15 December 2022
EMA/CHMP/14752/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Enhertu

International non-proprietary name: trastuzumab deruxtecan

Procedure No. EMEA/H/C/005124/II/0022

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

AC	Adjudication Committee
ADA	anti-drug antibody
ADC	antibody-drug conjugate
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AI	aromatase inhibitor
ASCO/CAP	American Society of Clinical Oncology/College of American Pathologists
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
BC	breast cancer
BICR	blinded independent central review
BRCA	germline breast cancer susceptibility gene
CDK4/6	cyclin-dependent kinase 4 and 6
CDx	companion diagnostic
CE	Conformité Européenne
CI	confidence interval
Cmax	maximum serum concentration
Cmin	minimum serum concentration
CNS	central nervous system
CR	complete response
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DAR	drug-to-antibody ratio
DCO	data cut-off
DoR	duration of response
DXd	the released payload, a topoisomerase I inhibitor derivative of exatecan
EAIR	exposure-adjusted incidence rate
ECOG PS	Eastern Cooperative Oncology Group performance status
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer

EQ-5D-5L	EuroQoL-5 dimensions-5 levels of severity
ER	exposure-response
ET	endocrine therapy
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
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
ICR	independent central review
IHC	immunohistochemistry
ILD	interstitial lung disease
INV	investigator assessment
IRR	infusion-related reaction
ISH	in situ hybridization
ITT	intent-to-treat
IUO	Investigational Use Only
IV	intravenous
IXRS	interactive web/voice response system
LV	left ventricular
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NAb	neutralizing antibody
nab	nanoparticle albumin-bound
NCA	noncompartmental analysis
NCCN	National Comprehensive Cancer Network
NE	not estimable
ORR	objective response rate

OS	overall survival
PARP	poly (ADP-ribose) polymerase
PBRER	Periodic Benefit Risk Evaluation Report
PD	progressive disease
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3 kinase catalytic subunit alpha
PK	pharmacokinetic(s)
PopPK	population pharmacokinetic(s)
PPS	Per-protocol Analysis Set
PR	partial response
PRO	Patient-reported outcome(s)
PT	preferred term
Q3W	every 3 weeks
QLQ-C30	Quality-of-life C-30
QLQ-BR45/BR323	Quality-of-life BR 45/BR23
RECIST v1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
SAE	serious adverse event
SAP	statistical analysis plan
SCE	summary of clinical efficacy
SCS	summary of clinical safety
SD	stable disease
SERM	selective estrogen receptor modulator
SMQ	Standardised MedDRA Query
SoC	standard of care
T-DXd	trastuzumab deruxtecan, Enhertu®
TEAE	treatment-emergent adverse event
TNBC	triple-negative breast cancer
TPC	treatment of physician's choice
TTDD	time to definitive deterioration
US	United States
v	Version
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 31 May 2022 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 and IIIB

Extension of indication to include treatment of unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior systemic therapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients with hormone receptor positive (HR+) breast cancer must additionally have received or be ineligible for endocrine therapy; for ENHERTU, based on final results from study DS8201-A-U303 (DESTINY-Breast04). This is a Phase III, multicentre, randomised, 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.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.4 of the RMP has also been submitted.
In addition, the Marketing authorisation holder (MAH) took the opportunity to update section 4.4 of the SmPC to update the dosing recommendation for corticosteroid treatment (e.g. prednisolone) with a daily dose.

The variation requested amendments to the Summary of Product Characteristics 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

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 20 September 2018 (EMEA/H/SA/3715/3/2018/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Aaron Sosa Mejia Co-Rapporteur: Paula Boudewina van Hennik

Timetable	Actual dates
Submission date	31 May 2022
Start of procedure:	18 June 2022
CHMP Rapporteur Assessment Report	5 August 2022
PRAC Rapporteur Assessment Report	11 August 2022
PRAC members comments	24 August 2022
CHMP Co-Rapporteur Critique	23 August 2022
Updated PRAC Rapporteur Assessment Report	25 August 2022
PRAC Outcome	1 September 2022
CHMP members comments	5 September 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	9 September 2022
Request for supplementary information (RSI)	15 September 2022
CHMP Rapporteur Assessment Report	15 November 2022
PRAC Rapporteur Assessment Report	18 November 2022
PRAC members comments	23 November 2022
Updated PRAC Rapporteur Assessment Report	24 November 2022
PRAC Outcome	1 December 2022
CHMP members comments	5 December 2022
Updated CHMP Rapporteur Assessment Report	8 December 2022
Opinion	15 December 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

The initially applied indication was as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior systemic therapy in the metastatic setting or developed disease recurrence during or within 6

months of completing adjuvant chemotherapy. Patients with hormone receptor positive (HR+) breast cancer must additionally have received or be ineligible for endocrine therapy.

Epidemiology and risk factors

Breast Cancer (BC) is the most commonly diagnosed cancer worldwide (11.7% of all cancer sites) and the leading cause of cancer death in women (15.5% of all cancer sites in 2020). In 2020, there was an estimated 2.26 million new cases of female BC globally, with an estimated 684,996 deaths due to BC (Globocan 2020).

Biologic features

According to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) recommendations for HER2 testing in BC, HER2 receptor status is classified as "HER2-positive" (tumors scoring 3+ or 2+ by immunohistochemistry [IHC] and HER2 gene amplification by in situ hybridization [ISH]) or "HER2 negative" (tumors scoring 2+ by IHC and no evidence of HER2 gene amplification by ISH or tumors scoring 1+ or 0 by IHC). Among patients with HER2-negative BC, approximately 50% have tumors with low HER2 expression (defined as tumors scoring 2+ or 1+ by IHC and no evidence of HER2 gene amplification). HER2-low tumors constitute a heterogeneous population that include both luminal-type hormone receptor-positive BC and hormone receptor-negative BC (triple-negative breast cancer [TNBC]).

