27 February 2025
EMA/109425/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Enhertu

International non-proprietary name: Trastuzumab deruxtecan

Procedure No. EMEA/H/C/005124/II/0048

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	anti-drug antibody
ADC	antibody-drug conjugate
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ASCO/CAP	American Society of Clinical Oncology/College of American Pathologists
BC	breast cancer
BICR	blinded independent central review
CDK 4/6	cyclin-dependent kinase 4 and 6
CDx	Companion diagnostic
CI	confidence interval
CMA	Conditional Marketing Authorisation
COVID-19	coronavirus disease 2019
CSP	clinical study protocol
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTD	common technical document
Ctrough	observed lowest concentration before the next dose is administered
DB-06	DESTINY-Breast06
DCO	data cut-off
DoR	duration of response
DXd	the released payload (MAAA-1181a)
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ER	estrogen receptor
ERA	environmental risk assessment
FAS	Full Analysis Set
FDA	Food and Drug Administration
GHS	Global Health Status
GI	gastrointestinal
HER2	human epidermal growth factor receptor 2

HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
ICH	International Council for Harmonisation
IHC	immunohistochemistry
ILD	interstitial lung disease
ISH	in situ hybridization
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous
LV	left ventricular
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mTOR	mammalian target of rapamycin
MTP	multiple testing procedure
N/A	not applicable
Nab	neutralizing antibody
NCCN	National Comprehensive Cancer Network
NE	not evaluable
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PFS2	time to second progression or death
PgR	progesterone receptor
PI3-K	phosphoinositide 3-kinase
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha protein coding
PK	pharmacokinetic(s)
PopPK	population PK
PPD	Pharmaceutical Product Development, Inc.
PPE	Palmar-plantar erythrodysaesthesia
PRO	Patient Reported Outcomes
PS	Performance status

PT	preferred term
Q3W	every 3 weeks
QLQ	Quality of Life (questionnaire)
RECIST v1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RCT	Randomised clinical trial
REC	Recommendation
SAE	serious adverse event
SAP	Statistical Analysis Plan
SMQ	Standardized MedDRA Query
SOB	Specific Obligation
SoC	standard of care
T-DXd	trastuzumab deruxtecan
TEAE	treatment-emergent adverse event
TPC	treatment of physician’s choice
US	United States of America
Vs	versus

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Daiichi Sankyo Europe GmbH submitted to the European Medicines Agency on 22 July 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to include treatment of adult patients with unresectable or metastatic HER2-low or HER2-ultralow breast cancer (BC) who have received at least one endocrine therapy in the metastatic setting for ENHERTU, based on results from study D9670C00001 (DESTINY-Breast06); this is a phase 3, randomized, multicentre, open-label study of trastuzumab deruxtecan (DS-8201a) compared with investigator's choice chemotherapy in, hormone receptor-positive, HER2-low and HER2-ultralow BC patients whose disease has progressed on endocrine therapy in the metastatic setting. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce editorial changes to the PI, to update the list of local representatives in the Package Leaflet and to update the PI according to the Excipients Guideline.

The variation requested amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/0001/2015 on the granting of a class waiver.

Information relating to orphan market exclusivity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 30 January 2020 (EMEA/H/SA/3715/1/FU/1/2019/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteurs appointed by the CHMP were:

CHMP Rapporteur: Boje Kvorning Pires Ehmsen CHMP Co-Rapporteur: Peter Mol

PRAC Rapporteur: Carla Torre

Timetable	Actual dates
Submission date	22 July 2024
Start of procedure:	17 August 2024
CHMP Rapporteur Assessment Report	9 October 2024
PRAC Rapporteur Assessment Report	18 October 2024
PRAC members comments	23 October 2024
CHMP Co-Rapporteur Assessment	23 October 2024
PRAC Outcome	31 October 2024
CHMP members comments	4 November 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	7 November 2024
Request for supplementary information (RSI)	14 November 2024
MAH's responses submitted to the CHMP on	13 December 2024
Re-start of procedure	30 December 2024
CHMP Rapporteur Assessment Report	29 January 2025
PRAC Rapporteur Assessment Report	31 January 2025
PRAC members comments	5 February 2025
Updated PRAC Rapporteur Assessment Report	6 February 2025
PRAC Outcome	13 February 2025
CHMP members comments	17 February 2025
Updated CHMP Rapporteur Assessment Report	21 February 2025
Opinion	27 February 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

The scope of this variation is to extend the existing therapeutic indication for Enhertu as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting, based on the results of phase III study DB-06.

Disease or condition

The MAH initially applied for the following indication:

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting (see section 5.1).

During the procedure the indication was amended. The agreed indication is as follows:

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment (see sections 4.2 and 5.1).

Epidemiology and risk factors

In Europe, over 531,000 patients were diagnosed with BC and over 141,000 patients died from the disease in 2021 (Sung et al 2021). Advanced BC, which includes both locally advanced (inoperable) and metastatic BC, remains incurable. The 5-year survival rate for metastatic BC is known to be 38% (Gennari et al. 2021).

Biologic features

Approximately 80-85% of patients with BC have tumours that are classified as HER2 negative, according to scoring recommended by the ASCO/CAP HER2 testing in BC guideline (Giuliani et al. 2016, Tarantino et al. 2023). Within what are traditionally considered HER2-negative BCs, there exists a spectrum of HER2 expression in tumours ranging from IHC 2+/ISH- and IHC 1+ to tumours that have lower than HER2 IHC 1+ expression or no HER2 expression and are determined as being IHC 0 according to scoring recommended by ASCO/CAP guidelines (Wolff et al 2018). Tumours that have HER2 IHC lower than 1+ but detectable HER2 staining, i.e. faint partial staining of the membrane in 10% or less of the cancer cells are referred to as HER2-ultralow tumours.

Based on literature of primary or metastatic hormone receptor-positive HER2-negative BC, approximately 60-65% of cases were HER2-low and approximately 20-25% were HER2 ultralow (Chen et al. 2023, Denkert et al. 2021, Mehta 2024, Viale et al. 2023).

Management

At the time the pivotal D9670C00001 study (DESTINY-Breast06 [Study DB 06 hereafter]) was initiated, patients with hormone receptor-positive, HER2-low (IHC 1+ and IHC 2+/ISH-) or HER2 ultralow (IHC 0 with membrane staining, described as IHC > 0 < 1+ in study DB-06) tumours followed the same treatment paradigm as for hormone receptor-positive, HER2 negative BC (NCCN 2024, Gennari et al. 2021, Shimoi et al. 2020), which includes multiple lines of endocrine therapy with or without targeted therapy (e.g., CDK 4/6 inhibitors) followed by single-agent chemotherapy (Cardoso et al. 2020).

Endocrine therapy, including aromatase inhibitors, selective ER modulators, and selective ER down regulators, as well as targeted therapies such as CDK 4/6 inhibitors, PI3-K inhibitors, and mTOR inhibitors have been shown to improve outcomes for patients with hormone receptor-positive, HER2 negative metastatic BC and are considered SoC for most patients in the metastatic setting (Allison et al. 2020, Andre et al. 2019, Matutino et al. 2018).

The optimal treatment sequence for patients with hormone receptor-positive (HR+), HER2-negative metastatic BC is considered to be the use of first-line endocrine therapy + CDK 4/6 inhibitors, followed by subsequent endocrine therapy with targeted therapies (e.g. mTOR or PI3-K inhibitors [for PIK3CA mutant tumours]) (NCCN 2024, Gennari et al. 2021, Cardoso et al. 2020). In patients whose disease has progressed after multiple lines of endocrine therapy with or without targeted therapies or who have a short median PFS on first-line endocrine-based therapy, chemotherapy is considered an appropriate option (Gennari et al. 2021).

When chemotherapy is recommended, the choice between single-agent and combination therapy is decided based on several factors to individualize therapy. Generally, sequential single-agent therapy is preferred over combination therapy (Cardoso et al. 2009, NCCN 2024, Cancer Facts and Figures 2024). Chemotherapy combinations may be used in selected patients with rapidly progressing disease and visceral crisis. Single-agent therapy options include taxanes, anti-metabolites (e.g. capecitabine) and anthracyclines. Because of the availability of many agents and the lack of clear superiority of one agent over others, there is no ideal sequence of treatments that can be applied to all patients.

In patients with HR+, HER2-negative BC who had received 0 to 1 prior line of chemotherapy for metastatic disease, single-agent chemotherapy led to a median PFS of approximately 6 to 7 months and a median OS of approximately 20 to 25 months (O'Shaughnessy at al. 2021a, O'Shaughnessy at al. 2021b, Robert et al. 2011, Baselga et al. 2017).

The ADC sacituzumab govitecan (Trodelvy) was recently approved based on the TROPiCS 02 study for patients with unresectable locally advanced or metastatic hormone receptor-positive, HER2-negative (IHC 0, IHC 1+ and IHC 2+/ISH−) BC who have received endocrine-based therapy and at least 2 additional systemic therapies in the metastatic setting based on improvement in median PFS over chemotherapy (5.5 months vs 4.0 months; HR: 0.66) (Rugo et al. 2022).

In patients with unresectable or metastatic HER2-low (IHC 1+ and IHC 2+/ISH-) BC, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy, T-DXd is an approved option regardless of hormone receptor status.

2.1.2. About the product

Enhertu (trastuzumab deruxtecan, T-DXd) is a HER2-directed antibody-drug conjugate (ADC) composed of a humanized anti-HER2 immunoglobulin G1 monoclonal antibody with the same amino

acid sequence as trastuzumab, covalently linked to the membrane-permeable topoisomerase I inhibitor payload DXd via a stable tetrapeptide based linker.

In Europe, Enhertu is currently approved as a Conditional Marketing Authorisation (CMA) as monotherapy for advanced HER2+ breast cancer in second or ulterior line of treatment (5.4 mg/kg Q3W), advanced HER2-low breast cancer after chemotherapy (5.4 mg/kg Q3W), advanced NSCLC HER2+ requiring systemic therapy following platinum-based chemotherapy with or without immunotherapy (5.4 mg/kg Q3W), and advanced HER2+ gastric or gastroesophageal adenocarcinoma after a trastuzumab-based regimen (6.4 mg/kg Q3W).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

This application is based on the phase 3 Randomized Clinical Trial DESTINY-Breast06 (study DB-06), which compared the efficacy and safety of T-DXd against investigator's choice chemotherapy (capecitabine, paclitaxel or nab-paclitaxel) in patients with HR+, HER2-low (IHC 1+ and IHC 2+/ISH-) and HER2-ultralow (IHC 0 with membrane staining, described as IHC > 0 < 1+ in the study) BC, whose disease had progressed on (a) at least 2 lines of endocrine therapy in the metastatic setting or (b) 1 line of prior endocrine therapy in the metastatic setting and demonstrated progression within 24 months of the start of adjuvant endocrine therapy, or within 6 months of starting first-line endocrine therapy in combination with a CDK 4/6 inhibitor in the metastatic setting.

The MAH received Scientific Advice from the CHMP on 30 January 2020 (EMEA/H/SA/3715/1/FU/1/2019/II). Overall, the study design was deemed acceptable. Considering that a low efficacy might be expected in the HER2-ultralow subgroup, subgroups' results should be considered in order to assess the consistency of the effect across the various HER2 expression levels. Anthracyclines were recommended to be included among the physician's choice comparator options, considering they are among the most widely used treatment options in this setting, and are also recommended by main guidelines. Depending on the actual magnitude of benefit in terms of PFS, the safety profile compared to SOC and the consistency of the effect among the various subgroups, mature OS data might be requested in order to conclude on the B/R in the ITT population.

2.1.4. General comments on compliance with GCP

The MAH has stated that their procedures, internal quality control measures, and audit programs provide reassurance that the clinical study program was carried out in accordance with Good Clinical Practice, as documented by the ICH, EMA, and the US FDA.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

A revised environmental risk assessment has not been provided (see discussion below) .

2.2.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

Trastuzumab deruxtecan is an antibody-drug conjugate (ADC) composed of a humanized anti-HER2 immunoglobulin G1 monoclonal antibody with the same amino acid sequence as trastuzumab, covalently linked to the membrane-permeable topoisomerase I inhibitor deruxtecan (DXd) via a stable tetrapeptide based linker. Antibodies are considered naturally occurring proteins, which are not expected to remain either stable or biologically active in the environment for any significant period. For the cytotoxic payload deruxtecan, the currently approved ERA implemented an Fpen based on a prevalence value for all breast cancer patients, irrespective of disease stage or previous treatments, as a worse case assumption. Therefore, this extension of indication will not result in any increase in the predicted environmental concentration of T-DXd, and based on the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*), no updated ERA is required. The justification for not providing an updated ERA is accepted.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application, does not lead to a significant increase in environmental exposure further to the use of trastuzumab deruxtecan. Considering the above data, trastuzumab deruxtecan is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The current application for T-DXd (Enhertu 5.4 mg/kg IV Q3W) for the treatment of adult patients with unresectable or metastatic HER2-low or HER2-ultralow BC is based on the results of pivotal study D9670C00001 (DESTINY-Breast06, hereafter referred to as study DB-06), a Phase III, randomized, multi-centre, open-label study of Trastuzumab Deruxtecan (T-DXd) versus investigator’s choice chemotherapy in HER2-low, Hormone Receptor-Positive breast cancer patients whose disease has progressed on endocrine therapy in the metastatic setting.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 1 Summary of T-DXd Efficacy Studies to Support the Proposed Indication

Study identifier; status; DCO	Objective(s) of the study	Study design/type of control	Test product, dosage regimen, route of administration	No. of patients randomised or enrolled/ treated	Patient population
Pivotal Study					
D9670C00001 (DESTINY-Breast06 [DB-06]) **Complete; DCO of 18 Mar 2024**	Efficacy, Safety and Tolerability, PK, HRQoL, Immunogenicity	Phase III, randomized, open-label multicenter, global study to assess the efficacy and safety of T-DXd vs investigator's choice single agent chemotherapy	T-DXd: 5.4 mg/kg IV infusion Q3W **OR** Investigator choice chemotherapy: Paclitaxel 80 mg/m^2 IV every week in 3-week cycles Capecitabine 1000 mg/m^2 or 1250 mg/m^2 twice daily orally 2 weeks on/1 week off in 3-week cycles Nab-paclitaxel 100 mg/m^2 IV every week for 3 weeks, then 1 week rest in 4-week cycles	Total: 866/851 T-DXd: 436/434 Investigator choice chemotherapy: 430/417	Advanced or metastatic hormone receptor-positive breast cancer with HER2-low (IHC 1+ and IHC 2+/ISH-) and HER2-ultralow (IHC 0 with membrane staining, described as IHC > 0 < 1+ in the study)

2.3.1. Bioanalytical methods

No new biopharmaceutical studies with different formulations were conducted.

No new methods were used to assay the drug substance and the drug product.

The bioanalytical methods used to determine serum concentrations of the intact drug (T-DXd), total anti-HER2 antibody and the released drug (DXd), and the detection of ADA, and nAb against T-DXd in study DB-06 are the same methods used supporting the initial marketing authorisation (EMEA/H/C005124) and subsequent BC applications (EMEA/H/C005124/II/14 & EMEA/H/C005124/II/22).

2.3.2. Pharmacokinetics

Study D9670C00001(Study DB-06)

Study design and disposition: Study DB-06 is a phase III, open-label (sponsor-blind), multi-center, randomized study to assess the efficacy and safety of T-DXd at 5.4 mg/kg Q3W compared with Investigator's choice single-agent chemotherapy (capecitabine, paclitaxel or nab-paclitaxel), in patients with hormone receptor-positive, HER2-low (IHC 1+ and IHC 2+/ISH-) and HER2-ultralow (IHC > 0 < 1+ BC).

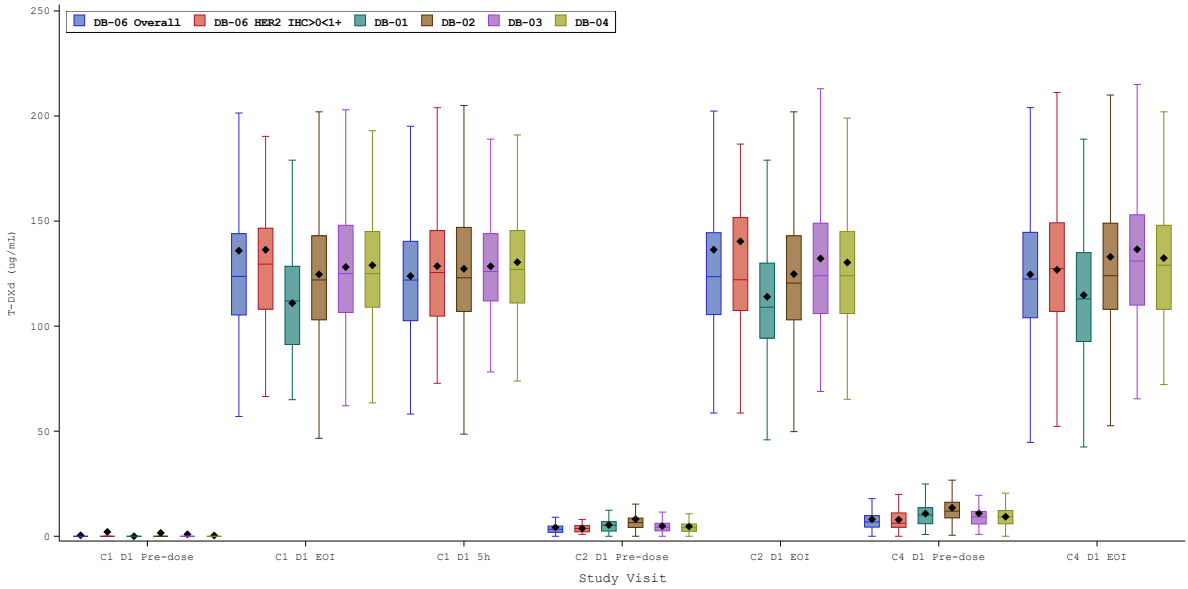
Clinical pharmacology objectives: To assess the PK of T-DXd and to investigate the immunogenicity of T DXd.

PK and immunogenicity sampling and measurements: In study DB-06 PK samples from patients who received T-DXd were collected pre-dose (within 6 hours before T DXd infusion) at Cycles 1, 2, 4, 6 and 8, post-dose end of infusion (within 15 minutes after end of T-DXd infusion) at Cycles 1, 2, and 4, and post-dose 5 hours (± 2 hours) after end of infusion at Cycle 1 only. In study DB-06, the serum concentrations of the intact drug (T-DXd), total anti-HER2 antibody and the released drug (DXd) were quantified. Blood samples for determination of anti-drug antibody (ADA) in serum was collected pre-infusion on Day 1 Cycle 1, Day 1 Cycle 2, and Day 1 Cycle 4, then on Day1 of every 4 cycles.

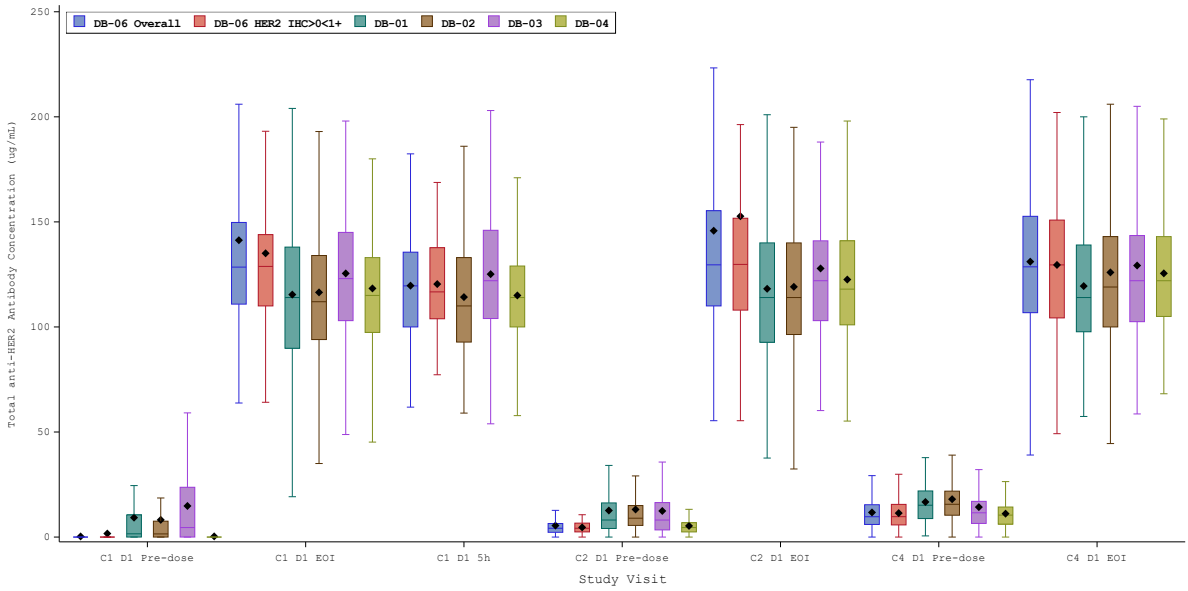
PK-results and immunogenicity results: Following T-DXd 5.4 mg/kg Q3W, T-DXd concentrations were similar to total anti-HER2 antibody concentrations (3.36 µg/mL [T-DXd] and 4.46 µg/mL [total anti-HER2 antibody] at Cycle 2 pre-dose [Ctrough]), and 6.90 µg/mL [T-DXd] and 10.47 µg/mL [total anti-HER2 antibody] at Cycle 4 pre-dose [Ctrough]). DXd exposure was lower than either T-DXd or total anti-HER2 antibody exposure (0.23 ng/mL at Cycle 2 pre-dose [Ctrough] and 0.35 ng/mL at Cycle 4 pre-dose [Ctrough]). In the HER2 IHC > 0 < 1+ subgroup, concentrations of total T-DXd, anti-HER2 and DXd were consistent with those observed in patients in the PK analysis set. The concentration levels shown in study DB-06 were consistent with concentration levels observed in other BC indications dosed at 5.4 mg/kg Q3W, see figure below.

Figure 1 Serum Concentration Box Plot (PK Population)

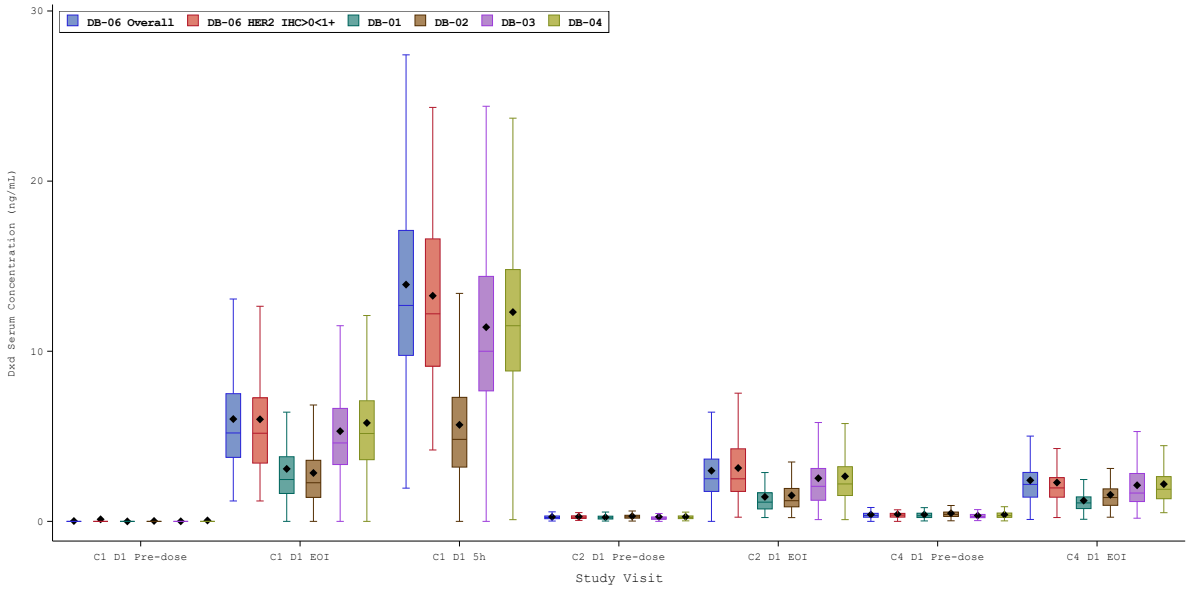
T-DXd serum concentrations (µg/mL)



Total anti-HER2 AB serum conc. (µg/mL)



DXd serum concentration (ng/mL)



Population Pharmacokinetic Evaluation of T-DXd: Prior population PK analyses have been conducted in support of multiple indications of T-DXd including the evaluation of various intrinsic and extrinsic covariates. The population PK evaluations in previous procedures confirmed there is no clinically meaningful PK difference among different tumor types and populations.

2.3.3. Pharmacodynamics

Primary and secondary pharmacology is described in the initial BC application (see initial MAA EMEA/H/C005124).

Immunogenicity results (study DB-06): In the HER2-low population, ADA prevalence (ADA+ prevalence at baseline or post-baseline) was 11.1% (48/433 patients), and ADA incidence (TE-ADA+) was 5.1% (22/433 patients), see table below. The results indicate that the majority of ADA+ patients were not classified as TE-ADA+. ADA responses were primarily transient in nature (20/22 TE-ADA+ patients, 4.6% of the ADA analysis set), and few ADA+ patients were TE-nAb+ (2/433, 0.5%). The median of maximum ADA titers in TE-ADA+ patients and patients who were ADA+ at baseline only were low, at the limit of detection of 45. The data suggest that the magnitude of ADA response to T-DXd in TE-ADA+ patients was no different than that of pre-existing ADA.

Comparison of results across clinical trials of T-DXd, 5.4 mg/kg

Immunogenicity data from 2331 ADA-evaluable patients in the following pools (comprising 11 clinical studies) were collected to assess T-DXd ADA responses and the impact of immunogenicity on clinical PK and safety:

T-DXd 5.4 mg/kg All BC Pool: consisting of studies J101, DB-01, DB-02, DB-03, DB-04, DB-06, and DP-01. This pool comprised 1740 patients from 7 studies that evaluated the safety and tolerability of T-DXd 5.4 mg/kg in BC across stage and line of treatment.

T-DXd 5.4 mg/kg All Solid Tumour Pool: consisting of studies J101, DB-01, DB-02, DB-03, DB-04, DB-06, DL-01, DL-02, DC-02, DP-01, and DP-02. This pool comprised 2331 patients from 11 studies that evaluated the safety and tolerability of T-DXd 5.4 mg/kg across various tumor types, stages, and lines of treatment.

Summary of Immunogenicity Response

The prevalence of ADA was 9.2% (160 of 1740 patients) in the T-DXd All BC Pool, and 8.4% (195 of 2331 patients) in the T-DXd All Solid Tumor Pool, see table below. The incidence of ADA was 2.6% (45 of 1740 patients) in the T-DXd All BC Pool and 2.1% (49 of 2331 patients) in the T-DXd All Solid Tumour Pool.

The majority of T-DXd-treated patients who had positive ADA results were ADA+ at baseline only. Across the pools, a total of 11 tested positive for neutralising anti-body (nAb), and 3 were classified as TE-nAb+. Across all pools, ADA response to T-DXd was mostly transient in nature. In TE-ADA+ patients, the median of the maximum titer was low relative to the MRD of 45. There was no apparent effect of ADA on the PK of T-DXd based on observed data and as also shown in previous population PK analysis.

Table 2 Summary of ADA Responses to T-DXd for DB-06 and Pools (Immunogenicity Analysis Set)

ADA category	DB-06 (5.4 mg/kg) (N = 433)	DB-06 HER2 IHC > 0 < 1+ (5.4 mg/kg) (N = 76)	All BC pool T-DXd (5.4 mg/kg) (N = 1740)	All solid tumor pool T-DXd (5.4 mg/kg) (N = 2331)
ADA+ prevalence at baseline or post-baseline [a], n (%)	48 (11.1)	5 (6.6)	160 (9.2)	195 (8.4)
Median of maximum titer	45.0	45.0	45.0	45.0
TE-ADA+ (ADA incidence) [b], n (%)	22 (5.1)	1 (1.3)	45 (2.6)	49 (2.1)
Median of maximum titer	45.0	45.0	45.0	45.0
ADA+ post-baseline only (treatment-induced ADA+ [c]) n (%)	22 (5.1)	1 (1.3)	45 (2.6)	49 (2.1)
Median of maximum titer	45.0	45.0	45.0	45.0
Treatment-boosted ADA+ [d], n (%)	0	0	0	0
Median of maximum titer	NC	NC	NC	NC
ADA+ prevalence at both baseline and post-baseline [e], n (%)	4 (0.9)	2 (2.6)	23 (1.3)	29 (1.2)
Median of maximum titer	67.5	45.0	45.0	45.0
ADA+ prevalence at baseline [f], n (%)	22 (5.1)	2 (2.6)	92 (5.3)	117 (5.0)
Median of maximum titer	45.0	270.0	90.0	90.0
TE-persistently ADA+ [g], n (%)	2 (0.5)	0	7 (0.4)	7 (0.3)
Median of maximum titer	225.0	NC	180.0	180.0
TE-transiently ADA+ [h], n (%)	20 (4.6)	1 (1.3)	38 (2.2)	42 (1.8)
Median of maximum titer	45.0	45.0	45.0	45.0
nAb+ prevalence at baseline or post-baseline [i], n (%)	3 (0.7)	0	10 (0.6)	11 (0.5)
Median of maximum titer [j]	202.5	NC	180.0	180.0
TE-nAb+ (nAb incidence) [k], n (%)	2 (0.5)	0	3 (0.2)	3 (0.1)
Median of maximum titer [j]	202.5	NC	45.0	45.0

[a] ADA+ prevalence at baseline or post-baseline: Patients with any positive ADA assessment at baseline or post-baseline. The percentage of these patients in a population is known as ADA prevalence.

[b] Treatment-emergent ADA+: Patients who were either treatment-boosted ADA+ or treatment-induced ADA+. The percentage of these patients in a population is known as ADA incidence.

[c] Treatment-induced ADA+: Patients who were ADA negative or missing at baseline and became ADA positive post-baseline.

[d] Treatment-boosted ADA+: Patients who were ADA+ at both baseline and post-baseline, but had a meaningful increase in ADA titer by at least 4-fold from baseline to post-baseline.

[e] ADA+ prevalence at both baseline and post-baseline: Patients with both a positive ADA assessment at baseline and any positive ADA assessment post-baseline.

[f] ADA+ prevalence at baseline: Patients with a positive ADA assessment at baseline and no positive ADA assessment at any post-baseline assessments.

[g] Treatment-emergent persistently ADA+: TE-ADA+ and having at least 2 post-baseline ADA+ measurements with ≥ 16 weeks between first and last positive.

[h] Treatment-emergent transiently ADA+: TE-ADA+ and having at least one post-baseline ADA+ measurement and not fulfilling the conditions for persistently positive.

[i] nAb+ prevalence at baseline or post-baseline: Patients with any positive nAb assessment at baseline or post-baseline. The percentage of these patients in a population is known as nAb prevalence.

[j] ADA titers in patients who are nAb+

[k] TE-nAb+: TE-ADA+ patients with any positive nAb assessment post-baseline. The percentage of these patients in a population is known as nAb incidence.

nAb test results not available for DB-01.

Immunogenicity analysis of pooled data from all conducted clinical trials of T-DXd

The immunogenicity paragraph in section 4.8 of the SmPC is being on the basis of immunogenicity data from the updated 5.4 mg/kg all solid tumour type pool and the 6.4 mg/kg all solid tumour type pool, see table below.

Table 3 Summary of Anti-drug Antibody Response to T-DXd by 5.4 mg/kg and 6.4 mg/kg Pools (Immunogenicity Analysis Set)

	All Solid Tumor Pool T-DXd 5.4 mg/kg (N = 2331)	**All Solid Tumor Pool T-DXd 6.4 mg/kg (N = 793)**	**Total (N = 3124)**
ADA positive prevalence at baseline or post-baseline, n (%)	195 (8.4)	62 (7.8)	257 (8.2)
Median of maximum titer	45.0	45.0	45.0
(Minimum, maximum)	(45, 1440)	(45, 1440)	(45, 1440)
Treatment-emergent ADA positive (ADA incidence), n (%)	49 (2.1)	21 (2.6)	70 (2.2)
Median of maximum titer	45.0	45.0	45.0
(Minimum, maximum)	(45, 720)	(45, 1440)	(45, 1440)
ADA positive post-baseline only (treatment-induced ADA positive), n (%)	49 (2.1)	20 (2.5)	69 (2.2)
Median of maximum titer	45.0	45.0	45.0
(Minimum, maximum)	(45, 720)	(45, 90)	(45, 720)
Treatment-boosted ADA positive, n (%)	0	1 (0.1)	1 (0.0)
Median of maximum titer	NC	1440.0	1440.0
(Minimum, maximum)	NC	(1440, 1440)	(1440, 1440)
ADA positive prevalence at both baseline and post-baseline, n (%)	29 (1.2)	7 (0.9)	36 (1.2)
Median of maximum titer	45.0	90.0	45.0
(Minimum, maximum)	(45, 1440)	(45, 1440)	(45, 1440)
ADA positive prevalence at baseline, n (%)	117 (5.0)	35 (4.4)	152 (4.9)
Median of maximum titer	90.0	45.0	45.0
(Minimum, maximum)	(45, 4050)	(45, 720)	(45, 4050)
Treatment-emergent persistently ADA positive, n (%)	7 (0.3)	1 (0.1)	8 (0.3)
Median of maximum titer	180.0	1440.0	270.0
(Minimum, maximum)	(45, 720)	(1440. 1440)	(45, 1440)
Treatment-emergent transiently ADA positive, n (%)	42 (1.8)	20 (2.5)	62 (2.0)
Median of maximum titer	45.0	45.0	45.0
(Minimum, maximum)	(45, 720)	(45, 90)	(45, 720)
NAb positive prevalence at baseline or post-baseline, n (%)	11 (0.5)	0	11 (0.4)
Median of maximum titer	180.0	NC	180.0
(Minimum, maximum)	(45, 1440)	NC	(45, 1440)
Treatment-emergent NAb positive (NAb incidence), n (%)	3 (0.1)	0	3 (0.1)

	All Solid Tumor Pool T-DXd 5.4 mg/kg (N = 2331)	All Solid Tumor Pool T-DXd 6.4 mg/kg (N = 793)	Total (N = 3124)
Median of maximum titer	45.0	NC	45.0
(Minimum, maximum)	(45, 360)	NC	(45, 360)

2.3.4. PK/PD modelling

Exposure-Response Analyses

Prior ER relationship analyses have been conducted which have confirmed no clinically relevant ER difference for both efficacy and safety endpoints at the dose levels evaluated for each study. In Study DB-06, the exposure, observed response, and safety endpoints in the HER2 >0 <1+ subgroup were consistent with the overall population; therefore, no ER analyses were performed.

2.3.5. Discussion on clinical pharmacology

This variation application to extend the use of T-DXd (Enhertu; 5.4 mg/kg IV Q3W) for the treatment of adult patients with HER2-low or HER2-ultralow BC is supported by the pivotal clinical study DB-06. The same drug product and dosing regimen was utilized as previously approved for treatment of HER2-positive BC. In study DB-06, the pharmacokinetics of T-DXd, total anti-HER2 AB (total AB) and payload DXd was investigated by sparse sampling (6 samples) over cycle 1, 2 and 4. PK-samples was taken after infusion of T-DXd, corresponding to ~Cmax, and pre-dose i.e. Ctrough. Therefore, both Cmax and Cmin of T-DXd, anti-HER2 total and DXd were determined, both after single dosing and multiple dosing. The serum concentration of T-DXd, anti-HER2 and DXd were adequately quantified with previously validated methods and summarized using descriptive statistics. The median (range), or geometric mean (geoCV%), serum concentration of T-DXd at the selected timepoints was comparable in both HER-2 low and HER-2 ultralow patients, additionally comparability was shown to data in other clinical studies of T-DXd, supporting already approved cancer indication, e.g. HER2 positive BC. Overall, the methodology used is considered adequate. The MAH has justified that no updated Pop-PK and ER analysis was conducted in the current application. Overall, the pharmacokinetics of T-DXd, anti-HER2 and DXd in BC was shown to be independent of HER-2 level. Immunogenicity was adequately evaluated in the DB-06 study using the already validated immunogenicity methods. Furthermore, a pooled immunogenicity analysis was conducted, including ADA-evaluable patients in an all BC-pool and an all solid tumour pool. The analysis showed that the immunogenicity in the DB-06 study is comparable to the two pools. Furthermore, there was no apparent effect between development of antibodies on the pharmacokinetics, safety and/or effectiveness of Enhertu. Finally, the immunogenicity paragraph in section 4.8 of the SmPC has been adequately updated on the basis of a pooled immunogenicity data analysis, including data all of 3124 patients treated with T-DXd.

2.3.6. Conclusions on clinical pharmacology

The pharmacokinetics and immunogenicity of T-DXd in adult patients with HER2-low or HER2-ultralow BC have been sufficiently investigated in the clinical study DB-06 and shown to be comparable to T-DXd in other approved BC indications. In conclusion, the clinical pharmacology is considered adequately described for the treatment of HER2-low and ultra-low BC subjects with T-DXd at the recommended dose 5.4 mg/kg Q3W.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

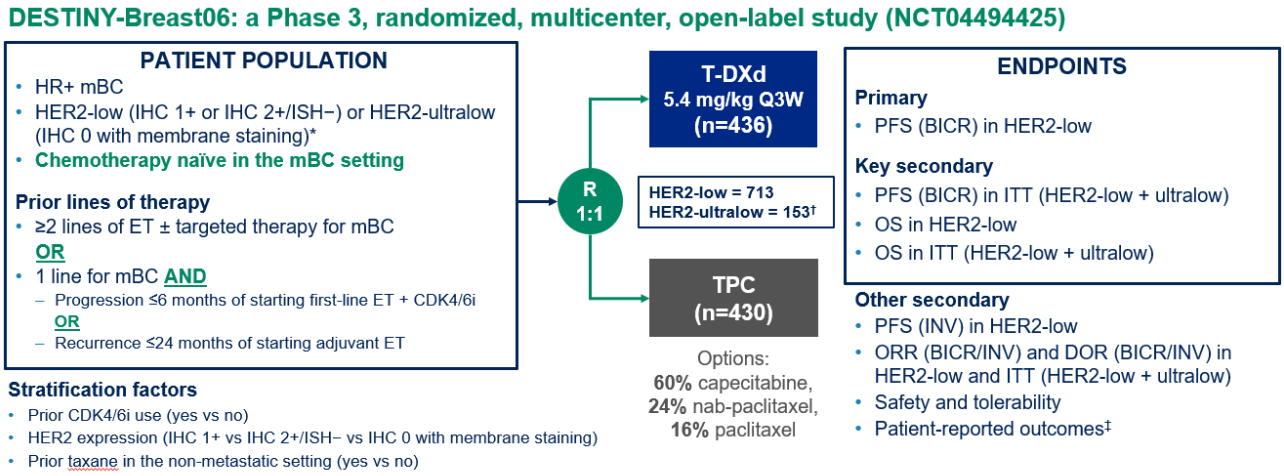
No dose-response studies were submitted as part of this application.

2.4.2. Main study

DESTINY-Breast06 – Study DB-06: A Phase III, Randomized, Multi-center, Open-label Study of Trastuzumab Deruxtecan (T-DXd) Versus Investigator's Choice Chemotherapy in HER2-low, Hormone Receptor-Positive Breast Cancer Patients whose Disease has Progressed on Endocrine Therapy in the Metastatic Setting

Methods

Figure 2 Study D9670C00001 (DESTINY-Breast06) Design



*Determined based on the most recent evaluable HER2 IHC sample prior to randomization; HER2-ultralow defined as faint, partial staining of the membrane in ≤10% of the cancer cells (also known as IHC >0<1+); †as determined by IRT (note: efficacy analyses in the HER2-ultralow subgroup were based on n=152 by central laboratory testing); ‡to be presented separately
BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DOR, duration of response; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; INV, investigator assessed; IRT, interactive response technology; ISH, in situ hybridization; ITT, intent-to-treat; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PD, progression disease; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice
NCT04494425. Updated April 12, 2024. Available from: https://clinicaltrials.gov/study/NCT04494425 (Accessed May 13, 2024)

Study participants

Main inclusion criteria

1 Male or female patients:

(a) ≥ 18 years of age – applicable for all countries participating in the study except Japan

(b) ≥ 20 years of age – applicable for Japan only

2 Pathologically documented breast cancer that:

(a) Is advanced or metastatic.

(b) Has a history of HER2-low or negative expression, defined as IHC 2+/ISH- or IHC 1+ (ISH- or untested) or IHC 0 (ISH- or untested) with a validated assay.

(c) Patients with historical HER2-low or HER2 IHC 0 expression must be confirmed by central laboratory testing to have HER2-low expression or HER2 IHC >0 <1+ expression, respectively. If the local HER2 result is not confirmed by the central laboratory result (i.e. must be HER2-low by most recent local HER2 test and HER2-low by central test or HER2 IHC 0 by most recent local HER2 test and HER2 IHC >0 <1+ by central test), the patient will not be eligible for the study.

o If a patient has had multiple historical/local HER2 results, the most recent result will be compared with the central laboratory HER2 results to confirm eligibility.

o If most recent local HER2 testing only classified the patient's tumour as HER2-negative (IHC status not available), eligibility will be determined by the central laboratory testing results.

(d) Was never previously reported as HER2-positive (IHC 3+ or ISH+) as per ASCO/CAP guidelines.

(e) Is documented as HR+ (either ER and/or PgR positive [ER or PgR ≥1%]) per ASCO/CAP guidelines (Hammond et al, 2010) in the metastatic setting. If a patient has had multiple ER/PgR results after metastatic disease, the most recent test result will be used to confirm eligibility.

3 Must have an adequate tumour tissue sample available for assessment of HER2 by central laboratory and other exploratory biomarker analyses and is preferred in FFPE blocks based on a mandatory FFPE tumor sample obtained at the time of metastatic disease or later; the most recently collected pre-randomization tumour sample from the time of metastatic disease or later that meets the tissue requirements specified in Section 8.6.1 is required. If no archival specimens are available, a newly acquired biopsy specimen is acceptable.

4 ECOG performance status of 0 or 1 at enrolment and randomization

5 Radiologic or objective evidence of disease progression on or after the last systemic therapy prior to starting study treatment.

6 Must have had disease progression on at least 2 previous lines of ET with or without a targeted therapy (such as CDK4/6, mTOR or PI3-K inhibitors; single agent anti-CDK4/6 therapy is considered a line) administered for the treatment of metastatic disease. Note that changes in dosing schedules, or discontinuations/re-starting of the same drugs or the addition of a targeted therapy to an ET without progression (e.g. adding a CDK4/6 to a current aromatase inhibitor regimen) will not be considered separate lines of therapy; however, disease progression within 24 months on adjuvant ET will count as 1 line.

7 No prior chemotherapy for advanced or metastatic breast cancer. Patients who have received chemotherapy in the neo-adjuvant or adjuvant setting are eligible, with a disease-free interval from completion of systemic chemotherapy to advanced or metastatic diagnosis of >12 months.

8 Life expectancy ≥12 weeks at screening.

9 At least 1 lesion, not previously irradiated, that can be measured accurately at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with CT or MRI which is suitable for accurate repeated measurements, or Non-measurable, bone-only disease that can be assessed by CT or MRI or X-Ray. Lytic or mixed lytic bone lesions that can be assessed by CT or MRI or X-Ray in the absence of measurable disease as defined above is acceptable; patients with sclerotic/osteoblastic bone lesions only in the absence of measurable disease are not eligible.

10 LVEF ≥ 50% within 28 days before randomization.

11 Adequate organ and bone marrow function within 14 days before randomization

12 Adequate treatment washout period before randomization/enrolment,

13 Evidence of post-menopausal status or negative serum pregnancy test for females of childbearing potential who were sexually active with a non-sterilized male partner

14 Female patients of childbearing potential who were sexually active with a non-sterilized male partner must use at least one highly effective method of contraception from the time of screening and must had agreed to continue using such precautions for 7 months after the last dose of study treatment.

15 Non-sterilized male patients who were sexually active with a female partner of childbearing potential must use a condom with spermicide from screening to 4 months after the final dose of study treatment.

16 Female patients must not donate, or retrieve for their own use, ova from the time of screening and throughout the study treatment period, and for at least 7 months after the last dose of study treatment.

Main exclusion criteria

1 Ineligible for all options in the investigator's choice chemotherapy arm.

2 Uncontrolled or significant cardiovascular disease including history of myocardial infarction within 6 months before randomization/enrollment, Uncontrolled hypertension; Uncontrolled and/or clinically important cardiac arrhythmias; Corrected QT interval by Fredericia's method (QTcF) prolongation to >470 ms (females) or >450 ms (male) based on average of screening triplicate 12-lead electrocardiogram (ECG) .

3 History of active primary immunodeficiency.

4 Clinically significant corneal disease in the opinion of the Investigator.

5 Has as a history of (non-infectious) ILD/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.

6 Patients with prior use of immunosuppressive medication within 14 days prior to first study dose, except for intranasal and inhaled corticosteroids or systemic corticosteroids at doses less than 10 mg/day of prednisone or equivalent.

7 Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder and any autoimmune, connective tissue or inflammatory disorders with potential pulmonary involvement and/or prior pneumonectomy.

8 Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals.

9 Patients with spinal cord compression or a history of leptomeningeal carcinomatosis. By Day 1 of the study, patients with central nervous system metastases must have been treated and must be asymptomatic and meet the following criteria: (a) No concurrent treatment, inclusive of but not limited to surgery, radiation, and/or corticosteroids.

10 Receipt of live, attenuated vaccine within 30 days prior to the first dose of study treatment.

11 Has unresolved toxicities from previous anticancer therapy,

12 Any concurrent chemotherapy, investigational product (IP), biologic, or hormonal therapy for cancer treatment.

13 Pregnant or breastfeeding female patients.

14 History of another primary malignancy within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, other solid tumors curatively treated, or contralateral breast cancer.

15 Previous treatment with anti-HER2 therapy.

16 Prior treatment with antibody drug conjugate that comprised an exatecan derivative that is a topoisomerase I inhibitor.

17 A pleural effusion, ascites or pericardial effusion that requires drainage, peritoneal shunt, or Cell-free and Concentrated Ascites Reinfusion Therapy (CART) (Drainage and CART are not allowed within 2 weeks prior to screening assessment).

Treatments

Table 4 Study Treatments and Duration

Compound	Dose	Route	Schedule
T-DXd	5.4 mg/kg	IV	Every 3 weeks
Capecitabine	1000 or 1250 mg/m^2	Oral	Twice daily orally for 2 weeks followed by a 1-week rest period in 3-week cycles
Paclitaxel	80 mg/m^2	IV	Every week in 3-week cycles
Nab-paclitaxel	100 mg/m^2	IV	Every week for 3 weeks followed by a 1-week rest period in 4-week cycles

Objectives/endpoints

Table 5 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of T-DXd compared with Investigator's choice chemotherapy in terms of PFS by BICR in the hormone receptor-positive, HER2-low (IHC 2+/ISH- and IHC 1+) population.	• PFS by BICR in the hormone receptor-positive, HER2-low population
Key Secondary	
• To assess the efficacy of T-DXd compared with Investigator's choice chemotherapy in terms of OS in the hormone receptor-positive, HER2-low population. • To assess the efficacy of T-DXd compared with Investigator's choice chemotherapy in terms of PFS by BICR and OS in the ITT population (HER2 IHC > 0 < 1+ and HER2-low)	• OS in the hormone receptor-positive, HER2-low population • PFS by BICR according to RECIST 1.1 in the ITT population (HER2 IHC > 0 < 1+ and HER2-low) • OS in the ITT Population

Other Secondary	
• To further assess the efficacy of T-DXd compared with Investigator's choice chemotherapy in terms of PFS by Investigator assessment, ORR, and DoR by BICR and Investigator assessment in the hormone receptor-positive, HER2-low population.	• PFS by Investigator assessment according to RECIST 1.1 in the hormone receptor-positive, HER2-low population. • ORR and DoR by BICR and by Investigator assessment according to RECIST 1.1 in the hormone receptor-positive, HER2-low population.
• To further assess the efficacy of T-DXd compared with Investigator's choice chemotherapy in terms of ORR and DoR by BICR and Investigator assessment in the ITT population	• ORR and DoR by BICR and by Investigator assessment in the ITT population (HER2 IHC > 0 < 1+ and HER2-low)
• To compare the effect of T-DXd with Investigator's choice chemotherapy in terms of PFS2 according to Investigator assessment, TFST, and TSST in the hormone receptor-positive, HER2-low population and the ITT population	• PFS2 in the hormone receptor-positive, HER2-low population and the ITT population. • TFST in the hormone receptor-positive, HER2-low population and the ITT population. • TSST in the hormone receptor-positive, HER2-low population and the ITT population.
• To assess the safety and tolerability profile of T-DXd compared with Investigator's choice chemotherapy	• AEs, changes from baseline in laboratory findings, ECHO/MUGA scans, ECGs, and vital signs
• To assess the PK of T-DXd	• T-DXd total anti-HER2 antibody and MAAA-1181a concentrations in serum
• To assess symptoms, functioning, and HRQoL in patients treated with T-DXd compared with Investigator's choice single-agent chemotherapy	• Change from baseline in EORTC QLQ-C30 and EORTC QLQ-BR45 scale scores. • Time to deterioration in EORTC QLQ-C30 scale scores
• To investigate the immunogenicity of T-DXd	• Number and percentage of patients who develop ADAs for T-DXd

Sample size

Approximately 850 patients were planned to be randomized in this study: 700 HER2-low (IHC 2+/ISH- and IHC 1+) patients and 150 HER2 IHC > 0 < 1+ patients. To ensure adequate representation of each subgroup of the HER2-low population, at least 240 patients in each HER2 IHC group (IHC 1+ and IHC 2+/ISH-) were planned to be randomized across both treatment arms (approximately 120 patients per arm).

To ensure that the majority of patients had received prior CDK4/6i therapy in the HER2-low population, no more than 343 patients (49% of 700 patients) who had not received prior therapy with CDK4/6i (e.g. palbociclib, abemaciclib, or ribociclib) were planned to be randomized; a similar proportion of patients who had not received prior CDK4/6 therapy were planned to be randomized in the HER2 IHC > 0 < 1+ population.

The study was powered to show statistical significance for the primary study endpoint of PFS. Based on a 2-sided significance level of 5%, a total of 456 PFS events (65% maturity) would provide at least 95% power to detect a hazard ratio of 0.55 (increase in median PFS from 5.5 to 10 months) in the HER2 low population, assuming an exponential distribution for both treatment groups.

The study was also powered to demonstrate a statistically significant difference in OS in the HER2-low population.

Randomisation

Patients were randomly assigned using IRT in a 1:1 ratio to treatment with T-DXd 5.4 mg/kg or Investigator's choice single-agent chemotherapy (capecitabine, paclitaxel or nab-paclitaxel). Patients were stratified according to prior CDK4/6i use (yes vs no), HER2 IHC expression (IHC 2+/ISH- vs IHC 1+ vs IHC > 0 < 1+) by central testing and prior taxane use in the non-metastatic setting (yes vs no).

Blinding (masking)

This was an open-label study for personnel at study sites. However, the study was conducted "sponsor-blind" and specific treatment assignment was via an IRT. To maintain the integrity of the study, sponsor personnel involved in the study did not undertake or have access to efficacy data aggregated by treatment arm prior to final data readout for the primary endpoint.

Statistical methods

The estimand framework has not been applied by the MAH.

Efficacy analyses sets:

FAS: The ITT population, also termed as FAS, included all randomized patients. Treatment arms were compared on the basis of randomized study treatment, regardless of the study treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment were included in the analysis in the treatment arm to which they were randomized.

HER2-low: The HER2-low population comprised the subset of patients included in the ITT population with HER2 IHC 2+/ISH- and IHC 1+ as determined by central laboratory testing.

HER2-ultra-low: The HER2 IHC >0 <1+ population comprised the subset of patients included in the ITT population with HER2 IHC >0 <1+ as determined by central laboratory testing and who were randomized ≥ 24 weeks prior to interim futility DCO.

Analysis methods:

Primary endpoint: PFS by BICR in the hormone receptor-positive, HER2-low population.

PFS distribution was compared between T-DXd and Investigator's choice chemotherapy using a stratified log-rank test adjusting for prior CDK4/6 inhibitor use (yes vs. no), and HER2 IHC expression (IHC 1+ vs. IHC 2+/ISH-).

The HR (T-DXd vs. Investigator's choice chemotherapy) and its CI were estimated from a stratified Cox proportional hazards model, based on the same stratification variables as for the log-rank test.

KM plots of PFS were presented by treatment group. Summaries of the number and percentage of patients experiencing a PFS event, the type of event (RECIST 1.1 progression or death) and the number and percentage of censored patients and detailed reason for censoring were provided along with median PFS and its CI for each treatment.

Of note, assumptions (proportional hazards within strata) for utilizing stratified log-rank test and stratified Cox analysis have been thoroughly investigated according to the SAP.

Definition of PFS, including censoring rules:

PFS was defined as the time from date of randomization until the date of objective radiological disease progression by BICR according to RECIST 1.1 or death (by any cause in the absence of progression). Patients who had not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient had disease progression or died immediately after 2 or more consecutive missed visits, the patient was censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits (note: not evaluable visit is not considered as missed visit). Given the scheduled visit assessment scheme (i.e. Q6W for the first 48 weeks, then Q9W thereafter), the definition of 2 missed visits (allowing for early and late visits) will change over time).

Sensitivity analyses for primary endpoint:

Evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled time points. The midpoint between the time of progression and the previous evaluable RECIST assessment (using the final date of the assessment) were to be analyzed using a stratified log-rank test, as described for the primary analysis of PFS.

Attrition bias were assessed by repeating the PFS analysis except that the actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of progression immediately following two or more missed tumour assessments were included. Within the same sensitivity analysis, patients who took subsequent therapy (note that for this analysis radiotherapy is not considered a subsequent anti-cancer therapy) prior to their last evaluable RECIST assessment or progression or death were censored at their last evaluable assessment prior to taking the subsequent therapy.

Ascertainment bias was assessed by analyzing Investigator-reported data. The stratified log-rank test was repeated on the programmatically derived PFS using the Investigator-reported data based upon RECIST. The HR and its CI were presented.

Of note, this analysis is to investigate coherence between BICR and investigator assessment.

Deviation bias was assessed by repeating the PFS analysis excluding patients with deviations that may affect the efficacy of trial therapy.

Tipping point analysis: To assess the potential impact of imbalanced censoring due to withdrawal of consent (6 treatment vs 17 chemotherapy) on the PFS results, a tipping point analysis was conducted by assuming a reduced risk for the chemotherapy arm patients who were censored due to withdrawal of consent compared to those still in follow-up (Jackson et al. 2014).

Lastly, a number of subgroup analyses were conducted.

