therapies, and on subsequent therapies (including ADCs) during the 12-month follow-up period, thereby adding valuable insight into this area.

As T-DXd is indicated for both HER2+ and HER2-low mBC, including HR+ disease, many patients will encounter T-DXd during their treatment. Therefore, it is beneficial to collect real-world data on AEs during T-DXd treatment, particularly for the large pool of HER2-low patients, of which less is known because the indication is newer. Between the HER2-low patients in DESTINY-Breast04 and the patients with HER2+ mBC in the DESTINY-Breast03 study, rates of most AEs were similar, with a few exceptions. In the HER2-low patients in DESTINY-Breast04, vomiting was less common (34 vs 52%), as was constipation (21 vs 37%) and diarrhea (22 vs 32%), compared with the HER2+ patients in DESTINY-Breast03 [10,20]. In both studies, the protocols recommended that patients receive prophylactic antiemetic agents such as 5-HT3 receptor antagonists or NK-1 receptor antagonists and/or steroids (e.g., dexamethasone) [10,20], as indicated in the T-DXd SmPC [9], as it is classified as having a moderate [21] or high emetogenic risk [11]. Furthermore, prophylactic or supportive treatment of AEs was available to patients at the investigator's discretion [10,20]. As DESTINY-Breast03 was performed earlier than DESTINY-Breast04, investigators may have had improved insight into management of AEs specific to T-DXd during the DESTINY-Breast04 trial, which could have led to the reduced proportions of observed gastric AEs during this study. Alternatively, HER2-low patients could be at lower risk of experiencing gastric AEs. Interestingly, fatigue was more common in DESTINY-Breast04 (48%) than DESTINY-Breast03 (31%) among patients receiving T-DXd, which may have been due to more progressed baseline disease states in DESTINY-Breast04. Management of fatigue might include support groups, low-intensity exercise and supportive care [22]. The DESTINY-Breast Respond HER2-low Europe NIS will collect data of these AEs in the clinic, producing useful guidance specific to HER2-low patients.

T-DXd treatment can be associated with certain SEIs; nausea and vomiting, fatigue, alopecia, ILD/pneumonitis, and decreased LVEF. ILD/pneumonitis and decreased LVEF are serious concerns, with fatal outcomes reported from ILD/pneumonitis. When selecting patients for treatment with T-DXd, risk factors for ILD/pneumonitis should be taken into account, and recommendations for management have been previously published [15,23]. Patients should be monitored for signs of ILD/pneumonitis and LVEF during treatment with T-DXd [9]. In patients treated with T-DXd in DESTINY-Breast04, drug-related ILD/pneumonitis occurred in 12.1%, including two patients who died due to pneumonitis. Left ventricular dysfunction occurred in 4.6% of patients [10]. Nausea and vomiting occurred in 73.0 and 34.0%, respectively, of patients receiving T-DXd in DESTINY-Breast04, which was higher than in patients receiving chemotherapy. The anti-nausea premedication was not precisely predefined in the study. Fatigue and alopecia were reported in 47.7 and 37.7% of patients receiving T-DXd, respectively. These rates were

similar to those in patients receiving chemotherapy [10], but are of interest due to their significant impact on quality of life.

Other potential AEs to note with T-DXd use include neutropenia, anemia, thrombocytopenia and alopecia, which occurred in 33.2, 33.2, 23.7 and 37.7% of patients receiving T-DXd in DESTINY-Breast04, respectively [10]. Neutropenia, anemia and thrombocytopenia may require modifications to the T-DXd dose, depending on reaction severity [9]. Patients at high risk of neutropenia or experiencing neutropenia of Grade ≥3 may benefit from primary granulocyte colony-stimulating factor. Screening for anemia through a complete blood count at each visit is recommended, and iron therapy, blood transfusions or erythropoiesis stimulating agents may be required. For thrombocytopenia, platelet transfusion or thrombopoietin receptor agonists may be useful. Alopecia does not pose a medical risk but can be psychologically distressing for the patient. Scalp cooling could help reduce alopecia but is not widely available. Treating physicians are encouraged to educate patients on alopecia before treatment, to increase acceptance [22].

The DESTINY-Breast Respond HER2-low Europe NIS will be the first to provide real-world evidence about T-DXd treatment in patients with HER2-low mBC in Europe. Data on effectiveness, safety and tolerability and treatment patterns of T-DXd will reflect those seen in the clinic, giving a more realistic view of patient treatment and outcomes than in clinical trials. This study will also include a larger pool of patients than previously studied, enabling greater detail of results. PROs, such as the nausea and vomiting diary and PGI-TT, will provide insight into the tolerability of T-DXd from the patient perspective, which is aimed to deepen understanding of effective management strategies for AEs and help toward maximizing patient quality of life. The study will provide data on geriatric patients treated with T-DXd, a group for which very limited data currently exist from clinical trials. The data gathered on HER2 testing practices are hoped to lead to a deeper level of understanding of biopsy collection and testing, and the networking and collaboration between oncologists and pathologists. This could help to guide future efforts of standardization and consistency across different European countries. As DESTINY-Breast Respond HER2-low Europe is a real-world NIS, the only exclusion criteria are pregnancy, and involvement in an interventional trial in the same timeframe. This approach prevents selection bias and allows recording of results as they appear naturally in routine clinical practice.