Management

Current therapeutic guidelines for patients with breast cancer exhibiting HER2-low expression are the same as those for patients with HER2 negative breast cancer. In the targeted metastatic setting, treatment recommendations are based on tumor hormone receptor status (positive or negative, i.e., presence or absence of estrogen and/or progesterone receptors), presence or absence of visceral crisis, and menopausal status (Gennari et al. ESMO. 2021).

The recommended treatment in the targeted second- and subsequent-line setting for patients with hormone receptor positive (HR+) disease, previously exposed to endocrine therapy (ET), are fulvestrant in combination with a CDK4/6 inhibitor. If a CDK4/6 inhibitor was not previously used, everolimus with either an AI, tamoxifen or fulvestrant, monotherapy with fulvestrant, a non-steroidal or a steroidal AI, or a selective oestrogen receptor modulator (SERM) is recommended. For patients with PIK3CA-mutated tumours, the preferred option is fulvestrant with alpelisib. Once metastatic hormone receptor-positive HER2-negative BC is refractory to ET, the standard of care (SoC) is sequential systemic single-agent chemotherapy. Because of the lack of clear superiority, no specific chemotherapy is recommended in clinical practice guidelines but the most commonly used regimens include anthracyclines (doxorubicin and liposomal doxorubicin), anti-metabolites (capecitabine and gemcitabine), microtubule inhibitors (vinorelbine and eribulin), and taxanes (paclitaxel). Combination therapies, although rarely used, may be useful in patients with rapid clinical progression or need for rapid symptom and/or disease control. Other available systemic therapies include PARP inhibitors for patients with BRCA germline mutations and alpelisib for patients with PIK3CA-mutated tumors.

For patients with HR-negative disease (Triple-negative disease (TNBC)), the available treatment options are as follows. For patients with PDL1-negative disease, the treatment in the first-line setting is sequential single agent chemotherapy using the same preferred chemotherapeutic options as those for patients with hormone receptor-positive HER2-negative BC refractory to ET. Regardless of BRCA status, for patients with TNBC previously treated with anthracyclines and taxanes in the adjuvant or

neoadjuvant setting, platinum agents are the preferred option. For patients with BRCA mutations, the recommendation is to use PARP inhibitors or platinum agents and for patients with PD L1-positive TNBC, the preferred therapeutic option in the first-line setting is an immune-checkpoint inhibitor in combination with chemotherapy. For the later line setting after at least two previous regimens, with at least one of them in the metastatic setting, the antibody-drug conjugate (ADC) sacituzumab govitecan is approved (see Trodelvy SmPC/EPAR).

Table 1 Treatment Options in Metastatic HER2-negative Breast Cancer Refractory to or Ineligible for Endocrine-based Therapy (modified)

Product Name	Relevant Indication	Dosing/ Administration	Efficacy Information
Doxorubicin Docetaxel	Doxorubicin: **2L+** For the treatment of ALL, AML, Hodgkin lymphoma, Non-Hodgkin lymphoma, metastatic BC, metastatic Wilms' tumor, metastatic neuroblastoma, metastatic soft tissue sarcoma, metastatic bone sarcomas, metastatic ovarian carcinoma, metastatic transitional cell bladder carcinoma, metastatic thyroid carcinoma, metastatic gastric carcinoma, metastatic bronchogenic carcinoma Docetaxel: **2L+** Single agent for locally advanced or metastatic BC after chemotherapy failure	Doxorubicin: 60 to 75 mg/m^2 IV infusion Q3W Docetaxel: 60 to 100 mg/m^2 single agent Q3W	Chan et al 1999 Doxorubicin (n = 165): ORR: 33.3% (95% CI: 26.1, 40.5) Median TTP: 21 weeks (95% CI not reported) Median OS: 14 months (95% CI not reported) Docetaxel (n = 161): ORR: 47.8% (95% CI: 40.1, 55.5) Median TTP: 26 weeks (95% CI not reported) Median OS: 15 months (95% CI not reported)
Paclitaxel	**2L+** Treatment of BC after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.	175 mg/m^2 IV over 3 hours Q3W or 80 mg/m^2 weekly	Nabholtz et al 1996 High-dose paclitaxel (175 mg/m^2; n = 235) ORR: 29% (95% CI: 23, 36) Median DoR: 8.2 months (range: 3.6 to 16.5+) Median TTP: 4.2 months (95% CI not reported) Median OS: 11.7 months (95% CI not reported)
Liposomal doxorubicin	**2L+** Monotherapy for patients with metastatic BC, where there is an increased cardiac risk associated with conventional doxorubicin	50 mg/m^2 Q4W	O'Brien et al 2004 Liposomal doxorubicin (n = 254): ORR: 33% (95% CI not reported) Median PFS: 6.9 months (95% CI not reported) (HR: 1.00 [95% CI: 0.82, 1.22]) Median OS: 21 months (95% CI not reported) (HR: 0.94 [95% CI: 0.74, 1.19]) Median DoR: 7.3 months (95% CI not reported)
Capecitabine	**2L+** As monotherapy in patients resistant to both	Monotherapy: 1250 mg/m^2	Blum et al 1999 (monotherapy) Capecitabine (n = 162):