Key secondary efficacy endpoints: PFS by BICR in ITT population, OS in HER2-low population, OS in ITT population.

PFS in the ITT population was treated similarly to PFS in the HER2-low population described above. This also applies for the sensitivity analyses.

Definition of OS:

OS was defined as the time from the date of randomization until death due to any cause regardless of whether the patient withdrew from randomized therapy or received another anticancer therapy (i.e. date of death or censoring – date of randomization + 1). Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive.

Analysis of OS in the HER2-low population is similar to analysis of PFS.

Multiple Testing Strategy

In order to strongly control the family-wise Type I error rate at the 5% 2-sided alpha level, a multiple testing procedure (MTP) with gatekeeping strategy was used across the primary and key secondary endpoints, as shown in the figure below.

The final analyses of PFS (DCO: 18 March 2024) was conducted after 457 BICR PFS events were reported between the combined T-DXd and chemotherapy arms (64% maturity) in the HER2-low population. The PFS HR favored T-DXd treatment and was statistically significant at the 5% alpha level.

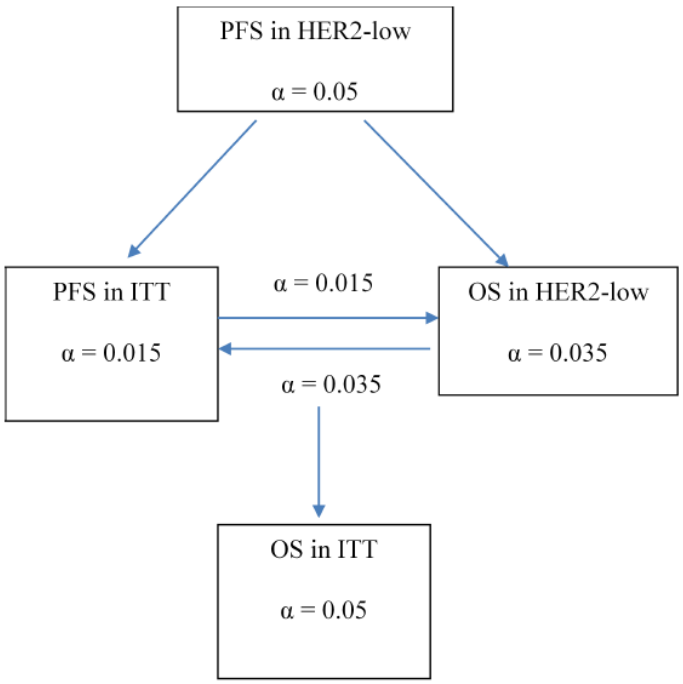
Therefore, per MTP, the 5% alpha was recycled and split to test PFS in the ITT Population (alpha: 1.5%) and OS in the HER2-low population (alpha: 3.5%).

The PFS HR in the ITT population favored the T-DXd treatment and was statistically significant at the 1.5% alpha level. Therefore, per MTP, the 1.5% alpha was recycled to test OS in the HER2-low population at 5% level.

The OS data in the HER2-low population were immature with a total of 282 events (39.6% maturity; 54% information fraction [282/521 OS events]). While OS in the HER2-low population indicated a trend favoring T-DXd treatment, it did not cross the pre-specified threshold of statistical significance. The OS data will be followed up further.

Per MTP, OS in the ITT population was not tested.

Figure 3 Multiple Testing Procedure



Timing of subsequent OS analyses:

The second interim OS analysis will occur when approximately 392 OS events have been observed in the HER2-low population (56% maturity or 80% information fraction). This was anticipated to occur

approximately 44 months after the first patient was randomized. It was expected that 477 OS events will be observed in the ITT population at this time.

The final OS analysis will be performed when approximately 489 OS events have been observed in the HER2-low population (70% maturity), which was expected to occur approximately 57 months after the first patient was randomized. At that time, it was estimated that 594 OS events will be observed in the ITT population.

Multiplicity due to interim analyses: For each hypothesis in OS (HER2-low population and ITT population) Lan DeMets spending function that approximates the O'Brien-Fleming alpha-spending approach (Lan and DeMets, 1983) was used to determine the significance level. Since a total of 282 OS events in the HER2-low population were observed at the time of DCO, the p-value boundary was 0.0046. The p-value boundary for the next interim analysis and the final analysis would have been determined based on the actual information fraction observed.

Other secondary endpoints: PFS by Investigator assessment, PFS2, ORR, DoR, TFST, TSST, HRQoL.

Note, of these endpoints only PFS by Investigator assessment, PFS2, ORR (and cORR) and DoR will be commented on below.

PFS by Investigator assessment: This was treated similarly to the primary endpoint, PFS (by BICR) in the HER2-low population.

ORR: ORR was defined as the percentage of patients with at least one visit response of complete or partial response (using RECIST 1.1). Data obtained up until progression, or last evaluable assessment in the absence of progression, was to be included in the assessment of ORR. However, patients who receive subsequent anticancer therapy (note that for this analysis radiotherapy is not considered a subsequent anticancer therapy) after discontinuing study treatment without progression and then respond were not included as responders in the ORR.

cORR: A confirmed response of CR/PR meant that a response of CR/PR was recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit.

ORR and cORR were analyzed by logistic regression in the HER2-low population, the ITT population and HER2-ultralow population.

DoR: For patients who achieved at least one visit response of CR or PR per RECIST 1.1, DoR was defined as the time from the date of first documented response until date of documented progression (using RECIST 1.1) or death in the absence of disease progression (i.e. date of PFS event or censoring – date of first response + 1). The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response was defined as the latest of the dates contributing towards the first visit response of PR or CR.

Medians in the different subgroups (HER2-low, ITT and HER2 ultra-low) were calculated using Kaplan-Meier technique.

PFS2: Time from randomization to second progression or death (PFS2) was analyzed in the HER2-low and ITT populations using identical methods as outlined for the primary endpoint and adjusting for the same set of covariates, but no subgroup analysis were to be performed. The HR for the treatment effect together with its CI was presented. Medians and KM plots will be presented to support the analysis.

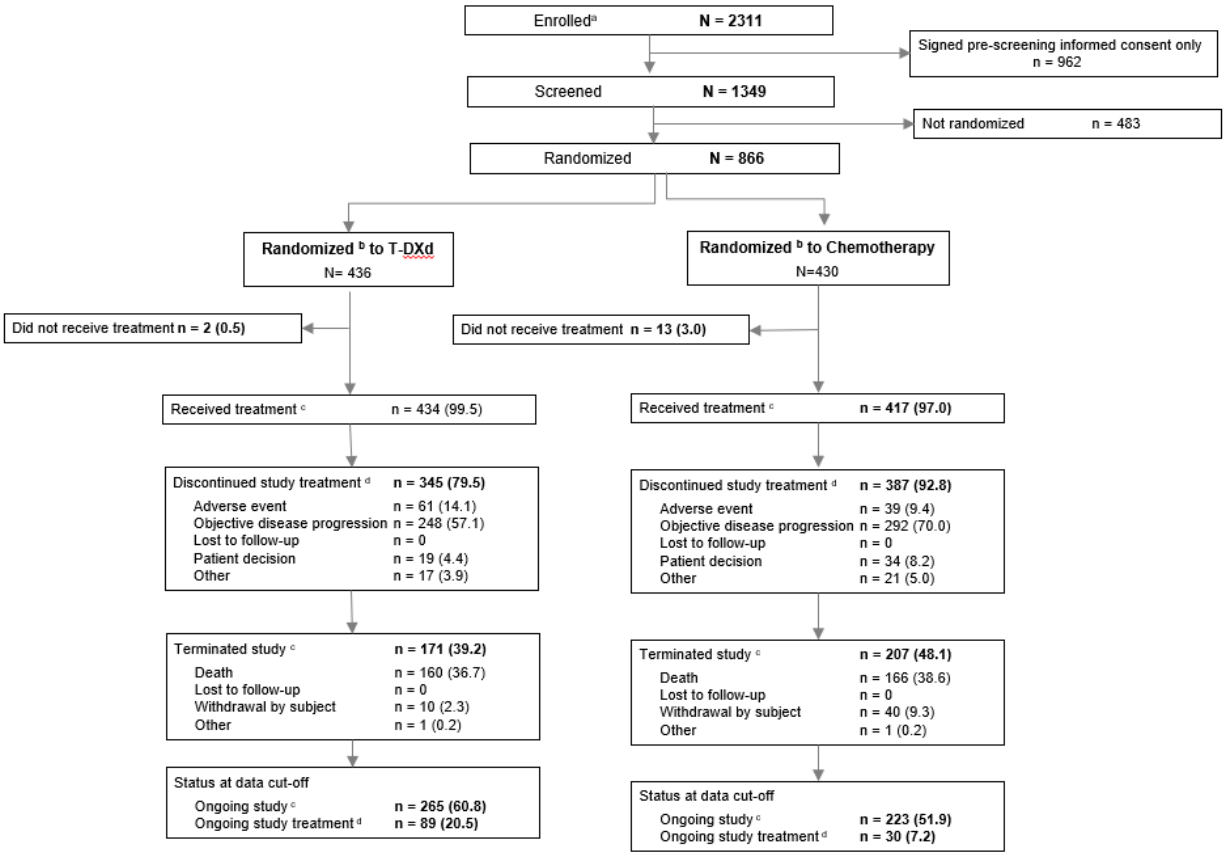
Interim futility analysis

An interim futility analysis was carried out after 70 patients have been randomized in the HER2 IHC >0 <1+ subgroup (approximately 35 per treatment group) and have had at least 24 weeks of follow-up from the point of randomization, have discontinued from study treatment or withdrawn from the study. A non-binding stopping boundary was applied to guide the decision of whether to limit recruitment to the HER2-low subgroup only. Confirmed ORR by Investigator assessments according to RECIST 1.1 in the HER2 IHC >0 <1+ analysis set was used in the interim futility analysis.

Results

Participant flow

Figure 4 Patient Disposition – Study DB-06 (All Patients)



[a] Informed consent signed (including patients who signed pre-screening informed consent form).
Percentages are calculated from the number of enrolled patients.
Percentages are calculated from the number of randomized patients.
Percentages are calculated from the number of patients who received treatment.

Table 6 Patient Disposition – All patients

	Number (%) of patients		
	T-DXd	Chemotherapy	Total
Patients enrolled[a]			2311
Patients randomized[b]	436 (18.9)	430 (18.6)	866 (37.5)
Patients who were not randomized[b]			1445 (62.5)
Death			13 (0.6)
Lost to follow-up			0
Screen failure			1347 (58.3)
Study terminated by Sponsor			0
Withdrawal by subject			72 (3.1)
Other			13 (0.6)
ITT population[c]	436 (100.0)	430 (100.0)	866 (100.0)
Patients who received treatment[c]	434 (99.5)	417 (97.0)	851 (98.3)
Patients who did not receive treatment[c]	2 (0.5)	13 (3.0)	15 (1.7)
Death	1 (0.2)	1 (0.2)	2 (0.2)
Lost to follow-up	0	0	0
Study terminated by Sponsor	0	0	0
Withdrawal by subject	1 (0.2)	11 (2.6)	12 (1.4)
Other	0	0	0
Unknown	0	1 (0.2)	1 (0.1)

	Number (%) of patients		
	T-DXd	Chemotherapy	Total
Patients ongoing study treatment at data cut-off[d]	89 (20.5)	30 (7.2)	119 (14.0)
Patients who discontinued treatment[d]	345 (79.5)	387 (92.8)	732 (86.0)
Subject decision	19 (4.4)	34 (8.2)	53 (6.2)
Adverse event	61 (14.1)	39 (9.4)	100 (11.8)
Severe non-compliance to protocol	0	1 (0.2)	1 (0.1)
Objective disease progression	248 (57.1)	292 (70.0)	540 (63.5)
Subject lost to follow-up	0	0	0
Pregnancy	0	0	0
Other	17 (3.9)	21 (5.0)	38 (4.5)
Death	5 (1.2)	4 (1.0)	9 (1.1)
Patients ongoing in study[c]	265 (60.8)	223 (51.9)	488 (56.4)
Patients who terminated study[c]	171 (39.2)	207 (48.1)	378 (43.6)
Death	160 (36.7)	166 (38.6)	326 (37.6)
Lost to follow-up	0	0	0
Study terminated by Sponsor	0	0	0
Withdrawal by subject	10 (2.3)	40 (9.3)	50 (5.8)
Other	1 (0.2)	1 (0.2)	2 (0.2)

[a] Informed consent signed (including patients who signed pre-screening informed consent form).
[b] Percentages are calculated from the number of enrolled patients.
[c] Percentages are calculated from the number of randomized patients.
[d] Percentages are calculated from number of patients who received treatment.
ITT population - all randomized patients.
T-DXd = trastuzumab deruxtecan.

Table 7 Main Reasons for Screen Failures in Study DB-06 Patients Who Were Not Randomised

Reason for Screen Failure		**Number of Patients**
Number of screen failed patients		483
Patients did not satisfy inclusion/exclusion criteria [a]		434
Inclusion 01	Male or female patients: (a) ≥ 18 years of age applicable for all countries participating in the study except Japan, (b) ≥ 20 years of age applicable for Japan only	1
Inclusion 02	Pathologically documented breast cancer (advanced or metastatic/history of HER2-low or negative expression/HER2-low or HER2 IHC > 0 < 1 expression by central lab/never previously reported as HER2-positive/documented as HR+).	192
Inclusion 03	Must have an adequate tumor tissue sample available for assessment of HER2 by central laboratory and other exploratory biomarker analyses	31
Inclusion 04	ECOG performance status of 0 or 1	19
Inclusion 05	Radiologic or objective evidence of disease progression on or after the last systemic therapy prior to starting study treatment	1
Inclusion 06	Must have had disease progression on: (a) endocrine therapy + CDK4/6 inhibitor within 6 months of starting first line treatment or (b) at least 2 previous lines of ET with or without a targeted therapy.	8
Inclusion 07	No prior chemotherapy for advanced or metastatic breast cancer. Patients who have received chemotherapy in the neo-adjuvant or adjuvant setting are eligible, as long as they have had a disease-free interval of > 12 m.	18
Inclusion 08	Life expectancy ≥ 12 weeks at screening	4
Inclusion 09	At least 1 lesion, not previously irradiated, that can be measured accurately at baseline as ≥10 mm in the longest diameter.	18
Inclusion 10	Left ventricular ejection fraction (LVEF) ≥ 50% within 28 days before randomization.	6
Inclusion 11	Adequate organ and bone marrow function within 14 days before randomization.	51

Reason for Screen Failure		Number of Patients
Inclusion 12	Adequate treatment washout period before randomization.	4
Inclusion 13	Evidence of post-menopausal status or negative serum pregnancy test for females of childbearing potential who are sexually active with a non-sterilized male partner.	1
Inclusion 15	Non-sterilized male patients who are sexually active with a female partner of childbearing potential must use a condom with spermicide from screening.	1
Exclusion 01	Ineligible for all options in the investigator's choice chemotherapy arm. Patients with contraindications to capecitabine, paclitaxel, and nab-paclitaxel treatment cannot be enrolled to the study.	2
Exclusion 02	Uncontrolled intercurrent illness, such as ongoing or active infection, uncontrolled hypertension, serious chronic gastrointestinal conditions, substantially increase risk of incurring adverse events, etc.	11
Exclusion 03	Uncontrolled or significant cardiovascular disease	7
Exclusion 04	Has as a history of (non-infectious) interstitial lung disease (ILD)/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.	11
Exclusion 06	Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disorder, and any autoimmune, connective tissue.	20
Exclusion 08	Has spinal cord compression or clinically active central nervous system metastases (untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms).	29
Exclusion 09	Active primary immunodeficiency, known human immunodeficiency virus (HIV) infection, or active hepatitis B or C infection.	4
Exclusion 11	Has unresolved toxicities from previous anticancer therapy, defined as toxicities not yet resolved to Grade ≤ 1 or baseline. May be enrolled with chronic Grade 2 toxicities	7
Exclusion 12 [b]	Any concurrent chemotherapy, investigational product (IP), biologic, or hormonal therapy for cancer treatment.	3

Reason for Screen Failure		Number of Patients
Exclusion 15	Previous treatment with anti-HER2 therapy	6
Exclusion 19	Has substance abuse or any other medical conditions such as psychological conditions	2
Other [c]		49

[a] Criteria as per the current CSP version. Patients may be counted more than once, if more than 1 criterion was failed.

[b] Any concurrent chemotherapy, investigational product (IP), biologic, or hormonal therapy for cancer treatment' criterion has been removed in CSP Amendment 2 (23 July 2021) due to overlap with Inclusion Criterion 12 Adequate treatment washout period before randomization.

[c] Includes patients who exceeded the 28-day re-screening window, died during screening, withdrew consent during the screening or when no randomization slots were available.

Source: Table 1

Recruitment

From 24 July 2020 to 13 April 2023, patients were recruited across Europe, Asia-Pacific, North America, and South America. A total of 866 patients were enrolled at 273 study centres in 28 countries worldwide: 50.8% in Europe, 11.0% in North America, 34.2% in Asia, and 4.0% in the Rest of World. The study population consisted of 713 patients (82.3%) whose tumours were HER2-low (IHC 1+ and IHC 2+/ISH-) per IRT and 152 patients (17.6%) whose tumours were HER2 IHC > 0 < 1+ per central laboratory categorization. The current DCO was at the time of the final analysis of PFS and at the first interim analysis (IA) of overall survival (OS) and safety data at the data cu-toff (DCO) of 18 March 2024.

Median follow-up for OS in the HER2-low population was 19.0 months.

Conduct of the study

Protocol amendments

The original clinical study protocol (CSP) (Version 1.0) was dated 20 March 2020. Important protocol amendments to the original CSP, including when those amendments came into effect with respect to the recruitment of patients and details of any associated substantial changes are shown in the below table.

Table 8 Protocol Amendments Related to Changes in Study Conduct

Amendment Number/Date	Section of CSP (Affected section of this report)	Key details of amendment	Main reason(s) for amendment
Amendments made *before* the start of patient recruitment			
CSP Amendment 1 (Version 2.0) 22 May 2020	Throughout CSP	Updated post-treatment follow-up schedule at 40 days window throughout the CSP from ±7 days to +7 days	Amended window for follow-up visit to allow for adequate safety follow-up, given the half-life of T-DXd.
	Throughout CSP	Guidance added on the management of T-DXd in respect to COVID-19 and associated treatments along with provision for additional blood samples for exploratory analyses of clinical benefit or safety.	Management guidelines, benefit/risk considerations, and additional reporting and sampling procedures were added to help assess potential impact of COVID-19 on data obtained in this study.
	1.3 Schedule of Assessments 5.1 Inclusion Criteria 6.5 Concomitant Therapy Appendix J (Sections 9.1, 9.3.1, 9.4.5)	Specified washout period prior to randomization for chloroquine/hydroxychloroquine and provided instructions related to restrictions and additional sample collection should T-DXd patients receive concomitant treatment with chloroquine or hydroxychloroquine.	A washout period and instructions related to restrictions and additional sample collections specified due to a possible interaction between T-DXd and chloroquine/ hydroxychloroquine.
	5.2 Exclusion Criteria (Section 9.3.2)	Added exclusion criterion for patients randomized in a previous T-DXd study	Added to discourage early patient withdrawal from earlier line T-DXd studies where patients are assigned to control
	5.2 Exclusion Criteria (Section 9.3.2)	Removal of exclusion criteria 5 (history of clinically significant corneal disease), 11 (infection relating to active tuberculosis [covered by separate criterion excluding ongoing or active infection]), 21 (drainage and CART not allowed within 2 weeks of randomization)	Removal of exclusion criterion 5 based on cumulative review of clinical data. Exclusion criterion 11 removed as already covered under exclusion criterion 2 Exclusion criterion 21 removed as not relevant for BC indication
	5.2 Exclusion Criteria (Section 9.3.2)	Amendment of exclusion criterion 6 for prior ILD to remove phrase on requiring steroid treatment. Patient's prior ILD no longer requires treatment with corticosteroid for patient to be excluded.	Updated exclusion criteria to exclude all patients with prior ILD to further mitigate the incidence of pulmonary toxicities.
	5.2 Exclusion Criteria (Section 9.3.2)	Updated exclusion criterion 3 to remove the phrase "unstable angina pectoris, clinically important cardiac arrhythmias, or a recent (< 6 months) cardiovascular event including, unstable angina pectoris, and stroke" and included the provision for a cardiologist consultation for patients with troponin levels above ULN at screening and without any myocardial related symptoms.	Updated to remove redundant text and include the need for cardiologist consultation in patients with elevated troponin levels, as defined by the manufacturer, to rule out any asymptomatic signs of myocardial infarction.
	1.3 Schedule of Assessments 8.2.7 Echocardiograms/ Multi-gated Acquisition Scans 8.3.11 Adverse Events of Special Interest 8.3.14.1 Specific Toxicity Management and Dose Modification Information for T-DXd (Section 9.1 and Section 9.7)	Updated ECG and troponin collection frequency.	Updated ECG measurements in line with the observations from a clinical study that showed no clinically meaningful impact of T-DXd on QTc. Data to date has shown that troponin-T testing is not an indicator of LVEF decrease and therefore troponin will be measured at screening and EOT and as clinically indicated.
	1.3 Schedule of Assessments 8.5.2 Immunogenicity Assessments (Section 9.1 and and Section 9.7)	Addition of ADA sample collection after 40-day (+7 day) follow-up for select patients	Provision of additional collection of ADA samples to monitor ADA positive patients at follow-up
	Appendix H Guidance for Management of Patients with Drug-Induced ILD/Pneumonitis and Appendix I Toxicity Management Guidelines for T-DXd (Section 9.1)	Update to ILD/pneumonitis management guidelines	Further recommendations provided on management of ILD/pneumonitis, in particular, more detailed recommendations around duration of systemic steroid treatment

Amendment Number/Date	Section of CSP (Affected section of this report)	Key details of amendment	Main reason(s) for amendment
	Appendix I Toxicity Management Guidelines for T-DXd (Section 9.1)	Updates to AST/ALT increased, cardiac toxicity, and QTc prolongation management guidelines and removal of troponin management guidelines.	Management of AST/ALT increased amended to provide greater clarity in patients with elevated AST/ALT at baseline. ECG QTc prolonged toxicity management guidelines amended to advise ruling out serum electrolyte related ECG changes. Data to date has shown that troponin testing is not an indicator of LVEF decrease. Troponin will only be measured at screening, at EOT and as clinically indicated.
Amendments made *after* the start of patient recruitment			
CSP Amendment 2 (Version 3.0) 23 July 2021	1.1 Synopsis; 1.2 Schema; 2.1 Study Rationale; 2.2.1 Background Information on the Disease to be Treated; 4.1 Overall Design; 5 Study Population; 5.1 Inclusion Criteria (Sections 9.1, 9.2, 9.3, 9.7, 9.8)	The study population was updated to include patients who progress on first-line ET + CDK4/6i within 6 months of starting therapy.	To expand study population who have progressed on ET + CDK4/6i and deemed appropriate to receive chemotherapy as next treatment.
	5.1 Inclusion Criteria (Section 9.3.1)	Inclusion criterion #12 updated to add non-antibody based immunotherapy washout period.	Added immunotherapy washout period, which was previously omitted by oversight.
	5.1 Inclusion Criteria; 5.3 Lifestyle Considerations (Section 9.3)	Updated text (Inclusion criteria #14 and 16) regarding females of childbearing potential.	To align with Sponsor standards for the T-DXd program, MHRA and PEI feedback and CTFG guidelines.
	5.1 Inclusion Criteria; 8.3.13.1 Paternal Exposure; Appendix A3 (Section 9.3)	Inclusion criterion #15 updated with text regarding male contraception and added text regarding preservation of sperm.	To align with Sponsor standards for the T-DXd program, MHRA and PEI feedback and CTFG guidelines.
	5.2 Exclusion Criteria (Section 9.3.2)	Updated Exclusion criterion #4 to exclude patients with history of (non-infectious) ILD/pneumonitis that required steroids.	Updated to allow patients with prior ILD/pneumonitis that did not require management with steroids to no longer be excluded; this is now aligned with Sponsor standards for the T-DXd program.
CSP Amendment 3 (Version 4.0) 27 April 2022	1.1 Synopsis; 9.1.1 Multiple Testing Procedure and 9.2 Sample Size Determination (Sections 9.8.3.1, 9.8.3.3)	Change in the MTP such that if PFS HER2-low is significant, the 5% alpha will be split between PFS ITT (1.5% alpha) and OS HER2-low (3.5% alpha). Change in the target number of events at the final OS analysis from 489 to 521 OS events in the HER2-low population; Expected information fraction at the first and second interim OS analyses were changed to 41% and 75% respectively.	To allow immediate allocation of alpha to PFS ITT if the primary endpoint is significant. Number of OS events in the HER2-low population that will trigger the final OS analysis was increased to achieve 80% power at 3.5% alpha.
	1.1 Synopsis; 9.1.1 Multiple Testing Procedure; 9.5.1 Interim Futility Analysis (Sections 9.8.3.1, 9.8.8)	Removal of the enrollment pause in the HER2 IHC > 0 < 1+ patient population during the futility analysis.	Clinical evidence from the DAISY study providing confidence for the efficacy of T-DXd in the HER2 IHC > 0 < 1+ population.
	5.1 Inclusion Criteria (Section 9.3.1)	Removal of the requirement for matched results between historical/local HER2 results and central test results (Inclusion criterion #2[c] of CSP version 3.0).	To ensure that the central HER2 test is the primary determinant for study eligibility to streamline enrollment procedures and reduce screen failures.
	5.1 Inclusion Criteria (Section 9.3.1)	Reduction in the minimum age for eligible patients in Japan from 20 years to 18 years (Inclusion criterion #1)	Revision of Japanese civil code
	5.2 Exclusion Criteria (Section 9.3.2)	Addition of statement that pre-screening for this study while a patient is on-treatment in another clinical study is acceptable (Exclusion criterion #18)	Clarification
	5.3 Lifestyle Considerations (Section 9.3.3)	Removal of bilateral tubal ligation as a recognized method of surgical sterilization	Correction

Amendment Number/Date	Section of CSP (Affected section of this report)	Key details of amendment	Main reason(s) for amendment
	5.4 Screen Failures (Section 9.3)	Update to clarify allowing rescreening of patients who previously were screen failed due to the local HER2 test result not confirmed by central HER2 testing.	Changes to Inclusion criterion #2.
	6.5 Concomitant Therapy (Section 9.4.5)	Addition of the recommendation to administer a combination regimen of 2 or 3 anti-emetic agents prior to each dose of T-DXd.	Alignment with Sponsor standards for the T-DXd program.
	6.6.1.1 T-DXd; 8.3.14.1 Specific Toxicity Management and Dose Modification Information for T-DXd (Section 9.1)	Increase in the permitted delay in T-DXd dosing from 49 days to 126 days since the previous dose.	Alignment with Sponsor standards for the T-DXd program.
	8.2.10.1 Pneumonitis (ILD) Investigation; 8.3.11 Adverse Events of Special Interest; 8.3.14.1 Specific Toxicity Management and Dose Modification Information for T-DXd (Section 9.1)	Addition of the requirement for patients with suspected ILD/pneumonitis to undergo a SARS-CoV-2 (COVID-19) test.	IDMC request
	9.5.1 Interim Futility Analysis (Section 9.8.8)	Addition of treatment recommendations for patients with HER2 IHC > 0 < 1+ in the event that recruitment in that subgroup is stopped	Clarification
	Appendix I (Section 9.1)	Increase in the time after which T-DXd should be discontinued in the case of Grade 1 ILD/pneumonitis occurring beyond cycle Day 22 from 49 days to 126 days since the previous dose	Alignment with Sponsor standards for the T-DXd program
	1.1 Synopsis, 1.3.2 Treatment Period, 1.3.3 Follow-up Period, 4.1 Overall Design, 7.1.2 Procedures forDiscontinuation of Study Treatment,	Clarified the mandatory requirement to perform an additional imaging assessment following Investigator-determined RECIST progression. Added requirement for submission of any available subsequent tumor assessment scans for central review until the primary	To reduce informative censoring in PFS by BICR when Investigator has assessed progression but BICR does not agree
	8.1.1 RECIST 1.1 Assessments, Appendix G, Guidelines for Evaluation of Objective Tumor Response using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors) (Sections 9.1, 9.5.1 and 9.8.3.2)	PFS analysis DCO or until the Sponsor notifies the site to discontinue (whichever is earlier). Added that subsequent imaging assessments should include brain scans for participants enrolled with stable brain metastases or if clinically indicated.	
CSP Amendment 4 (Version 5.0) 23 May 2023	1.1 Synopsis, 1.3.2 Treatment Period, 1.3.3 Follow-up Period, 4.1 Overall Design, 7.1.2 Procedures forDiscontinuation of Study Treatment, 8.1.1 RECIST 1.1 Assessments, Appendix G, Guidelines for Evaluation of Objective Tumor Response using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors) (Sections 9.1, 9.5.1 and 9.8.3.2)	Clarified the mandatory requirement to perform an additional imaging assessment following Investigator-determined RECIST progression. Added requirement for submission of any available subsequent tumor assessment scans for central review until the primary PFS analysis DCO or until the Sponsor notifies the site to discontinue (whichever is earlier). Added that subsequent imaging assessments should include brain scans for participants enrolled with stable brain metastases or if clinically indicated.	To reduce informative censoring in PFS by BICR when Investigator has assessed progression, but BICR does not agree
	2.3.1 Potential Risks of T-DXd 2.3.4 Overall Benefit/Risk Conclusion (Sections 9.2, 9.8.5)	Added text on higher incidence of ILD in patients with baseline moderate renal impairment and increased ILD education requirements for these patients	To provide guidance to Investigators regarding ILD education expectations
	1.3.2 Treatment Period	Added clarifications to wording on identification, evaluation and management of ILD	To align with Sponsor standards for the T-DXd program

Amendment Number/Date	Section of CSP (Affected section of this report)	Key details of amendment	Main reason(s) for amendment
	8.2.10 Other Safety Assessments Appendix H Toxicity Management Guidelines for T-DXd (Section 9.8.5)		
	9.4 Statistical Analyses (Section 9.8.3)	Clarified that additional analyses to be performed at the time of the PFS and OS analyses for the HER2 IHC > 0 < 1+ population will be specified in the SAP	To clarify the timing of additional analyses in the HER2 IHC > 0 < 1+ population

Changes to planned analyses

Table 9 Changes to Planned Analyses

Key details of change	Reason for change
• A revision to the MTP of the study to allow immediate allocation of alpha to PFS ITT if the primary endpoint is significant. Specifically, if PFS HER2-low was significant, the 5% alpha would be split between PFS ITT (1.5% alpha) and OS HER2-low (3.5% alpha). • To achieve 80% power for OS HER2-low at 3.5% alpha, the final OS analysis will be performed when approximately 521 OS events had been observed in the HER2-low population. • Expected information fraction at the first and second interim OS analyses were changed to 41% and 75% respectively.	• To allow immediate allocation of alpha to PFS ITT if the primary endpoint is significant. • Number of OS events in the HER2-low population that will trigger the final OS analysis was increased to achieve 80% power at 3.5% alpha

Protocol deviations

Table 10 Important Protocol Deviations (ITT Population)

Important protocol deviation [a]	Number (%) of Patients		
	T-DXd (N = 436)	Chemotherapy (N = 430)	Total (N = 866)
Number of patients with at least 1 important deviation	53 (12.2)	64 (14.9)	117 (13.5)
Inclusion criteria deviations	22 (5.0)	34 (7.9)	56 (6.5)
Exclusion criteria deviations	1 (0.2)	1 (0.2)	2 (0.2)
Deviations related to study procedure	13 (3.0)	17 (4.0)	30 (3.5)
Discontinuation criteria for study product met but patient not withdrawn from study treatment	9 (2.1)	3 (0.7)	12 (1.4)
Excluded medications taken	3 (0.7)	4 (0.9)	7 (0.8)
Investigational product deviation	2 (0.5)	8 (1.9)	10 (1.2)
Other important deviations	7 (1.6)	7 (1.6)	14 (1.6)

[a] IPDs before the start of treatment and during treatment

Note that the same patient may have had more than 1 IPD. The final count of patients with IPDs is to be decreased by 2 patients; 1 from "inclusion criteria deviations" category (inclusion criteria #6 IPD for patient E7807003 on chemotherapy arm was inactivated post DBL) and 1 from "discontinuation criteria for study product met but patient not withdrawn from study treatment" category (treatment through RECIST progression IPD for patient E4904003 on T-DXd arm was inactivated post DBL).

Baseline data

Table 11 Demographic Characteristics – Study DB-06

		ITT Population		HER2-low Population		HER2 IHC > 0 < 1+ Population	
		T-DXd	**Chemotherapy**	**T-DXd**	**Chemotherapy**	**T-DXd**	**Chemotherapy**
		(N = 436)	(N = 430)	(N = 359)	(N = 354)	(N = 76)	(N = 76)
Age (years)	N	436	430	359	354	76	76
	Mean	58.2	58.2	58.1	58.1	58.6	58.5
	SD	11.46	10.92	11.29	10.90	12.31	11.07
	Median	58.0	57.0	58.0	57.0	58.0	57.5
	Min	28	32	28	32	33	34
	Max	87	83	87	83	85	82
Age group (years) n (%)	< 65	302 (69.3)	297 (69.1)	252 (70.2)	244 (68.9)	49 (64.5)	53 (69.7)
	≥ 65	134 (30.7)	133 (30.9)	107 (29.8)	110 (31.1)	27 (35.5)	23 (30.3)
Sex n (%)	Male	0	1 (0.2)	0	1 (0.3)	-	-
	Female	436 (100)	429 (99.8)	359 (100)	353 (99.7)	76 (100)	76 (100)
Race n (%)	Black or African-American	4 (0.9)	3 (0.7)	1 (0.3)	3 (0.8)	3 (3.9)	0
	American Indian or Alaska Native	1 (0.2)	0	1 (0.3)	0	0	0
	Asian	154 (35.3)	151 (35.1)	122 (34.0)	127 (35.9)	32 (42.1)	24 (31.6)
	White	231 (53.0)	230 (53.5)	194 (54.0)	186 (52.5)	36 (47.4)	44 (57.9)
	Other	7 (1.6)	12 (2.8)	6 (1.7)	10 (2.8)	1 (1.3)	2 (2.6)
	Not reported	39 (8.9)	34 (7.9)	35 (9.7)	28 (7.9)	4 (5.3)	6 (7.9)

Age calculated at randomization.

Table 12 Baseline Disease Characteristics – Study DB-06

		Number (%) of patients					
		ITT Population		HER2-low Population		HER2 IHC > 0 < 1+ Population	
		T-DXd	**Chemotherapy**	**T-DXd**	**Chemotherapy**	**T-DXd**	**Chemotherapy**
		(N = 436)	**(N = 430)**	**(N = 359)**	**(N = 354)**	**(N = 76)**	**(N = 76)**
AJCC stage at diagnosis of breast cancer n (%)	Stage IV	133 (30.5)	132 (30.7)	111 (30.9)	104 (29.4)	22 (28.9)	28 (36.8)
ER expression at baseline n (%)[a]	<1%	4 (0.9)	2 (0.5)	3 (0.8)	2 (0.6)	1 (1.3)	0
	1-10%	17 (3.9)	12 (2.8)	15 (4.2)	11 (3.1)	2 (2.6)	1 (1.3)
	>10%	364 (83.5)	355 (82.6)	301 (83.8)	288 (81.4)	62 (81.6)	67 (88.2)
	Negative[b]	-	-	-	-	-	-
	Positive[b]	51 (11.7)	61 (14.2)	40 (11.1)	53 (15.0)	11 (14.5)	8 (10.5)
ER and PgR expression at baseline, combined n (%)[a, c]	ER-, PR-	1 (0.2)	0	-	-	1 (1.3)	0
	ER+, PR-	167 (38.3)	181 (42.1)	141 (39.3)	152 (42.9)	26 (34.2)	29 (38.2)
	ER-, PR+	3 (0.7)	2 (0.5)	3 (0.8)	2 (0.6)	-	-
	ER+, PR+	253 (58.0)	237 (55.1)	206 (57.4)	193 (54.5)	46 (60.5)	44 (57.9)
	ER+, PR missing	12 (2.8)	10 (2.3)	9 (2.5)	7 (2.0)	3 (3.9)	3 (3.9)
	ER missing, PR+	-	-	-	-	-	-
	ER missing, PR missing	-	-	-	-	-	-
HER2 expression at baseline by central laboratory n (%)[d]	IHC 0	1 (0.2)	1 (0.2)	1 (0.3)	1 (0.3)	-	-
	IHC > 0 < 1+	76 (17.4)	76 (17.7)	-	-	76 (100.0)	76 (100.0)
	IHC 1+	239 (54.8)	234 (54.4)	238 (66.3)	234 (66.1)	-	-

		Number (%) of patients					
		ITT Population		HER2-low Population		HER2 IHC > 0 < 1+ Population	
		T-DXd	Chemotherapy	T-DXd	Chemotherapy	T-DXd	Chemotherapy
		(N = 436)	(N = 430)	(N = 359)	(N = 354)	(N = 76)	(N = 76)
	IHC 2+/ISH-	117 (26.8)	118 (27.4)	117 (32.6)	118 (33.3)	-	-
	IHC 2+	3 (0.7)	1 (0.2)	3 (0.8)	1 (0.3)	-	-
Measurable disease at baseline by BICR[e] n (%)	Yes	393 (90.1)	389 (90.5)	326 (90.8)	324 (91.5)	67 (88.2)	65 (85.5)
	No	43 (9.9)	41 (9.5)	33 (9.2)	30 (8.5)	9 (11.8)	11 (14.5)
Measurable disease at baseline by Investigator assessment[f] n (%)	Yes	426 (97.7)	419 (97.4)	350 (97.5)	344 (97.2)	75 (98.7)	75 (98.7)
	No	10 (2.3)	11 (2.6)	9 (2.5)	10 (2.8)	1 (1.3)	1 (1.3)
Bone-only disease at baseline by Investigator assessment[g] n (%)	Yes	13 (3.0)	13 (3.0)	11 (3.1)	10 (2.8)	2 (2.6)	3 (3.9)
	No	423 (97.0)	417 (97.0)	348 (96.9)	344 (97.2)	74 (97.4)	73 (96.1)
Endocrine resistance at baseline[h] n (%)	Primary	128 (29.4)	140 (32.6)	105 (29.2)	116 (32.8)	23 (30.3)	24 (31.6)
	Secondary	308 (70.6)	288 (67.0)	254 (70.8)	236 (66.7)	53 (69.7)	52 (68.4)
	Missing	0	2 (0.5)	0	2 (0.6)	-	-
ECOG performance status at screening[i]	(0) Normal activity	252 (57.8)	257 (59.8)	207 (57.7)	218 (61.6)	44 (57.9)	39 (51.3)
	(1) Restricted activity	178 (40.8)	163 (37.9)	148 (41.2)	128 (36.2)	30 (39.5)	35 (46.1)
	(2) In bed less than or equal to 50% of the time	1 (0.2)	1 (0.2)	1 (0.3)	0	0	1 (1.3)
	Missing	5 (1.1)	9 (2.1)	3 (0.8)	8 (2.3)	2 (2.6)	1 (1.3)

[a] The most recent results available at study entry are summarized.

[b] 'Positive' and 'Negative' categories used when the percentage of tumor cells demonstrating positive nuclear staining was not available for ER/PR.

[c] ER/PR+ correspond to the results '1 to 10%', '> 10%' and 'Positive' and ER/PR- correspond to the results '< 1%' and 'Negative'.

[d] In 4 patients with HER2 IHC 2+, ISH was not evaluable per central lab. In 2 patients the final baseline HER2 IHC score per central lab was HER2 IHC 0; IPDs were reported for all 6 patients.

[e] Measurable disease defined as having at least one measurable lesion, not previously irradiated, which is ≥ 10 mm in the longest diameter (LD) (except lymph nodes which must have short axis ≥ 15 mm), with CT or MRI and which is suitable for accurate repeated measurements by BICR.

[f] Measurable disease defined as having at least one measurable lesion, not previously irradiated, which is ≥ 10 mm in the longest diameter (LD) (except lymph nodes which must have short axis ≥ 15 mm), with CT or MRI and which is suitable for accurate repeated measurements by Investigator assessment.

[g] 'Bone and locomotor' as only site of disease, with 'Bone' as the only anatomical location of target and non-target lesions by Investigator assessment.

[h] Primary endocrine resistance was defined as: relapse while on the first 2 years of adjuvant endocrine therapy, or progressive disease within first 6 months of first line endocrine therapy for metastatic breast cancer, while on endocrine therapy. Secondary (acquired) endocrine resistance was defined as: relapse while on adjuvant endocrine therapy but after the first 2 years, or relapse within 12 months of completing adjuvant endocrine therapy, or PD > 6 months after initiating endocrine therapy for metastatic breast cancer, while on endocrine therapy (ESO-ESMO ABC Guidelines)

[i] ECOG performance status at screening is derived as the last observed measurement prior to or on randomization. All 14 patients with missing ECOG status at baseline had ECOG 0 or 1 recorded in the eCRF within 6 days of randomization.

Table 13 Previous Disease Related Treatment Modalities – Study DB-06

	Number (%) of patients					
	ITT Population		HER2-low Population		HER2 IHC > 0 < 1+ Population	
	T-DXd	Chemotherapy	T-DXd	Chemotherapy	T-DXd	Chemotherapy
Previous treatment modalities	**(N = 436)**	**(N = 430)**	**(N = 359)**	**(N = 354)**	**(N = 76)**	**(N = 76)**
Median (range) number of prior lines of ET in the metastatic setting	2.0 (1 - 4)	2.0 (1 - 5)	2.0 (1 - 5)	2.0 (1 - 5)	2.0 (1 - 4)	2.0 (1 - 5)
Number of patients with at least one prior line of endocrine therapy in the metastatic setting[a]	435 (99.8)	428 (99.5)	358 (99.7)	352 (99.4)	76 (100)	76 (100)
Number of prior lines of ET in the metastatic setting						
1	65 (14.9)	82 (19.2)	54 (15.1)	67 (19.0)	11 (14.5)	15 (19.7)
1 prior line and time to progression from start of ET + CDK4/6i ≤ 6 months	37 (8.5)	40 (9.3)	33 (9.2)	33 (9.4)	4 (5.3)	7 (9.2)
Remaining patients with 1 prior line	28 (6.4)	42 (9.8)	21 (5.9)	34 (9.7)	7 (9.2)	8 (10.5)
2	295 (67.8)	288 (67.3)	242 (67.6)	236 (67.0)	52 (68.4)	52 (68.4)
≥ 3	75 (17.2)	58 (13.6)	62 (17.3)	49 (13.9)	13 (17.1)	9 (11.8)
Number of patients with at least one prior line of ET + CDK4/6i in the metastatic setting	388 (89.0)	385 (89.5)	318 (88.6)	316 (89.3)	69 (90.8)	69 (90.8)
Number of prior lines of ET + CDK4/6i in the metastatic setting[b]						
0	48 (11.0)	44 (10.3)	41 (11.4)	37 (10.5)	7 (9.2)	7 (9.2)
1	353 (81.0)	358 (83.4)	292 (81.3)	293 (83.0)	60 (78.9)	65 (85.5)
2	35 (8.0)	27 (6.3)	26 (7.2)	23 (6.5)	9 (11.8)	4 (5.3)
Hormonal therapy + targeted therapy (other than CDK4/6i)	143 (32.8)	127 (29.5)	120 (33.4)	105 (29.7)	22 (28.9)	22 (28.9)
Hormonal therapy + mTORi	104 (23.9)	102 (23.7)	89 (24.8)	81 (22.9)	15 (19.7)	21 (27.6)
Hormonal therapy + PIK3CAi	24 (5.5)	12 (2.8)	19 (5.3)	11 (3.1)	5 (6.6)	1 (1.3)
Hormonal therapy + PARPi	3 (0.7)	5 (1.2)	2 (0.6)	5 (1.4)	0	0
Hormonal therapy + Other	16 (3.7)	11 (2.6)	14 (3.9)	11 (3.1)	2 (2.6)	0
Adjuvant/Neoadjuvant setting prior treatment(s)[c]	291 (66.7)	281 (65.3)	240 (66.9)	237 (66.9)	51 (67.1)	44 (57.9)
Hormonal therapy	275 (63.1)	256 (59.5)	227 (63.2)	218 (61.6)	48 (63.2)	38 (50.0)
Cytotoxic chemotherapy	228 (52.3)	234 (54.4)	192 (53.5)	196 (55.4)	36 (47.4)	38 (50.0)
Taxane	179 (41.1)	177 (41.2)	151 (42.1)	151 (42.7)	28 (36.8)	26 (34.2)
Anthracycline	197 (45.2)	206 (47.9)	167 (46.5)	173 (48.9)	30 (39.5)	33 (43.4)
Cyclophosphamide	203 (46.6)	213 (49.5)	175 (48.7)	178 (50.3)	28 (36.8)	35 (46.1)
5-FU	79 (18.1)	73 (17.0)	68 (18.9)	56 (15.8)	11 (14.5)	17 (22.4)
Capecitabine	4 (0.9)	2 (0.5)	3 (0.8)	2 (0.6)	1 (1.3)	0
Other	33 (7.6)	20 (4.7)	25 (7.0)	15 (4.2)	8 (10.5)	5 (6.6)

[a] Percentages have been computed on the number of patients with at least one prior line of endocrine therapy in the metastatic setting

[b] Percentages have been computed on the number of patients with at least one prior line in the metastatic setting.

[c] Therapies reported are not mutually exclusive.

Table 14 Previous disease-related treatment modalities ITT population

Previous treatment modalities	Number (%) of patients		
	T-DXd (N=436)	Chemotherapy (N=430)	Total (N=866)
Median (Range) number of prior lines in the metastatic setting	2.0 (1 - 5)	2.0 (1 - 6)	2.0 (1 - 6)
Number of patients with at least one prior line in the metastatic setting	436 (100.0)	429 (99.8)	865 (99.9)
Number of prior lines in the metastatic setting[a]			
1	60 (13.8)	78 (18.2)	138 (16.0)
2	294 (67.4)	286 (66.7)	580 (67.1)
>=3	82 (18.8)	65 (15.2)	147 (17.0)
Median (Range) number of prior lines of endocrine therapy in the metastatic setting	2.0 (1 - 4)	2.0 (1 - 5)	2.0 (1 - 5)
Number of patients with at least one prior line of endocrine therapy in the metastatic setting	435 (99.8)	428 (99.5)	863 (99.7)
Number of prior lines of endocrine therapy in the metastatic setting[b]			
1	65 (14.9)	82 (19.2)	147 (17.0)
1 prior line and time to progression from start of ET + CDK4/6 inhibitors <= 6 months	37 (8.5)	40 (9.3)	77 (8.9)
Remaining patients with 1 prior line	28 (6.4)	42 (9.8)	70 (8.1)
2	295 (67.8)	288 (67.3)	583 (67.6)
>=3	75 (17.2)	58 (13.6)	133 (15.4)
Number of patients with at least one prior line of ET + CDK4/6i in the metastatic setting	388 (89.0)	385 (89.5)	773 (89.3)

Patients with therapies in more than one category are counted once in each category.
[a] Percentages have been computed on the number of patients with at least one prior line in the metastatic setting.
[b] Percentages have been computed on the number of patients with at least one prior line of endocrine therapy in the metastatic setting.
[c] Therapies reported are not mutually exclusive.
[d] Displays the line of therapy in which the patient received ET + CDK4/6i. Patients may be counted in more than one category.
[e] Includes blinded therapies or investigational agents.
Patients treated with Hormonal therapy and GnRH are summarized under Hormonal therapy.
ET = endocrine therapy. CDK = cyclin-dependent kinase. T-DXd = trastuzumab deruxtecan.

Numbers analysed

Table 15 Analysis Sets

	Number of Patients		
	T-DXd	Chemotherapy	Total
Patients randomized	436	430	866
Patients included in FAS (ITT population)	436	430	866
Patients included in HER2-low population	359	354	713
Patients included in HER2 IHC > 0 < 1+ population	76	76	152
Patients included in SAF	434	417	851
Patients excluded from SAF			15
Did not receive treatment			15
Patients included in HER2-low SAF	357	343	700
Patients excluded from HER2-low SAF			13
Did not receive treatment			13
Patients included in PK analysis set	432		432
Patients excluded from PK analysis set			434
Did not receive T-DXd			432
Had deviation considered to have impact upon PK			1
No post-dose data			1
Patients included in ADA evaluable set	433		433
Patients excluded from ADA evaluable set			433
Did not receive T-DXd			432
No baseline and/or post-baseline ADA data			1

HER2-low population - all patients in the ITT population with HER2 IHC 2+/ISH- and IHC 1+ as determined per the IRT data for the HER2 IHC expression.

HER2-low SAFfor the HER2 IHC expression.

HER2 IHC > 0 < 1+ population - all patients in the ITT population with HER2 IHC > 0 < 1+ as determined by central laboratory testing.

An earlier DCO date of 29 November 2023 was applied to ADA and PK data.

Outcomes and estimation

Primary endpoint – PFS by BICR (HER2-low population)

Table 16 Progression-free Survival by BICR (HER2-low population)

	T-DXd	Chemotherapy
	(N = 359)	(N = 354)
Total events[a], n (%)	225 (62.7)	232 (65.5)
RECIST progression	212 (59.1)	219 (61.9)
Death in the absence of progression	13 (3.6)	13 (3.7)
Censored patients, n (%)	134 (37.3)	122 (34.5)
Censored RECIST progression[b]	6 (1.7)	9 (2.5)
Censored death[c]	24 (6.7)	25 (7.1)
Progression-free at time of analysis	98 (27.3)	71 (20.1)
Lost to follow-up	0	0
Withdrawn consent	6 (1.7)	17 (4.8)
Other	0	0
Median progression-free survival (months)[d]	13.2	8.1
95% CI for median progression-free survival[d]	11.4, 15.2	7.0, 9.0
Hazard ratio[e]	0.62	
95% CI for hazard ratio[e]	0.52, 0.75	
2-sided p-value[f]	<0.0001	
Median (range) duration of follow-up in censored patients (months)	15.4 (0.0, 36.2)	8.1 (0.0, 36.0)

a Patients who had not progressed or died were censored at the latest evaluable RECIST assessment. Patients who progressed or died after two or more missed visits were censored at the latest evaluable RECIST assessment before the two missed visits. If there were no evaluable visits or no baseline assessment (unless the patient died within two visits of baseline), patients were censored at Day 1 (randomization).

b RECIST progression event occurred after two or more missed visits.

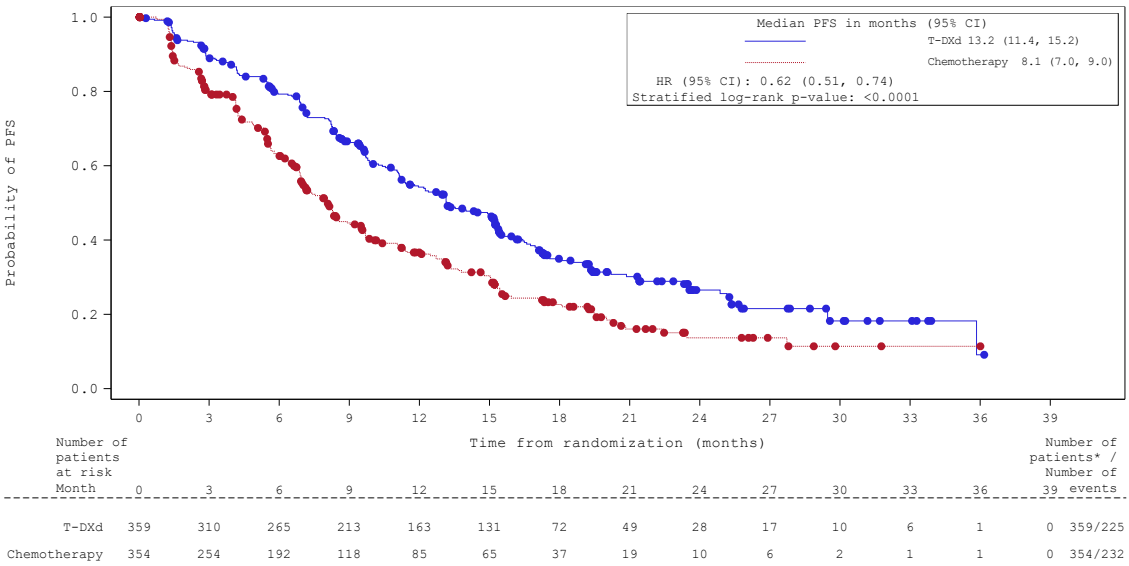
c Death which occurred after two or more missed visits in the absence of RECIST progression.

d Calculated using the KM technique. CI for median was derived based on Brookmeyer-Crowley method.

e The HR and confidence interval were calculated using a stratified Cox proportional hazards model, adjusting for prior CDK4/6i use (yes vs. no) and HER2 IHC expression (IHC 1+ vs. IHC 2+/ISH-) and ties handled by Efron approach. A HR < 1 favours T-DXd to be associated with a longer progression-free survival than Investigator's choice chemotherapy.

f The p-value was calculated using a stratified log-rank test, adjusting for prior CDK4/6i use (yes vs. no)and HER2 IHC expression (IHC 1+ vs. IHC 2+/ISH-). A p-value < 0.05 is significant.

Figure 5 Progression-free Survival by BICR, Kaplan-Meier plot (HER2-low Population)



Circle indicates a censored observation.
2-sided p-value. A p-value < 0.05 is significant

Secondary endpoint – OS (HER2-low population)

Table 17 Overall Survival, Primary Analysis (HER2-low Population)

	Number (%) of patients	
	T-DXd	Chemotherapy
	(N = 359)	(N = 354)
Death, n (%)	136 (37.9)	146 (41.2)
Censored patients, n (%)	223 (62.1)	208 (58.8)
Still in survival follow up[a]	215 (59.9)	182 (51.4)
Terminated prior to death[b]	8 (2.2)	26 (7.3)
Lost to follow-up	0	0
Withdrawn consent	8 (2.2)	26 (7.3)
Other	0	0
Median overall survival (months)[c]	28.9	27.1
95% CI for median overall survival[c]	25.7, 33.7	23.5, 29.9
Hazard ratio[d]	0.83	
95% CI for hazard ratio[d]	0.66, 1.05	
99.54% CI for hazard ratio[e]	0.59, 1.17	
2-sided p-value[f]	0.1299	
Median (range) duration of follow-up in all patients (months)	19.0 (0.1, 40.5)	18.3 (0.0, 42.9)
Median (range) duration of follow-up in censored patients (months)	21.1 (0.1, 40.5)	20.3 (0.0, 42.9)

g Included patients known to be alive at DCO.

h Included patients with unknown survival status or patients who were lost to follow-up.