Limitations of the study may include underreporting of AEs. This could occur between baseline and follow-up if events are difficult to remember or considered to be non-essential, but this is unlikely to be affected in the case of severe AEs and hospitalizations. Underreporting of treatment changes could also occur, but the risk of this is considered to be low. Sites are selected in a way that is designed to ensure representativeness of countries and regions, but their requirement for sufficient capabilities, interest and capacities to participate could affect representativeness of the study. Differences between countries or regions could occur, so this will be carefully examined during analysis. Discrepancies in how laboratories categorize HER2-low status may also impact this study and will be considered at the point of analysis. Lack of representation for ethnic minorities is a general concern in clinical trials [24], so inclusion of this demographic would be beneficial if possible, but this will depend on recruitment at individual sites. Finally, the non-interventional nature of the study could lead to missing data, and this will be considered during analysis.

Conclusion

The DESTINY-Breast Respond HER2-low Europe NIS will provide insights into the use of T-DXd treatment in patients with HER2-low mBC in the real-world across Europe. Information will be gathered on T-DXd effectiveness, safety and tolerability, treatment patterns, geriatric health status and HER2 testing in patients. This information will be useful for helping to guide clinicians on how best to treat patients with HER2-low mBC to maximize their benefit from T-DXd while minimizing AEs. See Box 2 for a summary.

Box 2. What this study adds to existing knowledge and clinical practice.

- The DESTINY-Breast Respond HER2-low Europe NIS will provide real-world insight into the effectiveness and T-DXd that is currently limited to findings from clinical trials.
- This study will be the first to provide prospective real-world data about T-DXd treatment in patients with HER2-low metastatic breast cancer, including underrepresented patient groups such as those aged 65 years and older.
- The information gathered about T-DXd treatment for HER2-low metastatic breast cancer is intended to provide knowledge which would be required in order to implement strategies aimed to improve patient outcomes.
- Characterizing the management of AEs associated with T-DXd in the real-world will help to optimize treatment and ensure maximum benefit.
- Through the use of pathologist surveys, HER2 testing practices across different European countries will be examined to provide information on differences in testing methodologies.

Executive summary

Background

- DESTINY-Breast Respond HER2-low Europe (NCT05945732) is a multi-center, multi-country, observational, prospective, non-interventional study (NIS) of trastuzumab deruxtecan (T-DXd) in patients with HER2-low mBC.

End points

- The study will provide information about T-DXd effectiveness, safety and tolerability, PROs and treatment patterns.
- The study will include a disease registry of patients treated with conventional chemotherapy to contextualize treatment patterns and effectiveness of T-DXd and conventional chemotherapy.
- The study will include a geriatric screening to provide data around T-DXd use in older patients.
- HER2 testing practices across different European countries will be examined through pathologist surveys.

Study population & schedule

- Approximately 1350 patients will be enrolled from 216 sites in 12 European countries.
- The study is planned to take place between 2023 and 2028.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2024-0015

Author contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Ethical conduct of research

Notification to or approval by Independent Ethics Committees and competent authorities or other organizations will be performed as required by national regulations in the participating countries before commencement of enrollment at a study center. Independent Ethics Committees include CEIm Hospital 12 de Octubre (Registration number: 23/608), CEIm Área de Salud Valladolid Este, Servicio de ordenación farmacéutica de la Dirección del Servicio Canario de la Salud, Comité de Ética de la Investigación con Medicamentos del Parc Taulí de Sabadell, El Comité de Ética de la Investigación -CEI- del Hospital Universitario Ramón y Cajal, Comitato Etico Area Nord Veneto (CET-ANV), Ethics Committee CER-VD, Cantonal Ethics Committee Zurich, Ethics Committee Northwest and Central Switzerland EKZN, Ethics Committe East Switzerland EKOS, Ethikkommission der Med. Universität Innsbruck (Registration number: 1175/2023), Ethikkommission der Johannes Kepler Universität Linz (Registration number: 1316/2023), Ethikkommission der Stadt Wien, Ethikkommission der Medizinischen Universität Wien, Ethikkommission des Landes Vorarlberg, Ethikkommission der Med. Universität Innsbruck, Etikkommission der med. Universität Graz, Ethikkommission des Landes Niederösterreich (Registration number: 26/006-2023), Ethikkommission des Landes Salzburg (Registration number: 1140/2023), Aerztliche Direktion MedUniInnsbruck (Registration number: 20240122-3360). Written Informed Consent Form (ICF) will be obtained from all patients. The ICF should be signed at the baseline data collection point after the investigator informed the patient about the participation, and patient agreed on participating in the study and prior to any data collection. The patient has the right to withdraw the consent at any time.

Data sharing statement

All data derived from the DESTINY-Breast Respond HER2-low study will be shared with the authors for interpretation and conclusions.

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