Product Name	Relevant Indication	Dosing/ Administration	Efficacy Information
	paclitaxel and an anthracycline-containing regimen	BID orally for 2 weeks followed by a 1-week reset period in 3-week cycles	ORR: 20% (95% CI: 14, 28) Median DoR: 8.1 months (95% CI not reported) Median TTP: 93 days (95% CI: 84, 106) Median OS: 12.8 months (95% CI not reported)
Gemcitabine	**1L+** In combination with paclitaxel, for first-line treatment of metastatic BC after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated	1250 mg/m^2 for 30 minutes on Day 1 and 8 of each 21-day cycle	Rha et al 2005 Gemcitabine (n = 41) ORR: 20% (95% CI not reported) Median DoR: 9 months (range: 2 to 25) Median PFS: 4.5 months (95% CI: 3, 5) Median OS: 11 months (95% CI: 4, 18).
Nab-paclitaxel	**2L+** Metastatic BC after failure of combination chemotherapy for metastatic disease or relapse with 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated	260 mg/m^2 IV Q3W	Gradishar et al 2005 Nab-paclitaxel (n = 229): ORR: 33.0% (95% CI: 27.1, 39.3) Median TTP: 23.0 weeks (95% CI not reported) Median OS: 65.0 weeks (95% CI not reported) Standard paclitaxel (n = 225): ORR: 19.0% (95% CI: 13.6, 23.8) Median TTP: 16.9 weeks (95% CI not reported) Median OS: 55.7 weeks (95% CI not reported)
Ixabepilone	**2L+** Monotherapy: treatment of metastatic or locally advanced BC in patients after failure of an anthracycline, a taxane, and capecitabine **2L+:** In combination with capecitabine: treatment of metastatic or locally advanced BC in patients after failure of an anthracycline and a taxane	40 mg/m^2 IV infusion over 3 hours Q3W	Thomas et al. 2007 Ixabepilone plus capecitabine (n = 375): ORR: 34.7% (95% CI: 29.9, 39.7) Median DoR: 6.4 months (95% CI: 5.6, 7.1) Median PFS: 5.8 months (95% CI: 5.45, 6.97) (HR: 0.75 [95% CI: 0.64, 0.88]; *P*-value = 0.0003) Capecitabine (n = 377): ORR: 14.3% (95% CI: 10.9, 18.3) Median DoR: 5.6 months (95% CI: 4.2, 7.5) Median PFS: 4.2 months (95% CI: 3.81, 4.50)
Eribulin	**2L+**: Treatment of patients with metastatic BC who have previously received at least 2 chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in	1.4 mg/m^2 IV over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.	EMBRACE Eribulin (n = 508): ORR: 12% (95% CI: 9.4, 15.5) Median DoR: 4.2 months (95% CI: 3.8, 5.0)

Product Name	Relevant Indication	Dosing/ Administration	Efficacy Information
	either the adjuvant or metastatic setting.		Median PFS: 3.7 months (95% CI: 3.3, 3.9) (HR: 0.87 [95% CI: 0.71, 1.05]; *P*-value = 0.137) Median OS: 13.1 months (95% CI: 11.8, 14.3) (HR: 0.81 [95% CI: 0.66, 0.99]; *P*-value = 0.041) Eribulin (n = 554): ORR: 11.0% (95% CI: 8.5, 13.9) Median PFS: 4.1 months (95% CI: 3.5, 4.3) (HR: 1.08 [95% CI: 0.93, 1.25]; *P*-value = 0.30) Median OS: 15.9 months (95% CI: 15.2, 17.6) (HR: 0.88 [95% CI: 0.77, 1.00]; *P*-value = 0.056)
Abemaciclib	**2L+** As monotherapy for the treatment of adult patients with hormone receptor-positive, HER2-negative advanced or metastatic BC with disease progression following ET and prior chemotherapy in the metastatic setting.	As monotherapy, 200 mg BID orally	MONARCH 1 Abemaciclib (n = 132) ORR: 19.7% (95% CI: 13.3, 27.5) Median DoR: 8.6 months (95% CI: 5.8, 10.2) Median PFS: 6.0 months (95% CI: 4.2, 7.5) Median OS: 17.7 months (95% CI: 16.0, not reached)
Hormone Receptor-negative Disease (Triple-negative Breast Cancer)			
Sacituzumab govitecan	**2L+** Unresectable locally advanced or metastatic TNBC who have received 2 or more prior systemic therapies, at least 1 of them for metastatic disease	10 mg/kg once weekly on Days 1 and 8 of continuous 21-day treatment cycles	ASCENT Sacituzumab govitecan (n = 235): ORR: 31% (95% CI not reported) Median DoR: 6.3 months (95% CI: 5.5, 9.0) Median PFS: 4.8 months (95% CI: 4.1, 5.8) (HR 0.43 [95% CI: 0.35, 0.54]; *P*-value <0.0001) Median OS: 11.8 months (95% CI: 10.5, 13.8) (HR 0.51 [95% CI: 0.41, 0.62]; *P*-value <0.0001)
Pembrolizumab	In combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (Combined Positive Score ≥10) (who have not received prior chemotherapy for metastatic disease)	200 mg Q3W or 400 mg Q6W as an IV infusion over 30 minutes	KEYNOTE-355 Pembrolizumab + chemotherapy (n = 220) ORR: 53% (95% CI: 46, 60) Median DoR: 19.3 months (95% CI: 9.9, 29.8) Median PFS: 9.7 months (95% CI: 7.6, 11.3) (HR: 0.65 [95% CI: 0.49, 0.86]; *P*-value = 0.012)

1L+ = first-line and subsequent lines; 2L+ = second-line and subsequent lines; ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; BC = breast cancer; BID = twice daily; CI = confidence interval; DoR = duration of response; ET = endocrine therapy; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; IV = intravenous; NE = not estimable; ORR = objective response rate; OS = overall survival; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival; Q3W = every 3 weeks; Q4W = every 4 weeks; Q6W = every

6 weeks; TNBC = triple-negative breast cancer; TPC = treatment of physician's choice; TTF = time to treatment failure; TTP = time to progression

Treatment outcomes with currently approved therapies in patients with metastatic HER2-negative breast cancer, who progressed on ET and at least 1 line of chemotherapy illustrate the high unmet medical need for new treatment options (Table 1). No targeted therapy is specifically approved for patients with HER2-low BC. The most recently approved single agents for patients with metastatic hormone receptor-positive HER2-low BC, who progressed on or are not eligible for ET are abemaciclib and eribulin. Abemaciclib has since been approved in earlier lines of therapy and is rarely used in the proposed setting where the cornerstone of treatment remains conventional chemotherapy.