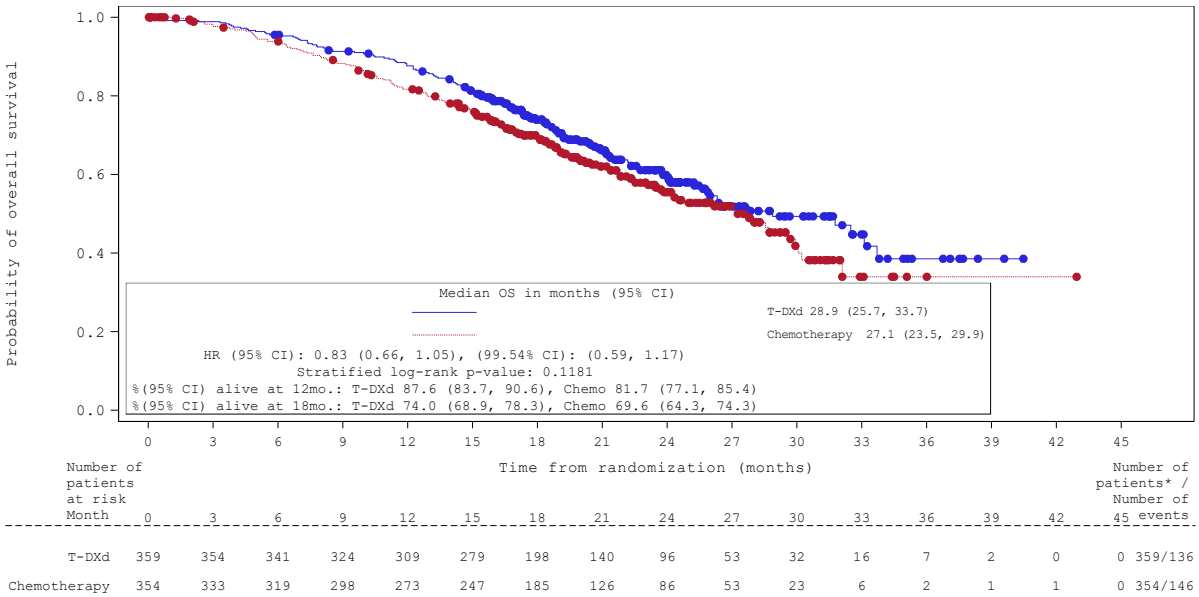
i Calculated using the KM technique. CI for median was derived based on Brookmeyer-Crowley method.

j The HR and CI were calculated using a Cox proportional hazards model with no stratification factors and ties handled by Efron approach. A HR < 1 favors T-DXd and is associated with a longer OS than Investigator's choice chemotherapy.

k Based on Lan DeMets alpha spending function with O'Brien-Fleming type boundary given the actual number of events observed.

l The p-value was calculated using a log-rank test with no stratification factors. A p-value < 0.0046 is significant.

Figure 6 Overall Survival, Kaplan-Meier Plot (HER2-low Population)



* Number of patients in HER2-low population.
Circle indicates a censored observation.
2-sided p-value. A p-value < 0.0046 is significant.

Secondary endpoint – PFS by BICR (ITT population)

Table 18 Progression-free Survival by BICR (ITT Population)

	T-DXd	Chemotherapy
	(N = 436)	(N = 430)
Total events[a], n (%)	269 (61.7)	271 (63.0)
RECIST progression	254 (58.3)	257 (59.8)
Death in the absence of progression	15 (3.4)	14 (3.3)
Censored patients, n (%)	167 (38.3)	159 (37.0)
Median progression-free survival (months)[b]	13.2	8.1
95% CI for median progression-free survival[b]	12.0, 15.2	7.0, 9.0
Hazard ratio[c]	0.64	
95% CI for hazard ratio[c]	0.54, 0.76	
2-sided p-value[d]	<0.0001	
Median (range) duration of follow-up in censored patients (months)	15.3 (0.0, 36.2)	7.2 (0.0, 36.0)

a Patients who had not progressed or died were censored at the latest evaluable RECIST assessment. Patients who progressed or died after two or more missed visits were censored at the latest evaluable RECIST assessment before the two missed visits. If there were no evaluable visits or no baseline assessment (unless the patient died within two visits of baseline), patients were censored at Day 1 (randomization).

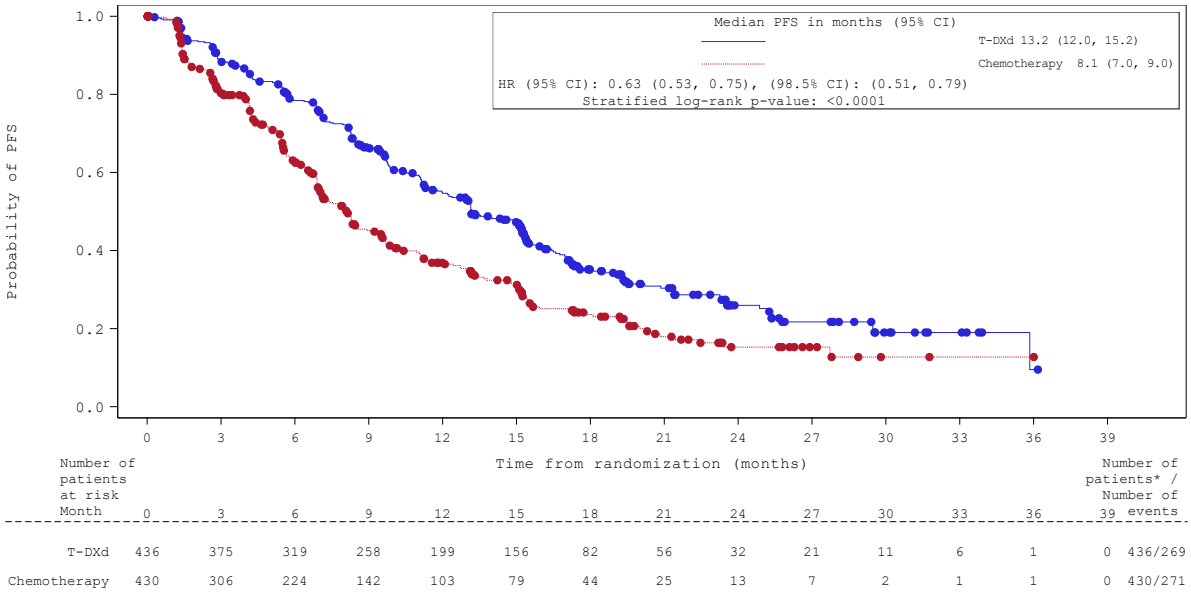
b Calculated using the KM technique. CI for median was derived based on Brookmeyer-Crowley method.

c The HR and CI were calculated using a Cox proportional hazards model with no stratification factors.

d The p-value was calculated using a log-rank test with no stratification factors

.

Figure 7 Progression-free Survival by BICR, Kaplan-Meier Plot – Study DB-06 (ITT Population)

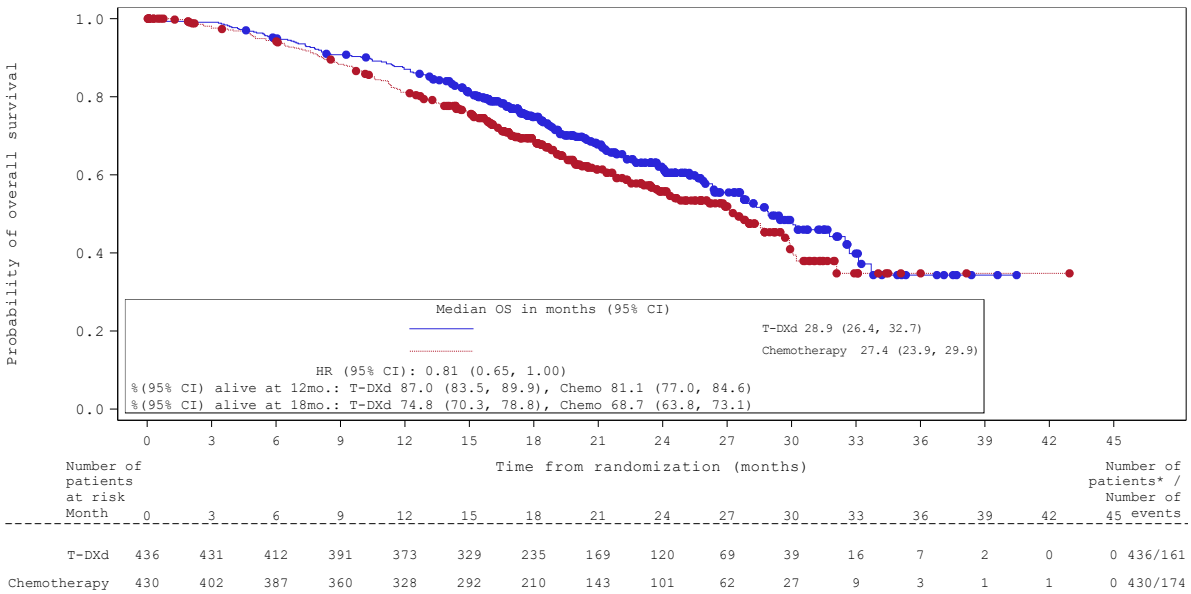


2-sided p-value. A p-value < 0.015 is significant.
Progression was determined by BICR according to RECIST 1.1.

Secondary endpoint – OS (ITT population)

As the efficacy data for OS in the HER2-low population was not statistically significant per the MTP, the OS analysis in the ITT population was not tested.

Figure 8 Overall survival, Kaplan-Meier Plot (ITT Population)



* Number of patients in ITT population. Circle indicates a censored observation.

The interim results of OS in the ITT population showed that the median OS was 28.9 months (95%CI: 26.4, 32.7) for T-DXd and 27.4 months (95%CI: 23.9, 29.9) for chemotherapy, HR: 0.81 [95%CI: 0.66, 1.01]).

Table 19 Overall survival, secondary analysis ITT population

	Number (%) of patients		
	T-DXd (N=436)	Chemotherapy (N=430)	Total (N=866)
Death, n (%)	161 (36.9)	174 (40.5)	
Censored patients, n (%)	275 (63.1)	256 (59.5)	
Still in survival follow-up[a]	265 (60.8)	223 (51.9)	
Terminated prior to death[b]	10 (2.3)	33 (7.7)	
Lost to follow-up	0	0	
Withdrawn consent	10 (2.3)	33 (7.7)	
Other	0	0	
Median overall survival (months)[c]	28.9	27.4	
95% CI for median overall survival[c]	26.4, 32.7	23.9, 29.9	
Hazard ratio[d]	0.81		
95% CI for hazard ratio[d]	0.66, 1.01		
Median (range) duration of follow-up in all patients (months)	18.6 (0.1, 40.5)	17.8 (0.0, 42.9)	18.2 (0.0, 42.9)
Median (range) duration of follow-up in censored patients (months)	20.6 (0.1, 40.5)	19.8 (0.0, 42.9)	
Percentage (95% CI) of patients alive at 12 months	87.0 (83.5, 89.9)	81.1 (77.0, 84.6)	
Percentage (95% CI) of patients alive at 18 months	74.8 (70.3, 78.8)	68.7 (63.8, 73.1)	

[a] Includes patients known to be alive at data cut-off.
[b] Includes patients with unknown survival status or patients who were lost to follow-up.
[c] Calculated using the Kaplan-Meier technique. CI for median is derived based on Brookmeyer-Crowley method.
[d] The hazard ratio and confidence interval were calculated using a Cox proportional hazards model with no stratification factors and ties handled by Efron approach. A hazard ratio < 1 favours T-DXd to be associated with a longer overall survival than Investigator's choice chemotherapy.
1 month = 30.4375 days.
CI = confidence interval. T-DXd = trastuzumab deruxtecan.

Secondary endpoint – PFS by INV (HER2-low population)

Table 20 Progression-free Survival by Investigator Assessment (HER2-low Population)

	T-DXd (N = 359)	Chemotherapy (N = 354)
Total events[a], n (%)	263 (73.3)	284 (80.2)
RECIST progression	246 (68.5)	275 (77.7)
Death in the absence of progression	17 (4.7)	9 (2.5)
Censored patients, n (%)	96 (26.7)	70 (19.8)
Median progression-free survival (months)[b]	12.8	7.0
95% CI for median progression-free survival[b]	11.1, 13.2	6.4, 7.5
Hazard ratio[c]	0.50	
95% CI for hazard ratio[c]	0.42, 0.60	
2-sided p-value[d]	<0.0001	
Median (range) duration of follow-up in censored patients (months)	19.2 (0.0, 37.9)	6.2 (0.0, 36.0)

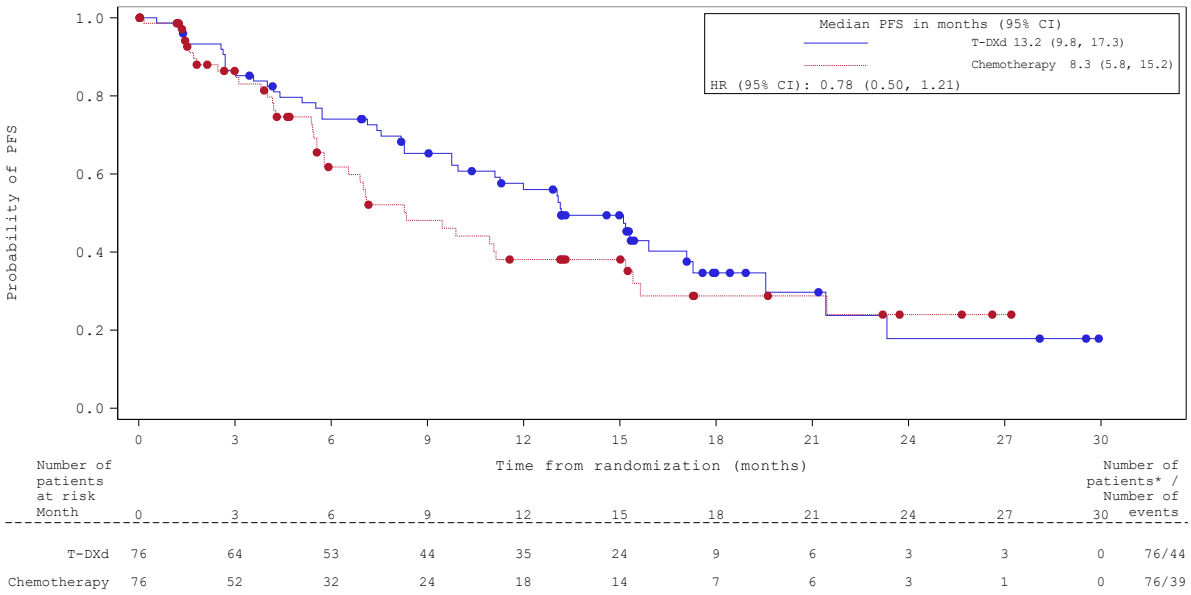
[a] Patients who had not progressed or died were censored at the latest evaluable RECIST assessment. Patients who progressed or died after two or more missed visits were censored at the latest evaluable RECIST assessment before the two missed visits. If there were no evaluable visits or no baseline assessment (unless the patient died within two visits of baseline), patients are censored at Day 1 (randomization).

[b] Calculated using the KM technique. CI for median was derived based on Brookmeyer-Crowley method.

[c] The HR and CI were calculated using a stratified Cox proportional hazards model, adjusting for prior CDK4/6i use (yes vs. no) and HER2 IHC expression (IHC 1+ vs. IHC 2+/ISH-) and ties handled by Efron approach. A HR < 1 favors T-DXd to be associated with a longer event time than Investigator's choice chemotherapy.

[d] The p-value was calculated using a stratified log-rank test, adjusting for prior CDK4/6i use (yes vs. no) and HER2 IHC expression (IHC 1+ vs. IHC 2+/ISH-).

Figure 9 Progression-free Survival by BICR, Kaplan-Meier plot (HER2 IHC > 0 < 1+ Population)



Progression was determined by BICR according to RECIST 1.1.

Secondary endpoint – ORR + DoR (HER2-low population)

Table 21 Objective response rate by BICR and Investigator assessment, logistic regression model HER2-low population

					Comparison between groups		
Endpoint	Group	N	Number (%) of patients with response	95% CI[c]	Odds ratio	95% CI	2-sided p-value
ORR by BICR[ab]	T-DXd	359	217 (60.4)	(55.2, 65.5)	2.51	1.86, 3.41	<0.0001
	Chemotherapy	354	134 (37.9)	(32.8, 43.1)			
ORR by Investigator Assessment[a]	T-DXd	359	217 (60.4)	(55.2, 65.5)	2.26	1.68, 3.05	<0.0001
	Chemotherapy	354	143 (40.4)	(35.2, 45.7)			
Confirmed ORR by BICR	T-DXd	359	203 (56.5)	(51.2, 61.7)	2.74	2.02, 3.73	<0.0001
	Chemotherapy	354	114 (32.2)	(27.4, 37.3)			
Confirmed ORR by Investigator Assessment	T-DXd	359	203 (56.5)	(51.2, 61.7)	2.71	2.00, 3.68	<0.0001
	Chemotherapy	354	115 (32.5)	(27.6, 37.6)			

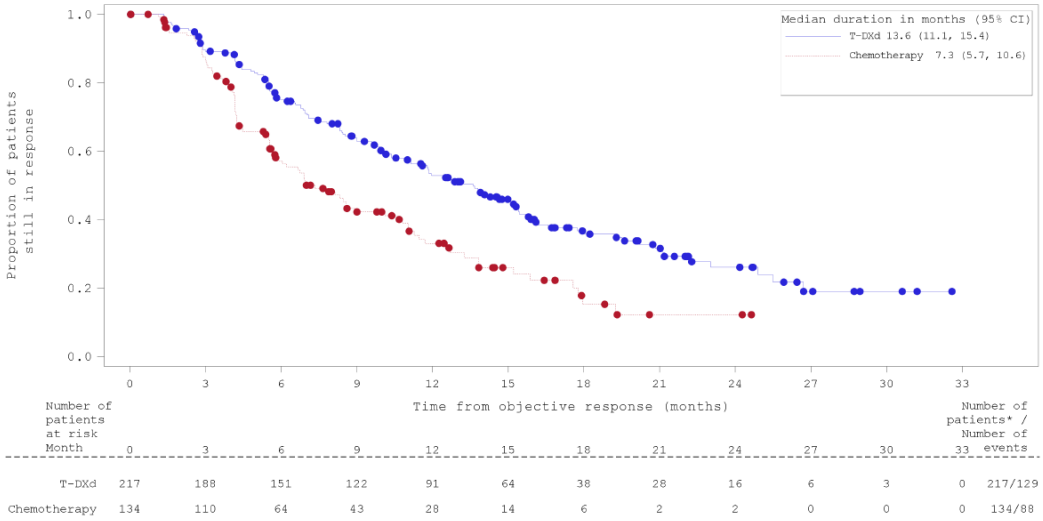
[a] Responses include unconfirmed responses.
[b] Primary analysis.
[c] 95% CI calculated using the Clopper Pearson method.
The odds ratio and confidence interval were calculated using a logistic regression model adjusting for prior CDK4/6 inhibitor use (yes vs. no) and HER2 IHC expression (IHC 1+ vs. IHC 2+/ISH-) as covariates in the model. An odds ratio > 1 favours T-DXd.
The stratification variables (prior CDK4/6 inhibitor use and HER2 IHC expression) were determined per the IRT (interactive response technology) data.
Response is determined according to RECIST 1.1.
BICR = blinded independent central review. CDK = cyclin-dependent kinase. CI = confidence interval. HER2 = human epidermal growth factor receptor 2. IHC = immunohistochemistry. ISH = in situ hybridization. ORR = objective response rate. T-DXd = trastuzumab deruxtecan.

Table 22 Duration of objective response (confirmed response) by BICR HER2-low population, patients with objective response (confirmed response) by BICRT

	T-DXd (N=203)	Chemotherapy (N=114)
Number of responders who subsequently progressed or died	119	74
Duration of response from onset of response (months)[ab]		
25th percentile	6.9	4.2
Median	14.1	8.6
75th percentile	25.5	15.9
Percentage remaining in response[b]		
At 3 months	93.5	92.8
At 6 months	78.8	63.8
At 9 months	67.0	48.0
At 12 months	55.4	36.4
At 15 months	48.2	28.5
At 18 months	37.5	16.8
At 21 months	33.1	13.4
At 24 months	27.3	13.4
At 27 months	19.9	NE
At 30 months	19.9	NE

[a] Duration of response is the time from the first documentation of CR/PR (which is subsequently confirmed) until the date of first documented progression, or death in the absence of progression. Patients who have not progressed or died are censored at their PFS censoring date.
[b] Calculated using Kaplan-Meier technique.
Response requires confirmation after 4 weeks.
Response is determined by BICR according to RECIST 1.1.
1 month = 30.4375 days.
BICR = blinded independent central review. CR = complete response. HER2 = human epidermal growth factor receptor 2. NE = not evaluable. PFS = progression-free survival. PR = partial response. T-DXd = trastuzumab deruxtecan.

Figure 10 Duration of Objective Response by BICR, Kaplan-Meier Plot (HER2-low Population)



Responses include unconfirmed responses.

Secondary endpoint – ORR +DoR (ITT population)

Table 23 Objective response rate by BICR and Investigator assessment, logistic regression model, patients with measurable disease at baseline ITT population

					Comparison between groups		
Endpoint	Group	N	Number (%) of patients with response	95% CI[c]	Odds ratio	95% CI	2-sided p-value
ORR by BICR[ab]	T-DXd	436	268 (61.5)	(56.7, 66.1)	2.76	2.10, 3.64	<0.0001
	Chemotherapy	430	158 (36.7)	(32.2, 41.5)			
ORR by Investigator Assessment[a]	T-DXd	436	268 (61.5)	(56.7, 66.1)	2.52	1.92, 3.32	<0.0001
	Chemotherapy	430	167 (38.8)	(34.2, 43.6)			
Confirmed ORR by BICR	T-DXd	436	250 (57.3)	(52.5, 62.0)	2.98	2.26, 3.94	<0.0001
	Chemotherapy	430	134 (31.2)	(26.8, 35.8)			
Confirmed ORR by Investigator Assessment	T-DXd	436	245 (56.2)	(51.4, 60.9)	2.91	2.20, 3.85	<0.0001
	Chemotherapy	430	132 (30.7)	(26.4, 35.3)			

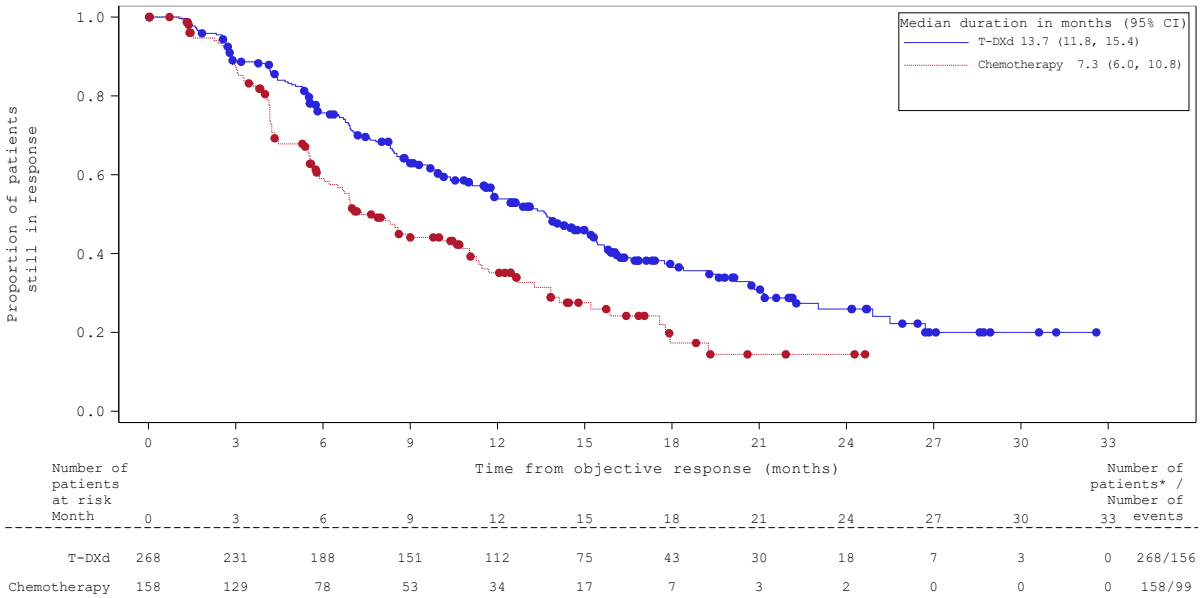
[a] Responses include unconfirmed responses.
[b] Primary analysis.
[c] 95% CI calculated using the Clopper Pearson method.
The odds ratio and confidence interval were calculated using a logistic regression model adjusting for prior CDK4/6 inhibitor use (yes vs. no) and HER2 IHC expression (IHC >0 <1+ vs. IHC 1+ vs. IHC 2+/ISH-) as covariates in the model. An odds ratio > 1 favours T-DXd.
The stratification variables (prior CDK4/6 inhibitor use and HER2 IHC expression) were determined per the IRT (interactive response technology) data.
Response is determined according to RECIST 1.1.
BICR = blinded independent central review. CDK = cyclin-dependent kinase. CI = confidence interval. HER2 = human epidermal growth factor receptor 2. IHC = immunohistochemistry. ISH = in situ hybridization. ORR = objective response rate. T-DXd = trastuzumab deruxtecan.

Table 24 Duration of objective response (confirmed response) by BICR ITT population, patients with objective response (confirmed response) by BICR

	T-DXd (N=250)	Chemotherapy (N=134)
Number of responders who subsequently progressed or died	142	83
Duration of response from onset of response (months)[ab]		
25th percentile	7.0	4.4
Median	14.3	8.6
75th percentile	25.5	17.6
Percentage remaining in response[b]		
At 3 months	93.6	93.1
At 6 months	79.9	65.0
At 9 months	67.3	49.9
At 12 months	56.9	38.8
At 15 months	48.5	30.4
At 18 months	38.5	19.1
At 21 months	32.6	15.9
At 24 months	27.4	15.9
At 27 months	21.1	NE
At 30 months	21.1	NE

[a] Duration of response is the time from the first documentation of CR/PR (which is subsequently confirmed) until the date of first documented progression, or death in the absence of progression. Patients who have not progressed or died are censored at their PFS censoring date.
[b] Calculated using Kaplan-Meier technique.
Response requires confirmation after 4 weeks.
Response is determined by BICR according to RECIST 1.1.
1 month = 30.4375 days.
BICR = blinded independent central review. CR = complete response. NE = not evaluable. PFS = progression-free survival. PR = partial response. T-DXd = trastuzumab deruxtecan.

Figure 11 Duration of Objective Response by BICR, Kaplan-Meier plot (ITT Population)



Responses include unconfirmed responses.

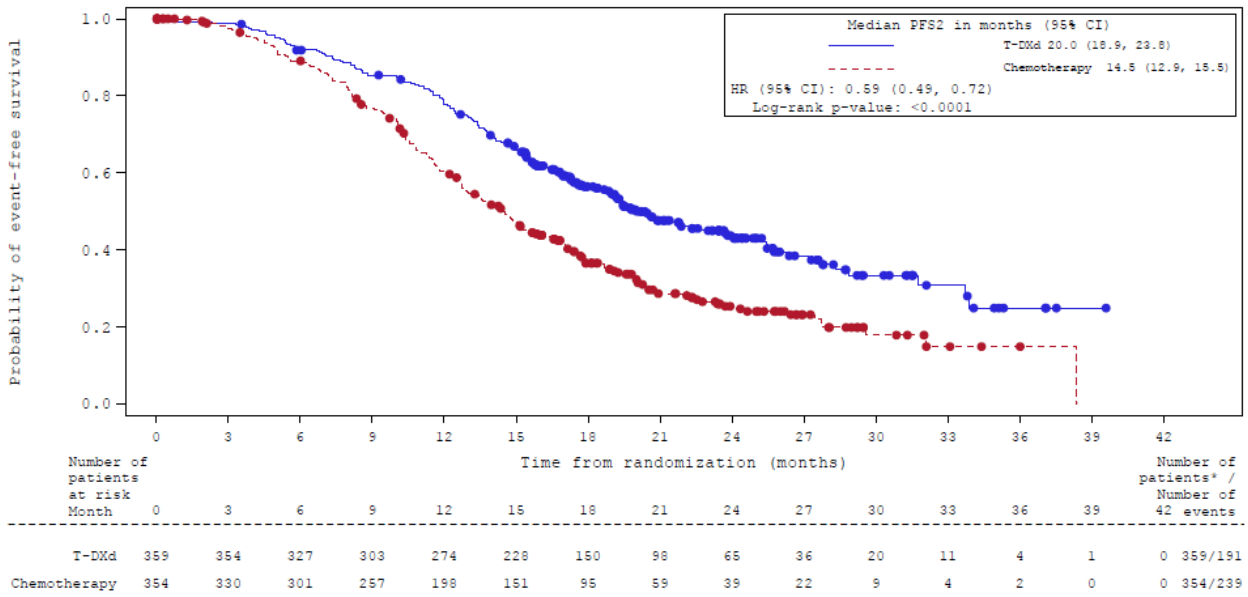
Secondary endpoint – PFS 2 (HER-2 low population)

Table 25 Time from randomization to second progression or death HER2- low population

	T-DXd (N=359)	Chemotherapy (N=354)
Total events[a], n (%)	191 (53.2)	239 (67.5)
Second progression	122 (34.0)	172 (48.6)
Objective radiological progression	106 (29.5)	148 (41.8)
Symptomatic progression in absence of objective radiological progression	12 (3.3)	17 (4.8)
Other	4 (1.1)	7 (2.0)
Death in the absence of second progression	69 (19.2)	67 (18.9)
Censored patients, n (%)	168 (46.8)	115 (32.5)
Second progression-free at time of analysis	163 (45.4)	96 (27.1)
Lost to follow-up	0	0
Withdrawn consent	5 (1.4)	19 (5.4)
Other[b]	0	0
Median time to second progression or death (months)[c]	20.0	14.5
95% CI for median time to second progression or death[c]	18.9, 23.8	12.9, 15.5
Hazard ratio[d]	0.59	
95% CI for hazard ratio[d]	0.49, 0.72	
2-sided p-value[e]	<0.0001	

[a] Patients alive and for whom a second disease progression has not been observed are censored at the earliest of: date of study termination, date last known alive, data cut-off or, if a patient has not had a first subsequent therapy, the date last known not to have received a first subsequent therapy.
[b] Other category includes patients discontinued the study for any other reason.
[c] Calculated using the Kaplan-Meier technique. CI for median is derived based on Brookmeyer-Crowley method.
[d] The hazard ratio and confidence intervals were calculated using a Cox proportional hazards model with no stratification factors and ties handled by Efron approach. A hazard ratio < 1 favours T-DXd to be associated with a longer event-free survival than Investigator's choice chemotherapy.
[e] The p-value was calculated using a log-rank test, with no stratification factors.
Second progression is determined by the Investigator according to local standard clinical practice.
1 month = 30.4375 days.
CI = confidence interval. HER2 = human epidermal growth factor receptor 2. T-DXd = trastuzumab deruxtecan.

Figure 12 Time from Randomization to Second Progression or Death, KaplanMeier plot (HER2-low Population)



* Number of patients in HER2-low population.
Circle indicates a censored observation.
2-sided p-value.
Second progression is determined by the Investigator according to local standard clinical practice.
1 month = 30.4375 days.
CI = confidence interval. HER2 = human epidermal growth factor receptor 2. HR = hazard ratio. NE = not evaluable. PFS2 = time from randomization to second progression or death. T-DXd = trastuzumab deruxtecan.

2-sided p-value.
Second progression was determined by the Investigator according to local standard clinical practice.

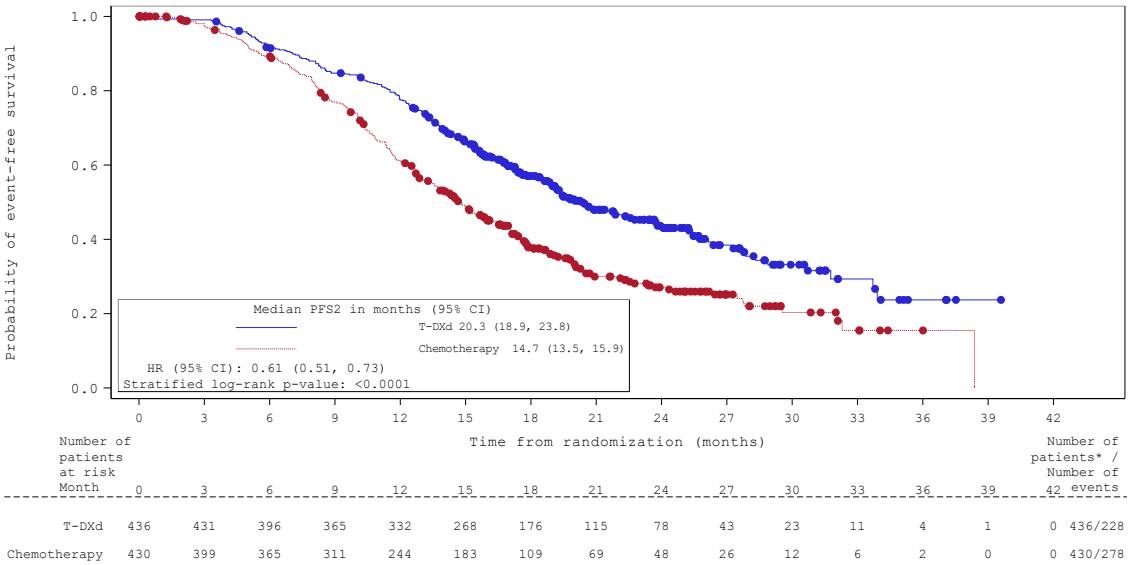
Secondary endpoint – PFS 2 (ITT population)

Table 26 Time from randomization to second progression or death ITT population

	T-DXd (N=436)	Chemotherapy (N=430)
Total events[a], n (%)	228 (52.3)	278 (64.7)
Second progression	149 (34.2)	201 (46.7)
Objective radiological progression	128 (29.4)	175 (40.7)
Symptomatic progression in absence of objective radiological progression	16 (3.7)	19 (4.4)
Other	5 (1.1)	7 (1.6)
Death in the absence of second progression	79 (18.1)	77 (17.9)
Censored patients, n (%)	208 (47.7)	152 (35.3)
Second progression-free at time of analysis	201 (46.1)	127 (29.5)
Lost to follow-up	0	0
Withdrawn consent	7 (1.6)	25 (5.8)
Other[b]	0	0
Median time to second progression or death (months)[c]	20.3	14.7
95% CI for median time to second progression or death[c]	18.9, 23.8	13.5, 15.9
Hazard ratio[d]	0.62	
95% CI for hazard ratio[d]	0.52, 0.74	
2-sided p-value[e]	<0.0001	

[a] Patients alive and for whom a second disease progression has not been observed are censored at the earliest of: date of study termination, date last known alive, data cut-off or, if a patient has not had a first subsequent therapy, the date last known not to have received a first subsequent therapy.
[b] Other category includes patients discontinued the study for any other reason.
[c] Calculated using the Kaplan-Meier technique. CI for median is derived based on Brookmeyer-Crowley method.
[d] The hazard ratio and confidence intervals were calculated using a Cox proportional hazards model with no stratification factors and ties handled by Efron approach. A hazard ratio < 1 favours T-DXd to be associated with a longer event-free survival than Investigator's choice chemotherapy.
[e] The p-value was calculated using a log-rank test, with no stratification factors.
Second progression is determined by the Investigator according to local standard clinical practice.
1 month = 30.4375 days.
CI = confidence interval. T-DXd = trastuzumab deruxtecan.

Figure 13 Time from Randomization to Second Progression or Death, Kaplan-Meier plot (ITT Population)



2-sided p-value.
Second progression was determined by the Investigator according to local standard clinical practice.

Secondary endpoint – TFST and TSST (ITT population)

Table 27 Time from randomization to first subsequent therapy or death ITT population

	T-DXd (N=436)	Chemotherapy (N=430)
Total events[a], n (%)	329 (75.5)	367 (85.3)
First subsequent therapy	284 (65.1)	329 (76.5)
Death in the absence of subsequent therapy	45 (10.3)	38 (8.8)
Censored patients, n (%)	107 (24.5)	63 (14.7)
Alive and with no subsequent therapy at time of analysis	103 (23.6)	45 (10.5)
Lost to follow-up	0	0
Withdrawn consent	4 (0.9)	18 (4.2)
Other[b]	0	0
Median time to first subsequent therapy or death (months)[c]	12.5	7.6
95% CI for median time to first subsequent therapy or death[c]	11.5, 13.9	6.9, 8.2
Hazard ratio[d]	0.54	
95% CI for hazard ratio[d]	0.46, 0.63	
2-sided p-value[e]	<0.0001	

[a] Patients alive and not known to have had a first subsequent anti-cancer therapy are censored at the earliest of: date of study termination, date last known alive, data cut-off or the last date that the patient was known not to have received a first subsequent anti-cancer therapy.
[b] Other category includes patients discontinued the study for any other reason.
[c] Calculated using the Kaplan-Meier technique. CI for median is derived based on Brookmeyer-Crowley method.
[d] The hazard ratio and confidence interval were calculated using a stratified Cox proportional hazards model, adjusting for prior CDK4/6 inhibitor use (yes vs. no) and HER2 IHC expression (IHC >0 <1+ vs. IHC 1+ vs. IHC 2+/ISH-) and ties handled by Efron approach. A hazard ratio < 1 favours T-DXd to be associated with a longer event-free survival than Investigator's choice chemotherapy.
[e] The p-value was calculated using a stratified log-rank test, adjusting for prior CDK4/6 inhibitor use (yes vs. no) and HER2 IHC expression (IHC >0 <1+ vs. IHC 1+ vs. IHC 2+/ISH-). 1 month = 30.4375 days. CDK = cyclin-dependent kinase. CI = confidence interval. HER2 = human epidermal growth factor receptor 2. IHC = immunohistochemistry. ISH = in situ hybridization. T-DXd = trastuzumab deruxtecan.

Table 28 Time from randomization to second subsequent therapy or death ITT population

	T-DXd (N=436)	Chemotherapy (N=430)
Total events[a], n (%)	223 (51.1)	276 (64.2)
Second subsequent therapy	129 (29.6)	191 (44.4)
Death in the absence of second subsequent therapy	94 (21.6)	85 (19.8)
Censored patients, n (%)	213 (48.9)	154 (35.8)
Alive and with no second subsequent therapy at time of analysis	209 (47.9)	136 (31.6)
Lost to follow-up	0	0
Withdrawn consent	4 (0.9)	18 (4.2)
Other[b]	0	0
Median time to second subsequent therapy or death (months)[c]	21.4	14.9
95% CI for median time to second subsequent therapy or death[c]	19.2, 23.8	13.5, 16.1
Hazard ratio[d]	0.60	
95% CI for hazard ratio[d]	0.50, 0.71	
2-sided p-value[e]	<0.0001	

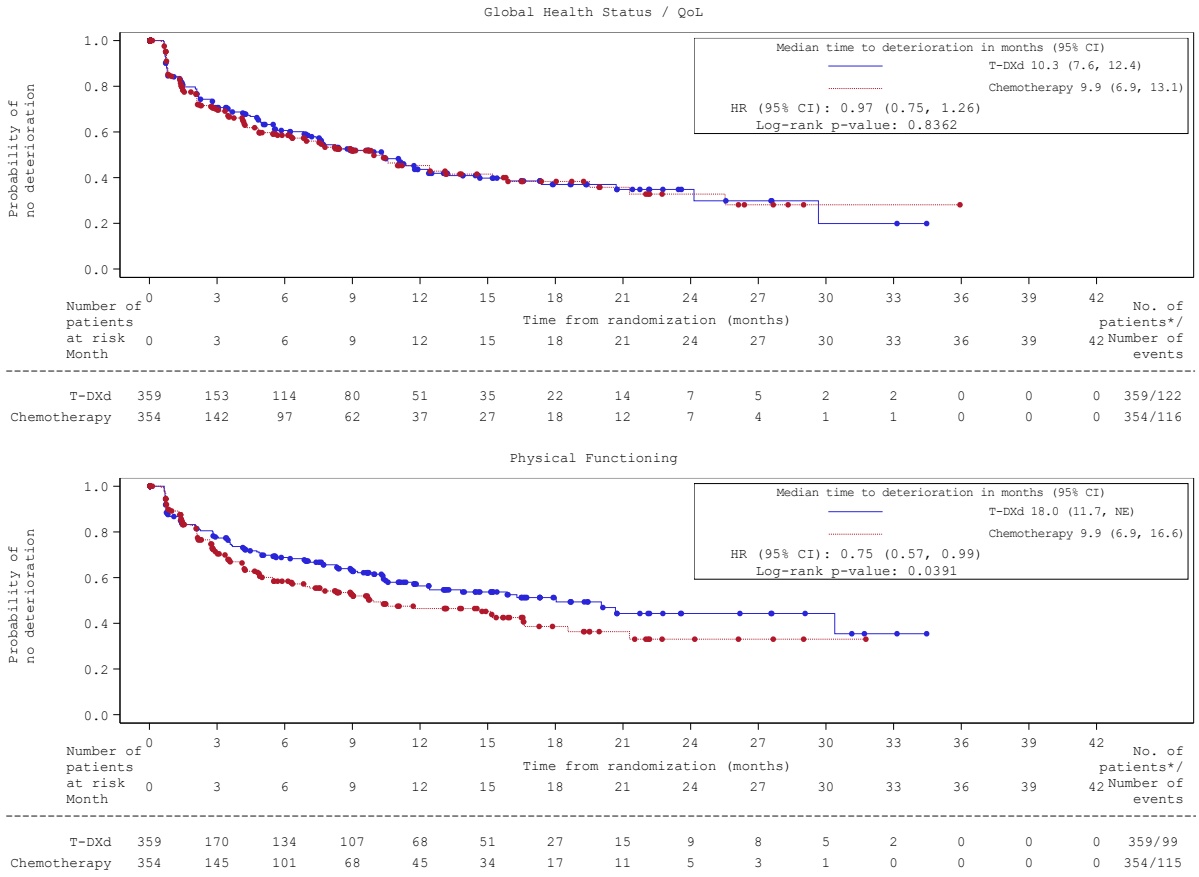
[a] Patients alive and not known to have had a second subsequent anti-cancer therapy are censored at the earliest of: date of study termination, date last known alive, data cut-off or the last date that the patient was known not to have received a second subsequent anti-cancer therapy.
[b] Other category includes patients discontinued the study for any other reason.
[c] Calculated using the Kaplan-Meier technique. CI for median is derived based on Brookmeyer-Crowley method.
[d] The hazard ratio and confidence intervals were calculated using a Cox proportional hazards model with no stratification factors and ties handled by Efron approach. A hazard ratio < 1 favours T-DXd to be associated with a longer event-free survival than Investigator's choice chemotherapy.
[e] The p-value was calculated using a log-rank test, with no stratification factors. 1 month = 30.4375 days. CI = confidence interval. T-DXd = trastuzumab deruxtecan.

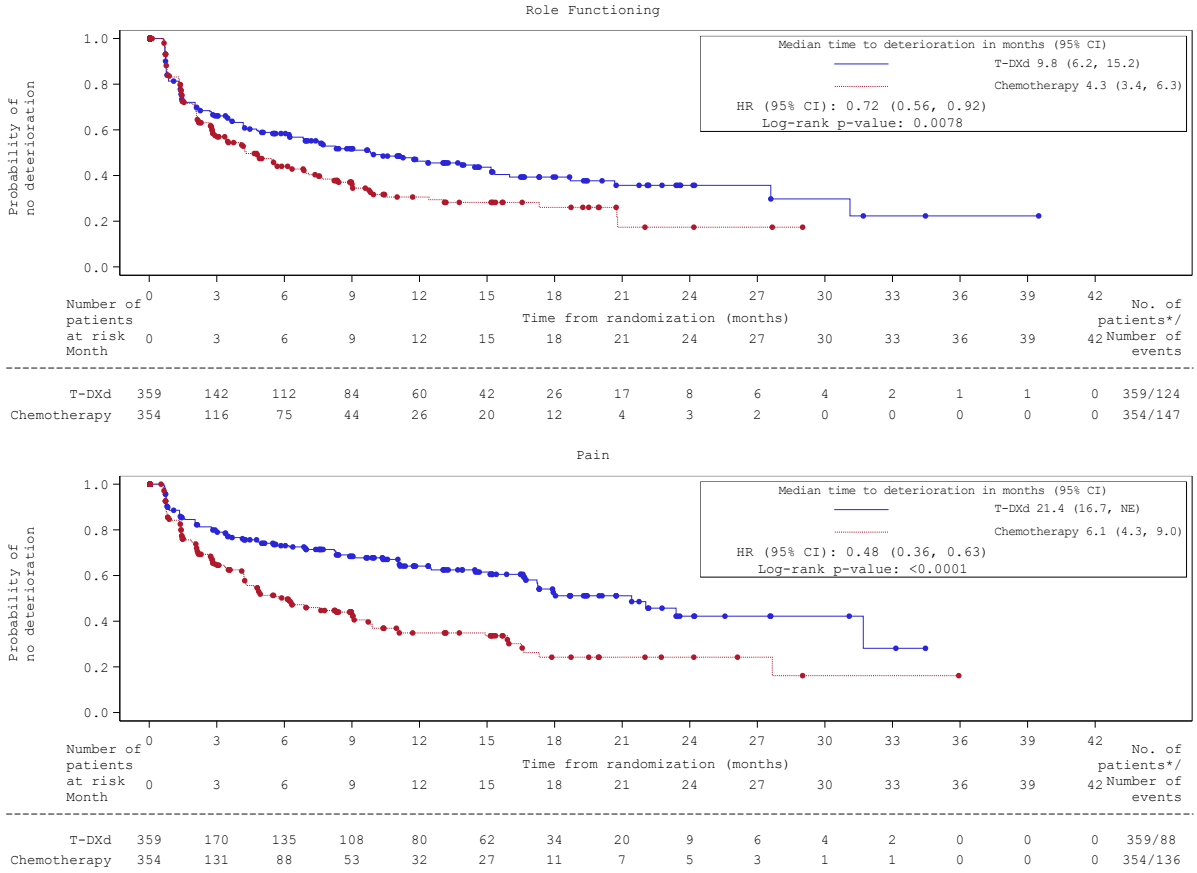
Patient-reported outcomes - EORTC QLQ-C30 and EORTC QLQ-BR45

As secondary outcome measures in the ITT population, PRO variables, as measured by EORTC QLQ-C30 and EORTC QLQ-BR45 PRO questionnaires, showed no differences in change from baseline over the first 7 months between the T-DXd arm and the chemotherapy arm in GHS/QoL and functioning,

but some differences were observed in symptoms. An improvement from baseline in pain was reported by patients in the T-DXd arm compared to chemotherapy, while a worsening of GI symptoms (nausea/vomiting, appetite loss and constipation) were reported by patients in the T-DXd arm compared to chemotherapy. A worsening of skin mucosis symptoms from baseline was reported by patients in the chemotherapy arm compared to the T-DXd arm. T-DXd also reduced the risk of deterioration for all pre-specified scales of physical functioning (by 28%), role functioning (by 25%) and pain (by 49%), compared to chemotherapy. The risk of deterioration in GHS/QoL was similar between the 2 arms. Results in the HER2-low population were consistent with the ITT population.

Figure 14 EORTC QLQ-C30, Time to Deterioration of Selected Scales, Kaplan-Meier Plot (HER2-low Population)

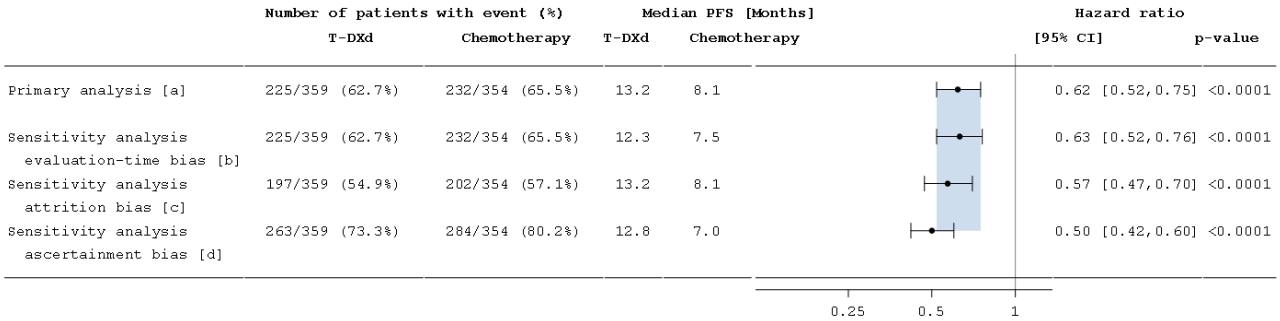




For the Pain scale: The hazard ratio and confidence interval were calculated using a stratified Cox proportional hazards model, adjusting for prior CDK4/6 inhibitor use (yes vs. no) and HER2 IHC expression (IHC 1+ vs. IHC 2+/ISH-) and ties handled by Efron approach. The p-value was calculated using a stratified log-rank test, adjusting for the same factors.
For other scales, the hazard ratios and confidence intervals were calculated using a Cox proportional hazards model with no stratification factors and ties handled by Efron approach. The p-value was calculated using a log-rank test, with no stratification factors.
A clinically meaningful deterioration is defined as a decrease from baseline ≥10 points in functional scales and GHS/QoL and as an increase from baseline ≥10 in symptom scales

Ancillary analyses

Figure 15 Forest Plot of Progression-free Survival by BICR, by Sensitivity Analyses (HER2-low Population)



[a] Patients who had not progressed or died were censored at the latest evaluable RECIST assessment. Patients who progressed or died after two or more missed visits were censored at the latest evaluable RECIST assessment before the two missed visits. If there were no evaluable visits or no baseline assessment (unless the

patient died within two visits of baseline), patients were censored at Day 1 (randomization). Progression was determined by BICR according to RECIST 1.1.

[b] In case of RECIST progression, the midpoint between the time of progression and the previous evaluable RECIST assessment was considered. For patients whose death was treated as a PFS event, the date of death was used. Progression was determined by BICR according to RECIST 1.1.

[c] The actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of progression immediately following two or more missed tumor assessments were included. Also, patients who took subsequent anti-cancer therapy (for this analysis radiotherapy was not considered a subsequent anti-cancer therapy) prior to their last evaluable RECIST assessment or progression or death were censored at their last evaluable assessment prior to taking the subsequent therapy. Progression was determined by BICR according to RECIST 1.1.

[d] Progression was determined by Investigator assessment according to RECIST 1.1.

HR (T-DXd: Investigator's choice chemotherapy), 95% CI for HR.
A HR < 1 favors T-DXd and is associated with a longer progression-free survival than Investigator's choice chemotherapy.
Grey band represents the 95% CI for the HR in the primary analysis.
The HR and CI were calculated using a stratified Cox proportional hazards model, adjusting for prior CDK4/6i use (yes vs. no) and HER2 IHC expression (IHC 1+ vs. IHC 2+/ISH-) and ties handled by Efron approach. The p-value was calculated using a stratified log-rank test, adjusting for prior CDK4/6i use (yes vs. no) and HER2 IHC expression (IHC 1+ vs. IHC 2+/ISH-).

Table 29 PFS by BICR, Sensitivity Analysis Without Applying Two Missed Visits Censoring Rule

	T-DXd	**Chemotherapy**
HER2-low population		
Number of patients	359	354
Total events, n (%) [a]	255 (71.0)	266 (75.1)
Censored patients	104 (29.0)	88 (24.9)
Median PFS, months, (95% CI) [b]	13.1 (11.3, 15.2)	8.2 (7.1, 9.6)
Hazard ratio (95% CI) [c]	0.65 (0.55, 0.78)	
2-sided p-value [d]	< 0.0001	
ITT population		
Number of patients	436	430
Total events, n (%) [a]	306 (70.2)	314 (73.0)
Censored patients	130 (29.8)	116 (27.0)
Median PFS, months, (95% CI) [b]	13.1 (11.4, 15.1)	8.3 (7.2, 9.6)
Hazard ratio (95% CI) [e]	0.66 (0.56, 0.77)	
2-sided p-value [f]	< 0.0001	
HER2 IHC > 0 < 1+ population		
Number of patients	76	76
Total events, n (%) [a]	51 (67.1)	48 (63.2)
Censored patients	25 (32.9)	28 (36.8)
Median PFS, months, (95% CI) [b]	13.1 (9.8, 17.1)	9.5 (6.5, 11.6)
Hazard ratio (95% CI) [e]	0.74 (0.50, 1.11)	
2-sided p-value [f]	0.1455	

[a] Patients who have not progressed or died are censored at the latest evaluable RECIST assessment. If there are no evaluable visits or no baseline assessment, patients are censored at Day 1 (randomization).

[b] Calculated using the Kaplan-Meier technique. CI for median is derived based on Brookmeyer-Crowley method.

[c] The hazard ratio and confidence interval were calculated using a stratified Cox proportional hazards model, adjusting for prior CDK4/6 inhibitor use (yes vs no), HER2 IHC expression (IHC 1+ vs IHC 2+/ISH-) and ties handled by Efron approach. A hazard ratio < 1 favors T-DXd to be associated with a longer progression-free survival than investigator's choice chemotherapy.

[d] The p-value was calculated using a stratified log-rank test, adjusting for prior CDK4/6 inhibitor use (yes vs no), HER2 IHC expression (IHC 1+ vs IHC 2+/ISH-).

[e] The hazard ratio and confidence interval were calculated using a Cox proportional hazards model with no stratification factors and ties handled by Efron approach. A hazard ratio < 1 favors T-DXd to be associated with a longer progression-free survival than investigator's choice chemotherapy.

[f] The p-value was calculated with no stratification factors.

Table 30 Concordance of Local and Central HER2 status in DB-06

HER2 Local		HER2 central						
		IHC 0		IHC 1+	IHC 2+ /ISH-	IHC 2+ /ISH+	IHC 3+	Total
		Absent membrane staining	With membrane staining					
			HER2-ultralow (IHC > 0 < 1+)	HER2-low				
IHC 0		123	140	70	15	1	0	349
IHC 1+	HER2-low	45	146	534	83	1	1	810
IHC 2+ / ISH-		20	50	146	236	6	2	460
IHC 2+/ ISH+		0	2	3	3	0	0	8
IHC 3+		1	1	0	0	0	0	2
Total		189	339	753	337	8	3	1629

Table 31 Disagreements between Investigator and Central Reviews of RECIST Progression (ITT Population)

	Number (%) of patients		Difference T-DXd vs Chemotherapy
	T-DXd (N = 436)	Chemotherapy (N = 430)	
RECIST progression[a] declared by:			
Investigator and central review	241 (55.3)	257 (59.8)	NA
Progression date agreement (within 2 weeks)	106 (24.3)	128 (29.8)	NA
Progression date ≥ 2 weeks earlier by central review than by Investigator	97 (22.2)	89 (20.7)	NA
Progression date ≥ 2 weeks earlier by Investigator than by central review	38 (8.7)	40 (9.3)	NA
RECIST progression disagreements	102 (23.4)	98 (22.8)	NA
Investigator but not central review	74 (17.0)	84 (19.5)	NA
Central review but not Investigator	28 (6.4)	14 (3.3)	NA
No Progression by both	93 (21.3)	75 (17.4)	NA
Early Discrepancy Rate[b]	0.36	0.36	-0.01[c]
Late Discrepancy Rate[d]	0.53	0.45	0.07

[a] Patients who had not progressed or died were censored at the latest evaluable RECIST assessment. Patients who progressed or died after two or more missed visits were censored at the latest evaluable RECIST assessment before the two missed visits. If there were no evaluable visits or no baseline assessment (unless the patient died within two visits of baseline), patients were censored at Day 1 (randomization).

[b] Early Discrepancy Rate was the frequency of Investigator-declared progressions before central review as a proportion of all Investigator progressions.

[c] Difference was calculated prior to rounding.

[d] Late Discrepancy Rate was the frequency of Investigator declared progressions after central review as a proportion of all discrepancies. Progression was determined according to RECIST 1.1.

Figure 16 Tipping Point Analysis – Change in the Estimated HR (ITT Population)

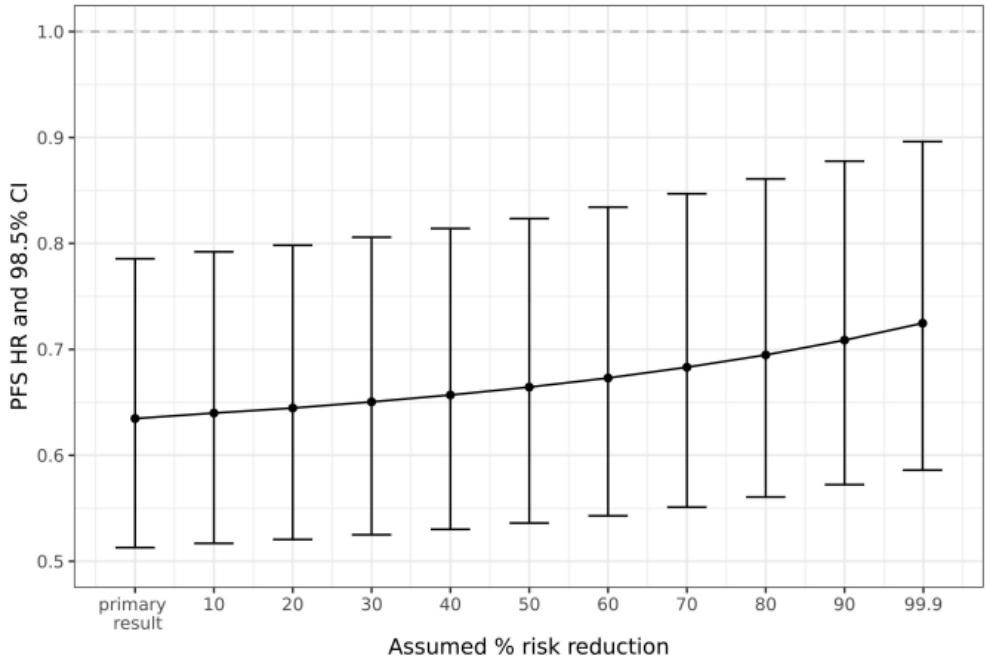
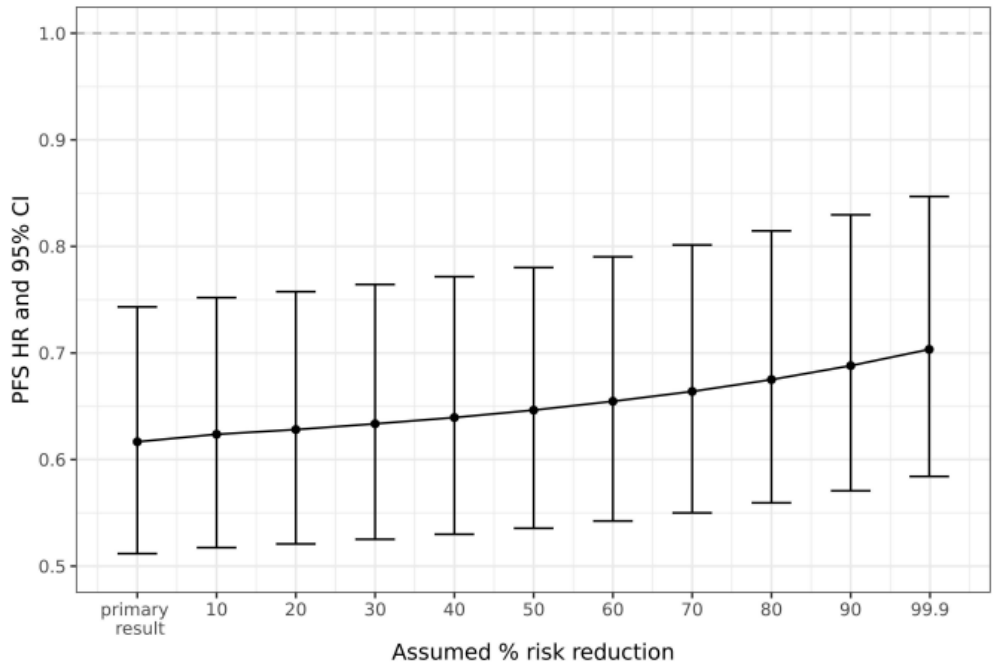


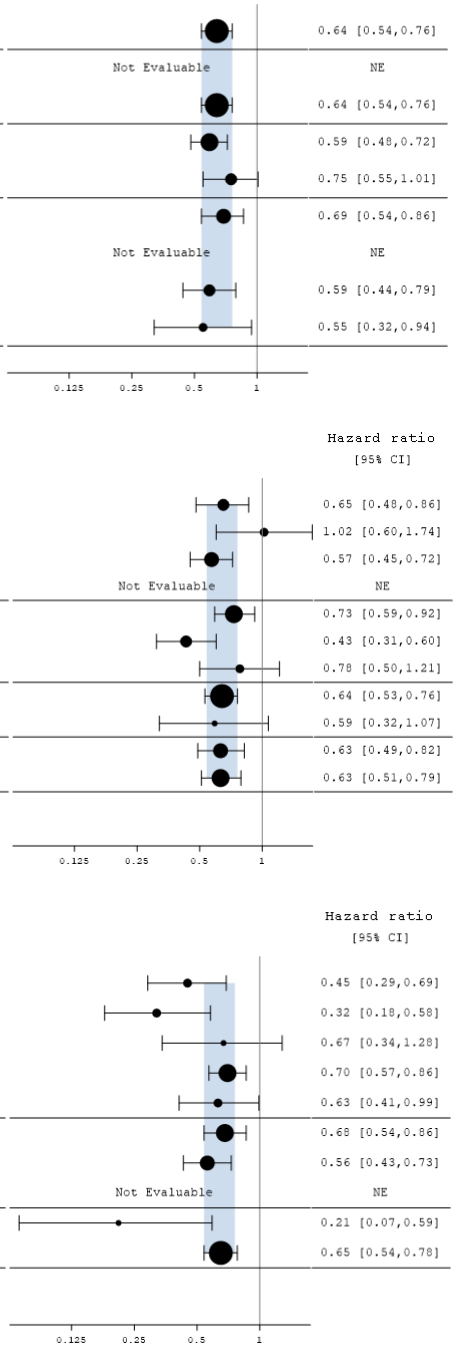
Figure 17 Tipping Point Analysis – Change in the Estimated HR (HER2-low Population)

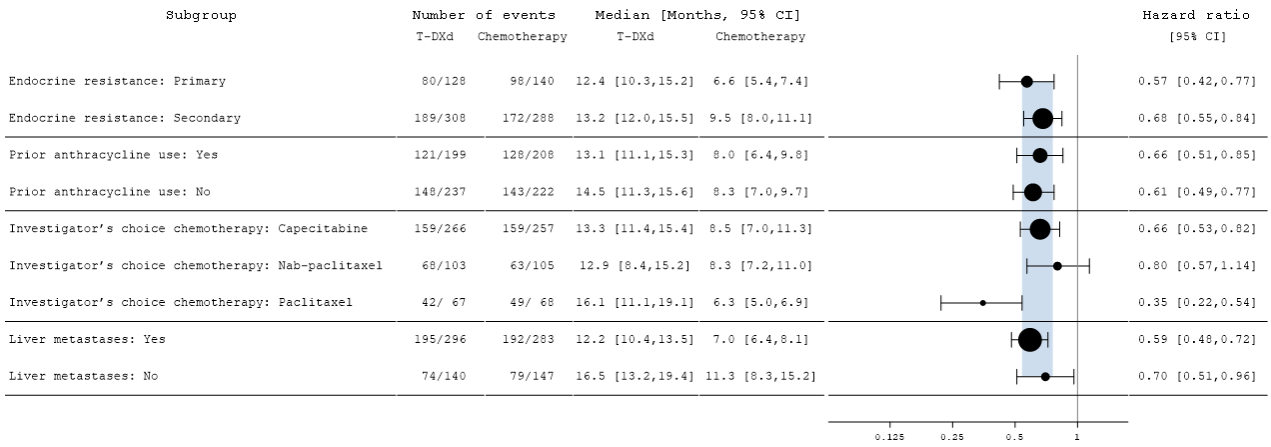


Subgroup analysis

Figure 18 Forest Plot of Progression-free Survival by BICR by Subgroup (ITT Population)

Subgroup	Number of events T-DXd	Number of events Chemotherapy	Median [Months, 95% CI] T-DXd	Median [Months, 95% CI] Chemotherapy	Hazard ratio [95% CI]
All patients	269/436	271/430	13.2 [12.0,15.2]	8.1 [7.0,9.0]	0.64 [0.54,0.76]
Sex: Male	0/ 0	1/ 1	NE [NE,NE]	1.2 [NE,NE]	NE
Sex: Female	269/436	270/429	13.2 [12.0,15.2]	8.1 [7.0,9.3]	0.64 [0.54,0.76]
Age at randomization: <65 years	186/302	186/297	13.3 [11.8,15.3]	7.4 [6.9,8.6]	0.59 [0.48,0.72]
Age at randomization: >=65 years	83/134	85/133	13.1 [9.7,15.6]	8.5 [7.1,11.5]	0.75 [0.55,1.01]
Race: White	148/231	142/230	13.0 [11.0,15.1]	8.2 [6.9,9.6]	0.69 [0.54,0.86]
Race: Black/African-American	2/ 4	2/ 3	NE [6.9,NE]	4.4 [1.2,NE]	NE
Race: Asian	88/154	101/151	15.2 [12.9,19.4]	8.2 [6.9,9.7]	0.59 [0.44,0.79]
Race: Other	31/ 47	26/ 46	15.0 [9.6,17.5]	7.1 [5.4,15.5]	0.55 [0.32,0.94]
Region: Asia	88/149	96/147	15.2 [12.4,19.3]	8.2 [6.9,9.7]	0.65 [0.48,0.86]
Region: North America	32/ 48	25/ 47	10.0 [8.4,13.1]	11.0 [6.8,15.4]	1.02 [0.60,1.74]
Region: Europe	143/227	139/213	13.5 [11.1,15.4]	7.3 [6.6,8.3]	0.57 [0.45,0.72]
Region: Rest of the World	6/ 12	11/ 23	13.3 [5.8,NE]	6.9 [4.2,NE]	NE
HER2 IHC expression: IHC 1+	157/239	150/234	13.1 [11.0,15.2]	8.2 [7.1,9.8]	0.73 [0.59,0.92]
HER2 IHC expression: IHC 2+/ISH-	65/117	80/118	15.2 [12.2,21.4]	7.0 [6.2,8.4]	0.43 [0.31,0.60]
HER2 IHC expression: IHC >0 <1+	44/ 76	39/ 76	13.2 [9.8,17.3]	8.3 [5.8,15.2]	0.78 [0.50,1.21]
Prior CDK4/6 inhibitor use: Yes	248/394	247/389	13.1 [11.3,15.2]	7.9 [6.9,8.6]	0.64 [0.53,0.76]
Prior CDK4/6 inhibitor use: No	21/ 42	24/ 41	16.1 [11.3,NE]	11.4 [7.1,20.6]	0.59 [0.32,1.07]
Prior taxane use in the non-metastatic setting: Yes	112/179	117/177	12.9 [9.9,14.0]	7.3 [6.3,9.3]	0.63 [0.49,0.82]
Prior taxane use in the non-metastatic setting: No	157/257	154/253	15.1 [11.4,16.5]	8.4 [7.1,9.7]	0.63 [0.51,0.79]
1 prior line	33/ 65	55/ 82	15.2 [9.7,19.1]	6.9 [5.5,8.4]	0.45 [0.29,0.69]
- 1 prior line and time to progression from start of ET + CDK4/6 inhibitors <= 6 months	18/ 37	32/ 40	15.2 [9.7,NE]	6.8 [4.2,8.4]	0.32 [0.18,0.58]
- Remaining patients with 1 prior line	15/ 28	23/ 42	15.2 [7.2,NE]	7.8 [5.3,20.0]	0.67 [0.34,1.28]
2 prior lines	188/295	179/288	13.2 [11.4,15.3]	8.3 [7.1,9.8]	0.70 [0.57,0.86]
>=3 prior lines	47/ 75	36/ 58	12.0 [8.7,17.3]	8.3 [6.4,11.3]	0.63 [0.41,0.99]
ER/PR status: ER+ PgR+	155/253	145/237	13.2 [11.3,15.3]	8.3 [6.9,10.4]	0.68 [0.54,0.86]
ER/PR status: ER+ PgR-	100/167	116/181	13.5 [11.3,16.1]	8.1 [6.9,9.5]	0.56 [0.43,0.73]
ER/PR status: ER- PgR+	3/ 3	2/ 2	4.2 [4.2,NE]	4.9 [4.2,NE]	NE
ER status: ER: 1-10%	11/ 17	10/ 12	15.3 [6.8,19.4]	4.4 [1.4,5.5]	0.21 [0.07,0.59]
ER status: ER: >10%	228/364	220/355	13.1 [11.3,15.2]	8.3 [7.3,9.7]	0.65 [0.54,0.78]





Hazard ratio (T-DXd: Investigator's choice chemotherapy), 95% CI for HR.

A hazard ratio < 1 favors T-DXd and is associated with a longer progression-free survival than Investigator's choice chemotherapy.

For the analysis on all patients, the hazard ratio and confidence interval were calculated using a stratified Cox proportional hazards model, adjusting for prior CDK4/6i use (yes vs no), and HER2 IHC expression (IHC > 0 < 1+ vs IHC 1+ vs IHC 2+/ISH-) and ties handled by Efron approach.

For the analysis in each subgroup, the hazard ratio and confidence interval were calculated using a Cox proportional hazards model with no stratification and ties handled by Efron approach.

Hazard ratio was not calculated in case of less than 20 events across both treatment groups in a subgroup.

Size of circle is proportional to the number of events.

Grey band represents the 95% confidence interval for the overall (all patients) hazard ratio.

Progression was determined by BICR according to RECIST 1.1.

Primary endocrine resistance was defined as: relapse while on the first 2 years of adjuvant endocrine therapy, or progressive disease within first 6 months of first line endocrine therapy for metastatic breast cancer, while on endocrine therapy. Secondary (acquired) endocrine resistance was defined as: relapse while on adjuvant endocrine therapy but after the first 2 years, or relapse within 12 months of completing adjuvant endocrine therapy, or PD > 6 months after initiating endocrine therapy for metastatic breast cancer, while on endocrine therapy.

Table 32 Summary of Efficacy Outcome Variables in Study DB-06 (ITT Population)

	ITT Population		HER2-low Population		HER2-ultralow Population	
	T-DXd	Chemotherapy	T-DXd	Chemotherapy	T-DXd	Chemotherapy
	(N = 436)	(N = 430)	(N = 359)	(N = 354)	(N = 76)	(N = 76)
Median duration of follow-up (range)	18.6 (0.1, 40.5)	17.8 (0.0, 42.9)	19.0 (0.1, 40.5)	18.3 (0.0, 42.9)	17.2 (3.4, 32.7)	16.1 (0.0, 38.1)
PFS by BICR						
Total progression events, n (%)	269 (61.7)	271 (63.0)	225 (62.7)	232 (65.5)	44 (57.9)	39 (51.3)
Median PFS (95% CI) (months) [a]	13.2 (12.0, 15.2)	8.1 (7.0, 9.0)	13.2 (11.4, 15.2)	8.1 (7.0, 9.0)	13.2 (9.8, 17.3)	8.3 (5.8, 15.2)
HR (95% CI)	0.64 (0.54, 0.76) [b]		0.62 (0.52, 0.75) [c]		0.78 (0.50, 1.21) [b]	
P-value (2-sided)	< 0.0001 [d]		< 0.0001 [e]		NA	
PFS by Investigator						
Total progression events, n (%)	315 (72.2)	341 (79.3)	263 (73.3)	284 (80.2)	52 (68.4)	57 (75.0)
Median PFS (95% CI) (months) [a]	13.1 (11.2, 13.4)	7.0 (6.3, 7.5)	12.8 (11.1, 13.2)	7.0 (6.4, 7.5)	14.6 (9.5, 15.4)	6.8 (4.6, 9.4)
HR (95% CI)	0.51 (0.44, 0.60) [b]		0.50 (0.42, 0.60) [c]		0.60 (0.41, 0.88) [b]	
P-value (2-sided) [nominal]	< 0.0001 [d]		< 0.0001 [f]		NA	
Interim OS						
Total death events, n (%)	161 (36.9)	174 (40.5)	136 (37.9)	146 (41.2)	25 (32.9)	28 (36.8)
Median OS (95% CI) (months) [a]	28.9 (26.4, 32.7)	27.4 (23.9, 29.9)	28.9 (25.7, 33.7)	27.1 (23.5, 29.9)	29.5 (27.9, NE)	27.4 (19.4, NE)
HR (95% CI) [b]	0.81 (0.66, 1.01)		0.83 (0.66, 1.05)		0.75 (0.43, 1.29)	
P-value (2-sided)	NA		0.1299 [g]		NA	
Overall survival rate at 12 months (%)	87.0	81.1	87.6	81.7	84.0	78.7
Overall survival rate at 18 months (%)	74.8	68.7	74.0	69.6	79.5	63.9
ORR by BICR, Logistic Regression Model						
Number (%) of patients with response [h]	268 (61.5)	158 (36.7)	217 (60.4)	134 (37.9)	51 (67.1)	24 (31.6)
Odds ratio (95% CI) [i]	2.76 (2.10, 3.64)		2.51 (1.86, 3.41)		4.42 (2.27, 8.86)	
P-value (2-sided) [nominal]	<0.0001		<0.0001		NA	
Confirmed ORR by BICR, Logistic Regression Model						
Number (%) of patients with response [j]	250 (57.3)	134 (31.2)	203 (56.5)	114 (32.2)	47 (61.8)	20 (26.3)
Odds ratio (95% CI) [i]	2.98 (2.26, 3.94)		2.74 (2.02, 3.73)		4.54 (2.31, 9.20)	
P-value (2-sided) [nominal]	< 0.0001		< 0.0001		NA	
DoR by BICR [k]						
Median (months)	13.7	7.3	13.6	7.3	13.7	11.4
PFS2 [l]						
Number of events (%) [m]	228 (52.3)	278 (64.7)	191 (53.2)	239 (67.5)	37 (48.7)	39 (51.3)
Median PFS2 (95% CI) (months) [a]	20.3 (18.9, 23.8)	14.7 (13.5, 15.9)	20.0 (18.9, 23.8)	14.5 (12.9, 15.5)	20.3 (16.8, 27.9)	16.4 (12.8, 32.3)
HR (95% CI) [b]	0.62 (0.52, 0.74)		0.59 (0.49, 0.72)		0.81 (0.52, 1.28)	
P-value (2-sided) [nominal]	< 0.0001 [d]		< 0.0001 [d]		NA	

[a] Calculated using the Kaplan-Meier technique. CI for median is derived based on Brookmeyer-Crowley method.
[b] The HR and CI were calculated using a Cox proportional hazards model with no stratification factors.
[c] The HR and CI were calculated using a stratified Cox proportional hazards model, adjusting for prior CDK 4/6 inhibitor use (yes vs no) and, HER2 IHC expression (IHC 1+ vs IHC 2+/ISH-) and ties handled by Efron approach. A HR < 1 favors T-DXd to be associated with a longer event time than investigator's choice chemotherapy.
[d] The p-value was calculated using a log-rank test, with no stratification factors.
[e] The p-value was calculated using a stratified log-rank test, adjusting for prior CDK 4/6 inhibitor use (yes vs no) and HER2 IHC expression (IHC 1+ vs IHC 2+/ISH-). A p-value <0.05 is significant.
[f] The p-value was calculated using a stratified log-rank text, adjusting for prior CDK 4/6 inhibitor use (yes vs no), HER2 IHC expression (IHC 1+ vs IHC 2+/ISH-).
[g] The p-value was calculated using a log-rank test, with no stratification factors. A p-value < 0.0046 is significant.
[h] Responses include unconfirmed responses.
[i] An odds ratio > 1 favors T-DXd. The odds ratio in the ITT and HER2-low populations and CI were calculated using a logistic regression model adjusting for prior CDK 4/6 inhibitor use (yes vs no) and HER2 IHC expression (IHC > 0 < 1+ vs IHC 1+ vs IHC 2+/ISH- for ITT, IHC 1+ vs IHC 2+/ISH- for HER2-low) as covariates in the model. No covariates were included for HER2-ultralow population.
[j] Responses include confirmed responses only.
[k] DoR is the time from the first documentation of CR/PR (including unconfirmed response) until the date of first documented progression, or death in the absence of progression. Patients who have not progressed or died are censored at their PFS censoring date. Median calculated using Kaplan-Meier technique.
[l] Second progression is determined by the investigator according to local standard clinical practice.
[m] Patients alive and for whom a second disease progression has not been observed are censored at the earliest of: date of study termination, date last known alive, DCO or, if a patient has not had a first subsequent therapy, the date last known not to have received a first subsequent therapy.
1 month = 30.4375 days.

In the HER2-ultralow population, the median duration of response in study DB-06 was 14.3 months (95% CI: 9.2, 20.7) and 14.1 months (95% CI: 5.9, not estimable) in patients randomised to Enhertu and chemotherapy, respectively.

Figure 19 Progression-free Survival by BICR, Kaplan-Meier plot in the HER2-ultralow Population of Study DB-06

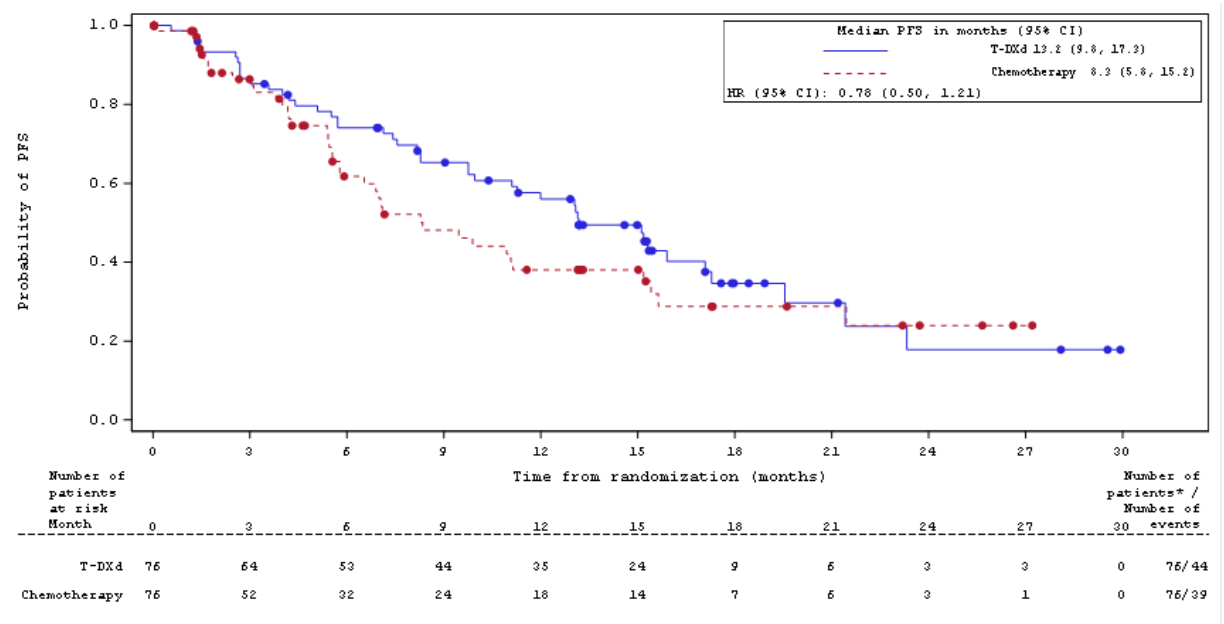
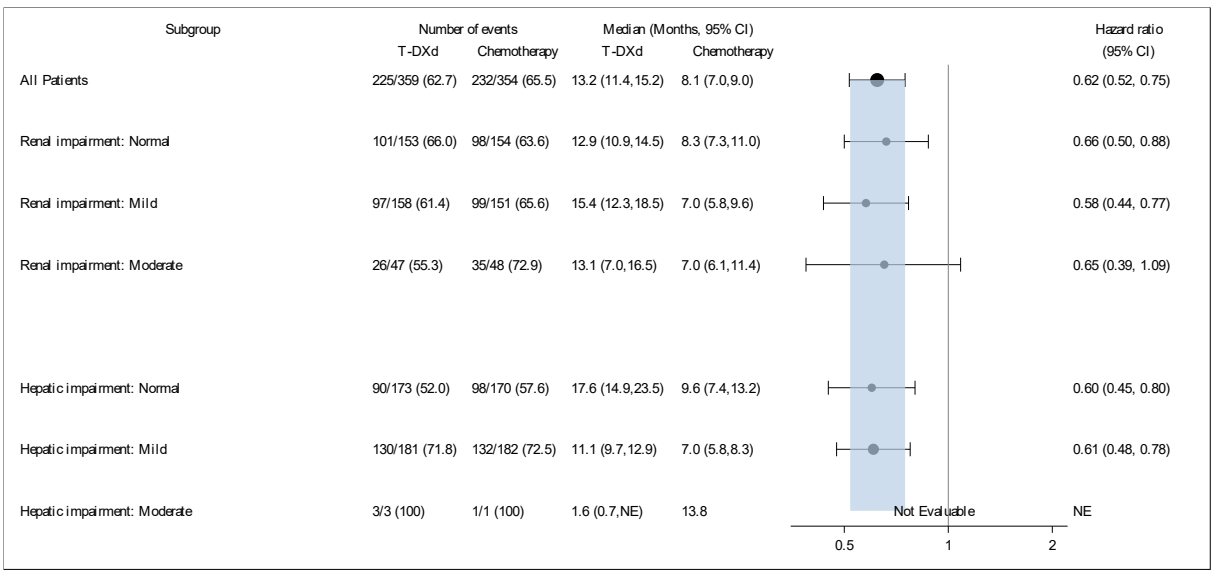
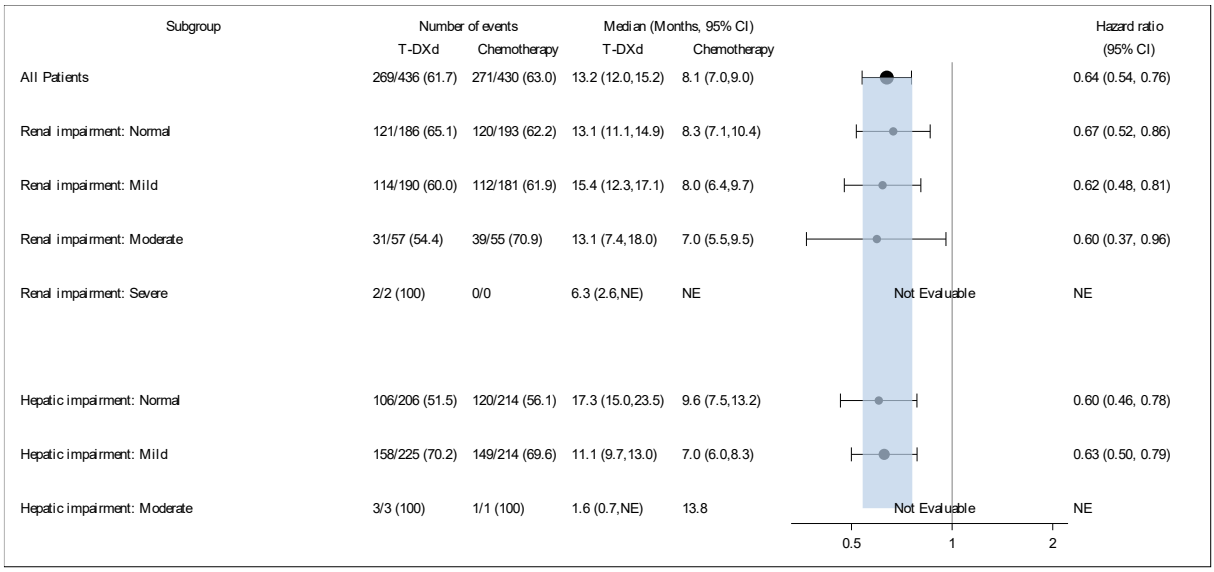


Figure 20 Progression-free Survival by BICR Forest Plot by Renal and Hepatic Impairment Subgroup (HER2-low Population)



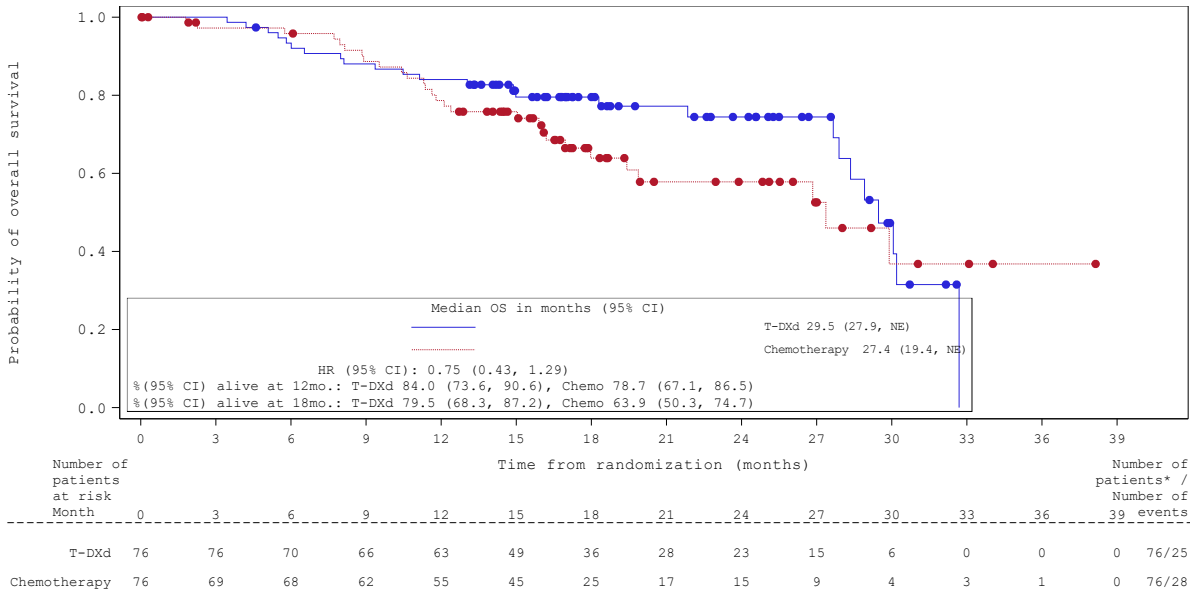
Hazard ratio (T-DXd : investigator's choice chemotherapy), 95% CI for HR. A hazard ratio < 1 favors T-DXd to be associated with a longer PFS than investigator's choice chemotherapy.
For the analysis in each subgroup, the hazard ratio and confidence interval were calculated using a Cox proportional hazards model with no stratification and ties handled by Efron approach.
Hazard ratio is not calculated in case of less than 20 events across both treatment groups in a subgroup. Size of circle is proportional to the number of events.
Grey band represents the 95% confidence interval for the all patients hazard ratio. Progression is determined by BICR according to RECIST 1.1.

Figure 21 Progression-free Survival by BICR Forest Plot by Renal and Hepatic Impairment Subgroup (ITT Population)



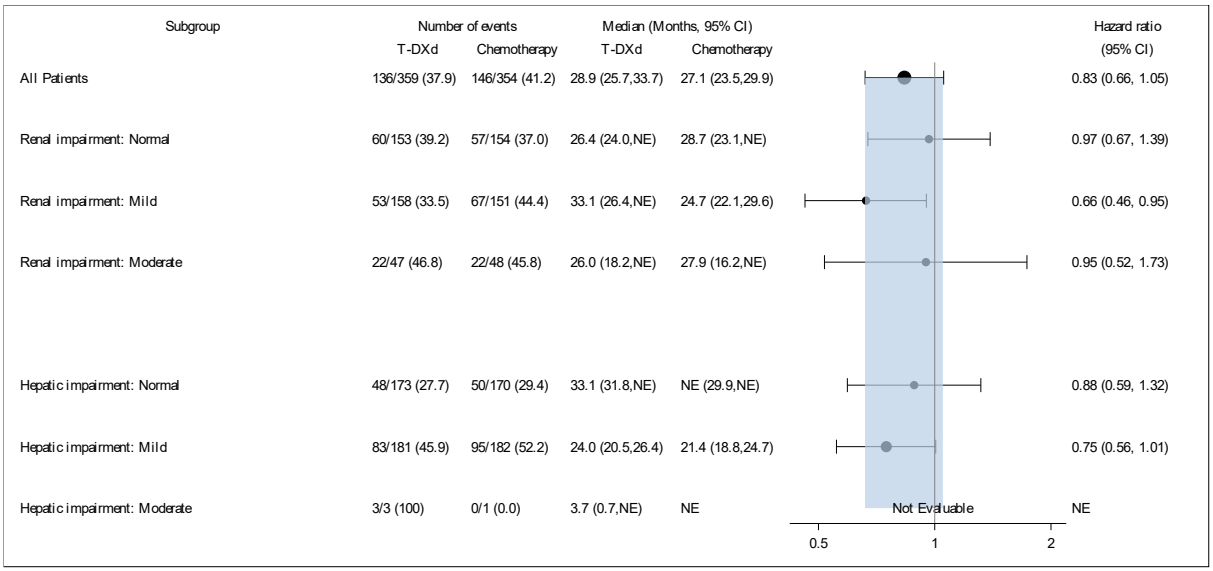
Hazard ratio (T-DXd : investigator's choice chemotherapy), 95% CI for HR. A hazard ratio < 1 favors T-DXd to be associated with a longer PFS than investigator's choice chemotherapy.
For the analysis in each subgroup, the hazard ratio and confidence interval were calculated using a Cox proportional hazards model with no stratification and ties handled by Efron approach.
Hazard ratio is not calculated in case of less than 20 events across both treatment groups in a subgroup. Size of circle is proportional to the number of events.
Grey band represents the 95% confidence interval for the all patients hazard ratio. Progression is determined by BICR according to RECIST 1.1.

Figure 22 Overall survival, Kaplan-Meier plot (HER2-ultralow Population)



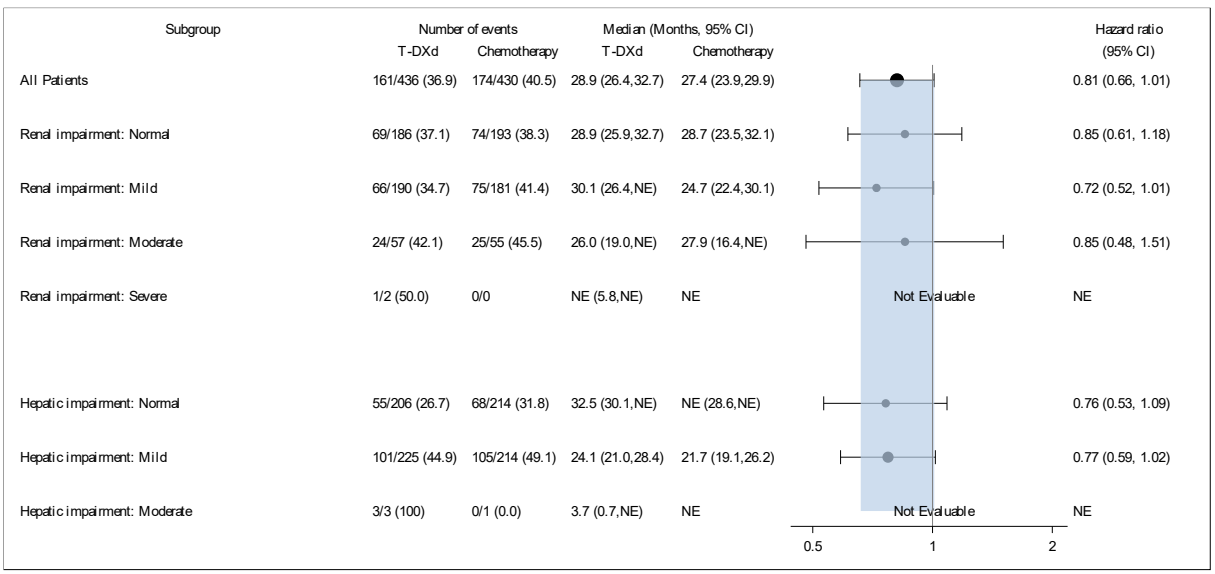
* Number of patients in HER2 IHC > 0 < 1+ population. Circle indicates a censored observation. 2-sided p-value. A p-value < 0.0046 is significant.

Figure 23 Overall Survival Forest Plot by Renal and Hepatic Impairment Subgroup (HER2-low Population)



Hazard ratio (T-DXd : investigator's choice chemotherapy), 95% CI for HR. A hazard ratio < 1 favors T-DXd to be associated with a longer overall survival than investigator's choice chemotherapy.
For the analysis in each subgroup, the hazard ratio and confidence interval were calculated using a Cox proportional hazards model with no stratification and ties handled by Efron approach.
Hazard ratio is not calculated in case of less than 20 events across both treatment groups in a subgroup. Size of circle is proportional to the number of events.
Grey band represents the 95% confidence interval for the all patients hazard ratio.

Figure 24 Overall Survival Forest Plot by Renal and Hepatic Impairment Subgroup (ITT Population)



Hazard ratio (T-DXd : investigator's choice chemotherapy), 95% CI for HR. A hazard ratio < 1 favors T-DXd to be associated with a longer overall survival than investigator's choice chemotherapy.
For the analysis in each subgroup, the hazard ratio and confidence interval were calculated using a Cox proportional hazards model with no stratification and ties handled by Efron approach.
Hazard ratio is not calculated in case of less than 20 events across both treatment groups in a subgroup. Size of circle is proportional to the number of events.
Grey band represents the 95% confidence interval for the all patients hazard ratio.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 33 Summary of Efficacy for trial DB-06

Title: A Phase 3, Randomized, multicenter, Open-label Study of Trastuzumab Deruxtecan (T-DXd) Versus Investigator's Choice Chemotherapy in HER2-low, Hormone Receptor-Positive Breast Cancer Patients whose Disease has Progressed on Endocrine Therapy in the Metastatic Setting (DESTINY-Breast06)			
Study identifier	Study Code: D9670C00001 EudraCT number: 2019-004493-26 NCT Number: NCT04494425		
Design	Study DESTINY-Breast06 (DB-06) was a Phase III, open-label, multi-centre, randomised study to assess the efficacy and safety of trastuzumab deruxtecan (T-DXd) compared with investigator's choice single-agent chemotherapy (capecitabine, paclitaxel, or nab-paclitaxel), in patients with advanced or metastatic breast cancer (BC) with hormone receptor positive, HER2-low or HER2-ultralow expression, and whose disease had progressed after 2 or more lines of prior endocrine therapy in the metastatic setting or after one prior line of endocrine therapy in the metastatic setting, if they progressed within 24 months of the start of adjuvant endocrine therapy or within 6 months of starting first line endocrine therapy in combination with a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor in the metastatic setting.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Treatment until progressive disease, unacceptable toxicity, or withdrawal of consent Not applicable Not applicable
Hypothesis	Superiority: Significant benefit of PFS		
Treatments groups	T-DXd (N=436)		T-DXd: 5.4 mg/kg IV infusion Q3W
	Investigator Choice Chemotherapy (N=430)		Paclitaxel: 80 mg/m^2 IV every week in 3-week cycles Capecitabine: 1000 or 1250 mg/m^2 twice daily orally for 2 weeks followed by a 1-week rest period in 3-week cycles Nab-paclitaxel: 100 mg/m^2 IV every week for 3 weeks followed by a 1-week rest period in 4-week cycles
Endpoints and definitions	Primary endpoint	PFS by BICR in the HER2-low population	Progression-free survival defined as the time from date of randomisation until the date of objective radiological disease progression by BICR according to RECIST 1.1 or death (by any cause in the absence of progression)
	Key Secondary	PFS by BICR in the ITT population	
	Key Secondary	OS in the HER2-low population	Overall survival defined as the time from the date of randomization until death due to any cause regardless of whether the patient withdrew from randomized therapy or received another anticancer therapy (ie, date of death or censoring – date of randomisation + 1).
	Key Secondary	OS in the ITT population	
	Other Secondary	ORR by BICR	Objective response rate defined as the percentage of patients with at least one visit response of CR or PR by BICR using RECIST 1.1

	Other Secondary	DOR by BICR	Duration of response rate defined as the time from date of first detection of objective response until the date of objective radiological disease progression by BICR, per RECIST 1.1 or death in the absence of progression
Database lock	DCO 18 March 2024 for PFS FA/OS IA		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	All efficacy analyses were performed on the FAS (ITT) population* which includes the hormone receptor-positive, HER2-low (IHC 2+/ISH- and IHC 1+) and HER2-ultralow (HER2 IHC > 0 < 1+) population; all randomized patients, including those randomized in error.		

Descriptive statistics and estimate variability	**Treatment group**	**T-DXd**	**Investigator's Choice Chemotherapy**
	ITT Population	**N=436**	**N=430**
	Number of events for PFS	269	271
	Number of events for OS	161	174
	PFS by BICR median (95% CI); months	13.2 (12.0, 15.2)	8.1 (7.0, 9.0)
	HR (95%CI)	0.64 (0.54, 0.76)	
	OS median (95%CI); months	28.9 (26.4 - 32.7)	27.4 (23.9 - 29.9)
	HR (95%CI)	0.81 (0.66, 1.01))	
	Confirmed ORR by BICR N (%) (95%CI)	250 57.3% (52.5%, 62.0%)	134 31.2% (26.8%, 35.8%)
	Confirmed DOR by BICR Median, months (95% CI)	14.3 (12.5, 15.9)	8.6 (6.9, 11.5)
Notes	*Results are only shown for the ITT population, since this is the target population for the sought indication		

Clinical studies in special populations

Table 34 Clinical studies in special populations

	Controlled Trials ITT Population Subjects number /total number (%)	Non-controlled trials.
Renal impairment[a]	114/866 (13.2)	0
Hepatic impairment patients[b]	4/866 (0.5)	0
Paediatric patients <18 years	0/866	0
Age 18-64	599/866 (69.2)	0

	Controlled Trials ITT Population Subjects number /total number (%)	Non-controlled trials.
Age 65-74	195/866 (22.5)	0
Age 75-84	69/866 (8.0)	0
Age 85+	3/866 (0.3)	0
Missing Age	0/866	0

[a] Including moderate and severe renal impairment where moderate renal impairment is serum creatinine clearance ≥ 30 but < 60 mL.min (Stage 3) and severe renal impairment is ≥ 15 but <30 mL/min (Stage 4 and Stage5).
[b] Including moderate and severe hepatic impairment where moderate hepatic impairment is total bilirubin ≥ 1.5 × ULN, ≤ 3.0 × ULN and any AST except for patients with Gilbert syndrome and severe hepatic impairment is total bilirubin ≥ 3.0 × ULN and any AST regardless of Gilbert syndrome

Supportive study

Not applicable.

In vitro biomarker test for patient selection for efficacy

To be eligible for the DB-06 study, patients had to have a history of HER2-negative status (IHC 0 [ISH- or untested], IHC 1+ [ISH- or untested] or IHC 2+/ISH-). However, the inclusion and randomization of patients in study DB-06 was based on prospective central laboratory assessment of HER2-ultralow (IHC > 0 < 1+) or HER2-low (IHC 1+ and IHC 2+/ISH-) status using the PATHWAY/VENTANA anti-HER2 (4B5) IUO assay and an approved HER2 ISH assay per manufacturers requirements for IHC 2+ cases.

The overall historical (local) versus central HER2 concordance data were summarized for cases which had both valid local HER2 test results in the eCRF, and central test results reported and is provided in the below table. HER2 IHC 0 scoring was separated into 2 categories ('IHC 0 absent membrane staining' or 'IHC 0 with membrane staining, described as IHC > 0 < 1+ in DB-06') for central test results but not for local test results since this is not currently part of standard clinical practice though these 2 categories are described within IHC 0 category in ASCO/CAP guidelines (Wolff et al. 2023). Therefore, concordance between local and central scoring for HER2-ultralow (IHC 0 with membrane staining) cannot be provided. Among cases that had a prior historical (local) HER2-low (IHC 1+ or IHC 2+/ISH-) result, 78.7% (999/1270) of cases were determined as HER2-low by central HER2 testing, and this is consistent with what was observed in DB-04 screening as 77.6% (Garrido et al. 2023). Differences in testing methodologies, lack of local pathologist training for determination of HER2 scores in the lower expression end, and intra-patient tumour heterogeneity can contribute to the observed differences between local and central assessment of HER2 expression.

Based on experience with HER2 testing following trastuzumab approval, where local versus central concordance for HER2-positivity scoring showed marked improvements over time (initial discordance for HER2 status of 52.4% was reduced to 8.4% in later studies) (Pfitzner et al. 2018), improvements in HER2-low and HER2-ultralow scoring is anticipated as more pathologists receive training and education, and HER2-low and HER2-ultralow assessment becomes standard routine clinical practice and is included in guidelines. Consistent with this, a study found improvements in HER2-low scoring after training (Ruschoff et al. 2023).

Table 35 Concordance of Local and Central HER2 status in DB-06

HER2 Local		HER2 central						
		IHC 0		IHC 1+	IHC 2+ /ISH-	IHC 2+ /ISH+	IHC 3+	Total
		Absent membrane staining	With membrane staining					
			HER2-ultralow (IHC > 0 < 1+)	HER2-low				
IHC 0		123	140	70	15	1	0	349
IHC 1+	HER2-low	45	146	534	83	1	1	810
IHC 2+ / ISH-		20	50	146	236	6	2	460
IHC 2+/ ISH+		0	2	3	3	0	0	8
IHC 3+		1	1	0	0	0	0	2
Total		189	339	753	337	8	3	1629

During the evaluation, the MAH further clarified the background for the HER2-testing.

Scientific rationale for the choice of the predictive in vitro biomarker test (including the prevalence) and cut-point selection

The primary population of the DESTINY-Breast06 (DB-06) study is the HER2-low population and the MAH therefore decided to use the same in vitro biomarker test i.e. PATHWAY/VENTANA anti-HER2 (4B5) assay, as used in the DESTINY-Breast04 study to select HER2-low BC patients. No substantial molecular differences have been demonstrated between HER2-low and HER2 IHC 0 BC tumours (including both absent membrane staining and with membrane staining cases). It is described in the ESMO expert consensus statement that HER2-low should not be considered a distinct molecular entity (Tarantino et al. 2023). The MAH therefore did not consider HER2-ultralow (IHC 0 with membrane staining), which is part of the HER2 IHC 0 BC tumours, as a distinct molecular entity either, and rather part of a heterogeneous group of tumours with a continuum of different HER2 expression levels from HER2-low to HER2 IHC 0 absent membrane staining, and that these groups can be distinguished by the use of PATHWAY/VENTANA anti-HER2 (4B5) assay.

Regarding the level of HER2 expression detected by the in vitro test, HER2 IHC assays used in clinical practice, including the PATHWAY/VENTANA anti-HER2 (4B5) assay, are optimized to detect overexpression of HER2 and not to detect basal levels of HER2 expression in normal breast tissue. Therefore, any staining detected with the PATHWAY/VENTANA anti-HER2 (4B5) assay, including HER2-ultralow (IHC 0 with membrane staining) indicates higher HER2 expression than in normal breast tissue.

Available clinical data were taken into consideration when selecting the cut-point for HER2 testing. At the time of study DB-06 design, there was limited clinical data on patients treated with T-DXd and classified as IHC 0 (both absent membrane staining and with membrane staining cases), but it was hypothesized that any detectable HER2 expression above that of normal breast tissue, including HER2-ultralow (IHC 0 with membrane staining), was required for a positive benefit/risk balance of T-DXd treatment. Based on the same rationale, those patients with no detectable HER2 staining (IHC 0

absent membrane staining) were not eligible for the study, and the MAH selected the HER2-ultralow cut-off as part of the DB-06 design.

A summary of HER2-low and HER2-ultralow prevalence from literature and screening data from study DB-06 is detailed in the below table. Among studies of primary or metastatic HR+ HER2- BC, approximately 20% to 25% were HER2-ultralow (Chen et al. 2023, Mehta 2024, Viale et al. 2023).

Table 36 HER2-ultralow and HER2-low Prevalence in HER2-negative BC

Data(n)/publication	IHC 0		IHC 1+ and 2+/ISH-
	Absent Membrane Staining	HER2-ultralow[a]	HER2-low
DB-06 Screening Datab HR+/HER2-negative BC[b] (n = 1742)	12.1%	21.8%	65.4%
HR+/HER2-negative BC (n = 1156) (Chen et al 2023)	5.4%	27.7%	66.9%
HER2-negative BC (n = 300) (Mehta 2024)	14% to 16%[c] of HER2-negative	21% to 24% c of HER2-negative	Not applicable
HR+/HER2-negative BC (n = 554) (Viale et al 2023)	17.5%	11.4%	71.1%

[a] IHC 0 with membrane staining

[b] All screened patients had a history of their tumour documented as HER2-negative. The data represents cases which had a valid HER2 status confirmed by central testing and had data entry on local HER2 status. 0.6% of cases were determined as HER2-positive (IHC 2+/ISH+ or IHC3+) by central testing. Source: IEMT 0166, CSR, Module 5.3.5.1.

[c] Assumes HER2 IHC 0 prevalence is 35% to 40% of HER2-negative BC cases and 60% of IHC 0 cases are HER2-ultralow

Analytical method including analytical and clinical validation strategy

Ventana has performed extensive analytical validation of the 4B5 assay for the detection of HER2-ultralow expression, specifically addressing the assay's analytical sensitivity, specificity, and robustness, as well as intra- and inter-instrument, reagent lot, pathologist, and laboratory precision and/or reproducibility for the HER2-ultralow IHC cut-off. All analytical studies, including the reproducibility studies, met Ventana's prespecified acceptance criteria.

In addition, Ventana also conducted tissue characterization studies to evaluate the impact of tumour heterogeneity on the assay performance, including i) a case heterogeneity study to characterize within-case heterogeneity by evaluating staining outcome from multiple blocks from the same subject case, ii) a block heterogeneity study to characterize within-block heterogeneity by evaluating staining outcome from multiple samples from the same tissue block, and iii) a primary vs metastatic tumour comparison study to characterize staining performance of the assay on the primary tumour versus subject-matched metastatic tumour sample.

Validation of the assay in relation to HER2-ultralow also considered sample preparation, including specimen type acceptability, and pre-analytical sample processing. Prior to participating in the study, all clinical sites were provided with guidance on appropriate sample preparation, this guidance was aligned with the VENTANA HER2 (4B5) package insert. The device package insert also detailed the compatible platform and scoring criteria. The clinical validity of the assay was demonstrated by assessing its performance in determining subject eligibility for enrolment in the DB-06 study.

In conclusion, the MAH has sufficiently clarified the scientific rationale for HER2 testing.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy assessment of the applied extension of indication is based on the pivotal study DESTINY-Breast06 (DB-06), which is a phase III randomised open-label two-arm study comparing trastuzumab deruxtecan (T-DXd) head to head with the current SoC in patients who were chemo-naïve and had received 1-2 lines of endocrine therapy (ET) +/- a CDK4/6 Inhibitor or had recurred within 24 months of starting adjuvant treatment. The proposed dosing regimen of 5.4 mg/kg IV Q3W is the same used for T-DXd in the approved breast cancer indications. Single-agent chemotherapy of Physician's choice (capecitabine, nab-paclitaxel or paclitaxel) used in the control arm is considered acceptable. Patients were randomised 1:1 to receive either T-DXd 5.4 mg/kg (N=436) IV Q3W or physician's choice of single-agent chemotherapy (N=430, capecitabine 60%, nab-paclitaxel 24%, or paclitaxel 16%). According to the MAH, anthracyclines were not considered an appropriate choice for the comparator arm due to the cumulative risk of cardiotoxicity associated with these agents, which limits treatment duration. Moreover, given the DB-06 study design, which entails treatment continuation until progression of disease, and the use of anthracyclines in the neoadjuvant/adjuvant setting, which also limits their use in the metastatic setting, it was considered that the use of anthracyclines as a choice of comparator would not be appropriate due to the maximum lifetime cumulative dose cap of these agents, potentially excluding patients from enrolling into the trial according to the MAH. Considering that baseline characteristics from the pivotal study showed that ~45-47% of the included patients have had prior anthracyclines (see section 5.1 of the SmPC), this precautionary measure of precluding this option may not have been necessary as more than half of patients could have received anthracyclines without safety concerns. The beneficial effect of T-DXd in patients who did not yet receive anthracyclines in the (neo-) adjuvant setting remains therefore uncertain. However, the MAH's justification is acknowledged. The study excluded patients with prior chemotherapy for advanced or metastatic disease, patients with a history of ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening, uncontrolled or significant cardiovascular disease, untreated and symptomatic brain metastases, or ECOG performance status >1. The exclusion criteria are similar to previous Enhertu studies and adequately described in section 5.1 of the SmPC.

T-DXd remains approved under a conditional marketing authorisation with the outstanding specific obligations to be fulfilled pertaining to of the approved indications in the gastric cancer and NSCLC setting. As the data submitted with the current variation application are considered comprehensive, no new specific obligation is being imposed.

A sample size of 866 patients randomized 1:1 to the two treatment arms is considered acceptable.

The current DCO was at the time of the final analysis of PFS and at the first interim analysis (IA) of overall survival (OS).

After the initial release (v1.0, 20 March 2020), and although the study protocol was amended 4 times, the protocol amendments do not appear to have had a major impact on the study outcome.