2.1.2. About the product

Enhertu, trastuzumab deruxtecan, is a HER2-targeted antibody-drug conjugate. The antibody is a humanised anti-HER2 IgG1 attached to deruxtecan, a topoisomerase I inhibitor (DXd) bound by a tetrapeptide-based cleavable linker. The antibody-drug conjugate is stable in plasma. The function of the antibody portion is to bind to HER2 expressed on the surface of certain tumour cells. After binding, the trastuzumab deruxtecan complex then undergoes internalisation and intracellular linker cleavage by lysosomal enzymes that are upregulated in cancer cells. Upon release, the membrane-permeable DXd causes DNA damage and apoptotic cell death. DXd, an exatecan derivative, is approximately 10 times more potent than SN-38, the active metabolite of irinotecan.

Enhertu is currently approved as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens. In November 2022, the CHMP gave a positive opinion for the treatment of adult patients with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

Enhertu is currently conditionally approved and the confirmatory study for the CMA is Study U301, a phase 3, multicentre, randomised, open-label, active-controlled study of T-DXd versus treatment of investigator's choice for HER2-positive, unresectable and/or metastatic breast cancer subjects pre-treated with prior standard of care HER2 therapies, including T-DM1. The due date for submission is estimated to 4Q 2022.

The recommended dose of Enhertu is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. The same posology is proposed for the applied indication.

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

The focus of this application is the randomized, active controlled Phase 3 Study DS8201-A-U303 (DESTINY-Breast04; hereinafter referred to as Study U303) in which the target population are patients with unresectable or metastatic HER2-low BC, who received T-DXd at the target dose of 5.4 mg/kg or treatment per physician's choice (TPC) in the second-line metastatic setting. It is agreed that the scientific advice given from the CHMP regarding the pivotal study U303 was generally followed.

2.1.4. General comments on compliance with GCP

The Applicant stated that all studies of trastuzumab deruxtecan were conducted in accordance with the ethical principles of Good Clinical Practice (GCP), according to International Council for Harmonisation (ICH) Harmonised Tripartite Guideline E6 and that all trials conformed to the Declaration of Helsinki

and informed, written consent was obtained from all patients as per GCP requirement.

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

The default $PEC_{SURFACEWATER}$ was above the PEC action limit for triggering a full ERA (see EPAR from initial MA). The PEC based on maximum daily dose was approximately 21-fold higher than if based on the actual dose regime recommended (once every 3 weeks). A PEC accounting for the actual dosing regimen would clearly be below the trigger (≤0.01 μg/L); however, the PEC was subsequently refined by utilising prevalence data on the newly claimed indication. In order to estimate refined $PEC_{SURFACEWATER}$, calculation of refined Fpen was based on breast cancer prevalence data as provided in the Globocan database. The prevalence data were not specifying the type of HER-2 status, hence, the new indication of HER-2 low status can be assumed included in the general prevalence of breast cancer. Therefore, no increase in consumption for calculation of refined Fpen is expected with this extension of indication.

Summary of main study results

Substance (INN/Invented Name): trastuzumab deruxtecan			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Log D_{OW} = 1.924 @ pH 5 Log D_{OW} = 1.799 @ pH 7 Log D_{OW} = 1.280 @ pH 9	Potential PBT No
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	<4.5	not B
	BCF	Not required	not B
Persistence	DT50 or ready biodegradability	Not required	not P
Toxicity	NOEC or CMR	Not required	not T
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater , default or refined (e.g. prevalence, literature)	0.00565	μg/L	> 0.01 threshold No
Other concerns (e.g. chemical class)			None

2.3. Clinical aspects

2.3.1. Introduction

The clinical package included in the current application is based on data from a Phase 3 study in subjects with HER2-low BC (Study U303) and data from nine prior studies. See below table.

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.

Table 2 Tabular overview of clinical studies

Study Number Module	Dev. Phase	Study Objectives	N	Dose	Sampling Time Points
J101 Module 5.3.3.2	1	Determination of the MTD or the RP2D of trastuzumab deruxtecan, assessment of the PK profiles of trastuzumab deruxtecan, DXd, and total anti-HER2 antibody, evaluation of efficacy, and assessment of safety and tolerability in subjects with advanced solid malignant tumors	292	0.8, 1.6, 3.2, 5.4, 6.4, and 8.0 mg/kg	Cycle 1: Predose, EOI, 2, 4, and 7 hours, and 1, 3, 7, 14 and 21[a] days after SOA Cycle 3: Predose, EOI, 4 hours, and 7 and 14 days after SOA. Cycles 2, 4, 6 and 8: Predose and EOI
J202[2]	2	Comparison of the efficacy and safety of trastuzumab deruxtecan and TPC in HER2-overexpressing advanced gastric or GEJ adenocarcinoma subjects who have progressed on two prior regimens including fluoropyrimidine agent, platinum agent and trastuzumab (brand, approved biosimilar)	231	6.4 mg/kg	Cycle 1, 3: Predose, EOI, 4 and 7 hours, and 7, 14 and 21[a] days after SOA Cycles 2, 4, 6 and 8: Predose and EOI
J102[3]	1	Assessment of the PK of trastuzumab deruxtecan after multiple dosing, assessment of the effect of T-DXd on the QTc interval, and evaluation of efficacy and safety in subjects with HER2-expressing metastatic and/or unresectable BC	51	6.4 mg/kg	Cycles 1 and 3: Predose, EOI, 2, 4, and 7 hours, and 1, 3, 7, 14 and 21[a] days after SOA Cycles 2, 4, 6 and 8: Predose and EOI
A103[4]	1	Assessment of the PK profiles of trastuzumab deruxtecan, DXd, and total anti-HER2 antibody, assessment of safety and tolerability of T-DXd, and investigation of anti-tumor activity in subjects with HER2-positive advanced and/or refractory gastric, GEJ adenocarcinoma, or BC	12	6.4 mg/kg	Cycles 1 and 3: Predose, EOI, 2, 4, and 7 hours, and 1, 3, 7, 14, and 21[a] days after SOA Cycles 2, 4, 6 and 8: Predose and EOI
A104[5]	1	Evaluation of the effects of ritonavir and itraconazole on the PK of trastuzumab deruxtecan and DXd, assessment of safety, and evaluation of efficacy in subjects with HER2-expressing advanced solid malignant tumors	40	5.4 mg/kg	Cycles 1, 4, 6 and 8: Predose and EOI Cycles 2 and 3: Predose, EOI, 2, 4, and 7 hours, and 1, 3, 7, 11, and 16 days after SOA