Baseline characteristics showed that the median age was ~58 years with ~69% of the patients being less than 65 years old and ~31% of the patients were ≥65 years, which is reflective of the targeted patient population. One male patient was included in the control arm (chemotherapy), which is acceptable since breast cancer is rare in men. The results from the pivotal trial are considered extrapolatable to men with HER2-low and ultralow metastatic breast cancer based on the common

biological and pharmacological rationale and in line with previous EMA decisions for T-DXd and other HER2-targeted treatments (e.g. trastuzumab). Most patients were White (~53%) or Asian (~35%), which was equally distributed between the arms. Hence, the fraction of patients representative of the EU population is considered acceptable for interpretation of the study results. Patients were most often of good ECOG Performance status (PS), and either of ECOC PS 0 (~60%) or ECOG PS 1, and the majority had tumours with HER2 expression on ICH of 1+ (~54%) or IHC2+/ISH- (~27%), which are both categorised as HER2-low, while only 17% were HER2-ultralow (IHC>0<1+). Approximately one third of patients had tumours with primary endocrine resistance, while the remaining had secondary endocrine resistance. 67% of patients had liver metastases, 32% had lung metastases, 8% had brain metastases, and 3% had bone-only metastases.

Prior lines of therapy were equally distributed between the treatment arms and in line with the inclusion criteria and the wording of the claimed therapeutic indication i.e. '*Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HR+ HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment (see sections 4.2 and 5.1)*'). Overall, the eligibility criteria adequately define the target population in need for chemotherapy, with the general note that the clinical trial population is considered healthier than the population treated in clinical practice. The wording of the indication initially applied for generally reflected the included study population, except for the additional specifications on rapid progression in case patients received only 1 line of ET in the metastatic setting. Due to concern that patients could be treated with Enhertu after only one line of ET in the metastatic setting in a broader sense, the wording of the indication was amended during the evaluation to include patients who are not considered suitable for endocrine therapy (ET) as the next line of treatment.

The primary objective of study DB-06 was to compare PFS benefit by blinded independent review (BICR) in the HER2-low population, and in the ITT population. OS in the HER2-low population and in the ITT population were secondary endpoints. The ITT comprises both the HER2-low and the HER2-ultralow populations. Other secondary efficacy endpoints were ORR, DoR, PFS by investigator and PFS2. The primary and secondary endpoints are considered acceptable and established in the current disease setting.

Efficacy data and additional analyses

The primary endpoint of **PFS by BICR assessment in the HER2-low population** was met and showed a statistically significant and clinically relevant improvement of 5.1 months from 8.1 months with chemotherapy to 13.2 months with T-DXd, HR 0.62 (95%CI: 0.52; 0.75). The data is considered mature with more than 60% events in both arms after a median duration of follow up of 19 months in the T-DXd arm and 18.3 months in the chemotherapy arm. The KM curves for PFS by BICR separates early and stay separated, so further updates are unlikely to change the benefit significantly due to the high number of events in both arms, although a third of the patients are censored. The sensitivity analyses provided support the primary analysis of PFS by BIRC.

The performance of the control arm is considered in line with what can be expected, as the median PFS with single-agent chemotherapy is approximately 6 to 7 months in patients who received 0 to 1 prior lines of chemotherapy in patients with advanced breast cancer, who has progressed on multiple lines of endocrine therapy +/- targeted therapy or has progressed rapidly on prior adjuvant or first-line endocrine therapy (O'Shaughnessy at al 2021, Robert at al. 2011). All of the included patients were chemotherapy-naïve in the metastatic setting and were less pre-treated, therefore the performance of the control arm is considered acceptable in this context.

The secondary endpoint of **OS in the HER2-low population** showed that, with ~40% of events at the time the first IA ,the median OS was 28.9 months in the T-DXd arm vs 27.1 months in the control arm; HR of 0.83 (95%CI: 0.66; 1.05). The KM curves for OS do not clearly separate but there is no sign of a detrimental effect. Considering that the targeted patient population are likely to have a relatively long OS and will receive further lines of treatment, this OS result is considered sufficient to grant an approval in the claimed indication as any future detriment on OS is considered unlikely. The interim results of OS in the ITT population were comparable to that of the HER2-low population, i.e. the median OS was 28.9 months (95%CI: 26.4, 32.7) for T-DXd and 27.4 months (95%CI: 23.9, 29.9) for chemotherapy (HR: 0.81; 95%CI: 0.66, 1.01). The next IA of OS is planned at 75% events and is expected around April 2025. The MAH is recommended to submit the results of the next interim OS analysis data as well as the final OS analysis data from study DB-06 when available (Recommendation (REC)).

PFS by BICR assessment in the **ITT** population also showed a statistically significant and clinically relevant improvement of 5.1 months from 8.1 months with chemotherapy to 13.2 months with T-DXd, HR 0.64 (95%CI: 0.54, 0.76). The KM curves also separates early and stay separated, so these results support the claimed indication for the ITT population, which includes both the HER2-low and the HER2-ultralow populations.

Since **OS in the HER2-low population** was not statistically significant, the OS analysis in the ITT population was not tested according to the testing hierarchy, which is considered acceptable. PFS by INV assessment in the HER2-low population showed slightly better results than for the ITT population.

Confirmed **ORR by BICR in the HER2-low population**, which was clinically and statistically significantly improved from 32.2% in the control arm to 56.5% with T-DXd. Complete responses (CR by BICR) were observed in 2.5% of the patients in the T-DXd arm and 0 patients in the chemotherapy arm, while the partial response (PR) was observed in 54.0% on T-DXd vs 32.2% for chemotherapy. The median duration of response (DoR) by BICR was longer for patients in the T-DXd arm i.e. 14.1 months vs 8.6 months with chemotherapy. These results are in line with the primary analysis of PFS and the improved ORR and DoR results are considered clinically relevant as a higher chance of a durable response is a key goal in the management of the targeted patient population with advanced progressive disease.

Confirmed **ORR by BICR in the ITT** population was clinically and statistically significantly improved from 31.2% in the control arm to 57.3% with T-DXd. CR was observed in 3.0% of the patients with T-DXd and 0 patients in the chemotherapy arm, while the rate of PR was 54.4% with T-DXd vs 31.2% in the chemotherapy arm. The median DoR by BICR was also longer for patients in the T-DXd arm i.e. 14.3 months vs 8.6 months with chemotherapy, which is in line with the primary analysis of PFS and the improved ORR and DoR results in the ITT population are considered supportive of the claimed indication.

In the absence of fully mature OS data, the provided **PFS2 results from the ITT population** are considered clinically important. The median PFS2 in the T-DXd arm was 20.3 months vs 14.7 months in the chemotherapy arm, HR 0.61 (95%CI: 0.51; 0.73), with the KM curves separating early and staying separated, so the patients on T-DXd have a longer time to the second progression on next-line therapy. This is considered reassuring and indicates that any detriment on OS is unlikely.

Considering the open-label design of the pivotal DB-06 study, the **patient-reported outcomes** should be interpreted with caution and are therefore not reflected in section 5.1 of the SmPC. No firm conclusion can be drawn and the conclusions in the safety section are considered more important in relation to the tolerability of T-DXd.

The **subgroup analyses** of PFS by BIRC in the ITT population are considered the most relevant for the sought indication, considering that the primary endpoint was PFS by BICR in the HER2-low population. The ITT population consists of both the HER2-low and the HER2-ultralow populations, and the subgroup analysis for both populations combined show that all of the point estimates are on the right side of one except for a small subgroup of those who were from the region of North America (HR 1.02 (95%CI: 0.60;1.74), N=80). This is not concerning as the point estimate is very close to one, no detrimental effect is observed and this may be due to a chance finding. Overall, the PFS benefit observed across the following prespecified subgroups, including HER2 expression, prior CDK4/6 inhibitor use (yes or no), prior taxane use in the non-metastatic setting (yes or no), and number of prior lines of endocrine therapy in the metastatic setting was in line with the primary analysis. Subgroup analyses based on renal and hepatic impairment have also been provided during the evaluation and these analyses support a beneficial effect independent of renal/hepatic impairment. No patients with severe renal impairment or moderate/severe hepatic impairment were included in the study.

The subgroup analysis of the **HER2-ultralow population** showed a median PFS of 13.2 months in patients who had T-DXd (N=76) versus 8.3 months in the control arm, HR 0.78 (95%CI: 0.50, 1.21). It is acknowledged that although this result is not statistically significant, the difference in PFS benefit observed is very similar to the primary analysis of the primary endpoint, and the numerical difference of 4.9 months is considered clinically relevant. The limited sample size of the HER2-ultralow population of 152 patients in total hampers the robustness of the results and is considered the reason for the not statistically significant results. However, the efficacy results from this subgroup is considered clinically relevant and the close similarity to the PFS, ORR and DoR and the PFS results from the HER2-low and the ITT populations are considered compelling, it is therefore concluded that T-DXd has similar and clinically relevant efficacy in the HER2-ultralow population as well. To conclude, it is considered acceptable to grant an indication of T-DXd for both the HER2-low and the HER2-ultralow populations, meaning the ITT population in study DB-06.

2.4.4. Conclusions on the clinical efficacy

The results from the pivotal study DB-06 show a statistically significant and clinically relevant superior efficacy of trastuzumab deruxtecan (T-DXd) compared to single-agent chemotherapy of Physician's choice regarding PFS by BIRC and INV, response rate, duration of response in the ITT population. Partly mature OS and PFS2 data indicates that any detriment on OS is unlikely and more mature OS data will be provided post-approval (REC).

To conclude, the efficacy of Enhertu as monotherapy is considered established for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment.

2.5. Clinical safety

Introduction

The current safety assessment is based on data from the pivotal study DESTINY-Breast06 (DB-06) (n=434 received T-DXd) and 2 safety pools: a BC Pool, comprising 1741 patients exposed to T-DXd from 7 studies. All Tumour Type (ATT) Pool, comprising 2335 patients exposed to T-DXd from 11

studies. The studies included in both pools evaluated safety and tolerability of T-DXd 5.4 mg/kg Q3W across stage and line of treatment.

The used data cut-off date for study DB-06 was 18 March 2024. Median (range) duration of follow-up of censored patients in the ITT population was 15.3 months in the T-DXd and 7.2 months in the chemotherapy arm.

Table 37 Summary of Clinical Studies constituting the All Tumour Type (ATT) Pool

Study Number (Study Name) Phase Status [a]	**Data Cut-off Date**	**Study Title**	**Number of Patients Treated with T-DXd 5.4 mg/kg or Active Control**
Breast Cancer			
D9670C00001 (DESTINY-Breast06; DB-06) Phase III Completed	18 Mar 2024	A Phase 3, Randomized, Multi-center, Open-label Study of Trastuzumab Deruxtecan (TDXd) Versus Investigator's Choice Chemotherapy in HER2-low, Hormone Receptor-positive Breast Cancer Patients whose Disease has Progressed on Endocrine Therapy in the Metastatic Setting	434 T-DXd 417 Chemotherapy
DS8201-A-U201 (DESTINY-Breast01; DB-01) Phase II Completed	08 Jun 2020	A Phase 2, Multicenter, Open-label Study of DS-8201a, an Anti-HER2-antibody Drug Conjugate (ADC), for HER2-positive, Unresectable and/or Metastatic Breast Cancer Subjects Previously Treated with T-DM1	184 T-DXd
DS8201-A-U301 (DESTINY-Breast02; DB-02) Phase III Completed	30 Jun 2022	A Phase 3, Multicenter, Randomized, Open-label, Active-controlled Study of Trastuzumab Deruxtecan (DS-8201A), an Anti-HER2-antibody Drug Conjugate, versus Treatment of Investigator's Choice for HER2-positive, Unresectable and/or Metastatic Breast Cancer Subjects Previously Treated with T-DM1	404 T-DXd 195 TPC
DS8201-A-U302 (DESTINY-Breast03; DB-03) Phase III Completed	25 Jul 2022	A Phase 3, Multicenter, Randomized, Open-label, Active-controlled Study of Trastuzumab Deruxtecan (DS-8201a), an Anti-HER2-antibody Drug Conjugate, versus Trastuzumab Emtansine (T-DM1) for HER2-positive, Unresectable and/or Metastatic Breast Cancer Subjects Previously Treated with Trastuzumab and Taxane	257 T-DXd 261 T-DM1
DS8201-A-U303 (DESTINY-Breast04; DB-04) Phase III Completed	11 Apr 2022	A Phase 3, Multicenter, Randomized, Open-label, Active-controlled Trial of Trastuzumab Deruxtecan (T-DXd), an Anti-HER2-antibody Drug Conjugate (ADC), versus Treatment of Physician's Choice for HER2-low, Unresectable and/or Metastatic Breast Cancer Subjects	371 T-DXd 172 TPC
NSCLC			
DS8201-A-U204 (DESTINY-Lung01; DL-01) Phase II Completed	03 Dec 2021	A Phase 2, Multicenter, Open-label, 2-cohort Study of Trastuzumab Deruxtecan (DS-8201a), an Anti-HER2-antibody Drug Conjugate (ADC), for HER2-overexpressing or -mutated, Unresectable and/or Metastatic Non-small Cell Lung Cancer (NSCLC)	41 T-DXd

Table 37 Summary of Clinical Studies constituting the All Tumour Type (ATT) Pool

Study Number (Study Name) Phase Status [a]	Data Cut-off Date	Study Title	Number of Patients Treated with T-DXd 5.4 mg/kg or Active Control
DS8201-A-U206 (DESTINY-Lung02; DL-02) Phase II Completed	23 Dec 2022	A Phase 2, Multicenter, Randomized Study of Trastuzumab Deruxtecan in Subjects with HER2-mutated Metastatic Non-small cell Lung Cancer (NSCLC)	101 T-DXd
Solid Tumors			
DS8201-A-J101 Phase I Completed	01 Aug 2019	Phase 1, Two-part, Multicenter, Non-randomized, Open-label, Multiple-dose, First-in-human Study of DS-8201a, in Subjects with Advanced Solid Malignant Tumors	91 T-DXd
D967MC00001 (DESTINY-PanTumor01; DP-01) Phase II Completed	25 Jan 2023	A Phase 2, Multicenter, Open-label Study to Evaluate the Efficacy and Safety of T-DXd for the Treatment of Unresectable and/or Metastatic Solid Tumors Harboring HER2-activating Mutations Regardless of Tumor Histology	102 T-DXd
D967VC00001 (DESTINY-PanTumor02; DP-02) Phase III Completed	08 Jun 2023	A Phase 2, Multicenter, Open-label Study to Evaluate the Efficacy and Safety of T-DXd (DS-8201a) for the Treatment of Selected HER2-expressing Tumors	267 T-DXd
Colorectal Cancer			
DS8201-A-U207 (DESTINY-CRC02; DC-02) Phase II Completed	01 Nov 2022	A Phase 2, Multicenter, Randomized Study of Trastuzumab Deruxtecan in Subjects with HER2-overexpressing Locally Advanced, Unresectable or Metastatic Colorectal Cancer	83 T-DXd

A study was defined as completed if the analyses for the primary objective had been performed.

Table 38 Number of Patients in the Safety Pools

Study	Number of Patients Treated	
	T-DXd 5.4 mg/kg All BC Pool	T-DXd 5.4 mg/kg All Tumor Types Pool
Total	**1741**	**2335**
DB-06	434	434
DB-01	184	184
DB-02	404	404
DB-03	257	257
DB-04	371	371
DL-01	NA	41
DL-02	NA	101

Table 38 Number of Patients in the Safety Pools

Study	Number of Patients Treated	
	T-DXd 5.4 mg/kg All BC Pool	T-DXd 5.4 mg/kg All Tumor Types Pool
DP-01	20	102
DP-02	NA	267
J101	71	91
DC-02	NA	83

Patient exposure

Table 39 Summary of Exposure (Safety Analysis Set)

	Number (%) of Patients			
	Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
Duration of treatment (months) [a]				
Mean	12.12	7.58	12.96	11.49
Std Dev	7.636	6.312	9.166	8.865
Median	11.02	5.62	10.58	8.97
Minimum, maximum	0.4, 39.6	0.1, 35.9	0.2, 45.1	0.2, 45.1
Duration of treatment category, n (%) [a]				
0 to ≤ 3 months	48 (11.1)	121 (29.0)	212 (12.2)	406 (17.4)
> 3 to ≤ 6 months	63 (14.5)	100 (24.0)	263 (15.1)	391 (16.7)
> 6 to ≤ 9 months	61 (14.1)	71 (17.0)	267 (15.3)	375 (16.1)
> 9 to ≤ 12 months	62 (14.3)	37 (8.9)	217 (12.5)	273 (11.7)
> 12 to ≤ 18 months	114 (26.3)	53 (12.7)	304 (17.5)	370 (15.8)
> 18 to ≤ 24 months	50 (11.5)	26 (6.2)	245 (14.1)	273 (11.7)
> 24 months	36 (8.3)	9 (2.2)	233 (13.4)	247 (10.6)
Number of cycles				
Mean	16.6	9.9	17.7	15.7
Std Dev	10.48	8.49	12.49	12.06
Median	15.0	8.0	14.0	12.0
Minimum, maximum	1, 56	1, 49	1, 60	1, 60
Number of cycles category, n (%)				
≤ 6 cycles	83 (19.1)	182 (43.6)	347 (19.9)	619 (26.5)
> 6 to ≤ 12 cycles	91 (21.0)	116 (27.8)	398 (22.9)	553 (23.7)
> 12 to- ≤ 18 cycles	85 (19.6)	55 (13.2)	298 (17.1)	384 (16.4)
> 18 to ≤ 24 cycles	84 (19.4)	33 (7.9)	225 (12.9)	265 (11.3)
> 24 to ≤ 30 cycles	43 (9.9)	15 (3.6)	177 (10.2)	200 (8.6)
> 30 cycles	48 (11.1)	16 (3.8)	296 (17.0)	314 (13.4)
Total patient-years of exposure [b]	438.5	263.5	1880.2	2235.2
Relative dose intensity (%) [c]				

	Number (%) of Patients			
	Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
Mean	92.90	87.54	96.87	96.01
Std Dev	11.072	15.494	8.057	9.155
Median	97.76	91.50	99.70	99.48
Minimum, maximum	45.1, 111.3	39.1, 131.9	45.1, 111.3	45.1, 199.6
Relative dose intensity category, n (%)				
≥ 90%	312 (71.9)	216 (51.8)	1542 (88.6)	1977 (84.7)
< 90% to ≥ 80%	66 (15.2)	66 (15.8)	105 (6.0)	189 (8.1)
< 80% to ≥ 60%	46 (10.6)	106 (25.4)	77 (4.4)	148 (6.3)
< 60%	10 (2.3)	23 (5.5)	17 (1.0)	21 (0.9)

[a] Duration of treatment (months) = (date of the last dose - date of the first dose + 1+ C days) / 30.44, where C = (scheduled number of days between doses - 1) and. 1 month = 365.25 / 12 = 30.44 days.

[b] Total patient-years of exposure = sum of duration of treatment (months) / 12.

[c] RDI derivation/definition for each study follows the study convention specified in CSR SAPs. RDI is the percentage of the actual dose intensity delivered relative to the intended dose intensity through treatment discontinuation. Actual treatment duration = total treatment duration, excluding duration of dose delays.

Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.
The pooled analysis group is based on tumor type and first dose received for patients in each study.

Adverse events

Table 40 Overview of Treatment-emergent Adverse Events (Safety Analysis Set)

	Number (%) of Patients			
	Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
Patients with any TEAE	429 (98.8)	397 (95.2)	1730 (99.4)	2317 (99.2)
TEAE with CTCAE Grade ≥ 3	229 (52.8)	185 (44.4)	941 (54.0)	1280 (54.8)
TEAE associated with an outcome of death	11 (2.5)	6 (1.4)	56 (3.2)	96 (4.1)
TEAE associated with study drug discontinuation	62 (14.3)	39 (9.4)	307 (17.6)	376 (16.1)
TEAE associated with study drug interruption	210 (48.4)	160 (38.4)	794 (45.6)	1039 (44.5)
TEAE associated with dose reduction	107 (24.7)	161 (38.6)	417 (24.0)	532 (22.8)
Drug-related TEAE	417 (96.1)	373 (89.4)	1689 (97.0)	2208 (94.6)
Drug-related TEAE with CTCAE Grade ≥ 3	176 (40.6)	131 (31.4)	750 (43.1)	971 (41.6)
Drug-related TEAE associated with an outcome of death	5 (1.2)	0	20 (1.1)	28 (1.2)
Drug-related TEAE associated with study drug discontinuation	56 (12.9)	33 (7.9)	266 (15.3)	317 (13.6)
Drug-related TEAE associated with study drug interruption	127 (29.3)	103 (24.7)	563 (32.3)	688 (29.5)
Drug-related TEAE associated with dose reduction	94 (21.7)	155 (37.2)	383 (22.0)	489 (20.9)
Treatment-emergent SAE	88 (20.3)	67 (16.1)	429 (24.6)	652 (27.9)
SAE with CTCAE Grade ≥ 3	68 (15.7)	54 (12.9)	332 (19.1)	522 (22.4)
SAE associated with an outcome of death	11 (2.5)	6 (1.4)	56 (3.2)	96 (4.1)
SAE associated with study drug discontinuation	24 (5.5)	11 (2.6)	105 (6.0)	134 (5.7)
SAE associated with study drug interruption	24 (5.5)	27 (6.5)	133 (7.6)	203 (8.7)
SAE associated with dose reduction	12 (2.8)	8 (1.9)	48 (2.8)	73 (3.1)
Drug-related SAE	46 (10.6)	24 (5.8)	208 (11.9)	281 (12.0)
Drug-related SAE with CTCAE Grade ≥ 3	35 (8.1)	19 (4.6)	144 (8.3)	203 (8.7)
Drug-related SAE associated with an outcome of death	5 (1.2)	0	20 (1.1)	28 (1.2)
Drug-related SAE associated with study drug discontinuation	21 (4.8)	7 (1.7)	81 (4.7)	94 (4.0)
Drug-related SAE associated with study drug interruption	8 (1.8)	6 (1.4)	46 (2.6)	62 (2.7)
Drug-related SAE associated with dose reduction	10 (2.3)	6 (1.4)	38 (2.2)	60 (2.6)

Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.

Table 41 Adverse Events Reported in ≥ 10% of Patients in Either Treatment Arm of Study DB-06, by Preferred Term (Safety Analysis Set)

	Number (%) of Patients			
	Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
Patients with any TEAE	429 (98.8)	397 (95.2)	1730 (99.4)	2317 (99.2)
Nausea	303 (69.8)	126 (30.2)	1294 (74.3)	1660 (71.1)
Alopecia	210 (48.4)	87 (20.9)	729 (41.9)	844 (36.1)
Anaemia	159 (36.6)	107 (25.7)	598 (34.3)	825 (35.3)
Diarrhoea	148 (34.1)	114 (27.3)	529 (30.4)	703 (30.1)
Vomiting	146 (33.6)	49 (11.8)	713 (41.0)	870 (37.3)
Constipation	137 (31.6)	62 (14.9)	594 (34.1)	741 (31.7)
Aspartate aminotransferase increased	117 (27.0)	44 (10.6)	394 (22.6)	476 (20.4)
Fatigue	117 (27.0)	83 (19.9)	587 (33.7)	753 (32.2)
Decreased appetite	114 (26.3)	48 (11.5)	529 (30.4)	715 (30.6)
COVID-19	106 (24.4)	52 (12.5)	209 (12.0)	282 (12.1)
Asthenia	99 (22.8)	71 (17.0)	342 (19.6)	462 (19.8)
Neutrophil count decreased	99 (22.8)	66 (15.8)	397 (22.8)	506 (21.7)
Alanine aminotransferase increased	93 (21.4)	48 (11.5)	317 (18.2)	388 (16.6)
White blood cell count decreased	79 (18.2)	53 (12.7)	324 (18.6)	384 (16.4)
Neutropenia	76 (17.5)	63 (15.1)	264 (15.2)	343 (14.7)
Headache	74 (17.1)	42 (10.1)	319 (18.3)	370 (15.8)
Cough	69 (15.9)	38 (9.1)	262 (15.0)	325 (13.9)
Platelet count decreased	61 (14.1)	15 (3.6)	296 (17.0)	385 (16.5)
Stomatitis	57 (13.1)	37 (8.9)	228 (13.1)	287 (12.3)
Hypokalaemia	56 (12.9)	15 (3.6)	201 (11.5)	271 (11.6)
Pyrexia	52 (12.0)	30 (7.2)	223 (12.8)	293 (12.5)
Dysgeusia	51 (11.8)	24 (5.8)	157 (9.0)	182 (7.8)
Dyspepsia	50 (11.5)	20 (4.8)	202 (11.6)	245 (10.5)
Blood alkaline phosphatase increased	48 (11.1)	17 (4.1)	165 (9.5)	193 (8.3)
Abdominal pain	45 (10.4)	35 (8.4)	199 (11.4)	266 (11.4)
Epistaxis	44 (10.1)	15 (3.6)	187 (10.7)	213 (9.1)
Oedema peripheral	36 (8.3)	59 (14.1)	146 (8.4)	186 (8.0)
Arthralgia	32 (7.4)	45 (10.8)	188 (10.8)	223 (9.6)
Peripheral sensory neuropathy	12 (2.8)	49 (11.8)	82 (4.7)	100 (4.3)
Palmar-plantar erythro-dysaesthesia syndrome	4 (0.9)	146 (35.0)	25 (1.4)	28 (1.2)

Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.

Table 42 Adverse Events of CTCAE Grade 3 or Higher Reported in ≥ 5% of Patients in Either Treatment Arm in Study DB-06, by Preferred Term (Safety Analysis Set)

	Number (%) of Patients			
	Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
Patients with any TEAE Grade ≥ 3	229 (52.8)	185 (44.4)	941 (54.0)	1280 (54.8)
Neutrophil count decreased	60 (13.8)	36 (8.6)	208 (11.9)	268 (11.5)
Anaemia	38 (8.8)	18 (4.3)	158 (9.1)	245 (10.5)
Neutropenia	37 (8.5)	35 (8.4)	122 (7.0)	160 (6.9)
White blood cell count decreased	25 (5.8)	20 (4.8)	102 (5.9)	117 (5.0)
Palmar-plantar erythro-dysaesthesia syndrome	0	31 (7.4)	1 (0.1)	1 (0.0)

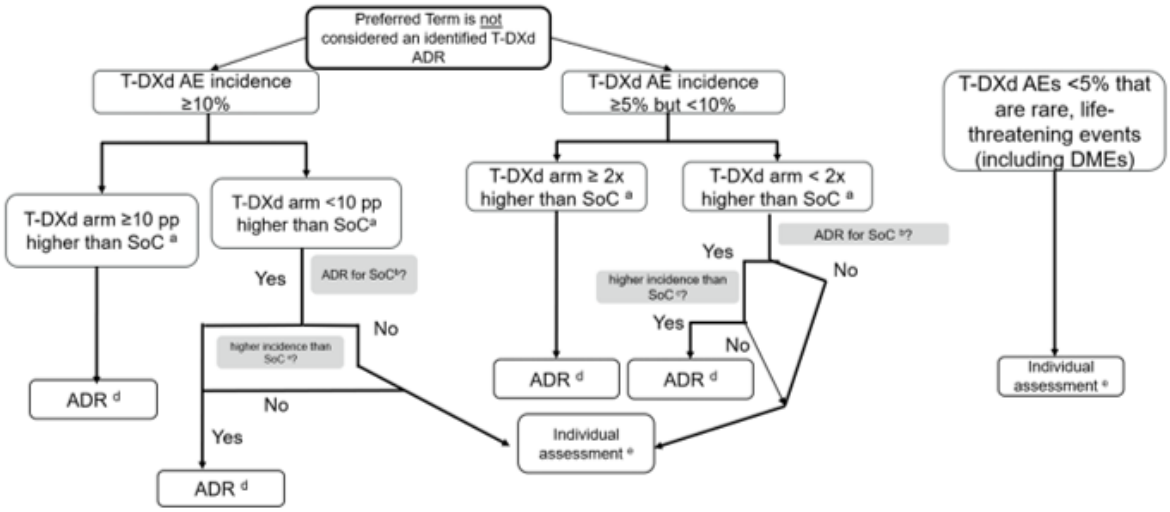
Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.
The pooled analysis group is based on first dose received for patients in each study.
PTs are sorted by descending frequency in the Study DB-06 T-DXd 5.4 mg/kg treatment arm.
If a patient had multiple occurrences of the same PT, the patient is counted once for the specific PT.
If a patient had multiple PTs, the patient is counted in each of the different PTs.

Adverse Drug Reactions

As ADR determination methodology, the MAH analysed systematically all-causality TEAEs from study DB-06. The MAH applied quantitative criteria to look for an imbalance in the incidence of TEAEs between treatment groups, examined pre-existing ADRs for changes in characteristics, and performed medical review of all ADR candidates including rare or life-threatening events. Events that were already identified as a T-DXd program-wide ADR continued to be classified as an ADR and TEAEs from study DB-06 were initially classified into 3 categories by incidence. Any imbalances observed between the T-DXd and Chemotherapy arms were meticulously assessed. In addition, the MAH reviewed laboratory and clinical measurements for any additional ADRs by looking at aspects such as trends, medians, means, and range of values. Through these various considerations, the MAH determined which TEAEs are considered an ADR. Relevant safety data from nonclinical studies, other clinical studies, class-effects, and AESIs (ILD/pneumonitis and LV dysfunction) were examined as well. This determination process was subjected to individual assessment based on frequency and severity of the events and/or evaluation of confounding factors and causality.

As a consequence of the updated All Tumour Type (ATT) Pool, the frequency of the following ADRs has been revised in section 4.8 of the SmPC: for lymphopenia, dizziness, dyspnoea and epistaxis from 'very common' to 'common', and for febrile neutropenia from 'uncommon' to 'common'.

Figure 25 Methodology of Adverse Drug reaction Determination in Study DB-06



Determination was based on the review for individual events.

[a] Comparators grouped to determine AE incidence (SoC = standard of care).

[b] Individual assessment if ADR not listed as an ADR for comparator.

[c] Product labels of each comparator assessed.

[d] If evidence suggest that the event is due to the underlying disease/alternative etiology, it may be determined as not as an ADR.

[e] If there is reasonable possibility of a causal relationship between the event and study drug, it may be determined as an ADR.

Table 43 Common Adverse Drug Reactions Reported in ≥ 10% of Patients with Any Event or ≥ 2% of Patients with Events of Grade 3 or 4 in the TDXd Arm of Study DB06, by MedDRA System Organ Class and Preferred Term/Grouped Term in Study DB06 (Safety Analysis Set)

MedDRA System Organ Class Preferred Term/Grouped Term	T-DXd 5.4 mg/kg (N = 434)					Chemotherapy (N = 417)				
	Frequency [a]	Number (%) of Subjects				Frequency [a]	Number (%) of Subjects			
		CTCAE Grade			SAE		CTCAE Grade			SAE
		All Grades	Grade 3 or 4	Grade 5			All Grades	Grade 3 or 4	Grade 5	
Patients with any ADR	--	428 (98.6)	193 (44.5)	3 (0.7)	39 (9.0)	--	370 (88.7)	118 (28.3)	0	20 (4.8)
Blood and lymphatic system disorders										
Neutropenia [b]	Very Common	169 (38.9)	96 (22.1)	0	1 (0.2)	Very Common	128 (30.7)	71 (17.0)	0	0
Anemia [b]	Very Common	162 (37.3)	38 (8.8)	0	3 (0.7)	Very Common	110 (26.4)	18 (4.3)	0	1 (0.2)
Leukopenia [b]	Very Common	105 (24.2)	31 (7.1)	0	0	Very Common	70 (16.8)	25 (6.0)	0	0
Thrombocytopenia [b]	Very Common	86 (19.8)	20 (4.6)	0	1 (0.2)	Common	21 (5.0)	1 (0.2)	0	0
Lymphopenia [b]	Very Common	47 (10.8)	14 (3.2)	0	0	Common	16 (3.8)	2 (0.5)	0	0
Gastrointestinal disorders										
Nausea	Very Common	303 (69.8)	9 (2.1)	0	3 (0.7)	Very Common	126 (30.2)	2 (0.5)	0	1 (0.2)
Diarrhoea	Very Common	148 (34.1)	10 (2.3)	0	1 (0.2)	Very Common	114 (27.3)	11 (2.6)	0	3 (0.7)

MedDRA System Organ Class Preferred Term/Grouped Term	T-DXd 5.4 mg/kg (N = 434)					Chemotherapy (N = 417)				
	Frequency [a]	Number (%) of Subjects				Frequency [a]	Number (%) of Subjects			
		CTCAE Grade			SAE		CTCAE Grade			SAE
		All Grades	Grade 3 or 4	Grade 5			All Grades	Grade 3 or 4	Grade 5	
Vomiting	Very Common	146 (33.6)	6 (1.4)	0	3 (0.7)	Very Common	49 (11.8)	1 (0.2)	0	1 (0.2)
Constipation	Very Common	137 (31.6)	3 (0.7)	0	1 (0.2)	Very Common	62 (14.9)	2 (0.5)	0	2 (0.5)
Abdominal pain [b]	Very Common	86 (19.8)	2 (0.5)	0	0	Very Common	58 (13.9)	1 (0.2)	0	1 (0.2)
Stomatitis [b]	Very Common	64 (14.7)	0	0	0	Very Common	46 (11.0)	2 (0.5)	0	0
Dyspepsia	Very Common	50 (11.5)	0	0	0	Common	20 (4.8)	0	0	0
General disorders and administration site conditions										
Fatigue [b]	Very Common	229 (52.8)	19 (4.4)	0	1 (0.2)	Very Common	166 (39.8)	10 (2.4)	0	0
Pyrexia	Very Common	52 (12.0)	1 (0.2)	0	0	Common	30 (7.2)	0	0	2 (0.5)
Hepatobiliary disorders										
Transaminases increased [b]	Very Common	159 (36.6)	18 (4.1)	0	1 (0.2)	Very Common	63 (15.1)	2 (0.5)	0	0
Infections and infestations										
Upper respiratory tract infection [b]	Very Common	81 (18.7)	0	0	0	Common	39 (9.4)	0	0	0
Investigations										
Blood alkaline phosphatase increased	Very Common	48 (11.1)	2 (0.5)	0	0	Common	17 (4.1)	1 (0.2)	0	0
Metabolism and nutrition disorders										
Decreased appetite	Very Common	114 (26.3)	6 (1.4)	0	2 (0.5)	Very Common	48 (11.5)	2 (0.5)	0	1 (0.2)
Hypokalaemia [b]	Very Common	57 (13.1)	20 (4.6)	0	5 (1.2)	Common	17 (4.1)	6 (1.4)	0	1 (0.2)
Musculoskeletal and connective tissue disorders										
Musculoskeletal pain [b]	Very Common	102 (23.5)	2 (0.5)	0	3 (0.7)	Very Common	94 (22.5)	8 (1.9)	0	4 (1.0)
Nervous system disorders										
Headache [b]	Very Common	76 (17.5)	2 (0.5)	0	0	Very Common	43 (10.3)	0	0	0
Dysgeusia	Very Common	51 (11.8)	1 (0.2)	0	0	Common	24 (5.8)	0	0	0
Respiratory, thoracic and mediastinal disorders										
Cough	Very Common	69 (15.9)	0	0	0	Common	38 (9.1)	0	0	0
Interstitial lung disease [c]	Very Common	49 (11.3)	3 (0.7)	3 (0.7)	11 (2.5)	Uncommon	1 (0.2)	0	0	0
Epistaxis	Very Common	44 (10.1)	0	0	0	Common	15 (3.6)	1 (0.2)	0	0
Skin and subcutaneous tissue disorders										

MedDRA System Organ Class Preferred Term/Grouped Term	T-DXd 5.4 mg/kg (N = 434)					Chemotherapy (N = 417)				
	Frequency [a]	Number (%) of Subjects				Frequency [a]	Number (%) of Subjects			
		CTCAE Grade			SAE		CTCAE Grade			SAE
		All Grades	Grade 3 or 4	Grade 5			All Grades	Grade 3 or 4	Grade 5	
Alopecia	Very Common	210 (48.4)	0	0	0	Very Common	87 (20.9)	2 (0.5)	0	0

[a] Within each pool, frequency was defined as follows: Very Common ≥ 1/10 subjects; Common ≥ 1/100 to < 1/10 patients; Uncommon ≥ 1/1000 to < 1/100 patients; Rare ≥ 1/10000 to < 1/1000 patients; Very rare < 1/10000 patients.

The PTs included in each grouped term are listed in Table 43.

Interstitial lung disease (AESI) includes PTs of bronchiectasis, interstitial lung disease, lower respiratory tract infection, pneumonia, pneumonia bacterial, pneumonitis, and pulmonary toxicity. These events were adjudicated as ILD and related to use of TDX-d.

System organ classes are presented by alphabetic order. PTs/grouped terms are presented by descending frequency in the Study DB-06 All Grades column**.**

If a subject had multiple occurrences of the same ADR, the patient was counted once for that specific ADR.

Table 44 All Adverse Drug reactions in T-DXd 5.4 mg/kg breast cancer pool and T-DXd 5.4 mg/kg all tumour types pool, by MedDRA System Organ Class, Preferred Term/Grouped Term and Frequency (Safety Analysis Set)

MedDRA System Organ Class Preferred Term/ Grouped Term	T-DXd 5.4 mg/kg breast cancer pool (N = 1741)					T-DXd 5.4 mg/kg all tumor types pool (N = 2335)				
	Frequency [1]	Number (%) of Subjects				Frequency [1]	Number (%) of Subjects			
		CTCAE Grade			SAE		CTCAE Grade			SAE
		All Grades	Grade 3 or 4	Grade 5			All Grades	Grade 3 or 4	Grade 5	
Subjects with any ADR	--	1724 (99.0)	785 (45.1)	21 (1.2)	222 (12.8)	--	2299 (98.5)	1044 (44.7)	33 (1.4)	334 (14.3)
Blood and lymphatic system disorders										
Neutropenia [a]	Very Common	633 (36.4)	323 (18.6)	0	4 (0.2)	Very Common	819 (35.1)	420 (18.0)	0	8 (0.3)
Anemia [b]	Very Common	611 (35.1)	159 (9.1)	0	17 (1.0)	Very Common	838 (35.9)	246 (10.5)	0	28 (1.2)
Leukopenia [c]	Very Common	413 (23.7)	119 (6.8)	0	0	Very Common	501 (21.5)	139 (6.0)	0	0
Thrombocytopenia [d]	Very Common	406 (23.3)	84 (4.8)	0	5 (0.3)	Very Common	539 (23.1)	127 (5.4)	0	13 (0.6)
Lymphopenia [e]	Very Common	193 (11.1)	80 (4.6)	0	0	Common	222 (9.5)	91 (3.9)	0	0
Febrile neutropenia	Uncommon	17 (1.0)	16 (0.9)	1 (0.1)	14 (0.8)	Common	24 (1.0)	22 (0.9)	1 (0.0)	19 (0.8)
Eye disorders										
Dry eye	Common	104 (6.0)	2 (0.1)	0	0	Common	116 (5.0)	2 (0.1)	0	0
Vision blurred [f]	Common	82 (4.7)	0	0	0	Common	95 (4.1)	1 (0.0)	0	0
Gastrointestinal disorders										
Nausea	Very Common	1294 (74.3)	89 (5.1)	0	17 (1.0)	Very Common	1660 (71.1)	115 (4.9)	0	25 (1.1)
Vomiting	Very Common	713 (41.0)	42 (2.4)	0	23 (1.3)	Very Common	870 (37.3)	55 (2.4)	0	35 (1.5)
Constipation	Very Common	594 (34.1)	8 (0.5)	0	5 (0.3)	Very Common	741 (31.7)	15 (0.6)	0	8 (0.3)
Diarrhoea	Very Common	529 (30.4)	36 (2.1)	0	5 (0.3)	Very Common	703 (30.1)	58 (2.5)	0	12 (0.5)
Abdominal pain [g]	Very Common	355 (20.4)	16 (0.9)	0	5 (0.3)	Very Common	455 (19.5)	24 (1.0)	0	13 (0.6)
Stomatitis [h]	Very Common	259 (14.9)	10 (0.6)	0	2 (0.1)	Very Common	325 (13.9)	11 (0.5)	0	2 (0.1)
Dyspepsia	Very Common	202 (11.6)	0	0	0	Very Common	245 (10.5)	1 (0.0)	0	0
Abdominal distension	Common	73 (4.2)	0	0	0	Common	89 (3.8)	1 (0.0)	0	1 (0.0)
Flatulence	Common	36 (2.1)	0	0	0	Common	45 (1.9)	0	0	0

MedDRA System Organ Class Preferred Term/ Grouped Term	T-DXd 5.4 mg/kg breast cancer pool (N = 1741)					T-DXd 5.4 mg/kg all tumor types pool (N = 2335)				
	Frequency [1]	Number (%) of Subjects CTCAE Grade			SAE	Frequency [1]	Number (%) of Subjects CTCAE Grade			SAE
		All Grades	Grade 3 or 4	Grade 5			All Grades	Grade 3 or 4	Grade 5	
Gastritis	Common	32 (1.8)	2 (0.1)	0	1 (0.1)	Common	38 (1.6)	3 (0.1)	0	1 (0.0)
General disorders and administration site conditions										
Fatigue [i]	Very Common	990 (56.9)	130 (7.5)	0	10 (0.6)	Very Common	1292 (55.3)	182 (7.8)	0	21 (0.9)
Pyrexia	Very Common	223 (12.8)	6 (0.3)	0	11 (0.6)	Very Common	293 (12.5)	10 (0.4)	0	16 (0.7)
Oedema peripheral	*NA	*NA	*NA	*NA	*NA	Common	186 (8.0)	3 (0.1)	0	3 (0.1)
Hepatobiliary disorders										
Transaminases increased [j]	Very Common	518 (29.8)	67 (3.8)	0	3 (0.2)	Very Common	622 (26.6)	81 (3.5)	0	3 (0.1)
Infections and infestations										
Upper respiratory tract infection [k]	Very Common	339 (19.5)	3 (0.2)	0	4 (0.2)	Very Common	380 (16.3)	3 (0.1)	0	4 (0.2)
Pneumonia	*NA	*NA	*NA	*NA	*NA	Common	126 (5.4)	31 (1.3)	7 (0.3)	43 (1.8)
Injury, poisoning and procedural complications										
Infusion related reaction [r]	Common	22 (1.3)	1 (0.1)	0	1 (0.1)	Common	25 (1.1)	1 (0.0)	0	1 (0.0)
Investigations										
Ejection fraction decreased [t]	Very Common	269 (15.5)	19 (1.1)	0	3 (0.2)	Very Common	325 (13.9)	24 (1.0)	0	5 (0.2)
Weight decreased	Very Common	246 (14.1)	8 (0.5)	0	1 (0.1)	Very Common	300 (12.8)	12 (0.5)	0	1 (0.0)
Blood alkaline phosphatase increased	Common	165 (9.5)	7 (0.4)	0	0	Common	193 (8.3)	11 (0.5)	0	0
Blood bilirubin increased [l]	Common	142 (8.2)	14 (0.8)	0	5 (0.3)	Common	176 (7.5)	20 (0.9)	0	6 (0.3)
Blood creatinine increased	Common	46 (2.6)	5 (0.3)	0	1 (0.1)	Common	85 (3.6)	7 (0.3)	0	2 (0.1)
Metabolism and nutrition disorders										
Decreased appetite	Very Common	529 (30.4)	29 (1.7)	0	4 (0.2)	Very Common	715 (30.6)	42 (1.8)	0	7 (0.3)
Hypokalaemia [m]	Very Common	208 (11.9)	63 (3.6)	0	12 (0.7)	Very Common	279 (11.9)	89 (3.8)	0	13 (0.6)
Dehydration	Common	46 (2.6)	7 (0.4)	0	5 (0.3)	Common	58 (2.5)	8 (0.3)	0	5 (0.2)
Musculoskeletal and connective tissue disorders										
Musculoskeletal pain [n]	Very Common	456 (26.2)	15 (0.9)	0	14 (0.8)	Very Common	551 (23.6)	21 (0.9)	0	19 (0.8)
Nervous system disorders										
Headache [o]	Very Common	329 (18.9)	5 (0.3)	0	2 (0.1)	Very Common	381 (16.3)	5 (0.2)	0	3 (0.1)
Dizziness	Common	170 (9.8)	4 (0.2)	0	1 (0.1)	Common	211 (9.0)	5 (0.2)	0	1 (0.0)
Dysgeusia	Common	157 (9.0)	1 (0.1)	0	0	Common	182 (7.8)	1 (0.0)	0	0
Respiratory, thoracic and mediastinal disorders										
Cough	Very Common	262 (15.0)	1 (0.1)	0	1 (0.1)	Very Common	325 (13.9)	2 (0.1)	0	1 (0.0)
Interstitial lung disease [s]	Very Common	226 (13.0)	15 (0.9)	18 (1.0)	64 (3.7)	Very Common	286 (12.2)	18 (0.8)	25 (1.1)	80 (3.4)
Epistaxis	Very Common	187 (10.7)	0	0	0	Common	213 (9.1)	2 (0.1)	0	1 (0.0)
Dyspnoea	Common	168 (9.6)	12 (0.7)	0	11 (0.6)	Common	219 (9.4)	21 (0.9)	1 (0.0)	20 (0.9)
Skin and subcutaneous tissue disorders										
Alopecia	Very Common	729 (41.9)	3 (0.2)	0	0	Very Common	844 (36.1)	3 (0.1)	0	0
Rash [p]	Common	170 (9.8)	2 (0.1)	0	1 (0.1)	Common	197 (8.4)	3 (0.1)	0	1 (0.0)
Pruritus	Common	86 (4.9)	1 (0.1)	0	0	Common	111 (4.8)	1 (0.0)	0	0
Skin hyperpigmentation [q]	Common	68 (3.9)	0	0	1 (0.1)	Common	81 (3.5)	0	0	1 (0.0)

*NA Oedema Peripheral and Pneumonia not determined as adverse drug reactions for breast cancer pool.
ADR = adverse drug reaction; CTCAE = Common Terminology Criteria for Adverse Events, version 5.0; MedDRA = Medical Dictionary for Regulatory Activities, version 26.1; N = total number of subjects treated; NA = not applicable; PT = preferred term; SAE = serious adverse event; T-DXd = trastuzumab deruxtecan.
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
System Organ Class are presented by alphabetic order. PTs/grouped terms are presented by descending frequency in the All Grades column of the T-DXd 5.4 mg/kg breast cancer pool.
If a subject had multiple occurrences of the same ADR, the subject was counted once for that specific ADR.
[1] Within each pool, frequency was defined as follows: Very Common >=1/10 subjects; Common >=1/100 to <1/10 subjects; Uncommon >=1/1000 to <1/100 subjects; Rare >=1/10000 to <1/1000 subjects; Very rare <1/10000 subjects.
[a] Neutropenia (grouped term) includes PTs of Neutrophil count decreased, Neutropenia.
[b] Anemia (grouped term) includes PTs of Haemoglobin decreased, Red blood cell count decreased, Anaemia, Haematocrit decreased.
[c] Leukopenia (grouped term) includes PTs of White blood cell count decreased, Leukopenia.
[d] Thrombocytopenia (grouped term) includes PTs of Platelet count decreased, Thrombocytopenia.
[e] Lymphopenia (grouped term) includes PTs of Lymphocyte count decreased, Lymphopenia.
[f] Vision blurred (grouped term) includes PTs of Vision blurred, Visual impairment.
[g] Abdominal pain (grouped term) includes PTs of Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Gastrointestinal pain.
[h] Stomatitis (grouped term) includes PTs of Stomatitis, Aphthous ulcer, Mouth ulceration, Oral mucosa erosion, Oral mucosal blistering, Oral mucosal eruption.
[i] Fatigue (grouped term) includes PTs of Fatigue, Asthenia, Malaise, Lethargy.
[j] Transaminases increased (grouped term) includes PTs of Transaminases increased, Aspartate aminotransferase increased, Alanine aminotransferase increased, Gamma-glutamyltransferase increased, Liver function test abnormal, Hepatic function abnormal, Liver function test increased, Hypertransaminasaemia.
[k] Upper respiratory tract infection (grouped term) includes PTs of Influenza, Influenza like illness, Upper respiratory tract infection, Nasopharyngitis, Pharyngitis, Sinusitis, Rhinitis, Laryngitis.
[l] Blood bilirubin increased (grouped term) includes PTs of Blood bilirubin increased, Hyperbilirubinaemia, Bilirubin conjugated increased, Blood bilirubin unconjugated increased.
[m] Hypokalaemia (grouped term) includes PTs of Hypokalaemia, Blood potassium decreased.
[n] Musculoskeletal pain (grouped term) includes PTs of Back pain, Myalgia, Pain in extremity, Musculoskeletal pain, Muscle spasms, Bone pain, Neck pain, Musculoskeletal chest pain, Limb discomfort.
[o] Headache (grouped term) includes PTs of Migraine, Headache, Sinus headache.
[p] Rash (grouped term) includes PTs of Rash, Rash pustular, Rash maculo-papular, Rash papular, Rash macular, Rash pruritic.
[q] Skin hyperpigmentation (grouped term) includes PTs of Skin hyperpigmentation, Skin discolouration, Pigmentation disorder.
[r] Infusion related reaction (grouped term) includes PTs of Hypersensitivity (n=2), Infusion related reaction (n=23)..
[s] Interstitial lung disease (grouped term) includes PTs of Acute respiratory failure (n=2), Alveolitis (n=2), Bronchiectasis (n=1), Disease progression (n=1), Hypersensitivity pneumonitis (n=1), Idiopathic interstitial pneumonia (n=1), Interstitial lung disease (n=109), Lower respiratory tract infection (n=1), Lung disorder (n=1), Lung infiltration (n=1), Lung opacity (n=4), Lymphangitis (n=1), Organising pneumonia (n=9), Pneumonia (n=9), Pneumonia bacterial (n=2), Pneumonia fungal (n=1), Pneumonitis (n=136), Pulmonary fibrosis (n=2), Pulmonary mass (n=1), Pulmonary toxicity (n=3), Radiation pneumonitis (n=4), Respiratory failure (n=5). These events were adjudicated as ILD..
[t] Ejection fraction decreased (grouped term) includes Laboratory parameters of LVEF decrease (n=312) and PTs of Cardiac failure (n=5), Cardiac failure acute (n=1), Cardiac failure chronic (n=1), Cardiac failure congestive (n=1), Ejection fraction decreased (n=99), Left ventricular dysfunction (n=3).

Table 45 Common Adverse Drug Reactions Reported in ≥ 10% of Patients with Any Event or ≥ 2% of Patients with Events of Grade 3 or 4 in the T-DXd 5.4 mg/kg Breast Cancer Pool or the T-DXd 5.4 mg/kg All Tumor Types Pool, by MedDRA System Organ Class and Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA System Organ Class	T-DXd 5.4 mg/kg BC Pool (N = 1741)					T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)				
Preferred Term/Grouped Term	Frequency [a]	Number (%) of Subjects				Frequency [a]	Number (%) of Subjects			
		CTCAE Grade			SAE		CTCAE Grade			SAE
		All Grades	Grade 3 or 4	Grade 5			All Grades	Grade 3 or 4	Grade 5	
Patients with any ADR	--	1721 (98.9)	776 (44.6)	20 (1.1)	220 (12.6)	--	2294 (98.2)	1032 (44.2)	32 (1.4)	330 (14.1)
Blood and lymphatic system disorders										
Neutropenia [b]	Very Common	633 (36.4)	323 (18.6)	0	4 (0.2)	Very Common	819 (35.1)	420 (18.0)	0	8 (0.3)
Anemia [b]	Very Common	611 (35.1)	159 (9.1)	0	17 (1.0)	Very Common	838 (35.9)	246 (10.5)	0	28 (1.2)
Leukopenia [b]	Very Common	413 (23.7)	119 (6.8)	0	0	Very Common	501 (21.5)	139 (6.0)	0	0
Thrombocytopenia [b]	Very Common	406 (23.3)	84 (4.8)	0	5 (0.3)	Very Common	539 (23.1)	127 (5.4)	0	13 (0.6)
Lymphopenia [b]	Very Common	193 (11.1)	80 (4.6)	0	0	Common	222 (9.5)	91 (3.9)	0	0
Gastrointestinal disorders										
Nausea	Very Common	1294 (74.3)	89 (5.1)	0	17 (1.0)	Very Common	1660 (71.1)	115 (4.9)	0	25 (1.1)
Vomiting	Very Common	713 (41.0)	42 (2.4)	0	23 (1.3)	Very Common	870 (37.3)	55 (2.4)	0	35 (1.5)
Constipation	Very Common	594 (34.1)	8 (0.5)	0	5 (0.3)	Very Common	741 (31.7)	15 (0.6)	0	8 (0.3)
Diarrhoea	Very Common	529 (30.4)	36 (2.1)	0	5 (0.3)	Very Common	703 (30.1)	58 (2.5)	0	12 (0.5)
Abdominal pain [b]	Very Common	355 (20.4)	16 (0.9)	0	5 (0.3)	Very Common	455 (19.5)	24 (1.0)	0	13 (0.6)
Stomatitis [b]	Very Common	259 (14.9)	10 (0.6)	0	2 (0.1)	Very Common	325 (13.9)	11 (0.5)	0	2 (0.1)
Dyspepsia	Very Common	202 (11.6)	0	0	0	Very Common	245 (10.5)	1 (0.0)	0	0
General disorders and administration site conditions										
Fatigue [b]	Very Common	990 (56.9)	130 (7.5)	0	10 (0.6)	Very Common	1292 (55.3)	182 (7.8)	0	21 (0.9)
Pyrexia	Very Common	223 (12.8)	6 (0.3)	0	11 (0.6)	Very Common	293 (12.5)	10 (0.4)	0	16 (0.7)
Hepatobiliary disorders										
Transaminases increased [b]	518 (29.8)	67 (3.8)	0	3 (0.2)	Very Common	622 (26.6)	81 (3.5)	0	3 (0.1)	0
Infections and infestations										
Upper respiratory tract infection [b]	339 (19.5)	3 (0.2)	0	4 (0.2)	Very Common	380 (16.3)	3 (0.1)	0	4 (0.2)	0
Investigations										

MedDRA System Organ Class Preferred Term/Grouped Term	T-DXd 5.4 mg/kg BC Pool (N = 1741)					T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)				
	Frequency [a]	Number (%) of Subjects				Frequency [a]	Number (%) of Subjects			
		CTCAE Grade			SAE		CTCAE Grade			SAE
		All Grades	Grade 3 or 4	Grade 5			All Grades	Grade 3 or 4	Grade 5	
Weight decreased	Very Common	246 (14.1)	8 (0.5)	0	1 (0.1)	Very Common	300 (12.8)	12 (0.5)	0	1 (0.0)
Metabolism and nutrition disorders										
Decreased appetite	Very Common	529 (30.4)	29 (1.7)	0	4 (0.2)	Very Common	715 (30.6)	42 (1.8)	0	7 (0.3)
Hypokalaemia [b]	Very Common	208 (11.9)	63 (3.6)	0	12 (0.7)	Very Common	279 (11.9)	89 (3.8)	0	13 (0.6)
Musculoskeletal and connective tissue disorders										
Musculoskeletal pain [b]	Very Common	456 (26.2)	15 (0.9)	0	14 (0.8)	Very Common	551 (23.6)	21 (0.9)	0	19 (0.8)
Nervous system disorders										
Headache [b]	Very Common	329 (18.9)	5 (0.3)	0	2 (0.1)	Very Common	381 (16.3)	5 (0.2)	0	3 (0.1)
Respiratory, thoracic and mediastinal disorders										
Cough	Very Common	262 (15.0)	1 (0.1)	0	1 (0.1)	Very Common	325 (13.9)	2 (0.1)	0	1 (0.0)
Interstitial lung disease [c]	Very Common	217 (12.5)	14 (0.8)	16 (0.9)	61 (3.5)	Very Common	276 (11.8)	17 (0.7)	23 (1.0)	77 (3.3)
Epistaxis	Very Common	187 (10.7)	0	0	0	Common	213 (9.1)	2 (0.1)	0	1 (0.0)
Skin and subcutaneous tissue disorders										
Alopecia	Very Common	729 (41.9)	3 (0.2)	0	0	Very Common	844 (36.1)	3 (0.1)	0	0

[a] Within each pool, frequency was defined as follows: Very Common ≥ 1/10 subjects; Common ≥ 1/100 to < 1/10 patients; Uncommon ≥ 1/1000 to < 1/100 patients; Rare ≥ 1/10000 to < 1/1000 patients; Very rare < 1/10000 patients.

[b] The PTs included in each grouped term are listed in Table.

[c] Interstitial lung disease (AESI) includes PTs of bronchiectasis, interstitial lung disease, lower respiratory tract infection, pneumonia, pneumonia bacterial, pneumonitis, and pulmonary toxicity. These events were adjudicated as ILD and related to use of T-DXd.

System organ classes are presented by alphabetic order. PTs/grouped terms are presented by descending frequency in the T-DXd 5.4 mg/kg BC Pool column**.**

If a subject had multiple occurrences of the same ADR, the patient was counted once for that specific ADR.

Table 46 Time to onset of Hematological Grouped Term ≥Grade 3 TEAEs in DB-06

	T-DXd (N = 434)	Chemotherapy (N = 417)
Selected TEAE: Hematological grouped term [a]		
Time to first onset (Days) [b]		
n	143	81
Mean	72.9	62.4
Standard deviation	116.07	112.53
Median	22.0	15.0
Minimum, maximum	-12, 855 [c]	0, 716
Selected TEAE: Neutropenia [d]		
Time to first onset (Days) [b]		
n	70	48

	T-DXd (N = 434)	Chemotherapy (N = 417)
Mean	54.6	51.6
Standard deviation	111.61	113.09
Median	21.0	15.0
Minimum, maximum	0, 855	7, 716
Selected TEAE: Anemia [e]		
Time to first onset (Days) [b]		
n	33	16
Mean	99.5	75.4
Standard deviation	130.18	105.98
Median	64.0	14.0
Minimum, maximum	-12, 572 [c]	0, 371
Selected TEAE: Leukopenia [f]		
Time to first onset (Days) [b]		
n	18	15
Mean	59.5	71.8
Standard deviation	95.80	118.07
Median	15.0	22.0
Minimum, maximum	6, 391	7, 461
Selected TEAE: Thrombocytopenia [g]		
Time to first onset (Days) [b]		
n	12	1
Mean	89.9	258.0
Standard deviation	131.31	NA
Median	19.5	258.0
Minimum, maximum	1, 372	258, 258
Selected TEAE: Lymphopenia [h]		
Time to first onset (Days) [b]		
n	10	1
Mean	117.1	42.0
Standard deviation	101.36	NA
Median	74.0	42.0
Minimum, maximum	14, 254	42, 42

[a] Hematological grouped term includes grouped terms neutropenia, anemia, leukopenia, thrombocytopenia, lymphopenia.
[b] Time to first onset (Days) = date of onset of the patient's first selected TEAE - date of the first dose + 1.
[c] Negative values indicate event start date before dosing and worsening of the same event after dosing.
[d] Includes the PTs of neutropenia and neutrophil count decreased.
[e] Includes the PTs of anaemia, haemoglobin decreased, haematocrit decreased, and red blood cell count decreased.
[f] Includes the PTs of leukopenia and white blood cell count decreased.
[g] Includes the PTs of platelet count decreased and thrombocytopenia.
[h] Includes the PTs of lymphopenia and lymphocyte count decreased.
A TEAE is defined as an adverse event that occurs, having been absent before the first dose of study drug, or has worsened in severity or seriousness after initiating the study drug until the 40-day (+ 7 days) safety follow-up visit

In the All Tumour Type (ATT) Pool, for the ADR neutropenia, median time to onset was 42 days (range: 1 day to 31.9 months), and median duration of the first event was 21 days (range: 1 day to 17.1 months).

Serious adverse event/deaths/other significant events

Table 47 Primary Cause of Any Deaths and On-treatment Deaths (Safety Analysis Set)

	Number (%) of Patients			
	Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
Any death	160 (36.9)	171 (41.0)	634 (36.4)	960 (41.1)
Adverse event	10 (2.3)	7 (1.7)	41 (2.4)	64 (2.7)
Disease progression	0	0	373 (21.4)	447 (19.1)
Disease under investigation	136 (31.3)	150 (36.0)	140 (8.0)	342 (14.6)
Unknown [a]	1 (0.2)	2 (0.5)	44 (2.5)	61 (2.6)
Other	13 (3.0)	12 (2.9)	36 (2.1)	46 (2.0)
On-treatment death [b]	12 (2.8)	13 (3.1)	52 (3.0)	123 (5.3)
Adverse event	8 (1.8)	6 (1.4)	29 (1.7)	49 (2.1)
Disease progression	0	0	15 (0.9)	34 (1.5)
Disease under investigation	4 (0.9)	6 (1.4)	4 (0.2)	32 (1.4)
Unknown	0	0	2 (0.1)	3 (0.1)
Other	0	1 (0.2)	2 (0.1)	5 (0.2)

[a] In Study DB-06 the "unknown" category consists of patients with missing primary cause of death on the eCRF.

[b] On-treatment death is defined as death occurred between first dose and 28 days following the last dose of study drug and before the initiation of the first subsequent anticancer therapy (whichever occurred first) for Study J101 and 47 days following the last dose of study treatment and before the initiation of the first subsequent anticancer therapy (whichever occurred first) for all other studies.

Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.
The pooled analysis group is based on tumor type and first dose received for patients in each study.
In Study DB-06, the reason for death of "disease under investigation" includes any death due to disease progression.

Table 48 Adverse Events Associated with an Outcome of Death Reported in a Least One Patient in Either Treatment Arm of Study DB-06, by Preferred Term (Safety Analysis Set)

	Number (%) of Patients			
	Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
Patients with any TEAE associated with an outcome of death	11 (2.5)	6 (1.4)	56 (3.2)	96 (4.1)
Interstitial lung disease	2 (0.5)	0	3 (0.2)	3 (0.1)
Sepsis	2 (0.5)	1 (0.2)	4 (0.2)	6 (0.3)
COVID-19 pneumonia	1 (0.2)	0	1 (0.1)	3 (0.1)
Cerebrovascular accident	1 (0.2)	0	1 (0.1)	3 (0.1)
Death	1 (0.2)	1 (0.2)	2 (0.1)	7 (0.3)
General physical health deterioration	1 (0.2)	0	3 (0.2)	3 (0.1)
Meningoencephalitis bacterial	1 (0.2)	0	1 (0.1)	1 (0.0)
Neutropenic sepsis	1 (0.2)	0	1 (0.1)	2 (0.1)
Peritonitis	1 (0.2)	0	1 (0.1)	1 (0.0)
Cardiac arrest	0	1 (0.2)	0	2 (0.1)

	Number (%) of Patients			
	Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
Haemorrhage intracranial	0	1 (0.2)	0	0
Pleural effusion	0	1 (0.2)	1 (0.1)	1 (0.0)
Pulmonary embolism	0	1 (0.2)	0	1 (0.0)

Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.
The pooled analysis group is based on first dose received for patients in each study.
PTs are sorted by descending frequency in the Study DB-06 T-DXd 5.4 mg/kg treatment arm.
If a patient had multiple occurrences of the same PT, the patient is counted once for the specific PT.
If a patient had multiple PTs, the patient is counted in each of the different PTs.

Table 49 Serious Adverse Events Reported in at Least 2 Patients in Either Treatment Arm in Study DB-06, by Preferred Term (Safety Analysis Set)

	Number (%) of Patients			
	Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
Patients with any TEAE	88 (20.3)	67 (16.1)	429 (24.6)	652 (27.9)
Interstitial lung disease	8 (1.8)	0	27 (1.6)	30 (1.3)
Pneumonitis	8 (1.8)	0	33 (1.9)	43 (1.8)
COVID-19	7 (1.6)	1 (0.2)	23 (1.3)	32 (1.4)
Febrile neutropenia	5 (1.2)	2 (0.5)	14 (0.8)	19 (0.8)
Hypokalaemia	5 (1.2)	1 (0.2)	12 (0.7)	13 (0.6)
Anaemia	3 (0.7)	1 (0.2)	17 (1.0)	28 (1.2)
General physical health deterioration	3 (0.7)	0	7 (0.4)	12 (0.5)
Nausea	3 (0.7)	1 (0.2)	17 (1.0)	25 (1.1)
Pulmonary embolism	3 (0.7)	3 (0.7)	6 (0.3)	9 (0.4)
Vomiting	3 (0.7)	1 (0.2)	23 (1.3)	35 (1.5)
Decreased appetite	2 (0.5)	1 (0.2)	4 (0.2)	7 (0.3)
Hypercalcaemia	2 (0.5)	2 (0.5)	7 (0.4)	7 (0.3)
Liver injury	2 (0.5)	0	3 (0.2)	3 (0.1)
Pneumocystis jirovecii pneumonia	2 (0.5)	0	6 (0.3)	7 (0.3)
Pneumothorax	2 (0.5)	0	4 (0.2)	5 (0.2)
Pyelonephritis	2 (0.5)	1 (0.2)	6 (0.3)	6 (0.3)
Sepsis	2 (0.5)	2 (0.5)	12 (0.7)	25 (1.1)
Cellulitis	1 (0.2)	5 (1.2)	10 (0.6)	11 (0.5)
Constipation	1 (0.2)	2 (0.5)	5 (0.3)	8 (0.3)
Diarrhoea	1 (0.2)	3 (0.7)	5 (0.3)	12 (0.5)
Pneumonia	1 (0.2)	3 (0.7)	26 (1.5)	43 (1.8)
Back pain	0	2 (0.5)	3 (0.2)	4 (0.2)
Cardiac failure	0	2 (0.5)	1 (0.1)	2 (0.1)
Cholangitis	0	3 (0.7)	0	4 (0.2)
Colitis	0	3 (0.7)	3 (0.2)	4 (0.2)

	Number (%) of Patients			
	Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
Femur fracture	0	3 (0.7)	1 (0.1)	1 (0.0)
Pleural effusion	0	5 (1.2)	8 (0.5)	16 (0.7)
Pyrexia	0	2 (0.5)	11 (0.6)	16 (0.7)

Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.
The pooled analysis group is based on first dose received for patients in each study.
PTs are sorted by descending frequency in the Study DB-06 T-DXd 5.4 mg/kg treatment arm.
If a patient had multiple occurrences of the same PT, the patient is counted once for the specific PT.
If a patient had multiple PTs, the patient is counted in each of the different PTs.

Table 50 Overview of Adjudicated Drug-related ILD (Safety Analysis Set)

Adjudication Result and CTCAE Grade by Adjudication Committee	Number (%) of Patients			
	Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
Total number of patients with events adjudicated by the ILD AC	75 (17.3)	5 (1.2)	299 (17.2)	379 (16.2)
Adjudicated as ILD				
Any grade	52 (12.0)	1 (0.2)	226 (13.0)	286 (12.2)
1	10 (2.3)	0	54 (3.1)	68 (2.9)
2	36 (8.3)	1 (0.2)	139 (8.0)	175 (7.5)
3	3 (0.7)	0	14 (0.8)	17 (0.7)
4	0	0	1 (0.1)	1 (0.0)
5	3 (0.7)	0	18 (1.0)	25 (1.1)
≥ 3	6 (1.4)	0	33 (1.9)	43 (1.8)
Adjudicated as drug-related ILD				
Any grade	49 (11.3)	1 (0.2)	217 (12.5)	276 (11.8)
1	7 (1.6)	0	51 (2.9)	65 (2.8)
2	36 (8.3)	1 (0.2)	136 (7.8)	171 (7.3)
3	3 (0.7)	0	14 (0.8)	17 (0.7)
4	0	0	0	0
5	3 (0.7)	0	16 (0.9)	23 (1.0)
≥ 3	6 (1.4)	0	30 (1.7)	40 (1.7)
Adjudicated as not drug-related ILD				
Any grade	3 (0.7)	0	9 (0.5)	10 (0.4)
1	3 (0.7)	0	4 (0.2)	4 (0.2)
2	0	0	3 (0.2)	4 (0.2)
3	0	0	0	0
4	0	0	0	0
5	0	0	2 (0.1)	2 (0.1)

Adjudication Result and CTCAE Grade by Adjudication Committee	Number (%) of Patients			
	Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
≥ 3	0	0	2 (0.1)	2 (0.1)
Adjudicated as not ILD	23 (5.3)	4 (1.0)	72 (4.1)	92 (3.9)
Pending adjudication [a, b]				
Any grade	0	0	1 (0.1)	1 (0.0)
1	0	0	0	0
2	0	0	0	0
3	0	0	1 (0.1)	1 (0.0)
4	0	0	0	0
5	0	0	0	0
≥ 3	0	0	1 (0.1)	1 (0.0)

[a] The CTCAE grade is based on investigator assessed grade.

[b] Patient 34050001 in Study U201 had an ILD case pending for adjudication.

Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.
The pooled analysis group is based on first dose received for patients in each study.
This table includes all events that were submitted to the ILD Adjudication Committee for adjudication.
Each patient is counted only in one of the last 4 summary blocks. For patients having ILD cases across the last 4 blocks, the patient is counted in the block according to the preceding order presented in the table. If a patient had multiple ILD events, the CTCAE grade is shown for the event with the worst grade. If a patient has both missing and non-missing CTCAE grades for a TEAE, the worst CTCAE grade is based on non-missing grade.

Adverse Events of Special Interest

Table 51 Preferred Terms in Adverse Events of Special Interest

Category	Preferred Terms
ILD/pneumonitis	Events of ILD/pneumonitis from PTs triggering adjudication, based on the current study MedDRA version for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure
Left ventricular dysfunction	Acute left ventricular failure Acute right ventricular failure Cardiac failure Cardiac failure acute Cardiac failure chronic Cardiac failure congestive Chronic left ventricular failure Chronic right ventricular failure Ejection fraction decreased Left ventricular dysfunction Left ventricular failure Right ventricular failure Ventricular failure

- **ILD/Pneumonitis**

Table 52 Drug Related ILD ILD/Pneumonitis by Preferred Terms (Safety Analysis Set)

	Number (%) of Patients			
	D9670C00001(DESTINY-Breast06)		Supportive Safety Pools	
MedDRA Preferred Term	T-DXd 5.4 mg/kg (N=434)	Investigator choice of chemotherapy (N=417)	T-DXd 5.4 mg/kg breast cancer pool (N=1741)	T-DXd 5.4 mg/kg all tumor types pool (N=2335)
Patients with ILD/Pneumonitis	58 (13.4)	2 (0.5)	234 (13.4)	290 (12.4)
Interstitial lung disease	30 (6.9)	2 (0.5)	101 (5.8)	119 (5.1)
Pneumonitis	28 (6.5)	0	133 (7.6)	171 (7.3)

Table 53 Treatment-Emergent ILD/Pneumonitis by Grouped Term, Preferred Term and Worst NCI CTCAE Grade (Safety Analysis Set)

	Number (%) of Patients			
	D9670C00001(DESTINY-Breast06)		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N=434)	Investigator choice of chemotherapy (N=417)	T-DXd 5.4 mg/kg breast cancer pool (N=1741)	T-DXd 5.4 mg/kg all tumor types pool (N=2335)
Selected TEAE: ILD/Pneumonitis				
Any selected TEAE	60 (13.8)	2 (0.5)	243 (14.0)	301 (12.9)
Worst NCI CTCAE Grade				
1	37 (8.5)	1 (0.2)	147 (8.4)	183 (7.8)
2	15 (3.5)	1 (0.2)	63 (3.6)	76 (3.3)
3	5 (1.2)	0	21 (1.2)	27 (1.2)
4	1 (0.2)	0	3 (0.2)	3 (0.1)
5	2 (0.5)	0	9 (0.5)	12 (0.5)
>=3	8 (1.8)	0	33 (1.9)	42 (1.8)
Outcome of the worst selected TEAE [1]				
Fatal	2 (3.3)	0	9 (3.7)	13 (4.3)
Not Recovered/Not Resolved	25 (41.7)	0	61 (25.1)	85 (28.2)
Ongoing	0	0	1 (0.4)	1 (0.3)
Recovering/Resolving	4 (6.7)	0	16 (6.6)	20 (6.6)
Recovered/Resolved with Sequelae	4 (6.7)	0	13 (5.3)	14 (4.7)
Recovered/Resolved	25 (41.7)	2 (100)	138 (56.8)	163 (54.2)
Missing/Unknown	0	0	5 (2.1)	5 (1.7)

Table 54 Analysis of ILD/Organising pneumonitis/Acute interstitial pneumonitis (Safety Analysis Set)

Table 2.7.4.2.2.1.c Analysis of ILD/Pneumonitis/Organising pneumonitis/Acute interstitial pneumonitis (Safety Analysis Set)

	Number (%) of Patients			
	D9670C00001(DESTINY-Breast06)		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N=434)	Investigator choice of chemotherapy (N=417)	T-DXd 5.4 mg/kg breast cancer pool (N=1741)	T-DXd 5.4 mg/kg all tumor types pool (N=2335)
Selected TEAE: ILD/Pneumonitis/Organising pneumonitis/Acute interstitial pneumonitis				
Any selected TEAE	60 (13.8)	2 (0.5)	250 (14.4)	310 (13.3)

Please refer to Table 50 Overview of Adjudicated Drug-related ILD (Safety Analysis Set) above.

Table 55 Overview of Investigator-reported ILD/Pneumonitis

	Number (%) of Patients			
	Study DB-06		**Supportive Safety Pools**	
	T-DXd 5.4 mg/kg (N = 434)	**Chemotherapy (N = 417)**	**T-DXd 5.4 mg/kg BC Pool (N = 1741)**	**T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)**
Patients with ILD/pneumonitis (any grade)	60 (13.8)	2 (0.5)	243 (14.0)	301 (12.9)
1	37 (8.5)	1 (0.2)	147 (8.4)	183 (7.8)
2	15 (3.5)	1 (0.2)	63 (3.6)	76 (3.3)
3	5 (1.2)	0	21 (1.2)	27 (1.2)
4	1 (0.2)	0	3 (0.2)	3 (0.1)
5	2 (0.5)	0	9 (0.5)	12 (0.5)

	Number (%) of Patients			
	Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
≥ 3	8 (1.8)	0	33 (1.9)	42 (1.8)
Serious ILD/pneumonitis	16 (3.7)	0	60 (3.4)	73 (3.1)
ILD/pneumonitis leading to study drug discontinuation	38 (8.8)	0	172 (9.9)	212 (9.1)
ILD/pneumonitis leading to study drug interruption	10 (2.3)	0	50 (2.9)	61 (2.6)

If a patient has multiple occurrences of the same preferred term, the patient is counted once for the specific preferred term. If a patient has more than one event per grouped term, the patient is counted once at the Grouped Term level. Within the same grouped term, if a patient has multiple preferred terms, the patient is counted in each of the different preferred terms.

Table 56 Investigator Assessment and ILD Adjudication Committee Assessment of Fatal ILD Events

Patient Description,	T-DXd Administration and Death Dates	Investigator Assessment	Adjudication Committee Assessment
Female, 79 White,	Received 7 doses of T-DXd; last dose on Day 128 Died on Day 170	Grade 1 ILD on Day 127 Maximum Grade 5 ILD Primary cause of death: AE of ILD	Adjudicated as Grade 1 drug-related ILD at onset Maximum Grade 5 drug-related ILD per AC
Female, 57 White,	Received 6 doses of T-DXd; last dose on Day 114 Died on Day 246	Grade 2 ILD on Day 125 Maximum Grade 3 ILD Primary cause of death: disease under investigation	Adjudicated as Grade 3 drug-related ILD at onset Maximum Grade 5 drug-related ILD per AC
Female, 76 Asian,	Received 10 doses of T-DXd; last dose on Day 196 Died on Day 210	Grade 3 bacterial pneumonia on Day 207; Grade 1 cytomegalovirus infection on Day 208; Grade 3 ILD on Day 209 Primary cause of death: disease under investigation	Adjudicated as Grade 3 drug related ILD at onset Maximum Grade 5 drug-related ILD per AC
Female, 82 Asian,	Received 6 doses of T-DXd; last dose on Day 113 Died on Day 138	Grade 1 ILD on Day 127, Maximum Grade 5 ILD Grade 4 COVID-19 on Day 130; Grade 4 Pneumocystis jirovecii pneumonia on Day 132 Primary cause of death: ILD Secondary cause of death: COVID-19	Adjudicated as not ILD. The ILD adjudication committee considered that this event was COVID-19 pneumonia

Table 57 Adjudicated Drug-Related Interstitial Lung Disease by Preferred Term and Worst NCI CTCAE Grade (Safety Analysis Set)

	Number (%) of Patients			
	D9670C00001(DESTINY-Breast06)		Supportive Safety Pools	
AESI Category MedDRA Preferred Term CTCAE Grade	T-DXd 5.4 mg/kg (N=434)	Investigator choice of chemotherapy (N=417)	T-DXd 5.4 mg/kg breast cancer pool (N=1741)	T-DXd 5.4 mg/kg all tumor types pool (N=2335)
Adjudicated Drug-related ILD	49 (11.3)	1 (0.2)	217 (12.5)	276 (11.8)
1	7 (1.6)	0	51 (2.9)	65 (2.8)
2	36 (8.3)	1 (0.2)	136 (7.8)	171 (7.3)
3	3 (0.7)	0	14 (0.8)	17 (0.7)
4	0	0	0	0
5	3 (0.7)	0	16 (0.9)	23 (1.0)
>=3	6 (1.4)	0	30 (1.7)	40 (1.7)
Interstitial lung disease	24 (5.5)	1 (0.2)	93 (5.3)	107 (4.6)
1	6 (1.4)	0	22 (1.3)	27 (1.2)
2	14 (3.2)	1 (0.2)	63 (3.6)	72 (3.1)
3	1 (0.2)	0	3 (0.2)	3 (0.1)
4	0	0	0	0
5	3 (0.7)	0	5 (0.3)	5 (0.2)
>=3	4 (0.9)	0	8 (0.5)	8 (0.3)

Table 58 Adjudicated Drug-related Interstitial Lung Disease by Preferred Term and Worst NCI CTCAE Grade (Safety Analysis Set)

	Number (%) of Patients			
	D9670C00001(DESTINY-Breast06)		Supportive Safety Pools	
AESI Category MedDRA Preferred Term CTCAE Grade	T-DXd 5.4 mg/kg (N=434)	Investigator choice of chemotherapy (N=417)	T-DXd 5.4 mg/kg breast cancer pool (N=1741)	T-DXd 5.4 mg/kg all tumor types pool (N=2335)
Pneumonitis	20 (4.6)	0	101 (5.8)	134 (5.7)
1	1 (0.2)	0	22 (1.3)	27 (1.2)
2	17 (3.9)	0	64 (3.7)	85 (3.6)
3	2 (0.5)	0	8 (0.5)	10 (0.4)
4	0	0	1 (0.1)	1 (0.0)
5	0	0	6 (0.3)	11 (0.5)
>=3	2 (0.5)	0	15 (0.9)	22 (0.9)
Bronchiectasis	1 (0.2)	0	1 (0.1)	1 (0.0)
1	0	0	0	0
2	1 (0.2)	0	1 (0.1)	1 (0.0)
3	0	0	0	0
4	0	0	0	0
5	0	0	0	0
>=3	0	0	0	0

Note: Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.
The pooled analysis group is based on first dose received for patients in each study.
Adjudicated ILD events include all adjudicated and considered study drug related events by adjudication committee.
CTCAE grade for adjudicated ILD is the adjudicated ILD grade.
Adverse Events are coded using MedDRA Version 26.1 and graded per CTCAE 5.0.
Preferred Terms are sorted by descending frequency in DB06 T-DXd 5.4 mg/kg.
If a patient has multiple occurrences of the same preferred term, the patient is counted once for the specific preferred term by worst adjudicated drug-related ILD grade.
If a patient has multiple preferred terms, the patient is counted in each of the different preferred terms.
T-DXd 5.4 mg/kg Breast cancer Pool: J101(N=71), DB01(N=184), DB02(N=404), DB03(N=257), DB04(N=371),DB06(N=434), DP01(N=20).
T-DXd 5.4 mg/kg all Tumor Types Pool: J101(N=91), DB01(N=184), DB02(N=404), DB03(N=257), DB04(N=371), DB06(N=434), DL01(N=41), DL02(N=101), DC02(N=83), DP01(N=102), DP02(N=267)
Date of Data cut-off: T-DXd 5.4 mg/kg breast cancer pool from studies J101 (01Aug2019), DB01 (08Jun2020), DB02 (30Jun2022), DB03 (25Jul2022), DB04 (11Apr2022), DB06 (18MAR2024), DP01 (25Jan2023)
T-DXd 5.4 mg/kg all tumor types cancer pool from J101 (01Aug2019), DB01 (08Jun2020), DB02 (30Jun2022), DB03 (25Jul2022), DB04 (11Apr2022), DB06 (18MAR2024), DL01(03Dec2021), DL02(23Dec2022), DC02 (01Nov2022), DP01 (25Jan2023), DP02 (08Jun2023)

Table 59 Characteristics of Events of ILD Adjudicated as Drug-related ILD (Safety Analysis Set)

	Number (%) of Patients			
	Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
Time to first onset of adjudicated drug-related ILD (days) [a]				
n	49	1	217	276
Mean	242.4	121.0	229.9	214.0
Std Dev	205.17	NA	179.03	175.37
Median	141.0	121.0	170.0	166.5
Minimum, maximum	37, 835	121, 121	26, 960	26, 960
Time to first onset of investigator-reported ILD for adjudicated drug-related ILD (days) [b]				
n	49	1	217	276
Mean	264.3	121.0	266.3	246.1
Std Dev	223.25	NA	199.66	192.24
Median	168.0	121.0	212.0	204.0
Minimum, maximum	38, 892	121, 121	26, 1163	19, 1163
Duration of first ILD event (days) [c, d]				
n	22	1	136	173
Mean	92.5	33.0	88.0	79.9
Std Dev	64.62	NA	86.97	80.80
Median	81.5	33.0	50.0	48.0
Minimum, maximum	7, 226	33, 33	1, 395	1, 395
Outcome of the worst ILD event [e]				
Not Recovered/Not Resolved	23 (46.9)	0	61 (28.1)	83 (30.1)
Recovered/Resolved	20 (40.8)	1 (100)	117 (53.9)	146 (52.9)
Recovering/Resolving	3 (6.1)	0	12 (5.5)	14 (5.1)
Recovered/Resolved with Sequelae	2 (4.1)	0	10 (4.6)	10 (3.6)
Fatal	1 (2.0) [f]	0	11 (5.1)	16 (5.8)
Ongoing	0	0	1 (0.5)	1 (0.4)
Missing/Unknown	0	0	5 (2.3)	6 (2.2)

[c] Time to first onset of adjudicated drug-related ILD (days) = onset date of first ILD adjudicated as drug related - first dose date + 1.

[d] Time to first onset of investigator-reported ILD (days) = onset date of first investigator-reported ILD adjudicated as drug related - first dose date + 1.

[e] Duration of first ILD = investigator-reported end date – investigator-reported onset date + 1. End date is censored for ongoing ILDs.

[f] Descriptive statistics are based on patients with AE start and end dates. Partial date is imputed per the SAP.

[g] The denominator for outcome of the worst ILD event is number of patients with adjudicated drug-related ILD.

[h] Outcome of death as recorded by the investigator on the AE eCRF.

Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.
The pooled analysis group is based on first dose received for patients in each study. Adjudicated ILD events include all events that were adjudicated and considered drug related by the Adjudication Committee.

Supplementary data on recovery from ILD/pneumonitis:

A detailed summary of the 23 patients in study DB-06 who had not recovered from ILD at the time of DCO is provided below:

- 8 patients died prior to DCO, (6 patients died of BC progression and 2 patients died of other reasons post study safety follow-up period) and for all those patients, the investigator confirmed that ILD was ongoing at the time of death.
- 1 patient fully withdrew consent and the investigator confirmed that per the last scan prior to withdrawal of consent the event of ILD was ongoing.
- The ILD event outcome for the above 9 patients can be considered final with a status of ILD not recovered.
- 14 patients were alive at the time of DCO:
    - 4 patients were receiving study treatment at the time of DCO and for all these patients ILD outcome was changed to recovered after the primary analysis database lock.
    - 10 patients had discontinued study treatment at the time of DCO. The ILD outcome was changed to recovered for 5 patients after the primary analysis database lock and 5 patients are still in follow up by the investigator with a current outcome of not recovered.

Overall, out of 23 patients who had not recovered from ILD at the time of DCO, 9 are now recovered, leading to a lower percentage of patients who have not recovered, more in line with what was observed in both pools.

Table 60 Summary of Follow Up Duration for Patients Who Had Not Resolved/Not Recovered Worst ILD

	Study DB-06	Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	T-DXd 5.4 mg/kg Breast Cancer Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
Follow-up duration from adjudicated ILD onset date (days)			
n	23	61	83
Mean	277.2	352.6	322.8
Standard deviation	222.25	245.83	240.68
Median	235.0	278.0	276.0
Minimum, maximum	4, 886	3, 1183	-286, 1183 [a]

[a] Negative value corresponds to a data entry error identified in a single patient in DESTINY-PanTumor02. The onset date was entered by the ILD AC as 03 Dec 2022 instead of the correct date 03 Dec 2021. This error was discovered after the database lock date for DB-06 and will be corrected at the next DESTINY-PanTumor02 DCO. All future analyses and submissions of the T-DXd 5.4 mg/kg All Tumor Types Pool will reflect this corrected data. The error does not impact the overall assessment and conclusions on ILD as an ADR for T-DXd.

Table 61 Analysis of ILD/Pneumonitis (Safety Analysis Set)

	Number (%) of Patients			
	D9670C00001(DESTINY-Breast06)		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N=434)	Investigator choice of chemotherapy (N=417)	T-DXd 5.4 mg/kg breast cancer pool (N=1741)	T-DXd 5.4 mg/kg all tumor types pool (N=2335)
Selected TEAE: ILD/Pneumonitis				
Time to first onset (Days) [2]				
n	60	2	201	259
Mean	244.8	99.0	247.6	229.7
Std Dev	192.66	31.11	186.11	177.99
Median	173.0	99.0	204.0	174.0
Min, Max	38, 892	77, 121	26, 1163	19, 1163
Duration of first event (Days) [3]	118.0	42.0	76.0	66.0
Median (95% CI) [4]	(69.0, 152.0)	(33.0, 51.0)	(55.0, 104.0)	(50.0, 84.0)
Patients with Censored Duration	31	0	70	91
n [5]	29	2	131	168
Mean	99.4	42.0	89.6	78.7
Std Dev	73.46	12.73	88.02	81.64
Median	84.0	42.0	52.0	46.5
Min, Max	7, 260	33, 51	1, 395	1, 395

Table 62 Characteristics of ILD by the ILD Adjudication Committee and Investigator (Safety Analysis Set)

	Number (%) of Patients			
	D9670C00001(DESTINY-Breast06)		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N=434)	Investigator choice of chemotherapy (N=417)	T-DXd 5.4 mg/kg breast cancer pool (N=1741)	T-DXd 5.4 mg/kg all tumor types pool (N=2335)
Time to first onset of Adjudicated ILD (Days) [1]				
n	52	1	226	286
Mean	242.9	121.0	226.4	212.0
Std Dev	204.62	NA	178.96	174.93
Median	144.5	121.0	168.0	166.0
Min, Max	-7, 835	121, 121	-9, 960	-9, 960

Note: Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.
The pooled analysis group is based on first dose received for patients in each study.
Adjudicated ILD events include all adjudicated as ILD events by adjudication committee.
Std Dev = Standard Deviation
[1] Time to First onset of Adjudicated ILD (Days) = onset date of first ILD adjudicated by AC - first dose date + 1.
T-DXd 5.4 mg/kg Breast cancer Pool: J101(N=71), DB01(N=184), DB02(N=404), DB03(N=257), DB04(N=371), DB06(N=434), DP01(N=20).
T-DXd 5.4 mg/kg all Tumor Types Pool: J101(N=91), DB01(N=184), DB02(N=404), DB03(N=257), DB04(N=371), DB06(N=434), DL01(N=41), DL02(N=101), DC02(N=83), DP01(N=102), DP02(N=267)
Date of Data cut-off: T-DXd 5.4 mg/kg breast cancer pool from studies J101 (01Aug2019), DB01 (08Jun2020), DB02 (30Jun2022), DB03 (25Jul2022), DB04 (11Apr2022), DB06 (18MAR2024), DP01 (25Jan2023)
T-DXd 5.4 mg/kg all tumor types cancer pool from J101 (01Aug2019), DB01 (08Jun2020), DB02 (30Jun2022), DB03 (25Jul2022), DB04 (11Apr2022), DB06 (18MAR2024), DL01(03Dec2021), DL02(23Dec2022), DC02 (01Nov2022), DP01 (25Jan2023), DP02 (08Jun2023)
Reference: ADAE2

	Number (%) of Patients			
	D9670C00001(DESTINY-Breast06)		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N=434)	Investigator choice of chemotherapy (N=417)	T-DXd 5.4 mg/kg breast cancer pool (N=1741)	T-DXd 5.4 mg/kg all tumor types pool (N=2335)
Outcome of the worst ILD event [1]				
Fatal	1 (1.9)	0	13 (5.8)	18 (6.3)
Not Recovered/Not Resolved	24 (46.2)	0	65 (28.8)	88 (30.8)
Ongoing	0	0	1 (0.4)	1 (0.3)
Recovering/Resolving	3 (5.8)	0	13 (5.8)	15 (5.2)
Recovered/Resolved with Sequelae	3 (5.8)	0	11 (4.9)	11 (3.8)
Recovered/Resolved	21 (40.4)	1 (100)	118 (52.2)	147 (51.4)
Missing/Unknown	0	0	5 (2.2)	6 (2.1)

Note: The pooled analysis group is based on first dose received for patients in each study.
Adjudicated ILD events include all adjudicated events by adjudication committee.
[1] The denominator for outcome of the worst ILD event is number of patients with adjudicated ILD.
T-DXd 5.4 mg/kg Breast cancer Pool: J101(N=71), DB01(N=184), DB02(N=404), DB03(N=257), DB04(N=371), DB06(N=434), DP01(N=20).
T-DXd 5.4 mg/kg all Tumor Types Pool: J101(N=91), DB01(N=184), DB02(N=404), DB03(N=257), DB04(N=371), DB06(N=434), DL01(N=41), DL02(N=101), DC02(N=83), DP01(N=102), DP02(N=267)
Date of Data cut-off: T-DXd 5.4 mg/kg breast cancer pool from studies J101 (01Aug2019), DB01 (08Jun2020), DB02 (30Jun2022), DB03 (25Jul2022), DB04 (11Apr2022), DB06 (18MAR2024), DP01 (25Jan2023)
T-DXd 5.4 mg/kg all tumor types cancer pool from J101 (01Aug2019), DB01 (08Jun2020), DB02 (30Jun2022), DB03 (25Jul2022), DB04 (11Apr2022), DB06 (18MAR2024), DL01(03Dec2021), DL02(23Dec2022), DC02 (01Nov2022), DP01 (25Jan2023), DP02 (08Jun2023)
Reference: ADAE

- **Left Ventricular Ejection Fraction Decrease**

Table 63 Events of Left Ventricular Dysfunction Reported in Any Patient in Either Treatment Arm of Study DB-06 (Safety Analysis Set)

MedDRA Preferred Term CTCAE Grade	Number (%) of Patients			
	Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
Patients with LV dysfunction	35 (8.1)	16 (3.8)	89 (5.1)	108 (4.6)
1	1 (0.2)	0	11 (0.6)	14 (0.6)
2	31 (7.1)	13 (3.1)	69 (4.0)	80 (3.4)
3	3 (0.7)	2 (0.5)	9 (0.5)	13 (0.6)
4	0	1 (0.2)	0	1 (0.0)
5	0	0	0	0
≥ 3	3 (0.7)	3 (0.7)	9 (0.5)	14 (0.6)
Ejection fraction decreased	35 (8.1)	12 (2.9)	84 (4.8)	99 (4.2)
1	1 (0.2)	0	8 (0.5)	10 (0.4)
2	31 (7.1)	11 (2.6)	68 (3.9)	79 (3.4)
3	3 (0.7)	1 (0.2)	8 (0.5)	10 (0.4)
4	0	0	0	0
5	0	0	0	0
≥ 3	3 (0.7)	1 (0.2)	8 (0.5)	10 (0.4)
Left ventricular dysfunction	1 (0.2)	1 (0.2)	3 (0.2)	3 (0.1)
1	0	0	2 (0.1)	2 (0.1)
2	0	1 (0.2)	0	0
3	1 (0.2)	0	1 (0.1)	1 (0.0)
4	0	0	0	0
5	0	0	0	0
≥ 3	1 (0.2)	0	1 (0.1)	1 (0.0)
Cardiac failure	0	3 (0.7)	3 (0.2)	5 (0.2)
1	0	0	1 (0.1)	2 (0.1)
2	0	1 (0.2)	1 (0.1)	1 (0.0)
3	0	1 (0.2)	1 (0.1)	2 (0.1)
4	0	1 (0.2)	0	0
5	0	0	0	0
≥ 3	0	2 (0.5)	1 (0.1)	2 (0.1)

Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.
The pooled analysis group is based on first dose received for patients in each study.
PTs are sorted by descending frequency in the Study DB-06 T-DXd 5.4 mg/kg treatment arm.
If a patient had multiple occurrences of the same PT, the patient is counted once for the specific PT by worst CTCAE grade.
If a patient had multiple PTs, the patient is counted in each of the different PTs.

Table 64 Summary of LVEF Values, Based on ECHO/MUGA Scan Data (Safety Analysis Set)

LVEF Parameter Criteria	Number (%) of Patients			
	Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
Patients with worst LVEF CTCAE grade post baseline, n (%)				
Nonmissing n [a]	396	332	1617	2075
Grade 2	58 (14.6)	26 (7.8)	246 (15.2)	296 (14.3)
Patients with LVEF measurement after worst grade	42	15	188	213
Recovered from worst grade to ≥ 90% of baseline, n (%) [b,c]	35 (83.3)	10 (66.7)	146 (77.7)	164 (77.0)
Grade 3	3 (0.8)	2 (0.6)	14 (0.9)	15 (0.7)
Patients with LVEF measurement after worst grade	2	2	11	12
Recovered from worst grade to ≥ 90% of baseline, n (%) [b,c]	2 (100)	1 (50.0)	7 (63.6)	7 (58.3)
LVEF measurements at baseline				
n	432	417	1738	2332
Mean	63.6	63.1	63.9	63.9
Std Dev	6.16	5.79	6.20	6.10
Median	63.0	63.0	64.0	64.0
Minimum, maximum	50, 81	50, 83	50, 86	50, 86
40% to 49%	0	0	0	0
20% to 39%	0	0	0	0
< 20%	0	0	0	0
Lowest LVEF measurement post baseline				
n	398	332	1620	2078
Mean	59.6	61.2	60.1	60.3
Std Dev	5.49	5.41	5.70	5.74
Median	60.0	61.0	60.0	60.0
Minimum, maximum	24, 79	42, 76	24, 79	24, 80
40% to 49%	11 (2.5)	6 (1.4)	46 (2.6)	52 (2.2)
20% to 39%	1 (0.2)	0	3 (0.2)	3 (0.1)
< 20%	0	0	0	0
Change from baseline to lowest post-baseline measurement				
n	396	332	1617	2075
Mean	-4.0	-1.9	-3.9	-3.7
Std Dev	5.63	5.42	5.53	5.48

LVEF Parameter Criteria	Number (%) of Patients			
	Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
Median	-3.0	-1.0	-3.0	-3.0
Minimum, maximum	-38, 14	-25, 19	-38, 18	-38, 18
10% to 19% decrease in absolute value	55 (12.7)	22 (5.3)	228 (13.1)	275 (11.8)
≥ 20% decrease in absolute value	3 (0.7)	2 (0.5)	13 (0.7)	14 (0.6)
Highest LVEF measurement post-baseline				
n	398	332	1620	2078
Mean	65.7	65.0	66.6	66.2
Std Dev	5.78	6.11	6.25	6.25
Median	65.0	65.0	66.0	66.0
Minimum, maximum	50, 81	49, 84	43, 90	43, 90
Change from baseline to highest post-baseline measurement				
n	396	332	1617	2075
Mean	2.1	1.9	2.6	2.3
Std Dev	5.63	5.42	5.75	5.73
Median	2.0	2.0	2.0	2.0
Minimum, maximum	-27, 22	-25, 26	-27, 24	-27, 24
10% to 19% increase in absolute value	37 (8.5)	19 (4.6)	174 (10.0)	211 (9.0)
≥ 20% increase in absolute value	2 (0.5)	2 (0.5)	8 (0.5)	9 (0.4)

[b] Nonmissing n is the number of subjects with both baseline and post-baseline data. Percentages are calculated using the nonmissing n as the denominator.

≥ 90% baseline since worst grade is defined as the highest post-baseline LVEF after the measurement with worst grade that is ≥ 90% of the baseline LVEF value.

Percentages are calculated using the number of subjects having worst post-baseline LVEF at the specific grade. If there is no LVEF measurement after the worst grade of LVEF, the subject is not included in the denominator.

The baseline value is defined as the last nonmissing value before initial administration of study treatment.

Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.

This analysis was based on ECHO/MUGA scan data.

The pooled analysis group is based on first dose received for patients in each study.

Per CTCAE, LVEF was defined as follows: Grade 2 = resting LVEF ≥ 40% to < 50% or a 10% to < 20% decrease from baseline; Grade 3 = resting LVEF ≥ 20% to < 40% or a ≥ 20% decrease from baseline; Grade 4 = resting LVEF < 20%.

Table 65 Analysis of LVEF (Safety Analysis Set)

LVEF Parameter Criteria	Study DB-06		Supportive Safety Pools	
	T-DXd (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg Breast Cancer Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
Worst grade post-baseline LVEF				
Non-missing n [a]	396	332	1617	2075
Grade 2	58 (14.6)	26 (7.8)	246 (15.2)	296 (14.3)
Patients with LVEF measurement since worst grade	42	15	188	213
≥ 90% baseline since worst grade, n (%) [b,c]	35 (83.3)	10 (66.7)	146 (77.7)	164 (77.0)
Time to worst grade				
n	58	26	246	296
Mean	244.0	222.7	270.7	258.7
Standard deviation	158.53	136.84	204.45	197.23
Median	173.5	190.0	190.5	185.5
Minimum, maximum	78, 714	51, 593	24, 1156	22, 1156
Time to first ≥ 90% baseline since worst grade				
n	35	10	146	164
Mean	352.9	287.4	356.7	357.9
Standard deviation	183.58	115.40	188.27	194.18
Median	281.0	266.5	320.0	327.5
Minimum, maximum	102, 818	130, 457	102, 1009	43, 1009
Grade 3	3 (0.8)	2 (0.6)	14 (0.9)	15 (0.7)
Patients with LVEF measurement since worst grade	2	2	11	12
≥ 90% baseline since worst grade, n (%) [b,c]	2 (100)	1 (50.0)	7 (63.6)	7 (58.3)
Time to worst grade (days)				
n	3	2	14	15
Mean	91.0	110.0	189.4	194.6
Standard deviation	11.27	1.41	145.40	141.57
Median	97.0	110.0	122.5	147.0
Minimum, maximum	78, 98	109, 111	78, 532	78, 532
Time to first ≥ 90% baseline since worst grade (days)				
n	2	1	7	7
Mean	129.0	126.0	251.0	251.0
Standard deviation	35.36	NA	190.70	190.70
Median	129.0	126.0	154.0	154.0
Minimum, maximum	104, 154	126, 126	104, 593	104, 593

[a] Non-missing n is the number of patients with both baseline and post-baseline data. Percentages are calculated using the non-missing n as denominator.

[b] ≥ 90% baseline since worst grade is defined as the highest post-baseline LVEF after the measurement with worst grade that is ≥ 90% of the baseline LVEF value.

[c] Percentages are calculated using the number of patients having worst post-baseline at the specific grade. If there is no LVEF measurements after the worst grade of LVEF, the patient is not included in the denominator.

The baseline value is defined as the last non-missing value before initial administration of study treatment.

Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.

This analysis was based on ECHO/MUGA scan data.

The pooled analysis group is based on first dose received for patients in each study.

Per CTCAE 5.0, Grade 2 LVEF decrease is defined by a resting ejection fraction of ≥ 40 - < 50%, or a 10 - < 20% drop from baseline. Grade 3 LVEF decrease is defined by a resting ejection fraction of ≥ 20 - < 40%, or a ≥ 20% drop from baseline. Grade 4 LVEF decrease is defined by a resting ejection fraction < 20%.

In the All Tumour Type (ATT) Pool, the ADR left ventricular dysfunction led to treatment interruption in 27/2335 (1.2%) patients. The median time to worst grade LVEF was 4.8 months, and the median time to recovery (≥90% baseline) from worst grade LVEF was 6.3 months.

- **To Immunogenicity**

Infusion-related reactions (IRRs) with T-DXd treatment occurred infrequently (n=5 (1.2%)), with an event of Grade ≥ 3 reported in 1 (0.2%) patient, who subsequently discontinued treatment. Of the 22 (5.1%) patients in the T-DXd arm who were identified as having treatment-emergent ADA positive status, no patient experienced an event of IRR.

Laboratory findings

Table 66 Summary of Shifts from Baseline to Worst Post-baseline CTCAE Grade in Anemia (Hemoglobin Decrease) (Safety Analysis Set)

	Baseline CTCAE Grade	Number (%) of Patients with Worst Post-Baseline CTCAE Grade						
		Normal	1	2	3	4	Total	Missing
T-DXd 5.4 mg/kg (N = 434)	Normal	36 (8.4)	167 (38.7)	39 (9.0)	13 (3.0)	0	255 (59.2)	2
	1	1 (0.2)	75 (17.4)	54 (12.5)	16 (3.7)	0	146 (33.9)	1
	2	0	1 (0.2)	21 (4.9)	8 (1.9)	0	30 (7.0)	0
	3	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	Total	37 (8.6)	243 (56.4)	114 (26.5)	37 (8.6)	0	431 (100)	3
	Missing	0	0	0	0	0	0	0
Chemotherapy (N = 417)	Normal	68 (16.6)	133 (32.4)	30 (7.3)	5 (1.2)	0	236 (57.6)	4
	1	1 (0.2)	84 (20.5)	52 (12.7)	9 (2.2)	0	146 (35.6)	2
	2	0	3 (0.7)	18 (4.4)	7 (1.7)	0	28 (6.8)	1
	3	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	Total	69 (16.8)	220 (53.7)	100 (24.4)	21 (5.1)	0	410 (100)	7
	Missing	0	0	0	0	0	0	0
T-DXd 5.4 mg/kg BC Pool (N = 1741)	Normal	245 (14.2)	599 (34.6)	193 (11.1)	56 (3.2)	0	1093 (63.1)	2
	1	3 (0.2)	229 (13.2)	234 (13.5)	58 (3.4)	0	524 (30.3)	1
	2	0	2 (0.1)	78 (4.5)	32 (1.8)	0	112 (6.5)	1
	3	0	0	2 (0.1)	0	0	2 (0.1)	0
	4	0	0	0	0	0	0	0
	Total	248 (14.3)	830 (47.9)	507 (29.3)	146 (8.4)	0	1731 (100)	4
	Missing	0	2	1	2	0	5	1
T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)	Normal	285 (12.3)	718 (30.9)	222 (9.6)	68 (2.9)	0	1293 (55.7)	3
	1	3 (0.1)	357 (15.4)	366 (15.8)	100 (4.3)	0	826 (35.6)	3
	2	0	6 (0.3)	127 (5.5)	68 (2.9)	0	201 (8.7)	1
	3	0	0	2 (0.1)	0	0	2 (0.1)	0
	4	0	0	0	0	0	0	0
	Total	288 (12.4)	1081 (46.6)	717 (30.9)	236 (10.2)	0	2322 (100)	7
	Missing	0	2	1	2	0	5	1

Percentages are calculated using the number of patients with both baseline and post-baseline measurements (n in the Total column) as the denominator.
The pooled analysis group is based on first dose received for patients in each study.
The baseline value is defined as the last nonmissing value before initial administration of study treatment.

Table 67 Summary of Shifts from Baseline to Worst Post-baseline CTCAE Grade in Platelet Count (Safety Analysis Set)

	Baseline CTCAE Grade	Number (%) of Patients with Worst Post-Baseline CTCAE Grade						
		Normal	1	2	3	4	Total	Missing
T-DXd 5.4 mg/kg (N = 434)	Normal	216 (50.1)	157 (36.4)	24 (5.6)	12 (2.8)	8 (1.9)	417 (96.8)	2
	1	0	7 (1.6)	2 (0.5)	4 (0.9)	0	13 (3.0)	1
	2	0	0	1 (0.2)	0	0	1 (0.2)	0

	Baseline CTCAE Grade	Number (%) of Patients with Worst Post-Baseline CTCAE Grade						
		Normal	1	2	3	4	Total	Missing
	3	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	Total	216 (50.1)	164 (38.1)	27 (6.3)	16 (3.7)	8 (1.9)	431 (100)	3
	Missing	0	0	0	0	0	0	0
Chemotherapy (N = 417)	Normal	292 (71.2)	93 (22.7)	4 (1.0)	2 (0.5)	2 (0.5)	393 (95.9)	7
	1	1 (0.2)	14 (3.4)	2 (0.5)	0	0	17 (4.1)	0
	2	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	Total	293 (71.5)	107 (26.1)	6 (1.5)	2 (0.5)	2 (0.5)	410 (100)	7
	Missing	0	0	0	0	0	0	0
T-DXd 5.4 mg/kg BC Pool (N = 1741)	Normal	785 (45.4)	586 (33.9)	104 (6.0)	52 (3.0)	16 (0.9)	1543 (89.2)	3
	1	4 (0.2)	107 (6.2)	54 (3.1)	16 (0.9)	3 (0.2)	184 (10.6)	1
	2	1 (0.1)	0	1 (0.1)	1 (0.1)	0	3 (0.2)	0
	3	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	Total	790 (45.7)	693 (40.1)	159 (9.2)	69 (4.0)	19 (1.1)	1730 (100)	4
	Missing	2	4	0	0	0	6	1
T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)	Normal	1074 (46.3)	764 (32.9)	138 (5.9)	75 (3.2)	27 (1.2)	2078 (89.6)	6
	1	8 (0.3)	131 (5.6)	71 (3.1)	23 (1.0)	6 (0.3)	239 (10.3)	1
	2	1 (0.0)	0	1 (0.0)	1 (0.0)	0	3 (0.1)	0
	3	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	Total	1083 (46.7)	895 (38.6)	210 (9.1)	99 (4.3)	33 (1.4)	2320 (100)	7
	Missing	2	5	0	0	0	7	1

Percentages are calculated using the number of patients with both baseline and post-baseline measurements (n in the Total column) as the denominator.
The pooled analysis group is based on first dose received for patients in each study.
The baseline value is defined as the last nonmissing value before initial administration of study treatment.

Table 68 Summary of Shifts from Baseline to Worst Post-baseline CTCAE Grade in Neutrophil Count (Safety Analysis Set)

	Baseline CTCAE Grade	Number (%) of Patients with Worst Post-Baseline CTCAE Grade						
		Normal	1	2	3	4	Total	Missing
T-DXd 5.4 mg/kg (N = 434)	Normal	106 (24.6)	73 (16.9)	133 (30.9)	91 (21.1)	13 (3.0)	416 (96.5)	3
	1	0	0	3 (0.7)	8 (1.9)	0	11 (2.6)	0
	2	0	0	1 (0.2)	3 (0.7)	0	4 (0.9)	0
	3	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	Total	106 (24.6)	73 (16.9)	137 (31.8)	102 (23.7)	13 (3.0)	431 (100)	3
	Missing	0	0	0	0	0	0	0
	Normal	188 (45.9)	54 (13.2)	83 (20.2)	55 (13.4)	17 (4.1)	397 (96.8)	7

	Baseline CTCAE Grade	Number (%) of Patients with Worst Post-Baseline CTCAE Grade						
		Normal	1	2	3	4	Total	Missing
Chemotherapy (N = 417)	1	1 (0.2)	1 (0.2)	1 (0.2)	8 (2.0)	0	11 (2.7)	0
	2	0	1 (0.2)	0	1 (0.2)	0	2 (0.5)	0
	3	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	Total	189 (46.1)	56 (13.7)	84 (20.5)	64 (15.6)	17 (4.1)	410 (100)	7
	Missing	0	0	0	0	0	0	0
T-DXd 5.4 mg/kg BC Pool (N = 1741)	Normal	535 (30.9)	311 (18.0)	497 (28.7)	241 (13.9)	30 (1.7)	1614 (93.3)	4
	1	1 (0.1)	9 (0.5)	39 (2.3)	40 (2.3)	9 (0.5)	98 (5.7)	0
	2	1 (0.1)	1 (0.1)	5 (0.3)	9 (0.5)	0	16 (0.9)	0
	3	0	2 (0.1)	0	0	0	2 (0.1)	0
	4	0	0	0	0	0	0	0
	Total	537 (31.0)	323 (18.7)	541 (31.3)	290 (16.8)	39 (2.3)	1730 (100)	4
	Missing	2	0	3	1	0	6	1
T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)	Normal	818 (35.3)	388 (16.7)	616 (26.6)	315 (13.6)	54 (2.3)	2191 (94.5)	7
	1	1 (0.0)	11 (0.5)	43 (1.9)	43 (1.9)	9 (0.4)	107 (4.6)	0
	2	1 (0.0)	3 (0.1)	5 (0.2)	10 (0.4)	0	19 (0.8)	0
	3	0	2 (0.1)	0	0	0	2 (0.1)	0
	4	0	0	0	0	0	0	0
	Total	820 (35.4)	404 (17.4)	664 (28.6)	368 (15.9)	63 (2.7)	2319 (100)	7
	Missing	2	0	3	1	0	6	3

Percentages are calculated using the number of patients with both baseline and post-baseline measurements (n in the Total column) as the denominator.
The pooled analysis group is based on first dose received for patients in each study.
The baseline value is defined as the last nonmissing value before initial administration of study treatment.