Study Number Module	Dev. Phase	Study Objectives	N	Dose	Sampling Time Points
U201 Module 5.3.5.2	2	Determination of the PK and RP2D of trastuzumab deruxtecan, evaluation of E-R relationships for efficacy and safety, and evaluation of efficacy and safety in HER2-positive, unresectable and/or metastatic BC subjects previously treated with T-DM1	253	5.4, 6.4, and 7.4 mg/kg	Part 1 PK: Cycle 1: Predose, EOI, 2, 4, and 7 hours, and 1, 3, 7, 14 and 21[a] days after SOA Cycle 2, 4, 6, and 8: Predose and EOI Cycle 3: Predose, EOI, and 4 and 7 hours after SOA Dose-finding/RP2D Evaluation: Cycle 1: Predose, EOI, 4 and 7 hours, and 7, 14 and 21[a] days after SOA Cycles 2, 4, 6, and 8: Predose and EOI Cycle 3: Predose, EOI, and 4 and 7 hours after SOA
U204[6]	2	Evaluation of the ORR of trastuzumab deruxtecan in HER2-overexpressing [redacted]/or HER2-mutated advanced NSCLC subjects	181	6.4 mg/kg	Cycle 1: Predose, EOI, 5 hours and 7, 14, and 21[a] days after SOA Cycles 2, 3, 4, and 6: Predose and EOI
U205[7]	2	Investigation of the efficacy of trastuzumab deruxtecan based on confirmed ORR, as assessed by an independent central imaging facility review using RECIST v1.1, in subjects with HER2-positive unresectable or metastatic gastric or GEJ adenocarcinoma that has progressed on or after a trastuzumab-containing regimen	79	6.4 mg/kg	Cycle 1: Predose, EOI, 5 ±2 hours and 8, 15 and 21[a] days after SOA Cycles 2, 3, 4, 6 and 8: Predose and EOI
U302[8]	3	Comparison of the efficacy of trastuzumab deruxtecan vs T-DM1 as measured by PFS for HER2-positive, unresectable and/or metastatic BC subjects previously treated with trastuzumab and taxane	524	5.4 mg/kg	Cycle 1: Predose, EOI, 5 hours and 21[a] days after SOA Cycles 2, 3, 4, 6, and 8: Predose and EOI
U303 Module 5.3.5.1	3	Comparison of PFS benefit of T-DXd to physician's choice in HER2-low, HR-positive BC, based on BICR	557	5.4 mg/kg	Cycle 1: Predose, EOI, 5 hours and 21[a] days after SOA Cycles 2, 3, 4 and subsequent: Predose and EOI

BC = breast cancer; BICR = blinded independent central review; Dev. = development; DXd = released payload (MAAA-1181a); EOI = end of infusion; E-R = exposure-response; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; N = number of subjects; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; ORR = objective response rate; PFS = progression-free survival; PK = pharmacokinetic(s); RECIST v1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; RP2D = recommended Phase 2 dose; SOA = start of administration; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

[a] If the schedule on Day 1 of the next cycle was delayed for 3 days or more, including if the subject could not continue onto the next cycle, blood sample was collected 21 days after the start of drug administration (±2 days). If the next schedule was not delayed, sampling at that point was not necessary.

2.3.2. Pharmacokinetics

Bioanalysis

For characterization of T-DXd PK, concentrations of T-DXd (the intact antibody-drug conjugate [ADC]), total anti-HER2 antibody, and DXd were measured by validated bioanalytical methods. Immunogenicity assessment for anti-T-DXd antibodies in serum was conducted using a validated bioanalytical method. The ADA positive samples were further analysed for detection of NAb against T-DXd.

Pop PK analyses

Data handling was performed using R (version 4.0.5 or higher) or SAS (version 9.4 or higher). NONMEM (version 7.4.3 or higher) was used for PK analyses. FOCE INTER was used for PopPK model development. Xpose and PsN (version 4.8.1) were used for model diagnostics and covariate testing. R

(version 4.0.5) in RStudio (version 1.1.383 or higher) was used for data exploration, post-processing of results and simulations based on the final models for T-DXd and DXd.

The Pop PK analysis was performed using PK data from four Phase 1 studies (Studies J101, J102, A103 and A104), four Phase 2 studies (Studies U201, J202, U204 and U205), and two Phase 3 studies (Studies U302 and U303) (see table 2). After inclusion of Study U303, the analysis dataset had 1128 (67%), 293 (18%), 199 (12%), and 55 (3%) subjects with BC, GC, NSCLC, and other cancers (including colorectal), respectively. Of these, 919 (55%) were HER2-positive, and 468 (28%) were HER2-low, with the remaining subjects (17%) having HER2-negative, mutant, overexpressing, or missing status. A summary of included PK data is shown in below table.