Table 69 Summary of Shifts from Baseline to Worst Post-baseline CTCAE Grade in Lymphocyte Count (Safety Analysis Set)

	Baseline CTCAE Grade	Number (%) of Patients with Worst Post-Baseline CTCAE Grade						
		Normal	1	2	3	4	Total	Missing
T-DXd 5.4 mg/kg (N = 434)	Normal	114 (26.5)	82 (19.0)	90 (20.9)	40 (9.3)	4 (0.9)	330 (76.6)	2
	1	2 (0.5)	6 (1.4)	30 (7.0)	18 (4.2)	1 (0.2)	57 (13.2)	0
	2	0	1 (0.2)	20 (4.6)	18 (4.2)	0	39 (9.0)	1
	3	0	0	0	5 (1.2)	0	5 (1.2)	0
	4	0	0	0	0	0	0	0
	Total	116 (26.9)	89 (20.6)	140 (32.5)	81 (18.8)	5 (1.2)	431 (100)	3
	Missing	0	0	0	0	0	0	0
Chemotherapy (N = 417)	Normal	162 (39.5)	74 (18.0)	51 (12.4)	11 (2.7)	0	298 (72.7)	6
	1	2 (0.5)	12 (2.9)	33 (8.0)	9 (2.2)	1 (0.2)	57 (13.9)	1
	2	2 (0.5)	4 (1.0)	35 (8.5)	8 (2.0)	1 (0.2)	50 (12.2)	0
	3	0	0	2 (0.5)	2 (0.5)	1 (0.2)	5 (1.2)	0
	4	0	0	0	0	0	0	0
	Total	166 (40.5)	90 (22.0)	121 (29.5)	30 (7.3)	3 (0.7)	410 (100)	7
	Missing	0	0	0	0	0	0	0

	Baseline CTCAE Grade	Number (%) of Patients with Worst Post-Baseline CTCAE Grade						
		Normal	1	2	3	4	Total	Missing
T-DXd 5.4 mg/kg BC Pool (N = 1741)	Normal	546 (31.6)	237 (13.7)	391 (22.6)	134 (7.7)	13 (0.8)	1321 (76.4)	2
	1	6 (0.3)	29 (1.7)	101 (5.8)	61 (3.5)	6 (0.3)	203 (11.7)	0
	2	6 (0.3)	2 (0.1)	60 (3.5)	95 (5.5)	4 (0.2)	167 (9.7)	2
	3	0	0	1 (0.1)	31 (1.8)	6 (0.3)	38 (2.2)	0
	4	0	0	1 (0.1)	0	0	1 (0.1)	0
	Total	558 (32.3)	268 (15.5)	554 (32.0)	321 (18.6)	29 (1.7)	1730 (100)	4
	Missing	3	0	1	2	0	6	1
T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)	Normal	731 (31.7)	294 (12.7)	515 (22.3)	183 (7.9)	20 (0.9)	1743 (75.5)	3
	1	7 (0.3)	46 (2.0)	133 (5.8)	71 (3.1)	8 (0.3)	265 (11.5)	2
	2	9 (0.4)	2 (0.1)	92 (4.0)	131 (5.7)	7 (0.3)	241 (10.4)	2
	3	0	0	3 (0.1)	46 (2.0)	10 (0.4)	59 (2.6)	0
	4	0	0	1 (0.0)	0	0	1 (0.0)	0
	Total	747 (32.4)	342 (14.8)	744 (32.2)	431 (18.7)	45 (1.9)	2309 (100)	7
	Missing	3	1	1	2	0	7	12

Percentages are calculated using the number of patients with both baseline and post-baseline measurements (n in the Total column) as the denominator.
The pooled analysis group is based on first dose received for patients in each study.
The baseline value is defined as the last nonmissing value before initial administration of study treatment.

Table 70 Summary of Shifts (Increase) from Baseline to Worst Post-baseline CTCAE Grade in Serum Creatinine (Safety Analysis Set)

	Baseline CTCAE Grade	Number (%) of Patients with Worst Post-Baseline CTCAE Grade						
		Normal	1	2	3	4	Total	Missing
T-DXd 5.4 mg/kg (N = 434)	Normal	384 (89.1)	12 (2.8)	24 (5.6)	4 (0.9)	0	424 (98.4)	3
	1	0	2 (0.5)	0	3 (0.7)	0	5 (1.2)	0
	2	0	0	1 (0.2)	1 (0.2)	0	2 (0.5)	0
	3	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	Total	384 (89.1)	14 (3.2)	25 (5.8)	8 (1.9)	0	431 (100)	3
	Missing	0	0	0	0	0	0	0
Chemotherapy (N = 417)	Normal	371 (90.7)	7 (1.7)	21 (5.1)	4 (1.0)	0	403 (98.5)	7
	1	1 (0.2)	4 (1.0)	1 (0.2)	0	0	6 (1.5)	0
	2	0	0	0	0	0	0	1
	3	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	Total	372 (91.0)	11 (2.7)	22 (5.4)	4 (1.0)	0	409 (100)	8
	Missing	0	0	0	0	0	0	0
T-DXd 5.4 mg/kg BC Pool (N = 1741)	Normal	1435 (82.9)	152 (8.8)	66 (3.8)	7 (0.4)	1 (0.1)	1661 (96.0)	7
	1	4 (0.2)	49 (2.8)	4 (0.2)	5 (0.3)	0	62 (3.6)	0
	2	0	1 (0.1)	4 (0.2)	2 (0.1)	0	7 (0.4)	0
	3	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	Total	1439 (83.2)	202 (11.7)	74 (4.3)	14 (0.8)	1 (0.1)	1730 (100)	7
	Missing	3	0	0	0	0	3	1
T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)	Normal	1834 (79.1)	223 (9.6)	108 (4.7)	12 (0.5)	1 (0.0)	2178 (94.0)	11
	1	5 (0.2)	97 (4.2)	17 (0.7)	6 (0.3)	0	125 (5.4)	1
	2	0	2 (0.1)	8 (0.3)	5 (0.2)	0	15 (0.6)	0
	3	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	Total	1839 (79.3)	322 (13.9)	133 (5.7)	23 (1.0)	1 (0.0)	2318 (100)	12
	Missing	4	0	0	0	0	4	1

Percentages are calculated using the number of patients with both baseline and post-baseline measurements (n in the Total column) as the denominator.
The pooled analysis group is based on first dose received for patients in each study.
The baseline value is defined as the last nonmissing value before initial administration of study treatment.

Table 71 Renal Function Abnormalities (Safety Analysis Set)

Creatinine clearance (mL/min)	Number (%) of Patients			
	Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
Nonmissing n [a]	431	409	1718	2308
Minimum post-baseline value				
< 30	12 (2.8)	6 (1.5)	32 (1.9)	59 (2.6)
30 to < 60	107 (24.8)	93 (22.7)	403 (23.5)	621 (26.9)
60 to < 90	211 (49.0)	179 (43.8)	807 (47.0)	1032 (44.7)
≥ 90 [c]	101 (23.4)	131 (32.0)	476 (27.7)	596 (25.8)

[a] Nonmissing n is the number of patients with both baseline and post-baseline data.
The pooled analysis group is based on first dose received for patients in each study.
CrCl was computed by the calculation by each site. Percentages are calculated using the nonmissing n as denominator.

Table 72 Summary of Shifts (Decrease) from Baseline to Worst Post-Baseline CTCAE Grade in Potassium (Hypokalemia) (Safety Analysis Set)

	Baseline CTCAE Grade	Number (%) of Patients with Worst Post-Baseline CTCAE Grade						
		Normal	1	2	3	4	Total	Missing
T-DXd 5.4 mg/kg (N = 434)	Normal	278 (64.5)	116 (26.9)	0	24 (5.6)	2 (0.5)	420 (97.4)	2
	1	3 (0.7)	1 (0.2)	0	5 (1.2)	2 (0.5)	11 (2.6)	1
	2	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	Total	281 (65.2)	117 (27.1)	0	29 (6.7)	4 (0.9)	431 (100)	3
	Missing	0	0	0	0	0	0	0
Chemotherapy (N = 417)	Normal	342 (83.8)	48 (11.8)	0	7 (1.7)	4 (1.0)	401 (98.3)	8
	1	1 (0.2)	4 (1.0)	0	1 (0.2)	0	6 (1.5)	0
	2	0	0	0	0	0	0	0
	3	0	1 (0.2)	0	0	0	1 (0.2)	0
	4	0	0	0	0	0	0	0
	Total	343 (84.1)	53 (13.0)	0	8 (2.0)	4 (1.0)	408 (100)	8
	Missing	1	0	0	0	0	1	0
T-DXd 5.4 mg/kg BC Pool (N = 1741)	Normal	1151 (66.6)	199 (11.5)	254 (14.7)	67 (3.9)	4 (0.2)	1675 (97.0)	4
	1	5 (0.3)	6 (0.3)	0	6 (0.3)	3 (0.2)	20 (1.2)	1
	2	3 (0.2)	0	18 (1.0)	8 (0.5)	2 (0.1)	31 (1.8)	0
	3	0	0	0	1 (0.1)	0	1 (0.1)	0
	4	0	0	0	0	0	0	0
	Total	1159 (67.1)	205 (11.9)	272 (15.7)	82 (4.7)	9 (0.5)	1727 (100)	5
	Missing	5	2	1	0	0	8	1
T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)	Normal	1537 (66.3)	300 (12.9)	300 (12.9)	95 (4.1)	7 (0.3)	2239 (96.6)	7
	1	9 (0.4)	14 (0.6)	0	11 (0.5)	3 (0.1)	37 (1.6)	1
	2	3 (0.1)	0	20 (0.9)	9 (0.4)	3 (0.1)	35 (1.5)	0
	3	0	1 (0.0)	2 (0.1)	1 (0.0)	0	4 (0.2)	0
	4	0	0	0	0	2 (0.1)	2 (0.1)	0
	Total	1549 (66.9)	315 (13.6)	322 (13.9)	116 (5.0)	15 (0.6)	2317 (100)	8
	Missing	6	2	1	0	0	9	1

Percentages are calculated using the number of patients with both baseline and post-baseline measurements (n in the Total column) as the denominator.
The pooled analysis group is based on first dose received for patients in each study.
The baseline value is defined as the last nonmissing value before initial administration of study treatment.

Table 73 Hepatic Function Abnormalities (Safety Analysis Set)

	Number (%) of Patients			
	Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
Alanine aminotransferase				
Nonmissing n [a]	431	408	1730	2320
Baseline ≥ ULN	164 (38.1)	142 (34.8)	483 (27.9)	577 (24.9)
Maximum post baseline				
≥ 3 × ULN	86 (20.0)	39 (9.6)	192 (11.1)	243 (10.5)

≥ 5 × ULN	25 (5.8)	9 (2.2)	44 (2.5)	64 (2.8)
≥ 6 × ULN	7 (1.6)	2 (0.5)	10 (0.6)	19 (0.8)
≥ 10 × ULN	5 (1.2)	2 (0.5)	7 (0.4)	10 (0.4)
≥ 20 × ULN	0	1 (0.2)	0	1 (0.0)
Aspartate aminotransferase				
Nonmissing n [a]	431	409	1729	2319
Baseline ≥ ULN	231 (53.6)	212 (51.8)	821 (47.5)	974 (42.0)
Maximum post baseline				
≥ 3 × ULN	95 (22.0)	51 (12.5)	250 (14.5)	311 (13.4)
≥ 5 × ULN	29 (6.7)	20 (4.9)	67 (3.9)	84 (3.6)
≥ 6 × ULN	11 (2.6)	7 (1.7)	23 (1.3)	32 (1.4)
≥ 10 × ULN	8 (1.9)	3 (0.7)	15 (0.9)	19 (0.8)
≥ 20 × ULN	2 (0.5)	1 (0.2)	5 (0.3)	6 (0.3)
ALT or AST				
Nonmissing n [a]	431	409	1730	2320
Baseline ≥ ULN	240 (55.7)	224 (54.8)	856 (49.5)	1032 (44.5)
Maximum post-baseline				
≥ 3 × ULN	121 (28.1)	67 (16.4)	319 (18.4)	398 (17.2)
≥ 5 × ULN	41 (9.5)	22 (5.4)	93 (5.4)	118 (5.1)
≥ 6 × ULN	14 (3.2)	8 (2.0)	26 (1.5)	38 (1.6)
≥ 10 × ULN	10 (2.3)	4 (1.0)	17 (1.0)	22 (0.9)
≥ 20 × ULN	2 (0.5)	2 (0.5)	5 (0.3)	7 (0.3)
Alkaline phosphatase				
Nonmissing n [a]	429	409	1729	2319
Baseline ≥ ULN	111 (25.9)	108 (26.4)	546 (31.6)	773 (33.3)
Maximum post-baseline				
≥ 1.5 × ULN	168 (39.2)	96 (23.5)	701 (40.5)	959 (41.4)
≥ 2 × ULN	105 (24.5)	67 (16.4)	429 (24.8)	606 (26.1)
Total bilirubin				
Nonmissing n [a]	430	408	1730	2320
Baseline ≥ ULN	7 (1.6)	11 (2.7)	58 (3.4)	80 (3.4)
Maximum post-baseline				
≥ 1.5 × ULN	35 (8.1)	31 (7.6)	134 (7.7)	191 (8.2)
≥ 2 × ULN	19 (4.4)	11 (2.7)	61 (3.5)	95 (4.1)
≥ 3 × ULN	8 (1.9)	6 (1.5)	25 (1.4)	42 (1.8)
TBL elevation concurrent with ALT or AST elevation [b]				
Nonmissing n [a]	430	408	1728	2318
ALT or AST ≥ 3 × ULN and TBL ≥ 2 × ULN	9 (2.1)	6 (1.5)	29 (1.7)	49 (2.1)
TBL elevation concurrent with ALT or AST elevation and ALP < 2 × ULN [b]				
Nonmissing n [a]	428	408	1725	2315
ALT or AST ≥ 3 × ULN and TBL ≥ 2 × ULN and ALP < 2 × ULN	5 (1.2)	3 (0.7)	17 (1.0)	26 (1.1)

[d] Nonmissing n is the number of patients with both baseline and post-baseline data. Percentages are calculated using the nonmissing n as denominator.

[e] "Concurrent" is defined as these abnormalities occurred within a 28-day window.
The pooled analysis group is based on tumor type and first dose received for patients in each study.
The baseline value is defined as the last nonmissing value before initial administration of study treatment.

ECG

Table 74 Summary of QT and QTcF Intervals (Safety Analysis Set)

	Number (%) of Patients			
	Study DB-06		**Supportive Safety Pools**	
	T-DXd 5.4 mg/kg (N = 434)	**Chemotherapy (N = 417)**	**T-DXd 5.4 mg/kg BC Pool (N = 1741)**	**T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)**
QT interval (msec)				
Nonmissing n [a]	410	364	1711	2215
New > 470 msec (female) or New > 450 msec (male) [b]	5 (1.2)	6 (1.6)	77 (4.5)	91 (4.1)
New > 480 msec [b]	2 (0.5)	5 (1.4)	37 (2.2)	43 (1.9)
New > 500 msec [b]	2 (0.5)	0	20 (1.2)	20 (0.9)
Increase from baseline > 30 msec	112 (27.3)	81 (22.3)	719 (42.0)	849 (38.3)
Increase from baseline > 60 msec	24 (5.9)	16 (4.4)	188 (11.0)	218 (9.8)
Maximum post-baseline value (msec)				
n	410	364	1711	2215
Mean	399.96	395.74	414.42	409.91
Std Dev	30.866	32.583	33.397	34.687
Median	400.00	395.00	414.00	410.00
Minimum, maximum	300, 578	311, 500	300, 610	280, 610
Maximum change from baseline value (msec)				
n	410	364	1711	2215
Mean	15.96	10.04	27.66	23.99
Std Dev	28.462	28.854	29.554	30.818
Median	14.67	8.00	25.83	22.67
Minimum, maximum	-76.7, 148	-62, 115	-76.7, 248.3	-112, 248.3
QTcF interval (msec)				
Nonmissing n [a]	410	364	1711	2213
New > 470 msec (female) or New > 450 msec (male) [b]	15 (3.7)	4 (1.1)	157 (9.2)	188 (8.5)
New > 480 msec [b]	8 (2.0)	4 (1.1)	91 (5.3)	101 (4.6)
New > 500 msec [b]	1 (0.2)	2 (0.5)	32 (1.9)	35 (1.6)
Increase from baseline > 30 msec	66 (16.1)	37 (10.2)	459 (26.8)	539 (24.4)
Increase from baseline > 60 msec	7 (1.7)	5 (1.4)	94 (5.5)	107 (4.8)
Maximum post-baseline value (msec)				

	Number (%) of Patients			
	Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
n	410	364	1711	2213
Mean	428.72	423.85	438.81	435.53
Std Dev	22.968	23.648	26.775	27.100
Median	427.00	422.00	435.78	433.10
Minimum, maximum	367, 633	373, 564	367, 694.4	323, 694.4
Maximum change from baseline value (msec)				
n	410	364	1711	2213
Mean	12.73	8.15	21.53	19.07
Std Dev	21.298	19.814	26.032	26.990
Median	12.00	7.00	17.66	15.74
Minimum, maximum	-40, 183	-48.3, 149	-72.5, 277.2	-98, 337

[f] Nonmissing n is the number of patients with both baseline and post-baseline data. Percentages are calculated using the nonmissing n as denominator.

[g] New is defined as an abnormal ECG finding at post-baseline that is not present at baseline.

The pooled analysis group is based on first dose received for patients in each study.
The baseline value is defined as the last nonmissing value before initial administration of study treatment.
If multiple ECG measurements are taken at the baseline, the average of all baseline values will be used as baseline.

Safety in special populations

Intrinsic factors

Table 75 Overall Summary of Treatment-emergent Adverse Events by Age Group (Safety Analysis Set)

Parameter	< 65 years				≥ 65 years			
	Study DB-06		Supportive Safety Pools		Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 302)	Chemo-therapy (N = 286)	T-DXd 5.4 mg/kg BC Pool (N = 1320)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 1661)	T-DXd 5.4 mg/kg (N = 132)	Chemo-therapy (N = 131)	T-DXd 5.4 mg/kg BC Pool (N = 421)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 674)
Duration of treatment (months) [a]								
Median	11.45	5.52	10.82	9.66	10.50	7.36	9.95	8.10
Minimum, maximum	0.7, 33.3	0.1, 26.9	0.2, 44.0	0.2, 44.0	0.4, 39.6	0.2, 35.9	0.4, 45.1	0.4, 45.1
Patients with any TEAE	301 (99.7)	272 (95.1)	1313 (99.5)	1651 (99.4)	128 (97.0)	125 (95.4)	417 (99.0)	666 (98.8)

Parameter	< 65 years				≥ 65 years			
	Study DB-06		Supportive Safety Pools		Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 302)	Chemo-therapy (N = 286)	T-DXd 5.4 mg/kg BC Pool (N = 1320)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 1661)	T-DXd 5.4 mg/kg (N = 132)	Chemo-therapy (N = 131)	T-DXd 5.4 mg/kg BC Pool (N = 421)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 674)
TEAEs with worst CTCAE Grade ≥ 3 [b]	154 (51.0)	115 (40.2)	686 (52.0)	865 (52.1)	75 (56.8)	70 (53.4)	255 (60.6)	415 (61.6)
Treatment-emergent SAEs	52 (17.2)	38 (13.3)	299 (22.7)	408 (24.6)	36 (27.3)	29 (22.1)	130 (30.9)	244 (36.2)
TEAEs associated with study drug discontinuation	38 (12.6)	23 (8.0)	211 (16.0)	244 (14.7)	24 (18.2)	16 (12.2)	96 (22.8)	132 (19.6)
TEAEs associated with study drug interruption	152 (50.3)	101 (35.3)	588 (44.5)	724 (43.6)	58 (43.9)	59 (45.0)	206 (48.9)	315 (46.7)
TEAEs associated with dose reduction	75 (24.8)	98 (34.3)	308 (23.3)	371 (22.3)	32 (24.2)	63 (48.1)	109 (25.9)	161 (23.9)
TEAEs associated with an outcome of death [c]	5 (1.7)	2 (0.7)	37 (2.8)	50 (3.0)	6 (4.5)	4 (3.1)	19 (4.5)	46 (6.8)
Patients with any drug-related TEAE [d]	295 (97.7)	256 (89.5)	1284 (97.3)	1586 (95.5)	122 (92.4)	117 (89.3)	405 (96.2)	622 (92.3)
Drug-related TEAEs with worst CTCAE Grade ≥ 3 [b]	116 (38.4)	82 (28.7)	545 (41.3)	659 (39.7)	60 (45.5)-	49 (37.4)	205 (48.7)	312 (46.3)
Drug-related treatment-emergent SAEs	27 (8.9)	14 (4.9)	143 (10.8)	172 (10.4)	19 (14.4)	10 (7.6)	65 (15.4)	109 (16.2)

Parameter	< 65 years				≥ 65 years			
	Study DB-06		Supportive Safety Pools		Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/ kg (N = 302)	Chemo-therapy (N = 286)	T-DXd 5.4 mg/ kg BC Pool (N = 1320)	T-DXd 5.4 mg/ kg All Tumor Types Pool (N = 1661)	T-DXd 5.4 mg/ kg (N = 132)	Chemo-therapy (N = 131)	T-DXd 5.4 mg/ kg BC Pool (N = 421)	T-DXd 5.4 mg/ kg All Tumor Types Pool (N = 674)
Drug-related TEAEs associated with study drug discontinuation	37 (12.3)	19 (6.6)	180 (13.6)	205 (12.3)	19 (14.4)	14 (10.7)	86 (20.4)	112 (16.6)
Drug-related TEAEs associated with study drug interruption	90 (29.8)	67 (23.4)	412 (31.2)	475 (28.6)	37 (28.0)	36 (27.5)	151 (35.9)	213 (31.6)
Drug-related TEAEs associated with dose reduction	65 (21.5)	95 (33.2)	287 (21.7)	347 (20.9)	29 (22.0)	60 (45.8)	96 (22.8)	142 (21.1)
Drug-related TEAEs associated with an outcome of death [c]	2 (0.7)	0	13 (1.0)	14 (0.8)	3 (2.3)	0	7 (1.7)	14 (2.1)

[c] Duration of treatment (months) = (date of the last dose - date of the first dose + a cycle length (day))/30.44. 1 month = 365.25/12 = 30.44 days

[d] A patient was counted once at the maximum severity.

For specific TEAEs associated with outcome of death, refer to.

If relationship was missing, the TEAE was considered to be related to the drug.

Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.

Table 76 All Adverse Drug Reactions in At Least 65 Years of Age in T-DXd 5.4 mg/kg breast cancer pool and T-DXd 5.4 mg/kg all tumour types pool, by MedDRA System Organ Class, Preferred Term/Grouped Term and Frequency (Safety Analysis Set)

MedDRA System Organ Class Preferred Term/ Grouped Term	T-DXd 5.4 mg/kg breast cancer pool (N = 421)					T-DXd 5.4 mg/kg all tumor types pool (N = 674)				
	Frequency [1]	Number (%) of Subjects				Frequency [1]	Number (%) of Subjects			
		CTCAE Grade			SAE		CTCAE Grade			SAE
		All Grades	Grade 3 or 4	Grade 5			All Grades	Grade 3 or 4	Grade 5	
Subjects with any ADR	--	415 (98.6)	204 (48.5)	6 (1.4)	67 (15.9)	--	656 (97.3)	322 (47.8)	16 (2.4)	133 (19.7)

Table 77 All Adverse Drug Reactions in Subjects Less than 65 Years in T-DXd 5.4 mg/kg breast cancer pool and T-DXd 5.4 mg/kg all tumour types pool. By MedDRA System Organ Class, Preferred Term/Grouped Term and Frequency (Safety Analysis Set)

MedDRA System Organ Class Preferred Term/ Grouped Term	T-DXd 5.4 mg/kg breast cancer pool (N = 1320)					T-DXd 5.4 mg/kg all tumor types pool (N = 1661)				
	Frequency [1]	Number (%) of Subjects				Frequency [1]	Number (%) of Subjects			
		CTCAE Grade			SAE		CTCAE Grade			SAE
		All Grades	Grade 3 or 4	Grade 5			All Grades	Grade 3 or 4	Grade 5	
Subjects with any ADR	--	1306 (98.9)	572 (43.3)	14 (1.1)	153 (11.6)	--	1638 (98.6)	710 (42.7)	16 (1.0)	197 (11.9)

Table 78 AEs by age range

	T-DXd				Chemotherapy			
MedDRA Terms	Age <65 n (%)	Age 65-74 n (%)	Age 75-84 n (%)	Age 85+ n (%)	Age <65 n (%)	Age 65-74 n (%)	Age 75-84 n (%)	Age 85+ n (%)
Total Subjects Number per Category	301	97	33	3	285	96	36	0
Total AEs	300 (99.7)	95 (97.9)	31 (93.9)	3 (100)	271 (95.1)	90 (93.8)	36 (100)	0
Serious AEs – Total	52 (17.3)	25 (25.8)	11 (33.3)	0	37 (13.0)	19 (19.8)	11 (30.6)	0
- Fatal	5 (1.7)	2 (2.1)	4 (12.1)	0	2 (0.7)	3 (3.1)	1 (2.8)	0
- Hospitalization/ prolong existing hospitalization	49 (16.3)	23 (23.7)	11 (33.3)	0	33 (11.6)	19 (19.8)	11 (30.6)	0
- Life-threatening	5 (1.7)	4 (4.1)	3 (9.1)	0	1 (0.4)	4 (4.2)	0	0
- Disability/incapacity	1 (0.3)	0	1 (3.0)	0	2 (0.7)	0	1(2.8)	0
- Other (medically significant)	11 (3.7)	4 (4.1)	0	0	6 (2.1)	5 (5.2)	2 (5.6)	0
AE leading to treatment discontinuation	38 (12.6)	14 (14.4)	10 (30.3)	0	23 (8.1)	11 (11.5)	5 (13.9)	0
Psychiatric disorders[a]	38 (12.6)	9 (9.3)	6 (18.2)	0	16 (5.6)	9 (9.4)	7 (19.4)	0
Nervous system disorders[a]	122 (40.5)	35 (36.1)	11 (33.3)	1 (33.3)	126 (44.2)	45 (46.9)	17 (47.2)	0
Accidents and injuries[b]	16 (5.3)	9 (9.3)	4 (12.1)	2 (66.7)	17 (6.0)	10 (10.4)	4 (11.1)	0
Cardiac disorders[a]	23 (7.6)	8 (8.2)	2 (6.1)	2 (66.7)	14 (4.9)	8 (8.3)	3 (8.3)	0
Vascular disorders[a]	40 (13.3)	18 (18.6)	2 (6.1)	0	32 (11.2)	13 (13.5)	7 (19.4)	0
Cerebrovascular disorders [c]	1 (0.3)	0	0	0	1 (0.4)	0	1 (2.8)	0
Infections and infestations [a]	172 (57.1)	48 (49.5)	12 (36.4)	1 (33.3)	99 (34.7)	45 (46.9)	17 (47.2)	0
Anticholinergic syndrome	0	0	0	0	0	0	0	0
Quality of life decreased	0	0	0	0	0	0	0	0
Sum of orthostatic hypotension, fall, loss of consciousness, syncope, dizziness, ataxia [d]	29 (9.6)	10 (10.3)	5 (15.2)	2 (66.7)	21 (7.4)	9 (9.4)	7 (19.4)	0

[a] MedDRA System Organ Class (SOC).

[b] Accidents and Injuries MedDRA Standardised MedDRA Query (SMQ; narrow search).
[c] Includes central nervous system haemorrhages and cerebrovascular conditions SMQ (narrow search)
[d] Grouped term including PTs of orthostatic hypotension, fall, loss of consciousness, syncope, dizziness, and ataxia. The PT of fracture was removed to avoid duplication given all fractures are included in the Accidents and Injuries SMQ.
Includes AEs with an onset date or worsening on or after the date of first dose and up to and including 47 days following the date of last dose of study medication or before the initiation of the first subsequent cancer therapy (whichever occurs first).
MedDRA version 26.1.

Table 79 Subgroup Analysis of Overall Summary of Treatment-Emergent Adverse Events in Patients ≥ 75 (Safety Analysis Set)

Age: >=75 years

	Number (%) of Patients			
	D9670C00001(DESTINY-Breast06)		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N=36)	Investigator choice of chemotherapy (N=36)	T-DXd 5.4 mg/kg breast cancer pool (N=86)	T-DXd 5.4 mg/kg all tumor types pool (N=147)
Treatment-Emergent Adverse Events (TEAE)	34 (94.4)	36 (100)	84 (97.7)	145 (98.6)
TEAE with CTCAE Grade >= 3	24 (66.7)	20 (55.6)	48 (55.8)	90 (61.2)
TEAE associated with an outcome of death	4 (11.1)	1 (2.8)	4 (4.7)	14 (9.5)
TEAE associated with study drug discontinuation	10 (27.8)	5 (13.9)	24 (27.9)	35 (23.8)
TEAE associated with study drug interruption	16 (44.4)	12 (33.3)	37 (43.0)	67 (45.6)
TEAE associated with dose reduction	7 (19.4)	20 (55.6)	21 (24.4)	31 (21.1)
Drug-Related TEAE (Related TEAE)	32 (88.9)	32 (88.9)	82 (95.3)	136 (92.5)
Related TEAE with CTCAE Grade >= 3	22 (61.1)	15 (41.7)	42 (48.8)	69 (46.9)
Related TEAE associated with an outcome of death	3 (8.3)	0	3 (3.5)	5 (3.4)
Related TEAE associated with study drug discontinuation	10 (27.8)	4 (11.1)	24 (27.9)	32 (21.8)
Related TEAE associated with study drug interruption	10 (27.8)	6 (16.7)	26 (30.2)	42 (28.6)
Related TEAE associated with dose reduction	7 (19.4)	19 (52.8)	17 (19.8)	27 (18.4)

Table 80 Overall Summary of Treatment-emergent Adverse Events by Race (Safety Analysis Set)

Parameter	White				Asian				Other			
	Study DB-06		Supportive Safety Pools		Study DB-06		Supportive Safety Pools		Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 231)	Chemo-therapy (N = 223)	T-DXd 5.4 mg/kg BC Pool (N = 878)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 1172)	T-DXd 5.4 mg/kg (N = 153)	Chemo-therapy (N = 147)	T-DXd 5.4 mg/kg BC Pool (N = 681)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 928)	T-DXd 5.4 mg/kg (N = 50)	Chemo-therapy (N = 477)	T-DXd 5.4 mg/kg BC Pool (N = 178)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 231)
Duration of treatment (months) [a]												
Median	10.35	5.59	10.27	8.87	11.50	7.36	11.04	9.59	12.22	4.17	11.86	9.66
Minimum, maximum	0.4, 37.1	0.1, 26.9	0.2, 39.1	0.2, 39.1	0.7, 39.6	0.1, 35.9	0.7, 45.1	0.7, 45.1	0.6, 30.6	0.2, 22.0	0.6, 39.0	0.6, 39.0
Patients with any TEAE	227 (98.3)	214 (96.0)	871 (99.2)	1159 (98.9)	153 (100)	138 (93.9)	679 (99.7)	925 (99.7)	49 (98.0)	45 (95.7)	176 (98.9)	229 (99.1)
TEAEs with worst CTCAE Grade ≥ 3 [b]	114 (49.4)	110 (49.3)	452 (51.5)	605 (51.6)	93 (60.8)	59 (40.1)	397 (58.3)	553 (59.6)	22 (44.0)	16 (34.0)	89 (50.0)	119 (51.5)
Treatment-emergent SAEs	48 (20.8)	43 (19.3)	227 (25.9)	333 (28.4)	32 (20.9)	16 (10.9)	160 (23.5)	253 (27.3)	8 (16.0)	8 (17.0)	40 (22.5)	64 (27.7)
TEAEs associated with study drug discontinuation	33 (14.3)	22 (9.9)	143 (16.3)	177 (15.1)	26 (17.0)	7 (4.8)	133 (19.5)	165 (17.8)	3 (6.0)	10 (21.3)	31 (17.4)	34 (14.7)
TEAEs associated with study drug interruption	110 (47.6)	95 (42.6)	371 (42.3)	474 (40.4)	80 (52.3)	51 (34.7)	343 (50.4)	461 (49.7)	20 (40.0)	14 (29.8)	77 (43.3)	101 (43.7)
TEAEs associated with dose reduction	49 (21.2)	93 (41.7)	187 (21.3)	236 (20.1)	50 (32.7)	52 (35.4)	189 (27.8)	249 (26.8)	8 (16.0)	16 (34.0)	39 (21.9)	45 (19.5)
TEAEs associated with an outcome of death [c]	7 (3.0)	4 (1.8)	40 (4.6)	61 (5.2)	2 (1.3)	2 (1.4)	12 (1.8)	28 (3.0)	2 (4.0)	0	4 (2.2)	7 (3.0)

Parameter	White				Asian				Other			
	Study DB-06		Supportive Safety Pools		Study DB-06		Supportive Safety Pools		Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 231)	Chemo-therapy (N = 223)	T-DXd 5.4 mg/kg BC Pool (N = 878)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 1172)	T-DXd 5.4 mg/kg (N = 153)	Chemo-therapy (N = 147)	T-DXd 5.4 mg/kg BC Pool (N = 681)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 928)	T-DXd 5.4 mg/kg (N = 50)	Chemo-therapy (N = 477)	T-DXd 5.4 mg/kg BC Pool (N = 178)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 231)
Patients with any drug-related TEAE [d]	221 (95.7)	200 (89.7)	847 (96.5)	1096 (93.5)	151 (98.7)	132 (89.8)	668 (98.1)	891 (96.0)	45 (90.0)	41 (87.2)	170 (95.5)	217 (93.9)
Drug-related TEAEs with worst CTCAE Grade ≥ 3 [b]	79 (34.2)	68 (30.5)	334 (38.0)	423 (36.1)	79 (51.6)	50 (34.0)	345 (50.7)	461 (49.7)	18 (36.0)	13 (27.7)	69 (38.8)	85 (36.8)
Drug-related treatment-emergent SAEs	24 (10.4)	12 (5.4)	102 (11.6)	134 (11.4)	18 (11.8)	6 (4.1)	85 (12.5)	119 (12.8)	4 (8.0)	6 (12.8)	20 (11.2)	27 (11.7)
Drug-related TEAEs associated with study drug discontinuation	28 (12.1)	18 (8.1)	118 (13.4)	142 (12.1)	25 (16.3)	6 (4.1)	119 (17.5)	143 (15.4)	3 (6.0)	9 (19.1)	29 (16.3)	32 (13.9)
Drug-related TEAEs associated with study drug interruption	60 (26.0)	58 (26.0)	232 (26.4)	271 (23.1)	55 (35.9)	36 (24.5)	276 (40.5)	351 (37.8)	12 (24.0)	9 (19.1)	52 (29.2)	63 (27.3)
Drug-related TEAEs associated with dose reduction	45 (19.5)	88 (39.5)	166 (18.9)	211 (18.0)	42 (27.5)	52 (35.4)	178 (26.1)	234 (25.2)	7 (14.0)	15 (31.9)	37 (20.8)	42 (18.2)
Drug-related TEAEs associated with an outcome of death [c]	3 (1.3)	0	15 (1.7)	19 (1.6)	2 (1.3)	0	5 (0.7)	7 (0.8)	0	0	0	2 (0.9)

[a] Duration of treatment (months) = (date of the last dose - date of the first dose + a cycle length (day))/30.44. 1 month = 365.25/12 = 30.44 days.
[b] A patient was counted once at the maximum severity.
[c] For specific TEAEs associated with outcome of death, refer to Table 15.
[d] If relationship was missing, the TEAE was considered to be related to the drug.
Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.

Table 81 Overall Summary of Treatment-emergent Adverse Events by ECOG Performance Status (Safety Analysis Set)

Parameter	ECOG PS = 0				ECOG PS = 1			
	Study DB-06		Supportive Safety Pools		Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 251)	Chemo-therapy (N = 246)	T-DXd 5.4 mg/kg BC Pool (N = 990)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 1245)	T-DXd 5.4 mg/kg (N = 177)	Chemo-therapy (N = 162)	T-DXd 5.4 mg/kg BC Pool (N = 743)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 1080)
Duration of treatment (months) [a]								
Median	11.70	6.24	11.71	10.18	9.95	5.55	9.66	7.75
Minimum, maximum	0.7, 39.6	0.1, 32.0	0.4, 44.0	0.4, 44.0	0.4, 32.1	0.1, 35.9	0.2, 45.1	0.2, 45.1
Patients with any TEAE	248 (98.8)	234 (95.1)	982 (99.2)	1235 (99.2)	175 (98.9)	154 (95.1)	740 (99.6)	1073 (99.4)
TEAEs with worst CTCAE Grade ≥ 3 [b]	125 (49.8)	101 (41.1)	497 (50.2)	623 (50.0	101 (57.1)	80 (49.4)	440 (59.2)	653 (60.5)
Treatment-emergent SAEs	41 (16.3)	42 (17.1)	197 (19.9)	271 (21.8)	46 (26.0)	24 (14.8)	230 (31.0)	379 (35.1)
TEAEs associated with study drug discontinuation	31 (12.4)	19 (7.7)	171 (17.3)	203 (16.3)	31 (17.5)	20 (12.3)	136 (18.3)	173 (16.0)
TEAEs associated with study drug interruption	124 (49.4)	92 (37.4)	452 (45.7)	549 (44.1)	83 (46.9)	62 (38.3)	339 (45.6)	486 (45.0)
TEAEs associated with dose reduction	60 (23.9)	101 (41.1)	202 (20.4)	258 (20.7)	45 (25.4)	58 (35.8)	213 (28.7)	272 (25.2)
TEAEs associated with an outcome of death [c]	5 (2.0)	5 (2.0)	21 (2.1)	26 (2.1)	6 (3.4)	1 (0.6)	34 (4.6)	69 (6.4)
Patients with any drug-related TEAE [d]	241 (96.0)	218 (88.6)	964 (97.4)	1193 (95.8)	171 (96.6)	147 (90.7)	718 (96.6)	1007 (93.2)
Drug-related TEAEs with worst CTCAE Grade ≥ 3 [b]	91 (36.3)	74 (30.1)	400 (40.4)	492 (39.5)	83 (46.9)	54 (33.3)	347 (46.7)	476 (44.1)
Drug-related treatment-emergent SAEs	20 (8.0)	15 (6.1)	97 (9.8)	128 (10.3)	26 (14.7)	9 (5.6)	111 (14.9)	153 (14.2)
Drug-related TEAEs associated with study drug discontinuation	28 (11.2)	17 (6.9)	147 (14.8)	172 (13.8)	28 (15.8)	16 (9.9)	119 (16.0)	145 (13.4)
Drug-related TEAEs associated with study drug interruption	75 (29.9)	58 (23.6)	330 (33.3)	382 (30.7)	50 (28.2)	40 (24.7)	231 (31.1)	304 (28.1)
Drug-related TEAEs associated with dose reduction	54 (21.5)	99 (40.2)	188 (19.0)	240 (19.3)	38 (21.5)	54 (33.3)	193 (26.0)	247 (22.9)
Drug-related TEAEs associated with an outcome of death [c]	1 (0.4)	0	7 (0.7)	10 (0.8)	4 (2.3)	0	13 (1.7)	18 (1.7)

[a] Duration of treatment (months) = (date of the last dose - date of the first dose + a cycle length (day))/30.44. 1 month = 365.25/12 = 30.44 days.
[b] A patient was counted once at the maximum severity.
[c] For specific TEAEs associated with outcome of death, refer to Table 15.
[d] If relationship was missing, the TEAE was considered to be related to the drug.
Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.

Table 82 Overall Summary of Treatment-emergent Adverse Events by Renal Function (Safety Analysis Set)

Parameter	Normal Renal Function				Mild Renal Impairment				Moderate Renal Impairment			
	Study DB-06		Supportive Safety Pools		Study DB-06		Supportive Safety Pools		Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 185)	Chemo-therapy (N = 187)	T-DXd 5.4 mg/kg BC Pool (N = 888)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 1106)	T-DXd 5.4 mg/kg (N = 190)	Chemo-therapy (N = 175)	T-DXd 5.4 mg/kg BC Pool (N = 649)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 902)	T-DXd 5.4 mg/kg (N = 57)	Chemo-therapy (N = 55)	T-DXd 5.4 mg/kg BC Pool (N = 195)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 317)
Duration of treatment (months) [a]												
Median	11.76	5.65	11.22	9.74	10.91	5.59	10.35	8.76	8.28	5.59	8.71	7.03
Minimum, Maximum	0.6, 32.1	0.2, 32.0	0.4, 44.0	0.4, 44.0	1.3, 39.6	0.1, 35.9	0.2, 45.1	0.2, 45.1	0.4, 37.1	0.2, 18.8	0.4, 38.6	0.4, 38.6
Patients with any TEAE	184 (99.5)	178 (95.2)	883 (99.4)	1098 (99.3)	187 (98.4)	164 (93.7)	645 (99.4)	896 (99.3)	56 (98.2)	55 (100)	193 (99.0)	313 (98.7)
TEAEs with worst CTCAE ≥Grade 3 [b]	105 (56.8)	67 (35.8)	482 (54.3)	598 (54.1)	87 (45.8)	79 (45.1)	334 (51.5)	476 (52.8)	35 (61.4)	39 (70.9)	117 (60.0)	197 (62.1)
Treatment-emergent SAEs	37 (20.0)	29 (15.5)	221 (24.9)	290 (26.2)	32 (16.8)	22 (12.6)	142 (21.9)	243 (26.9)	18 (31.6)	16 (29.1)	64 (32.8)	116 (36.6)
TEAEs associated with study drug discontinuation	25 (13.5)	15 (8.0)	140 (15.8)	159 (14.4)	24 (12.6)	16 (9.1)	108 (16.6)	140 (15.5)	12 (21.1)	8 (14.5)	55 (28.2)	73 (23.0)
TEAEs associated with study drug interruption	93 (50.3)	65 (34.8)	401 (45.2)	488 (44.1)	95 (50.0)	70 (40.0)	297 (45.8)	398 (44.1)	21 (36.8)	25 (45.5)	91 (46.7)	148 (46.7)

Parameter	Normal Renal Function				Mild Renal Impairment				Moderate Renal Impairment			
	Study DB-06		Supportive Safety Pools		Study DB-06		Supportive Safety Pools		Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 185)	Chemo-therapy (N = 187)	T-DXd 5.4 mg/kg BC Pool (N = 888)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 1106)	T-DXd 5.4 mg/kg (N = 190)	Chemo-therapy (N = 175)	T-DXd 5.4 mg/kg BC Pool (N = 649)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 902)	T-DXd 5.4 mg/kg (N = 57)	Chemo-therapy (N = 55)	T-DXd 5.4 mg/kg BC Pool (N = 195)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 317)
TEAEs associated with dose reduction	44 (23.8)	65 (34.8)	218 (24.5)	256 (23.1)	47 (24.7)	66 (37.7)	142 (21.9)	192 (21.3)	16 (28.1)	30 (54.5)	54 (27.7)	81 (25.6)
TEAEs associated with an outcome of death [c]	4 (2.2)	1 (0.5)	23 (2.6)	31 (2.8)	5 (2.6)	4 (2.3)	23 (3.5)	41 (4.5)	2 (3.5)	1 (1.8)	10 (5.1)	23 (7.3)
Patients with any drug-related TEAE [d]	179 (96.8)	166 (88.8)	864 (97.3)	1053 (95.2)	181 (95.3)	155 (88.6)	627 (96.6)	851 (94.3)	55 (96.5)	52 (94.5)	189 (96.9)	294 (92.7)
Drug-related TEAEs with worst CTCAE Grade ≥ 3 [b]	77 (41.6)	44 (23.5)	377 (42.5)	451 (40.8)	68 (35.8)	58 (33.1)	268 (41.3)	361 (40.0)	30 (52.6)	29 (52.7)	99 (50.8)	152 (47.9)
Drug-related treatment-emergent SAEs	20 (10.8)	12 (6.4)	114 (12.8)	131 (11.8)	14 (7.4)	6 (3.4)	59 (9.1)	94 (10.4)	12 (21.1)	6 (10.9)	35 (17.9)	56 (17.7)
Drug-related TEAEs associated with study drug	24 (13.0)	12 (6.4)	119 (13.4)	132 (11.9)	20 (10.5)	14 (8.0)	93 (14.3)	117 (13.0)	12 (21.1)	7 (12.7)	51 (26.2)	65 (20.5)

Parameter	Normal Renal Function				Mild Renal Impairment				Moderate Renal Impairment			
	Study DB-06		Supportive Safety Pools		Study DB-06		Supportive Safety Pools		Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 185)	Chemo-therapy (N = 187)	T-DXd 5.4 mg/kg BC Pool (N = 888)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 1106)	T-DXd 5.4 mg/kg (N = 190)	Chemo-therapy (N = 175)	T-DXd 5.4 mg/kg BC Pool (N = 649)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 902)	T-DXd 5.4 mg/kg (N = 57)	Chemo-therapy (N = 55)	T-DXd 5.4 mg/kg BC Pool (N = 195)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 317)
discontinuation												
Drug-related TEAEs associated with study drug interruption	61 (33.0)	40 (21.4)	288 (32.4)	331 (29.9)	52 (27.4)	48 (27.4)	205 (31.6)	259 (28.7)	14 (24.6)	15 (27.3)	66 (33.8)	94 (29.7)
Drug-related TEAEs associated with dose reduction	39 (21.1)	61 (32.6)	201 (22.6)	236 (21.3)	41 (21.6)	64 (36.6)	130 (20.0)	175 (19.4)	14 (24.6)	30 (54.5)	49 (25.1)	75 (23.7)
Drug-related TEAEs associated with an outcome of death [c]	2 (1.1)	0	7 (0.8)	8 (0.7)	1 (0.5)	0	7 (1.1)	10 (1.1)	2 (3.5)	0	6 (3.1)	10 (3.2)

[e] Duration of treatment (months) = (date of the last dose - date of the first dose + a cycle length (day))/30.44. 1 month = 365.25/12 = 30.44 days.
A patient was counted once at the maximum severity.
For specific TEAEs associated with outcome of death, refer to.
If relationship was missing, the TEAE was considered to be related to the drug.
Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.

Table 83 Overall Summary of Treatment-emergent Adverse Events by Hepatic Function (Safety Analysis Set)

Parameter	Normal Hepatic Functions				Mild Hepatic impairment			
	Study DB-06		Supportive Safety Pools		Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 205)	Chemo-therapy (N = 210)	T-DXd 5.4 mg/kg BC Pool (N = 930)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 1370)	T-DXd 5.4 mg/kg (N = 225)	Chemo-therapy (N = 205)	T-DXd 5.4 mg/kg BC Pool (N = 792)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 937)
Duration of treatment (months) [a]								
Median	13.27	6.39	12.40	9.69	9.89	5.52	9.23	8.34
Minimum, maximum	0.7, 37.1	0.1, 35.9	0.4, 44.0	0.4, 44.0	0.4, 39.6	0.2, 26.9	0.2, 45.1	0.2, 45.1
Patients with any TEAE	204 (99.5)	200 (95.2)	923 (99.2)	1358 (99.1)	222 (98.7)	195 (95.1)	789 (99.6)	932 (99.5)
TEAEs with worst CTCAE Grade ≥ 3 [b]	103 (50.2)	81 (38.6)	479 (51.5)	720 (52.6)	123 (54.7)	103 (50.2)	446 (56.3)	536 (57.2)
Treatment-emergent SAEs	40 (19.5)	28 (13.3)	219 (23.5)	377 (27.5)	46 (20.4)	38 (18.5)	201 (25.4)	260 (27.7)
TEAEs associated with study drug discontinuation	28 (13.7)	16 (7.6)	159 (17.1)	208 (15.2)	33 (14.7)	23 (11.2)	144 (18.2)	163 (17.4)
TEAEs associated with study drug interruption	101 (49.3)	76 (36.2)	426 (45.8)	611 (44.6)	109 (48.4)	83 (40.5)	358 (45.2)	415 (44.3)
TEAEs associated with dose reduction	52 (25.4)	79 (37.6)	222 (23.9)	309 (22.6)	54 (24.0)	80 (39.0)	190 (24.0)	214 (22.8)
TEAEs associated with an outcome of death [c]	5 (2.4)	3 (1.4)	25 (2.7)	55 (4.0)	6 (2.7)	3 (1.5)	29 (3.7)	38 (4.1)
Patients with any drug-related TEAE [d]	196 (95.6)	188 (89.5)	899 (96.7)	1290 (94.2)	218 (96.9)	183 (89.3)	773 (97.6)	896 (95.6)
Drug-related TEAEs with worst CTCAE Grade ≥ 3 [b]	82 (40.0)	58 (27.6)	386 (41.5)	538 (39.3)	92 (40.9)	72 (35.1)	352 (44.4)	416 (44.4)
Drug-related treatment-emergent SAEs	17 (8.3)	7 (3.3)	100 (10.8)	148 (10.8)	27 (12.0)	17 (8.3)	105 (13.3)	127 (13.6)
Drug-related TEAEs associated with study drug discontinuation	25 (12.2)	14 (6.7)	141 (15.2)	176 (12.8)	30 (13.3)	19 (9.3)	122 (15.4)	137 (14.6)
Drug-related TEAEs associated with study	58 (28.3)	50 (23.8)	299 (32.2)	392 (28.6)	69 (30.7)	53 (25.9)	257 (32.4)	289 (30.8)

Parameter	Normal Hepatic Functions				Mild Hepatic impairment			
	Study DB-06		Supportive Safety Pools		Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 205)	Chemo-therapy (N = 210)	T-DXd 5.4 mg/kg BC Pool (N = 930)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 1370)	T-DXd 5.4 mg/kg (N = 225)	Chemo-therapy (N = 205)	T-DXd 5.4 mg/kg BC Pool (N = 792)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 937)
drug interruption								
Drug-related TEAEs associated with dose reduction	45 (22.0)	77 (36.7)	204 (21.9)	284 (20.7)	48 (21.3)	76 (37.1)	174 (22.0)	196 (20.9)
Drug-related TEAEs associated with an outcome of death [c]	3 (1.5)	0	10 (1.1)	17 (1.2)	2 (0.9)	0	9 (1.1)	10 (1.1)

[f] Duration of treatment (months) = (date of the last dose - date of the first dose + a cycle length (day))/30.44. 1 month = 365.25/12 = 30.44 days.
A patient was counted once at the maximum severity.
For specific TEAEs associated with outcome of death, refer to.
If relationship was missing, the TEAE was considered to be related to the drug.
Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.

Extrinsic Factors

Table 84 Overall Summary of Treatment-emergent Adverse Events by Geographic Region: Asia and North America (Safety Analysis Set)

Parameter	Asia				North America			
	Study DB-06		Supportive Safety Pools		Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 148)	Chemo-therapy (N = 144)	T-DXd 5.4 mg/kg BC Pool (N = 645)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 877)	T-DXd 5.4 mg/kg (N = 47)	Chemo-therapy (N = 46)	T-DXd 5.4 mg/kg BC Pool (N = 269)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 368)
Duration of treatment (months) [a]								
Median	11.52	7.34	11.17	9.66	10.41	6.88	8.97	8.15
Minimum, maximum	0.7, 39.6	0.1, 35.9	0.7, 45.1	0.7, 45.1	1.3, 30.6	0.2, 25.1	0.7, 32.4	0.7, 32.4
Patients with any TEAE	148 (100)	135 (93.8)	643 (99.7)	874 (99.7)	47 (100)	46 (100)	268 (99.6)	366 (99.5)
TEAEs with worst CTCAE Grade ≥ 3 [b]	92 (62.2)	60 (41.7)	381 (59.1)	525 (59.9)	19 (40.4)	25 (54.3)	132 (49.1)	189 (51.4)
Treatment-emergent SAEs	35 (23.6)	18 (12.5)	153 (23.7)	241 (27.5)	8 (17.0)	5 (10.9)	70 (26.0)	104 (28.3)
TEAEs associated with study drug discontinuation	25 (16.9)	6 (4.2)	130 (20.2)	160 (18.2)	3 (6.4)	7 (15.2)	40 (14.9)	46 (12.5)
TEAEs associated with study	79 (53.4)	48 (33.3)	328 (50.9)	441 (50.3)	23 (48.9)	22 (47.8)	100 (37.2)	131 (35.6)

Parameter	Asia				North America			
	Study DB-06		Supportive Safety Pools		Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 148)	Chemo-therapy (N = 144)	T-DXd 5.4 mg/kg BC Pool (N = 645)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 877)	T-DXd 5.4 mg/kg (N = 47)	Chemo-therapy (N = 46)	T-DXd 5.4 mg/kg BC Pool (N = 269)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 368)
drug interruption								
TEAEs associated with dose reduction	49 (33.1)	49 (34.0)	182 (28.2)	239 (27.3)	7 (14.9)	24 (52.2)	49 (18.2)	69 (18.8)
TEAEs associated with an outcome of death [c]	3 (2.0)	2 (1.4)	12 (1.9)	28 (3.2)	1 (2.1)	0	11 (4.1)	18 (4.9)
Patients with any drug-related TEAE [d]	146 (98.6)	128 (88.9)	633 (98.1)	843 (96.1)	44 (93.6)	44 (95.7)	261 (97.0)	346 (94.0)
Drug-related TEAEs with worst CTCAE Grade ≥ 3 [b]	76 (51.4)	50 (34.7)	330 (51.2)	440 (50.2)	13 (27.7)	19 (41.3)	98 (36.4)	129 (35.1)
Drug-related treatment-emergent SAEs	19 (12.8)	8 (5.6)	81 (12.6)	113 (12.9)	4 (8.5)	4 (8.7)	31 (11.5)	38 (10.3)
Drug-related TEAEs associated with study drug discontinuation	24 (16.2)	5 (3.5)	116 (18.0)	138 (15.7)	3 (6.4)	6 (13.0)	35 (13.0)	40 (10.9)
Drug-related TEAEs associated with study drug interruption	54 (36.5)	33 (22.9)	264 (40.9)	336 (38.3)	12 (25.5)	18 (39.1)	66 (24.5)	79 (21.5)
Drug-related TEAEs associated with dose reduction	41 (27.7)	49 (34.0)	171 (26.5)	224 (25.5)	7 (14.9)	23 (50.0)	42 (15.6)	59 (16.0)
Drug-related TEAEs associated with an outcome of death [c]	2 (1.4)	0	4 (0.6)	6 (0.7)	0	0	5 (1.9)	7 (1.9)

[g] Duration of treatment (months) = (date of the last dose - date of the first dose + a cycle length (day))/30.44. 1 month = 365.25/12 = 30.44 days

A patient was counted once at the maximum severity.
For specific TEAEs associated with outcome of death, refer to.
If relationship was missing, the TEAE was considered to be related to the drug.
Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.