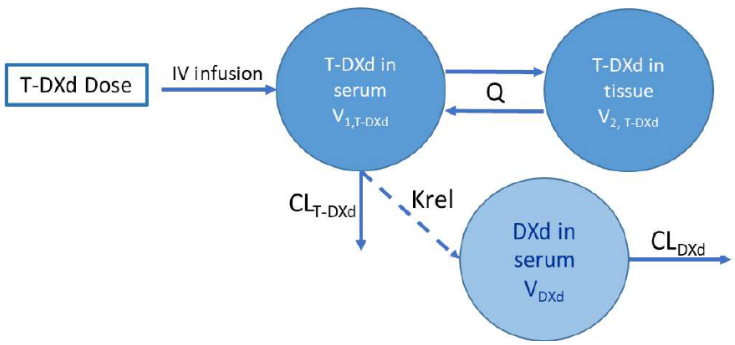
Table 3 Summary of PK data

Category	Previous data		U303		Overall	
	T-DXd	DXd	T-DXd	DXd	T-DXd	DXd
Subjects						
Total Subjects	1327	1327	371	371	1698	1698
Subjects with evaluable observations	1313	1313	362	361	1675	1674
PK Observations						
Evaluable non-BQL observations included	19551 (92.0%)	19681 (92.7%)	3770 (89.0%)	3572 (85.0%)	23321 (91.5%)	23253 (91.4%)
Co-medication inhibitor excluded	105 (0.5%)	104 (0.5%)	76 (1.8%)	75 (1.8%)	181 (0.7%)	179 (0.7%)
Other excluded	201 (0.9%)	201 (0.9%)	18 (0.4%)	17 (0.4%)	219 (0.9%)	218 (0.9%)
Outlier excluded	105 (0.5%)	23 (0.1%)	0 (0%)	0 (0%)	105 (0.4%)	23 (0.1%)
Post-dose BQL excluded	101 (0.5%)	34 (0.2%)	11 (0.3%)	3 (0.1%)	112 (0.4%)	37 (0.1%)
Pre-dose BQL excluded	1195 (5.6%)	1199 (5.6%)	359 (8.5%)	354 (8.4%)	1554 (6.1%)	1553 (6.1%)
Re-analyzed PK observations (non-BQL)	0 (0%)	0 (0%)	0 (0%)	181 (4.3%)	0 (0%)	181 (0.7%)
Total observations	21258	21242	4234	4202	25492	25444

Abbreviations: BQL = below the limit of quantitation; PK = pharmacokinetic.
Source: DS8201_303-subject_count.csv, DS8201_303-observation_count.csv, 2022-02-22-ds8201_303_eda.r.

The previous PopPK analysis that included data from all studies, except for Study U303, was used for model development. The T-DXd data was described by a two-compartment model with linear elimination, and DXd was described by a one-compartment model, with time-varying release of drug from T-DXd (figure below).

Figure 1 Structural model schematic



Abbreviations: CL_{DXd} = clearance of DXd; $CL_{T\text{-}DXd}$ = clearance of T-DXd; IV = intravenous; Krel = release rate constant; Q = distributional clearance for T-DXd; $V_{1,T\text{-}DXd}$ = central volume of T-DXd; $V_{2,T\text{-}DXd}$ = peripheral volume of T-DXd; V_{DXd} = volume of DXd.

A sequential modelling approach was used to re-estimate model parameters with the updated analysis dataset. First the T-DXd parameter estimates and corresponding covariate effects were re-estimated using only the PK data for T-DXd. The effects of Asian from Japan on V2,T-DXd changed by >20% relative to the prior estimates. This effect was retained in the T-DXd model as removal increased the OFV by 34 units. Region was correlated with race-country. No new covariate correlations were identified. The final T-DXd model (run010) suggested that CL,T-DXd increased with increasing body weight, baseline tumour size, and for GC, NSCLC or other cancers; CL,T-DXd decreased with increasing albumin and being Asian from Japan; V1,T-DXd increased with increasing body weight, in males and for GC; and V2,T-DXd decreased in Asian subjects from Japan. The final Pop PK parameters for T-DXd is shown in below table.

Table 4 Final Pop PK parameters for T-DXd

Variable	Estimate		Between-Subject Variability		
	Typical Value	RSE (%)	Magnitude (%CV)	RSE (%)	Shrinkage (%)
Clearance ($CL_{T\text{-}DXd}$, L/day)	0.410	0.933	23.8	2.13	11.1
Central Volume of Distribution ($V_{1,T\text{-}DXd}$, L)	2.68	0.478	15.1	1.86	8.63
Distributional Clearance ($Q_{T\text{-}DXd}$, L/day)	0.198	1.25	29.0	4.26	40.0
Peripheral Volume of Distribution ($V_{2,T\text{-}DXd}$, L)	6.64	3.08	79.7	3.07	24.0
Albumin (g/L) on $CL_{T\text{-}DXd}$	-0.480	10.0	-	-	-
Race-country (Japan) on $CL_{T\text{-}DXd}$	-0.0928	13.6	-	-	-
Tumor Size (mm) on $CL_{T\text{-}DXd}$	0.0533	16.1	-	-	-
Body Weight (kg) on $CL_{T\text{-}DXd}$	0.385	8.14	-	-	-
GC on $CL_{T\text{-}DXd}$	0.175	12.4	-	-	-
NSCLC and Other Cancers (not BC or GC) on $CL_{T\text{-}DXd}$	0.0968	19.0	-	-	-
Body Weight (kg) on $V_{1,T\text{-}DXd}$	0.430	4.65	-	-	-
Sex (Male) on $V_{1,T\text{-}DXd}$	0.136	10.3	-	-	-
GC on $V_{1,T\text{-}DXd}$	0.0976	15.2	-	-	-
Race-country (Japan) on $V_{2,T\text{-}DXd}$	-0.269	9.43	-	-	-
Residual Variability					
Proportional Residual Error Std Dev	0.167	0.216	-	-	-
Additive Residual Error Std Dev (ng/mL)	1059	1.72	-	-	-
Covariance of $CL_{T\text{-}DXd}$ and $V_{1,T\text{-}DXd}$	0.0179	3.42	-	-	-

BC = breast cancer; $CL_{T\text{-}DXd}$ = elimination clearance of T-DXd; CV = coefficient of variation; ETA = random between-subject effect; GC = gastric cancer; NSCLC = non-small cell lung cancer; $Q_{T\text{-}DXd}$ = distributional clearance; RSE = relative standard error; Std Dev = standard deviation; SE = standard error; sqrt = square root; T-DXd = trastuzumab deruxtecan; $V_{1,T\text{-}DXd}$ = T-DXd central volume of distribution; $V_{2,T\text{-}DXd}$ = T-DXd peripheral volume of distribution

Note: RSE of parameter estimates were calculated as 100 × (SE/typical value); RSE of between-subject variability magnitude was calculated as 100 × (SE/variance estimate)/2. CV (%) for between-subject variability estimates were based on the estimated variances. Shrinkage (%) was calculated as 100 × (1-Std Dev[ETA]/sqrt[variance]). Overall residual unexplained variability shrinkage was estimated to be 9.08%. The correlation coefficient between $CL_{T\text{-}DXd}$ and $V_{1,T\text{-}DXd}$ was estimated as 0.505.

-: not applicable

Source: Module 5.3.3.5 Population PK Analysis Report PMx019, Table 4-6

The DXd parameters and corresponding covariate effects were then re-estimated based on the whole updated dataset with parameters for T-DXd fixed. With the addition of Study U303, the covariate effects of GC and NSCLC on CL,DXd and FL-DP1 formulation, NSCLC and race-country (non-Asian) on the V,DXd changed by >20% compared to the same parameters in the previous DXd PopPK model. The effects of GC and NSCLC on CL,DXd and FL-DP1 formulation on V,DXd were no longer significant following backward deletion (p>0.001) and were removed. Removal of NSCLC and race-country (non-Asian) effects on V,DXd resulted in a significant increase in OFV of 26 and 93 units and therefore they were retained. Covariate correlations were identified between race-country, region, weight and BSA. Thus, race-country was not tested. Parameter estimates for the final DXd model (run034) are presented in Table 5. Residual variability was modelled with a proportional error structure and estimated to be 30% with 7.51% shrinkage.

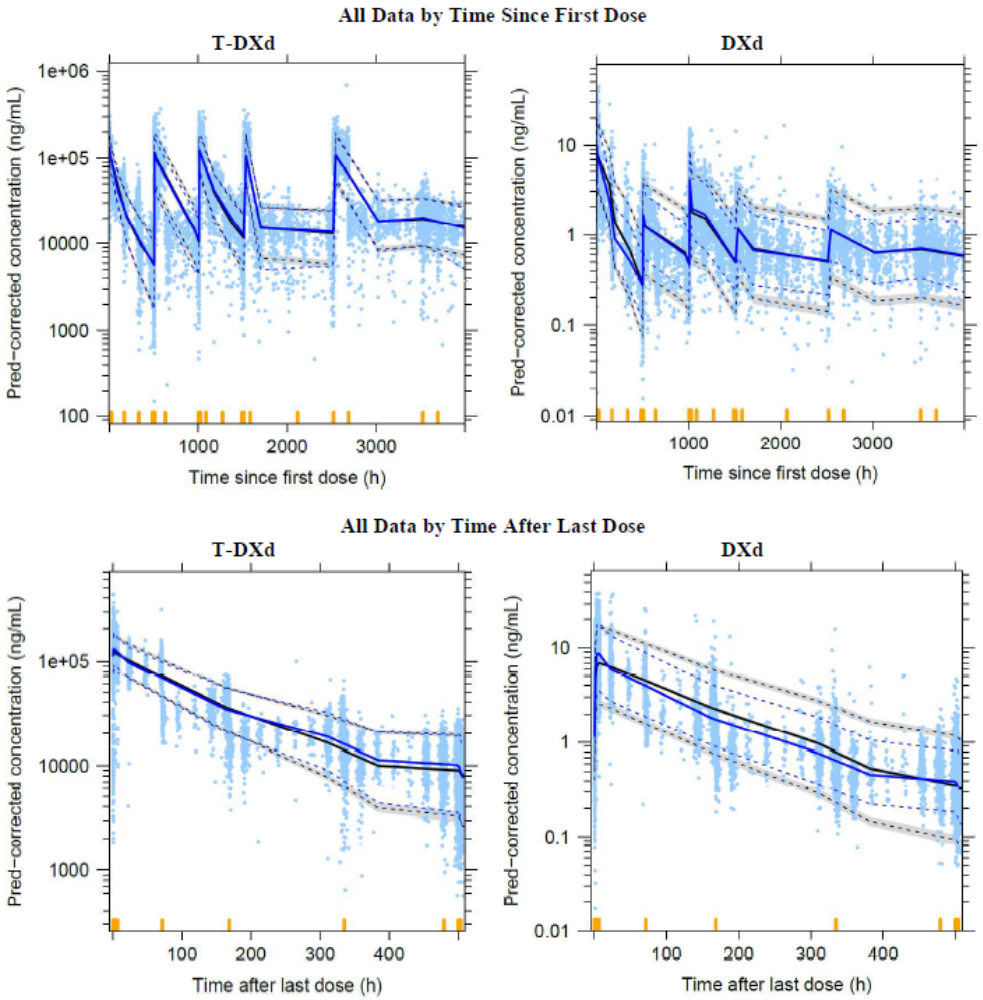
Table 5 Parameter estimates for the final DXd model

Variable	Estimate		Between-Subject Variability		
	Typical Value	RSE (%)	Magnitude (%CV)	RSE (%)	Shrinkage (%)
DXd Clearance (CL_{DXd}, L/h)	19.6	2.20	30.1	3.59	33.0
DXd Volume of Distribution (V_{DXd}, L)	Fixed 17*BSA	-	47.0	2.59	21.1
Release Rate (K_{rel}, 1/h)	0.0196	2.16	32.9	3.55	25.4
Fraction of K_{rel} at Cycle >1 (FPC1)	0.741	0.969	26.7	2.70	26.2
Exponent of Cycle effect on K_{rel} (FPC2)	-0.158	2.60	-	-	-
Ritonavir on CL_{DXd}	-0.121	14.2	-	-	-
Itraconazole on CL_{DXd}	-0.111	19.4	-	-	-
AST (U/L) on CL_{DXd}	-0.195	10.3	-	-	-
Total Bilirubin (µmol/L) on CL_{DXd}	-0.147	14.2	-	-	-
Body Weight (kg) on CL_{DXd}	0.316	16.3	-	-	-
Age (years) on V_{DXd}	0.630	10.1	-	-	-
FL-DP2 Formulation on V_{DXd}	0.583	12.1	-	-	-
NSCLC on V_{DXd}	-0.204	21.6	-	-	-
Race-Country (Non-Asian) on V_{DXd}	-0.244	8.91	-	-	-
Residual Unexplained Variability					
Proportional Residual Error Std Dev	0.304	0.351	-	-	-