Table 85 Overall Summary of Treatment-emergent Adverse Events by Geographic Region: Europe and Rest of the World (Safety Analysis Set)

Parameter	Europe				Rest of World			
	Study DB-06		Supportive Safety Pools		Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 227)	Chemo-therapy (N = 206)	T-DXd 5.4 mg/kg BC Pool (N = 687)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 934)	T-DXd 5.4 mg/kg (N = 12)	Chemo-therapy (N = 21)	T-DXd 5.4 mg/kg BC Pool (N = 140)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 156)
Duration of treatment (months) [a]								
Median	10.71	5.19	10.32	8.64	11.50	5.49	14.00	13.06
Minimum, maximum	0.4, 37.1	0.1, 26.9	0.2, 39.0	0.2, 39.0	0.6, 21.1	0.2, 23.3	0.6, 39.1	0.6, 39.1
Patients with any TEAE	223 (98.2)	198 (96.1)	680 (99.0)	922 (98.7)	11 (91.7)	18 (85.7)	139 (99.3)	155 (99.4)
TEAEs with worst CTCAE Grade ≥ 3 [b]	112 (49.3)	94 (45.6)	347 (50.5)	477 (51.1)	6 (50.0)	6 (28.6)	81 (57.9)	89 (57.1)
Treatment-emergent SAEs	43 (18.9)	40 (19.4)	170 (24.7)	264 (28.3)	2 (16.7)	4 (19.0)	36 (25.7)	43 (27.6)
TEAEs associated with study drug discontinuation	32 (14.1)	25 (12.1)	120 (17.5)	152 (16.3)	2 (16.7)	1 (4.8)	17 (12.1)	18 (11.5)
TEAEs associated with study drug interruption	103 (45.4)	81 (39.3)	302 (44.0)	393 (42.1)	5 (41.7)	9 (42.9)	64 (45.7)	74 (47.4)
TEAEs associated with dose reduction	49 (21.6)	85 (41.3)	154 (22.4)	189 (20.2)	2 (16.7)	3 (14.3)	32 (22.9)	35 (22.4)
TEAEs associated with an outcome of death [c]	6 (2.6)	3 (1.5)	28 (4.1)	44 (4.7)	1 (8.3)	1 (4.8)	5 (3.6)	6 (3.8)
Patients with any drug-related TEAE [d]	216 (95.2)	185 (89.8)	658 (95.8)	868 (92.9)	11 (91.7)	16 (76.2)	137 (97.9)	151 (96.8)
Drug-related TEAEs with worst CTCAE Grade ≥ 3 [b]	81 (35.7)	59 (28.6)	261 (38.0)	335 (35.9)	6 (50.0)	3 (14.3)	61 (43.6)	67 (42.9)
Drug-related treatment-emergent SAEs	21 (9.3)	11 (5.3)	83 (12.1)	114 (12.2)	2 (16.7)	1 (4.8)	36 (25.7)	43 (27.6)
Drug-related TEAEs associated with study drug discontinuation	27 (11.9)	21 (10.2)	101 (14.7)	124 (13.3)	2 (16.7)	1 (4.8)	14 (10.0)	15 (9.6)
Drug-related TEAEs associated with study drug interruption	57 (25.1)	46 (22.3)	192 (27.9)	227 (24.3)	4 (33.3)	6 (28.6)	41 (29.3)	46 (29.5)
Drug-related TEAEs associated with dose reduction	44 (19.4)	80 (38.8)	142 (20.7)	175 (18.7)	2 (16.7)	3 (14.3)	28 (20.0)	31 (19.9)
Drug-related TEAEs associated with an outcome of death [c]	2 (0.9)	0	10 (1.5)	13 (1.4)	1 (8.3)	0	1 (0.7)	2 (1.3)

[a] Duration of treatment (months) = (date of the last dose - date of the first dose + a cycle length (day))/30.44. 1 month = 365.25/12 = 30.44 days
[b] A patient was counted once at the maximum severity.
[c] For specific TEAEs associated with outcome of death, refer to Table 15.
[d] If relationship was missing, the TEAE was considered to be related to the drug.
Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.

Safety related to drug-drug interactions and other interactions

No interactions with strong cytochrome P450 3A and organic anion transporting polypeptide 1B inhibitors were observed in a dedicated drug-drug interaction study (DS8201-A-A104) with ritonavir and itraconazole in subjects with BC.

No new information on drug interactions is available since the time of study DS8201-A-A104 (submitted as part of EMEA/H/C/005124).

Discontinuation due to adverse events

Interruption due to adverse events

Table 86 Drug Related ILD/Pneumonitis Associated with Study Drug Interruption by Preferred Term (Safety Analysis Set)

	Number (%) of Patients			
	D9670C00001(DESTINY-Breast06)		Supportive Safety Pools	
MedDRA Preferred Term	T-DXd 5.4 mg/kg (N=434)	Investigator choice of chemotherapy (N=417)	T-DXd 5.4 mg/kg breast cancer pool (N=1741)	T-DXd 5.4 mg/kg all tumor types pool (N=2335)
Patients with ILD/Pneumonitis	10 (2.3)	0	50 (2.9)	61 (2.6)
Interstitial lung disease	9 (2.1)	0	26 (1.5)	33 (1.4)
Pneumonitis	1 (0.2)	0	24 (1.4)	28 (1.2)

Table 87 Adverse Events Associated with Study Drug Interruption in ≥ 2% of Patients in Either Treatment Arm of Study DB-06, by Preferred Term (Safety Analysis Set)

	Number (%) of Patients			
	Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
Patients with any TEAE associated with study drug interruption	210 (48.4)	160 (38.4)	794 (45.6)	1039 (44.5)
COVID-19	63 (14.5)	27 (6.5)	121 (7.0)	155 (6.6)
Neutrophil count decreased	33 (7.6)	17 (4.1)	151 (8.7)	182 (7.8)
Neutropenia	30 (6.9)	20 (4.8)	99 (5.7)	114 (4.9)
Anaemia	15 (3.5)	3 (0.7)	77 (4.4)	106 (4.5)
Pyrexia	12 (2.8)	4 (1.0)	32 (1.8)	40 (1.7)
Pneumonia	10 (2.3)	5 (1.2)	35 (2.0)	46 (2.0)
White blood cell count decreased	10 (2.3)	6 (1.4)	55 (3.2)	59 (2.5)
Interstitial lung disease	9 (2.1)	0	27 (1.6)	35 (1.5)
Diarrhoea	4 (0.9)	9 (2.2)	15 (0.9)	21 (0.9)
Palmar-plantar erythrodysaesthesia syndrome	1 (0.2)	17 (4.1)	2 (0.1)	2 (0.1)

Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.
The pooled analysis group is based on first dose received for patients in each study.
PTs are sorted by descending frequency in the Study DB-06 T-DXd 5.4 mg/kg treatment arm.
If a patient had multiple occurrences of the same PT, the patient is counted once for the specific PT.
If a patient had multiple PTs, the patient is counted in each of the different PTs.

Table 88 Treatment-Emergent Adverse Events PTs of ILD/Pneumonitis and COVID-19

	Study DB-06		Supportive Safety Pools	
	T-DXd (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
Subjects with concurrent ILD/pneumonitis and COVID-19 PTs	4 (0.9)	0	5 (0.3)	7 (0.3)
Subjects with concurrent ILD/pneumonitis and grouped term of COVID-19	4 (0.9)	0	6 (0.3)	8 (0.3)

Patients are counted only once per each category.
COVID-19 grouped term includes preferred terms Asymptomatic COVID-19, Congenital COVID-19, Coronavirus infection, Coronavirus test positive, COVID-19, COVID-19 pneumonia, COVID-19 treatment, Multisystem inflammatory syndrome in children, Post-acute COVID-19 syndrome, SARS-CoV-2 antibody test positive, SARS-CoV-2 carrier, SARS-CoV-2 RNA decreased, SARS-CoV-2 RNA fluctuation, SARS-CoV-2 RNA increased, SARS-CoV-2 sepsis, SARS-CoV-2 test false negative, SARS-CoV-2 test positive, SARS-CoV-2 viraemia, Suspected COVID-19, Vaccine derived SARS-CoV-2 infection.

Table 89 Adverse Drug Reactions Associated with Dose Interruption in T-DXd 5.4 mg/kg breast cancer pool and T-DXd 5.4 mg/kg breast cancer pool and T-DXd 5.4 mg/kg all tumour types pool, by MedDRA System Organ Class, Preferred Term/Grouped Term and Frequency (Safety Analysis Set)

MedDRA System Organ Class Preferred Term/Grouped Term	Number (%) of Subjects	
	T-DXd 5.4 mg/kg breast cancer pool (N = 1741)	T-DXd 5.4 mg/kg all tumor types pool (N = 2335)
Subjects with any ADR associated with Study Drug Interruption	602 (34.6)	762 (32.6)
Blood and lymphatic system disorders		
Neutropenia [a]	243 (14.0)	289 (12.4)
Anemia [b]	78 (4.5)	107 (4.6)
Leukopenia [c]	68 (3.9)	74 (3.2)
Thrombocytopenia [d]	49 (2.8)	57 (2.4)
Lymphopenia [e]	7 (0.4)	8 (0.3)
Febrile neutropenia	6 (0.3)	6 (0.3)
Eye disorders		
Dry eye	1 (0.1)	1 (0.0)
Gastrointestinal disorders		
Nausea	23 (1.3)	33 (1.4)
Diarrhoea	15 (0.9)	21 (0.9)
Vomiting	12 (0.7)	16 (0.7)
Stomatitis [f]	8 (0.5)	10 (0.4)
Abdominal pain [g]	7 (0.4)	12 (0.5)
Constipation	3 (0.2)	3 (0.1)
Gastritis	3 (0.2)	4 (0.2)
General disorders and administration site conditions		
Fatigue [h]	77 (4.4)	110 (4.7)
Pyrexia	32 (1.8)	40 (1.7)
Oedema peripheral	2 (0.1)	4 (0.2)

MedDRA System Organ Class Preferred Term/Grouped Term	Number (%) of Subjects	
	T-DXd 5.4 mg/kg breast cancer pool (N = 1741)	T-DXd 5.4 mg/kg all tumor types pool (N = 2335)
Hepatobiliary disorders		
Transaminases increased [i]	37 (2.1)	41 (1.8)
Infections and infestations		
Upper respiratory tract infection [j]	55 (3.2)	70 (3.0)
Pneumonia	35 (2.0)	46 (2.0)
Injury, poisoning and procedural complications		
Infusion related reaction [p]	4 (0.2)	5 (0.2)
Investigations		
Blood bilirubin increased [k]	30 (1.7)	34 (1.5)
Ejection fraction decreased [r]	22 (1.3)	27 (1.2)
Blood creatinine increased	4 (0.2)	6 (0.3)
Blood alkaline phosphatase increased	1 (0.1)	3 (0.1)
Weight decreased	1 (0.1)	1 (0.0)
Metabolism and nutrition disorders		
Hypokalaemia [l]	16 (0.9)	21 (0.9)
Decreased appetite	7 (0.4)	8 (0.3)
Dehydration	3 (0.2)	3 (0.1)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain [m]	4 (0.2)	4 (0.2)
Nervous system disorders		
Dizziness	4 (0.2)	5 (0.2)
Headache [n]	2 (0.1)	3 (0.1)
Dysgeusia	0	1 (0.0)
Respiratory, thoracic and mediastinal disorders		
Interstitial lung disease [q]	48 (2.8)	61 (2.6)
Dyspnoea	15 (0.9)	19 (0.8)
Cough	14 (0.8)	17 (0.7)
Epistaxis	1 (0.1)	2 (0.1)
Skin and subcutaneous tissue disorders		
Pruritus	1 (0.1)	1 (0.0)
Rash [o]	1 (0.1)	3 (0.1)

ADR = adverse drug reaction; MedDRA = Medical Dictionary for Regulatory Activities, version 26.1; N = total number of subjects treated; PT = preferred term; T-DXd = trastuzumab deruxtecan.
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
System Organ Class are presented by alphabetic order. PTs/grouped terms are presented by descending frequency in the T-DXd 5.4 mg/kg breast cancer pool.
If a subject had multiple occurrences of the same ADR, the subject was counted once for that specific ADR.
[a] Neutropenia (grouped term) includes PTs of Neutrophil count decreased, Neutropenia.
[b] Anemia (grouped term) includes PTs of Haemoglobin decreased, Red blood cell count decreased, Anaemia, Haematocrit decreased.
[c] Leukopenia (grouped term) includes PTs of White blood cell count decreased, Leukopenia.
[d] Thrombocytopenia (grouped term) includes PTs of Platelet count decreased, Thrombocytopenia.
[e] Lymphopenia (grouped term) includes PTs of Lymphocyte count decreased, Lymphopenia.
[f] Stomatitis (grouped term) includes PTs of Stomatitis, Aphthous ulcer, Mouth ulceration, Oral mucosa erosion, Oral mucosal blistering, Oral mucosal eruption.
[g] Abdominal pain (grouped term) includes PTs of Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Gastrointestinal pain.
[h] Fatigue (grouped term) includes PTs of Fatigue, Asthenia, Malaise, Lethargy.
[i] Transaminases increased (grouped term) includes PTs of Transaminases increased, Aspartate aminotransferase increased, Alanine aminotransferase increased, Gamma-glutamyltransferase increased, Liver function test abnormal, Hepatic function abnormal, Liver function test increased, Hypertransaminasaemia.
[j] Upper respiratory tract infection (grouped term) includes PTs of Influenza, Influenza like illness, Upper respiratory tract infection, Nasopharyngitis, Pharyngitis, Sinusitis, Rhinitis, Laryngitis.
[k] Blood bilirubin increased (grouped term) includes PTs of Blood bilirubin increased, Hyperbilirubinaemia, Bilirubin conjugated increased, Blood bilirubin unconjugated increased.
[l] Hypokalaemia (grouped term) includes PTs of Hypokalaemia, Blood potassium decreased.
[m] Musculoskeletal pain (grouped term) includes PTs of Back pain, Myalgia, Pain in extremity, Musculoskeletal pain, Muscle spasms, Bone pain, Neck pain, Musculoskeletal chest pain, Limb discomfort.
[n] Headache (grouped term) includes PTs of Migraine, Headache, Sinus headache.
[o] Rash (grouped term) includes PTs of Rash, Rash pustular, Rash maculo-papular, Rash papular, Rash macular, Rash pruritic.
[p] Infusion related reaction (grouped term) includes PTs of Administration related reaction, Anaphylactic reaction, Hypersensitivity, Infusion related reaction and Infusion related hypersensitivity reaction.
[q] Interstitial lung disease (grouped term) includes PTs of Bronchiectasis, Interstitial lung disease, Lung opacity, Pneumonia, Pneumonia bacterial, Pneumonitis, Pulmonary toxicity, Radiation pneumonitis, Respiratory failure. These events were adjudicated as ILD and related to use of T-DXd.

Discontinuation due to adverse events

Table 90 Summary of Patient Disposition (Safety Analysis Set)

	Number (%) of Patients			
	Study DB-06		Supportive Safety Pools	
	T-DXd 5.4 mg/kg (N = 434)	Chemotherapy (N = 417)	T-DXd 5.4 mg/kg BC Pool (N = 1741)	T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)
Patients ongoing study drug at DCO	89 (20.5)	30 (7.2)	356 (20.4)	402 (17.2)
Patients discontinued from study drug, by primary reason	345 (79.5)	387 (92.8)	1385 (79.6)	1933 (82.8)
Progressive disease [a]	0	0	602 (34.6)	735 (31.5)
Clinical progression [a]	0	0	56 (3.2)	75 (3.2)
Objective disease progression [a]	248 (57.1)	292 (70.0)	255 (14.6)	456 (19.5)
Subjective disease progression [a]	0	0	1 (0.1)	27 (1.2)
Adverse event	61 (14.1)	39 (9.4)	300 (17.2)	366 (15.7)
Death	5 (1.2)	4 (1.0)	26 (1.5)	57 (2.4)
Withdrawal by subject	0	0	75 (4.3)	80 (3.4)
Severe non-compliance to protocol	0	0	0	0
Physician decision	0	0	18 (1.0)	27 (1.2)
Subject decision	19 (4.4)	34 (8.2)	19 (1.1)	34 (1.5)
Lost to follow-up	0	0	1 (0.1)	2 (0.1)
Protocol deviation	0	1 (0.2)	1 (0.1)	1 (0.0)
Pregnancy	0	0	0	0
Study terminated by Sponsor	0	0	0	0
Due to COVID-19 pandemic	0	0	0	0
Other	12 (2.8)	17 (4.1)	31 (1.8)	73 (3.1)

[a] These 4 terms are considered synonymous, with differences due to differences in the terms used in the individual studies in the pools.

Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.
The pooled analysis group is based on first dose received for patients in each study.

Table 91 Adverse Drug Reactions Associated with Study Drug Discontinuation in T-DXd 5.4 mg/kg breast cancer pool and T-DXd 5.4 mg/kg all tumour types pool, by MedDRA System Organ Class, Preferred Term/Groped Term and Frequency (Safety Analysis Set)

MedDRA System Organ Class Preferred Term/Grouped Term	Number (%) of Subjects T-DXd 5.4 mg/kg breast cancer pool T-DXd 6.4 mg/kg (N = 1741)			T-DXd 5.4 mg/kg all tumor types pool (N = 2335)		
	All Grades	Grade 3 or 4	Grade 5	All Grades	Grade 3 or 4	Grade 5
Subjects with any ADR associated with Study Drug Discontinuation	224 (12.9)	55 (3.2)	12 (0.7)	274 (11.7)	63 (2.7)	17 (0.7)
Blood and lymphatic system disorders						
Thrombocytopenia [a]	10 (0.6)	7 (0.4)	0	12 (0.5)	8 (0.3)	0
Neutropenia [b]	5 (0.3)	5 (0.3)	0	5 (0.2)	5 (0.2)	0
Anemia [c]	2 (0.1)	2 (0.1)	0	4 (0.2)	4 (0.2)	0
Febrile neutropenia	1 (0.1)	0	1 (0.1)	1 (0.0)	0	1 (0.0)
Leukopenia [d]	1 (0.1)	1 (0.1)	0	1 (0.0)	1 (0.0)	0
Lymphopenia [e]	1 (0.1)	1 (0.1)	0	1 (0.0)	1 (0.0)	0
Gastrointestinal disorders						
Vomiting	2 (0.1)	0	0	2 (0.1)	0	0
Diarrhoea	1 (0.1)	1 (0.1)	0	1 (0.0)	1 (0.0)	0
Nausea	1 (0.1)	0	0	1 (0.0)	0	0
General disorders and administration site conditions						
Fatigue [f]	8 (0.5)	6 (0.3)	0	9 (0.4)	6 (0.3)	0
Pyrexia	1 (0.1)	1 (0.1)	0	1 (0.0)	1 (0.0)	0
Hepatobiliary disorders						
Transaminases increased [g]	4 (0.2)	4 (0.2)	0	4 (0.2)	4 (0.2)	0
Infections and infestations						
Pneumonia	13 (0.7)	2 (0.1)	3 (0.2)	16 (0.7)	3 (0.1)	4 (0.2)
Injury, poisoning and procedural complications						
Infusion related reaction [k]	1 (0.1)	1 (0.1)	0	1 (0.0)	1 (0.0)	0
Investigations						
Ejection fraction decreased [m]	8 (0.5)	4 (0.2)	0	9 (0.4)	5 (0.2)	0
Blood bilirubin increased [h]	3 (0.2)	2 (0.1)	0	5 (0.2)	2 (0.1)	0
Weight decreased	1 (0.1)	1 (0.1)	0	1 (0.0)	1 (0.0)	0
Metabolism and nutrition disorders						
Hypokalaemia [i]	4 (0.2)	4 (0.2)	0	5 (0.2)	5 (0.2)	0
Decreased appetite	1 (0.1)	1 (0.1)	0	1 (0.0)	1 (0.0)	0
Nervous system disorders						
Dysgeusia	1 (0.1)	1 (0.1)	0	1 (0.0)	1 (0.0)	0
Respiratory, thoracic and mediastinal disorders						
Interstitial lung disease [l]	157 (9.0)	13 (0.7)	9 (0.5)	195 (8.4)	14 (0.6)	13 (0.6)
Dyspnoea	3 (0.2)	0	0	4 (0.2)	1 (0.0)	0
Cough	1 (0.1)	0	0	1 (0.0)	0	0
Skin and subcutaneous tissue disorders						
Skin hyperpigmentation [j]	2 (0.1)	0	0	2 (0.1)	0	0

ADR = adverse drug reaction; MedDRA = Medical Dictionary for Regulatory Activities, version 26.1; N = total number of subjects treated; PT = preferred term; T-DXd = trastuzumab deruxtecan.
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
System Organ Class are presented by alphabetic order. PTs/grouped terms are presented by descending frequency in the All Grades column of the T-DXd 5.4 mg/kg breast cancer pool.
If a subject had multiple occurrences of the same ADR, the subject was counted once for that specific ADR.
[a] Thrombocytopenia (grouped term) includes PTs of Platelet count decreased, Thrombocytopenia.
[b] Neutropenia (grouped term) includes PTs of Neutrophil count decreased, Neutropenia.
[c] Anemia (grouped term) includes PTs of Haemoglobin decreased, Red blood cell count decreased, Anaemia, Haematocrit decreased.
[d] Leukopenia (grouped term) includes PTs of White blood cell count decreased, Leukopenia.
[e] Lymphopenia (grouped term) includes PTs of Lymphocyte count decreased, Lymphopenia.
[f] Fatigue (grouped term) includes PTs of Fatigue, Asthenia, Malaise, Lethargy.
[g] Transaminases increased (grouped term) includes PTs of Transaminases increased, Aspartate aminotransferase increased, Alanine aminotransferase increased, Gamma-glutamyltransferase increased, Liver function test abnormal, Hepatic function abnormal, Liver function test increased, Hypertransaminasaemia.
[h] Blood bilirubin increased (grouped term) includes PTs of Blood bilirubin increased, Hyperbilirubinaemia, Bilirubin conjugated increased, Blood bilirubin unconjugated increased.
[i] Hypokalaemia (grouped term) includes PTs of Hypokalaemia, Blood potassium decreased.
[j] Skin hyperpigmentation (grouped term) includes PTs of Skin hyperpigmentation, Skin discolouration, Pigmentation disorder.
[k] Infusion related reaction (grouped term) includes PTs of Administration related reaction, Anaphylactic reaction, Hypersensitivity, Infusion related reaction and Infusion related hypersensitivity reaction.
[l] Interstitial lung disease (grouped term) includes PTs of Alveolitis, Idiopathic interstitial pneumonia, Interstitial lung disease, Lung disorder, Organising pneumonia, Pneumonia, Pneumonitis, Pulmonary fibrosis, Pulmonary mass, Pulmonary toxicity. These events were adjudicated as ILD..
[m] Ejection fraction decreased (grouped term) includes PTs of Cardiac failure, Cardiac failure congestive, Ejection fraction decreased, Left ventricular dysfunction.

Table 92 Adverse Events Associated with Study Drug Discontinuation in at Least 2 Patients in Either Treatment Arm of Study DB-06, by Preferred Term (Safety Analysis Set)

	Number (%) of Patients			
	Study DB-06		**Supportive Safety Pools**	
	T-DXd 5.4 mg/kg (N = 434)	**Chemotherapy (N = 417)**	**T-DXd 5.4 mg/kg BC Pool (N = 1741)**	**T-DXd 5.4 mg/kg All Tumor Types Pool (N = 2335)**
Patients with any TEAE associated with study drug discontinuation	62 (14.3)	39 (9.4)	307 (17.6)	376 (16.1)
Pneumonitis	23 (5.3)	0	103 (5.9)	131 (5.6)
Interstitial lung disease	15 (3.5)	0	69 (4.0)	81 (3.5)
Platelet count decreased	3 (0.7)	0	8 (0.5)	9 (0.4)
General physical health deterioration	2 (0.5)	0	2 (0.1)	2 (0.1)
Hypokalaemia	2 (0.5)	0	4 (0.2)	5 (0.2)
Asthenia	1 (0.2)	3 (0.7)	4 (0.2)	4 (0.2)
Angina pectoris	0	3 (0.7)	0	0
Colitis	0	3 (0.7)	1 (0.1)	1 (0.0)
Fatigue	0	2 (0.5)	4 (0.2)	5 (0.2)
Neuropathy peripheral	0	2 (0.5)	1 (0.1)	1 (0.0)

Adverse Drug reactions leading to dose reduction

Table 93 Adverse Drug reactions Associated with Dose Reduction in T-DXd 5.4 mg/kg breast cancer pool and T-DXd 5.4 mg/kg all tumour types pool, by MedDRA System Organ Class, Preferred Term/Grouped Term and Frequency (Safety Analysis Set)

MedDRA System Organ Class Preferred Term/Grouped Term	Number (%) of Subjects	
	T-DXd 5.4 mg/kg breast cancer pool (N = 1741)	T-DXd 5.4 mg/kg all tumor types pool (N = 2335)
Subjects with any ADR associated with Dose Reduction	366 (21.0)	474 (20.3)
Blood and lymphatic system disorders		
Neutropenia [a]	60 (3.4)	81 (3.5)
Thrombocytopenia [b]	38 (2.2)	54 (2.3)
Anemia [c]	22 (1.3)	27 (1.2)
Leukopenia [d]	13 (0.7)	13 (0.6)
Febrile neutropenia	7 (0.4)	12 (0.5)
Lymphopenia [e]	2 (0.1)	2 (0.1)
Eye disorders		
Dry eye	1 (0.1)	1 (0.0)
Vision blurred [f]	1 (0.1)	1 (0.0)
Gastrointestinal disorders		
Nausea	88 (5.1)	111 (4.8)
Vomiting	28 (1.6)	33 (1.4)
Diarrhoea	21 (1.2)	34 (1.5)
Stomatitis [g]	8 (0.5)	8 (0.3)
Abdominal pain [h]	6 (0.3)	8 (0.3)
Abdominal distension	2 (0.1)	2 (0.1)
Constipation	2 (0.1)	4 (0.2)
Gastritis	2 (0.1)	2 (0.1)
Dyspepsia	1 (0.1)	2 (0.1)
General disorders and administration site conditions		
Fatigue [i]	91 (5.2)	118 (5.1)
Oedema peripheral	2 (0.1)	2 (0.1)
Pyrexia	1 (0.1)	3 (0.1)
Hepatobiliary disorders		
Transaminases increased [j]	17 (1.0)	19 (0.8)
Infections and infestations		
Pneumonia	4 (0.2)	6 (0.3)
Investigations		
Blood bilirubin increased [k]	15 (0.9)	17 (0.7)
Weight decreased	12 (0.7)	15 (0.6)
Blood creatinine increased	3 (0.2)	4 (0.2)
Metabolism and nutrition disorders		
Decreased appetite	19 (1.1)	25 (1.1)
Hypokalaemia [l]	5 (0.3)	6 (0.3)
Dehydration	2 (0.1)	2 (0.1)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain [m]	1 (0.1)	1 (0.0)
Nervous system disorders		
Headache [n]	5 (0.3)	5 (0.2)
Dizziness	4 (0.2)	5 (0.2)
Dysgeusia	1 (0.1)	1 (0.0)
Respiratory, thoracic and mediastinal disorders		
Interstitial lung disease [p]	20 (1.1)	24 (1.0)
Dyspnoea	1 (0.1)	2 (0.1)
Epistaxis	0	1 (0.0)
Skin and subcutaneous tissue disorders		
Alopecia	3 (0.2)	4 (0.2)
Rash [o]	2 (0.1)	2 (0.1)

Post marketing experience

Since the first approval of TDXd on 20 December 2019 through 19 December 2023 (the DCO of the latest PBRER), the estimated cumulative patient exposure was 42,929.2 patient-years. No new safety concerns have been identified based on post-marketing safety reports.

2.5.1. Discussion on clinical safety

The size of the safety pool and the length of exposure to T-DXd is adequate for safety assessment. The MAH presented a safety data set, based on the patients included in the pivotal DB-06 study and an All

Tumours Pool (ATT Pool), including 2335 patients exposed to T-DXd 5.4 mg/kg IV Q3W. The median duration of T-DXd treatment in the DB-06 study was 11.02 months and 72.8% of patients in the BC Pool (which included the pivotal DB-06 study) were exposed to T-DXd for more than 6 months and 45% were exposed for more than 12 months.

Almost all patients in the pivotal DB-06 study experienced at least one **adverse event** (AE). The most common AEs during T-DXd treatment are in the broad categories of gastrointestinal and haematological toxicities, as well as alopecia and fatigue. The incidences of these toxicities are in line with those of the ATT Pool, in which the most common were nausea (71.1%), fatigue or asthenia (if grouped occurring in 52%), vomiting (37.3%), alopecia (36.1%), anaemia (35.3%) and neutropenia (35.1%).

The reported incidences of **treatment-related adverse events** with T-DXd in the pivotal DB-06 study were overall very similar to the incidences of the AEs reported in the DB-06 study. The most common ADRs were all notably more frequent in the T-DXd arm than in the chemotherapy arm. The gastrointestinal ADRs were, with regards to nausea (69.8%), vomiting (33.6%) and constipation (31.6%), more than twice as frequent in the T-DXd arm as in the chemotherapy arm. The haematological ADRs were all significantly more substantial than in the chemotherapy arm, as seen for the respective incidences of neutropenia (38.9% vs. 30.7%), anaemia (37.3% vs. 26.4%), thrombocytopenia (19.8% vs. 5.0%) and lymphopenia (10.8% vs. 3.8%). This pattern also applies to fatigue (52.8% vs. 39.8%) and alopecia (48.4% versus 20.9%).

Of note, **COVID-19** was twice as frequent in the T-DXd arm as in the chemotherapy arm of the pivotal study DB-06. This is presumed to be due to more frequent testing for COVID-19 in the T-DXd arm, since testing was part of the ILD-workup, and thus indicating more frequent respiratory symptoms in this group. Another explanation for the higher frequency of COVID-19 cases may also be the median 5 months longer treatment time on T-DXd and the resulting longer time at risk of encountering COVID-19. The exposure-adjusted incidence rate for the event was balanced between the two arms (0.24 in the T-DXd arm vs 0.20 in the chemotherapy arm). The explanations presented by the MAH are considered sufficient to justify the absence of an increased risk of COVID-19 infection during T-DXd treatment compared with chemotherapy.

Grade ≥ 3 AEs were seen in approximately half of the T-DXd treated population, both in the T-DXd arm of the pivotal study DB-06 and in the Safety Pools (54.8%). The chemotherapy arm had a 10% lower occurrence of grade ≥ 3 AEs. In both groups the grade ≥ 3 AEs were mainly haematological (neutropenia and anaemia). The incidence of grade ≥ 3 AEs in the other most common toxicities, such as nausea, other gastrointestinal AEs and fatigue, was low in the T-DXd arm.

AEs of special interest are ILD/pneumonitis and LVEF decrease.

ILD/pneumonitis occurred in more than 10% in the T-DXd arm, and thus classifies as a very common AE. Clinically, ILD and pneumonitis have similar presentations, implications and are managed according to the same treatment algorithm. For these reasons it is essential to present their occurrence as one category, i.e. ILD/pneumonitis The methodology used by the MAH for ascertaining the diagnosis of ILD/pneumonitis was the adoption of an adjudication committee (AC), blinded to treatment arm. All cases with suspected ILD/pneumonitis were reviewed by the AC. In the ATT Pool 16.2% of the ITT were referred for adjudication and 12.2% of the ITT were adjudicated by the AC as having ILD/pneumonitis. ILD/pneumonitis was the main reason for treatment-related fatal events (1.1%) as well as the main reason for drug-related discontinuation of treatment (8.4%). In 28.1% of the cases, the patients had not recovered from ILD/pneumonitis at a median follow up of ~9.4 months. Although the number of fatalities due to ILD/pneumonitis was reported as 2, it is noted that 8 patients had unresolved ILD/pneumonitis at the time of death. ILD/pneumonitis continues to be the greatest

risk of T-DXd treatment. The management of ILD/pneumonitis is adequately described in sections 4.2, 4.4 and 4.8 of the SmPC and it is an important identified risk in the RMP.

Decrease in left ventricular ejection fraction to a grade 2 occurred in 14.6% of the T-DXd treated patients of the pivotal study, which is in line with the ATT Pool. There were few or no patients with LVEF decrease at a grade ≥ 3. The management of left ventricular dysfunction is adequately described in sections 4.2, 4.4 and 4.8 of the SmPC and left ventricular dysfunction is an important identified risk in the RMP.

Serious adverse events (SAEs) were seen in 20.3% in the T-DXd arm of study DB-06, which is lower than in the ATT Pool (27.9%). The most commonly observed SAE in the T-DXd arm was ILD/pneumonitis, which was classified as an SAE in 3.6% of patients. ILD grade 5 occurred in 3 patients and was the most frequent cause of treatment-related death in the T-DXd arm.

Discontinuation of treatment due to AEs was seen in 14.1% in the T-DXd arm and in 9.8% in the chemotherapy arm. The primary cause of discontinuation due to an AE was ILD/pneumonitis, accounting for 8.8%. Haematological toxicity led to drug discontinuation in very few cases in the pivotal study. There were 3 cases of discontinuation due to thrombocytopenia and 1 discontinuation due to anaemia in the T-DXd arm. In the chemotherapy arm, there was only one case of discontinuation in this category (neutropenia). This is in line with the Safety Pools. To conclude, the main cause of drug-related discontinuation of T-DXd was ILD/pneumonitis.

Overall, the toxicity profile of T-DXd is considerable. This is stressed by the high number of symptomatic AEs present in ≥ 10% of patients (17 categories for the T-DXd arm). Although the shorter duration of treatment in the chemotherapy arm may affect the generally lower incidence of AEs in this arm, toxicities such as nausea, vomiting, constipation, fatigue and alopecia were notably more frequent in the T-DXd arm. Particularly the observation that most AEs occur during the first 6 treatment cycles of T-DXd, indicates that the higher incidence of AEs in the T-DXd arm is not alone explained by the longer exposure time to T-DXd treatment, but underscores a worse safety profile with T-DXd treatment than with chemotherapy. Peripheral sensory neuropathy and Palmar-plantar erythrodysaesthesia (PPE) were characteristic of chemotherapy and rarely occur with T-DXd. The risk of any gastrointestinal toxicity related to T-DXd is high, with nausea taking the lead as the most common ADR in this category, and combined with the high risk of fatigue, has potential to significantly impact quality of life during treatment. Alopecia as well is considered an important ADR. On the positive side, there were only a few high grade gastrointestinal and hematological AEs and they seldomly led to dose interruption or discontinuation. Overall the toxicities were manageable. As stated above, the most serious risk of T-DXd treatment is still ILD/pneumonitis.

2.5.2. Conclusions on clinical safety

Based on safety data from 2335 patients with breast cancer and other tumours, who have had relevant exposure to the approved dose of trastuzumab deruxtecan (T-DXd 5.4 mg/kg iv Q3W), no clinically significant changes of the known safety profile nor any new safety findings were detected. In study DB-06, the safety profile of T-DXd was compared to chemotherapy (investigators choice of capecitabine, paclitaxel or nab-paclitaxel) after prior exposure to two lines of endocrine therapy. The toxicities observed with T-DXd are considered notably more frequent, numerous and for some also different in character, than those observed with chemotherapy. ILD/pneumonitis is still the greatest risk in the treatment with T-DXd and the occurrence of drug-related fatal cases stresses the importance of continuous monitoring of this AESI, as reflected in the SmPC and the RMP. In the targeted setting of metastatic breast cancer, the observed toxicities of T-DXd are considered acceptable and manageable.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version 9.0 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 9.0 is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

Table 94 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Interstitial lung disease/Pneumonitis • Left ventricular dysfunction
Important potential risks	• Embryo-foetal toxicity • Product confusion-related medication errors
Missing information	• Use in patients with severe hepatic impairment • Long-term safety

Pharmacovigilance plan

Table 95 Ongoing and Planned Additional Pharmacovigilance Activities

Study: **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation: None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances: None				
Category 3 – Required additional pharmacovigilance activities : None				

Risk minimisation measures

Table 96 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Interstitial Lung Disease/Pneumonitis	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Patient Information Leaflet Section 2 Patient Information Leaflet Section 4 Recommendations for ILD/pneumonitis monitoring and detecting early signs and symptoms of ILD/pneumonitis are included in SmPC Section 4.4. Dose modification guidance and recommendation for corticosteroid treatment for managing the risk of ILD/pneumonitis are included in SmPC Section 4.2. Recommendation for careful monitoring of patients with moderate or severe renal impairment is included in SmPC Section 4.2. Additional risk minimisation activities: HCP Guide and Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire Additional pharmacovigilance activities: None
Left ventricular dysfunction	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Patient Information Leaflet Section 2 Recommendations for monitoring of left ventricular dysfunction are included in SmPC Section 4.4. Dose modification guidance for managing the risk of left ventricular dysfunction is included in SmPC Section 4.2. Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risks		
Embryo-foetal toxicity	Routine risk minimisation measures: SmPC Section 4.4 SmPC Section 4.6 Patient Information Leaflet Section 2 Recommendations for pregnancy monitoring and contraception usage are included in SmPC Section 4.4 and SmPC Section 4.6. Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Product confusion-related medication error	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 6.6 Pack and vials: specific livery for ENHERTU on the packaging and specific colours for vial cap and bottle to distinguish from other trastuzumab containing products Additional risk minimisation activities:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risks		
	HCP Guide	
Missing Information		
Use in patients with severe hepatic impairment	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 5.2 Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Long-term safety	Routine risk minimisation measures: None Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

HCP = healthcare professional; ILD = interstitial lung disease; PK = pharmacokinetic; SmPC = Summary of Product Characteristics

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template 10.4 and the Excipients guideline, which were reviewed and accepted by the CHMP.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- In accordance with articles 59(3) and 61(1) of Directive 2001/83/EC, the MAH completed a full user test of the PIL during the review of the initial Marketing Authorisation Application (MAA) for Enhertu (EMEA/H/C/005124/0000).
- Enhertu is prescribed by a physician and administered intravenously under the supervision of a healthcare professional at a hospital/clinic setting. The posology, administration and method of reconstitution for the extension of indication is unchanged.
- The updates to the PIL, including the safety sections, are not significant and utilise well recognised lay terms. Furthermore, the PIL will be kept identical in format size, colours, layout/design as illustrated in the agreed mock-ups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The recommended indication reflecting the data evaluated is:

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment (see sections 4.2 and 5.1).

3.1.2. Available therapies and unmet medical need

Metastatic HER2-low (tumour status defined as a score of IHC 1+ or IHC 2+/ISH-) and HER2-ultralow (tumour status described as IHC 0 with membrane staining (IHC >0<1+)) breast cancer remains an uncurable disease. Although treatment with single-agent chemotherapy has improved the disease outcomes for patients with unresectable locally advanced or metastatic breast cancer, the disease invariably progresses.

When the disease has progressed after multiple lines of endocrine therapy with or without targeted therapies or who have a short median PFS on first-line endocrine-based therapy, chemotherapy is considered the most appropriate option. Single-agent therapy is preferred over combination therapy (Cardoso et al. 2009, NCCN 2024, Cancer Facts and Figures 2024) and chemotherapy combinations are only used in patients with rapidly progressing disease and visceral crisis. Single-agent chemotherapy options include taxanes, anti-metabolites (e.g., capecitabine) and anthracyclines. In patients similar to the sought indication, who have HR+, although classified as HER2-negative breast cancer, and have received 0 to 1 prior line of chemotherapy for metastatic disease, single-agent chemotherapy led to a median PFS of approximately 6 to 7 months and a median OS of approximately 20 to 25 months (O'Shaughnessy et al. 2021a, O'Shaughnessy at al 2021b, Robert et al. 2011, Baselga et al. 2017). At this time, T-DXd is approved in HER2-low breast cancer following one line of chemotherapy and there are no approved HER2-targeting therapies for the HER2-ultralow population.

Overall, the modest benefits for patients with HER2-low or HER2-ultralow BC, who have received at least 1 line of endocrine therapy in the metastatic setting illustrate the high unmet medical need for new treatment options to delay progression and improve survival outcomes in the targeted earlier-line setting.

3.1.3. Main clinical studies

The current application is based on a single pivotal study DESTINY-Breast06 or DB-06: a phase III randomised open-label two-arm study comparing trastuzumab deruxtecan (T-DXd) head to head with the current SoC in the targeted setting of HER2-low and HER2-ultralow advanced breast cancer i.e. single-agent chemotherapy by Physician's choice (either capecitabine, nab-paclitaxel, paclitaxel). Eligible patients had disease progression on at least 2 lines of endocrine therapy in the metastatic setting or one line of endocrine therapy in the metastatic setting and demonstrated progression within 24 months of the start of adjuvant endocrine therapy, or within 6 months of starting first line endocrine therapy in combination with a CDK 4/6 inhibitor in the metastatic setting.

866 patients were recruited from 273 study centres in 28 countries and the median duration of follow-up for OS in the HER2-low population was 19.0 months at the DCO of 18 March 2024, which is at the time of the final analysis of PFS and the first interim analysis (IA) of overall survival (OS). The pivotal study was fully recruited, and a relevant fraction of the patients is considered representative of the EU population (~62% from Europe or North America).

The study population (ITT) consisted of 713 patients (82.3%) whose tumours were HER2-low and 152 patients (17.6%) whose tumours were HER2-ultralow.

3.2. Favourable effect

The primary endpoint in study DB-06, PFS by BICR assessment in the HER2-low population, showed an improvement of 5.1 months from 8.1 months (95%CI: 7.0, 9.0) with chemotherapy to 13.2 months (95%CI: 11.4, 15.2) with T-DXd, HR 0.62 (95%CI: 0.52; 0.75) at the DCO of 18 March 2024. The data is considered mature with 62.7% events in the active T-DXd arm and 65.5% events in the control arm.

Below, the favourable effects are reflected for the entire study population (ITT), since this is the relevant population for the applied indication.

PFS by BICR assessment in the ITT population was a secondary endpoint and its results were in line with the primary endpoint showing an improvement of 5.1 months from 8.1 months with chemotherapy to 13.2 months with T-DXd, HR 0.64 (95%CI: 0.54, 0.76). The data is considered mature with 61.7% events in the active T-DXd arm and 63.0% events in the control arm.

Since the Interim Analysis (IA) of OS in the HER2-low population was not statistically significant, the confirmatory testing at the IA stopped, and OS was not formally tested in the ITT population. Therefore, all subsequent results are descriptive. At the IA, the HR for OS in the ITT population was 0.81 (95%CI: 0.66; 1.01) and 0.83 (95%CI: 0.66, 1.05) in the HER2-low population.

Confirmed ORR by BICR in the ITT population was improved from 31.2% in the control arm to 57.3% with T-DXd. CR was observed in 3.2% of the patients with T-DXd and 0 patients in the chemotherapy arm, while the rate of PR was 58.3% with T-DXd vs 36.7% in the chemotherapy arm.

The median duration of response (DoR) by BICR was longer for patients in the T-DXd arm i.e. 13.7 months (95%CI: 11.8; 15.4) vs 7.3 months with chemotherapy (95%CI: 6.0; 10.8).

The median PFS2 in the T-DXd arm was 20.3 months vs 14.7 months in the chemotherapy arm, HR 0.61 (95%CI: 0.51; 0.73). The KM curves for PFS2 separate early and remain separated.

The median treatment duration was 11.0 months in the T-DXd and 5.6 months in the chemotherapy arm.

3.3. Uncertainties and limitations about favourable effects

The limited sample size of the HER2-ultralow population of 152 patients represents an uncertainty on the treatment effect of T-DXd in the HR+ HER2-ultralow population due to the lower number of patients and events/unpowered analysis.

The comparator arm may be considered suboptimal for patients who did not receive prior anthracyclines (around ~55% of the included patients in study DB-06 (see section 5.1 of the SmPC)) especially since about 30% of patients presented with de-novo Stage IV disease. The beneficial effect

of T-DXd in patients without prior use of anthracyclines is therefore uncertain. Nevertheless, a detrimental effect is considered unlikely.

3.4. Unfavourable effects

Almost all patients in both treatment arms in the pivotal study DB-06 experienced at least one **adverse event** (AE) and most of these were treatment-related. The majority of the AEs were at least twice as frequent in the T-DXd arm compared to the chemotherapy arm. All reported AE incidences for the T-DXd arm were within the same magnitude of the AE incidences reported in the All Tumour Pool (ATT Pool), with the exception of COVID-19 (24.4% in the T-DXd arm versus 12.5% in the chemotherapy arm of the DB-06 study) and no new categories of AEs were observed. In the ATT Pool, the most frequently observed events were nausea (71.1%), fatigue (52%), vomiting (37.3%), alopecia (36.1%), neutropenia (36.4%), anaemia (35.3%), constipation (31.7%) and diarrhoea (30.1%). **Treatment-related AEs** (ADRs) with T-DXd in the DB-06 study were also mainly gastrointestinal and haematological in nature, at nearly the same incidences as reported for the AEs. The incidences of ADRs in the T-DXd arm of the DB-06 study are in line with those of the ATT Pool.

In the DB-06 study 52.8% and 44.4% had a **grade ≥ 3 AE** in the T-DXd arm and chemotherapy arm respectively. The most common grade ≥ 3 AEs were neutropenia (22.3% versus 17%) and anaemia (8.8% versus 4.3%). The very common AEs, such as nausea, other gastrointestinal AEs and fatigue, seldomly were grade ≥ 3. This is in line with the data from the Safety Pools (BC and ATT).

Adverse events of special interest are ILD/pneumonitis and left ventricular ejection fraction decrease. ILD/pneumonitis continues to be the greatest risk for T-DXd treatment, with an incidence of 12.2%. Most events were Grade 1 or Grade 2, but there were three Grade 3 or 4 events (0.7%) and three Grade 5 events in the T-DXd arm. A decrease in left ventricular ejection fraction to a grade 2 occurred in 14.6% of the T-DXd treated patients of the pivotal study, which is in line with the ATT Pool.

In the T-DXd arm and the chemotherapy arm of the pivotal study, **Serious AEs** (SAEs) were observed in 20.3% in the T-DXd arm and 16.1% in the chemotherapy arm. In patients treated with T-DXd in 2.5% an AE was reported with the outcome of death, which was considered to be drug-related in 1.2% (ILD in 2 patients, sepsis in 2 patients and general physical health deterioration in 1 patient). In the chemotherapy arm, in 1.4% an AE was reported with an outcome of death and none of the cases were drug-related. The most commonly observed SAE in the DB-06 study was interstitial lung disease/pneumonitis (3.6%), which is in line with the most common SAE in the ATT Pool of 3.1% and was associated with death in 3 patients.

The main cause of **discontinuation of treatment** in the pivotal study, was objective disease progression in both treatment arms, which was 57.1% in the T-DXd arm and 70% in the chemotherapy arm. Discontinuation of treatment due to AEs was seen in 14.1% in the T-DXd arm and in 9.8% in the chemotherapy arm. The primary cause of discontinuation was ILD/pneumonitis (8.8%).

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 97 Effects Table for Enhertu (T-DXd) for advanced HR+, HER2-low and HER2-ultralow breast cancer (data cut-off: 18 March 2024)

Effect	Short description	Unit	Treatment T-DXd N= 436	Control Chemo-therapy N=430	Uncertainties / Strength of evidence
Favourable Effects (ITT population)					
PFS by BICR	Progression-free survival	Months (95%CI)	13.2 12.0; 15.2	8.1 7.0; 9.0	HR 0.64 (0.54; 0.76) 61.7% vs 63% events Strength: Independent of HER2 expression level Uncertainty: Effect size HER2-ultralow subgroup due to low number of events /unpowered analysis
OS	Overall survival	Months	28.9 26.4; 32.7	27.4 23.9; 29.9	36.9% vs 40.5% events, HR 0.81(NS) Uncertainty: Exploratory analysis due to immature data
ORR by BICR	Overall response rate	%	57.3	31.2	Confirmed ORR reported
DOR by BICR	Duration of response	Months	13.7	7.3	
Unfavourable Effects-					
Grade ≥3 AEs		%	52.8	44.4	
SAEs		%	20.3	16.1	
AEs leading to discontinuation		%	14.3	9.4	
AEs associated with death		%	2.5	1.4	
ILD/pneumonitis		%	12.2	(0.2 – 1.2)	
LVEF decrease ≥ grade 2		%	15.0	8.4	

Abbreviations: BICR: Blinded independent review; NS: Not statistically significant; AE: Adverse Event; SAE: Serious Adverse Event.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

At the DCO of 18 March 2024, the primary endpoint of PFS by BICR in the HER2-low population was met and showed a statistically significant and clinically relevant improvement of 5.1 months from 8.1 months with chemotherapy to 13.2 months with T-DXd, HR 0.62 after a median follow up of almost 19 months and more than 60% of events in both arms. The secondary endpoint of OS in the HER2-low population show that with partly mature data at the time of the first IA (~40% events), the median OS was 28.9 months in the T-DXd arm vs 27.1 months in the control arm; HR of 0.83 (95%CI: 0.66; 1.05). The KM curves for OS do not clearly separate but there is no sign of a detriment.

The results of PFS by BICR assessment in the ITT population were in line with the primary analysis and also showed an improvement of 5.1 months from 8.1 months with chemotherapy to 13.2 months with T-DXd, HR 0.64 (95%CI: 0.54, 0.76).

Of note, the subgroup analysis of the HER2-ultralow population showed a median PFS of 13.2 months in patients who had T-DXd (N=76) versus 8.3 months in the control arm, HR 0.78, and although this result is not statistically significant, the difference in PFS benefit observed is very similar to the primary analysis of the primary endpoint, and the numerical difference of 4.9 months is considered clinically relevant. The limited sample size of the HER2-ultralow population of 152 patients in total is considered the reason for the not statistically significant results. However, the efficacy results from the HER2-ultralow population is considered clinically relevant and the close similarity to the PFS, ORR and DoR and the PFS results from the HER2-low and the ITT populations are considered compelling, allowing to conclude that T-DXd has similar and clinically relevant efficacy in the HER2-ultralow population as well. Therefore, it is considered acceptable to grant an indication for T-DXd for both the HER2-low and the HER2-ultralow populations, meaning the ITT population in study DB-06.

In the absence of fully mature OS data, the provided PFS2 results from the ITT population are considered clinically important. The median PFS2 in the T-DXd arm was 20.3 months vs 14.7 months in the chemotherapy arm, HR 0.61, so the patients on T-DXd have a longer time to the second progression on next-line therapy. This is considered reassuring and indicates that any detriment on OS is unlikely. The MAH is recommended to submit the results of the next interim OS analysis data as well as the final OS analysis data from study DB-06 when available (Recommendation (REC)).

The safety profile of T-DXd was not changed with the added safety data from the pivotal study DB-06 and the main reported adverse events of trastuzumab deruxtecan are still haematological and gastrointestinal toxicities, which were rarely of high grade and seem to be manageable, while the major safety concern remains the risk of ILD/pneumonitis.

The clinically meaningful improvements in efficacy are shown in a direct head-to-head comparison with the current standard of care i.e. singe-agent chemotherapy, and although the toxicities of chemotherapy could be interpreted as less severe compared to T-DXd in the pivotal study DB-06, the safety profile of T-DXd is considered manageable. The risk of severe and potentially fatal toxicity is considered balanced against the markedly improved efficacy observed with T-DXd in study DB-06.

3.7.2. Balance of benefits and risks

When the advanced breast cancer has progressed in patients after multiple lines of endocrine therapy with or without targeted therapies or who have a short median PFS on first-line endocrine-based therapy, single-agent chemotherapy is considered the standard of care however with modest benefits for patients with HER2-low or HER2-ultralow BC, highlighting the high unmet medical need for new treatment options to delay progression and improve survival outcomes in this setting.

Based on the results from the DB-06 study, T-DXd as monotherapy for the treatment of adult patients with unresectable or metastatic HR+ HER2-low or HER2-ultralow breast cancer has demonstrated a statistically significant and clinically relevant benefit in PFS.

The safety profile of T-DXd is non-negligible and ILD/pneumonitis remains an important safety concern.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

Overall, the B/R balance of Enhertu in the new claimed indication is considered positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to include treatment of adult patients with unresectable or metastatic HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment for ENHERTU, based on results from study D9670C00001 (DESTINY-Breast06); this is a phase 3, randomized, multicentre, open-label study of trastuzumab deruxtecan (DS-8201a) compared with investigator's choice chemotherapy in, hormone receptor-positive, HER2-low and HER2-ultralow BC patients whose disease has progressed on endocrine therapy in the metastatic setting. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 9.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce editorial changes to the PI, and to update the PI according to the Excipients Guideline. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

The variation leads to amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II, IIIA and IIIB and to the Risk Management Plan are recommended.

This recommendation is subject to the following amended conditions:

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Additional risk minimisation measures

Prior to the launch of trastuzumab deruxtecan in each member state, the Marketing Authorisation Holder (MAH) must agree on the content and format of the educational programme (Healthcare Professional [HCP] Guide, Patient Card for ILD/pneumonitis and HCP Guide for product confusion-

related medication errors), including communication media, distribution modalities, and other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at:

I) ensuring early recognition of interstitial lung disease (ILD)/pneumonitis, to allow prompt appropriate treatment and to mitigate worsening of the condition.

II) improving HCP awareness of the potential risk for product confusion-related medication errors due to the availability of multiple trastuzumab-containing products and trastuzumab emtansine

The MAH shall ensure that in each member state where trastuzumab deruxtecan is marketed, all HCPs and patients who are expected to administer/be administered trastuzumab deruxtecan are provided with the following educational materials:

I) **Healthcare Professional (HCP) Guide for ILD/pneumonitis**

The HCP Guide contains the following key elements:

- Summary of important findings of trastuzumab deruxtecan-induced ILD/pneumonitis (eg, frequency, grade, time to onset) observed in the clinical trial setting
- Description of the appropriate monitoring and evaluation of ILD/pneumonitis in patients receiving trastuzumab deruxtecan
- Detailed description of management of ILD/pneumonitis in patients treated with trastuzumab deruxtecan including guidance on drug interruption, reduction and treatment discontinuation for ILD/pneumonitis
- Reminder to HCP that they should repeat the information about signs and symptoms of ILD/pneumonitis at each patient visit, including when the patient should seek attention from an HCP (eg, the symptoms to watch for; the importance to adhere to scheduled appointments)
- Reminder to HCP to provide the patient with the Patient Card (PC), including advice that the PC should be kept with the patient at all times

II) **Healthcare Professional Guide for prevention of medication errors**

The HCP Guide contains the following key elements:

- Alert to HCPs about a potential risk of confusion between Enhertu (trastuzumab deruxtecan) and other trastuzumab-containing products and the HER2-targeted antibody-drug conjugate Kadcyla (trastuzumab emtansine)
- Mitigation measures for prescribing errors due to similarities in active ingredient names and measures to avoid errors during prescription phase by physicians
- Comparison of commercial appearance between Enhertu (trastuzumab deruxtecan) and other trastuzumab-containing products and the HER2-targeted antibody-drug conjugate Kadcyla (trastuzumab emtansine)
- Potential mitigation strategies to avoid errors during preparation phase by pharmacists
- Detailed Information about the dosage, method of administration and preparation as well as instructions to avoid medication errors during administration phase by nurses

III) **Patient Card**

The Patient Card contains the following key elements:

- Description of the important risks of ILD/pneumonitis associated with the use of trastuzumab deruxtecan
- Description of key signs and symptoms of ILD/pneumonitis and guidance on when to seek attention from an HCP
- Contact details of the trastuzumab deruxtecan prescriber
- Cross-reference to Patient Information Leaflet