AST = aspartate aminotransferase; BSA = body surface area; CL_{DXd} = elimination clearance of DXd; CV = coefficient of variation; DXd = released payload (MAAA-1181a); ETA = random between-subject effect; FL-DP2 = frozen liquid drug product 2; FPC1 = fraction of K_{rel} after Cycle 1; FPC2 = exponent of Cycle effect on K_{rel}; K_{rel} = release rate constant; NSCLC = non-small cell lung cancer; RSE = relative standard error; Std Dev = standard deviation; SE = standard error; sqrt = square root; V_{DXd} = volume of distribution.
Note: RSE of parameter estimate was calculated as 100 × (SE/typical value); RSE of between-subject variability magnitude was calculated as 100 × (SE/variance estimate)/2. CV% for the between-subject variability estimates were based on the estimated variances. Shrinkage (%) was calculated as 100 × (1-Std Dev[ETA]/sqrt[variance]).
Overall residual unexplained variability shrinkage was estimated to be 7.51%.
-: not applicable
Source: Module 5.3.3.5 Population PK Analysis Report PMx019, Table 4-8

Prediction-corrected VPCs are presented in the below figures.

Figure 2 Prediction-corrected VPC for the T-DXd and DXd PopPK model (run034)

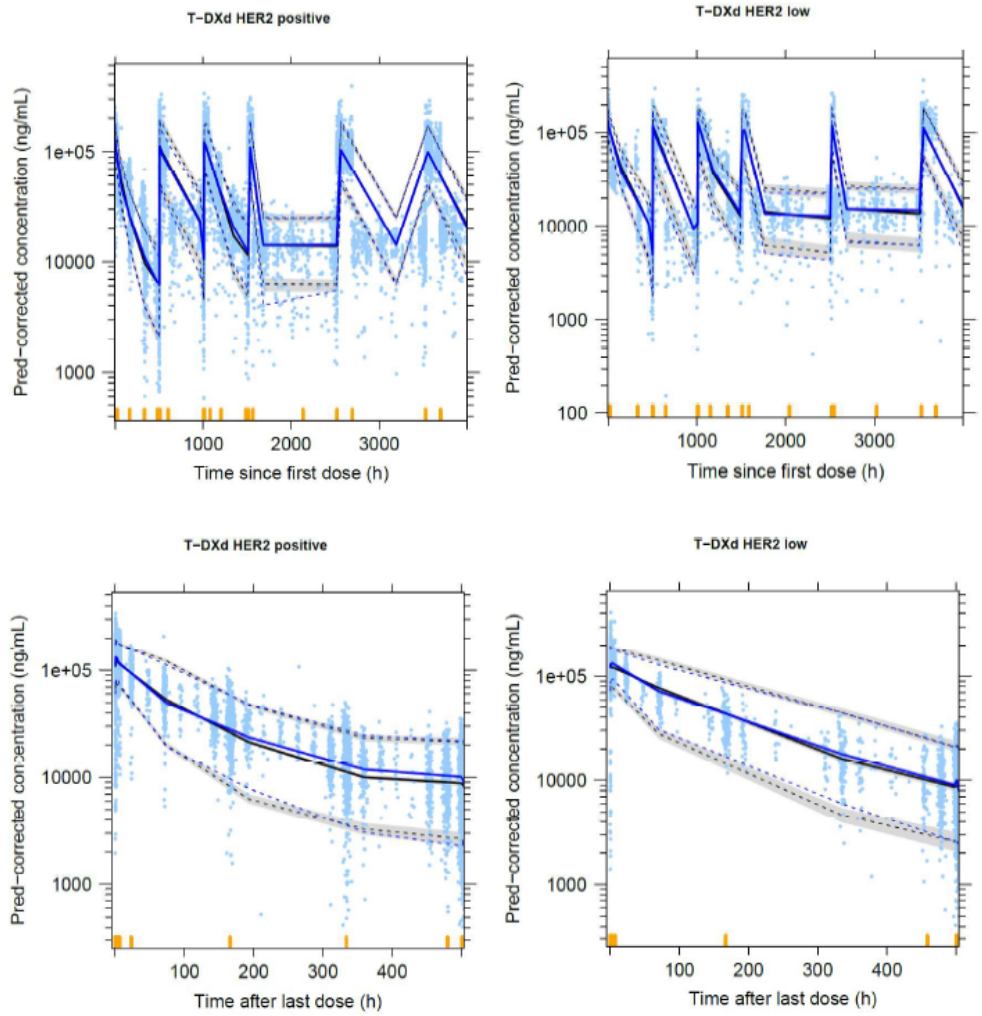


Abbreviations: PopPK = population pharmacokinetics; pred = prediction; VPC = visual predictive check.

Note: Left plot is the prediction-corrected VPC for T-DXd and the right plot is the prediction-corrected VPC for DXd. Blue dots are prediction-corrected observed concentrations; blue lines are 50th (solid), 5th (dashed), and 95th (dashed) percentiles of observed concentrations; and black lines are 50th (solid), 5th (dashed), and 95th (dashed) percentiles of simulations. Gray bands are 95% prediction interval for corresponding black lines based on 500 simulations. Short yellow lines indicate bin intervals.

Source: VPC-TIME-both-all-data034.pdf, VPC-TAD-both-all-data-034.pdf, 2022-02-23-ds8201-303-gof.r.

Figure 3 Prediction-corrected VPC for the final T-DXd PopPK model (run034), stratified by HER2 status

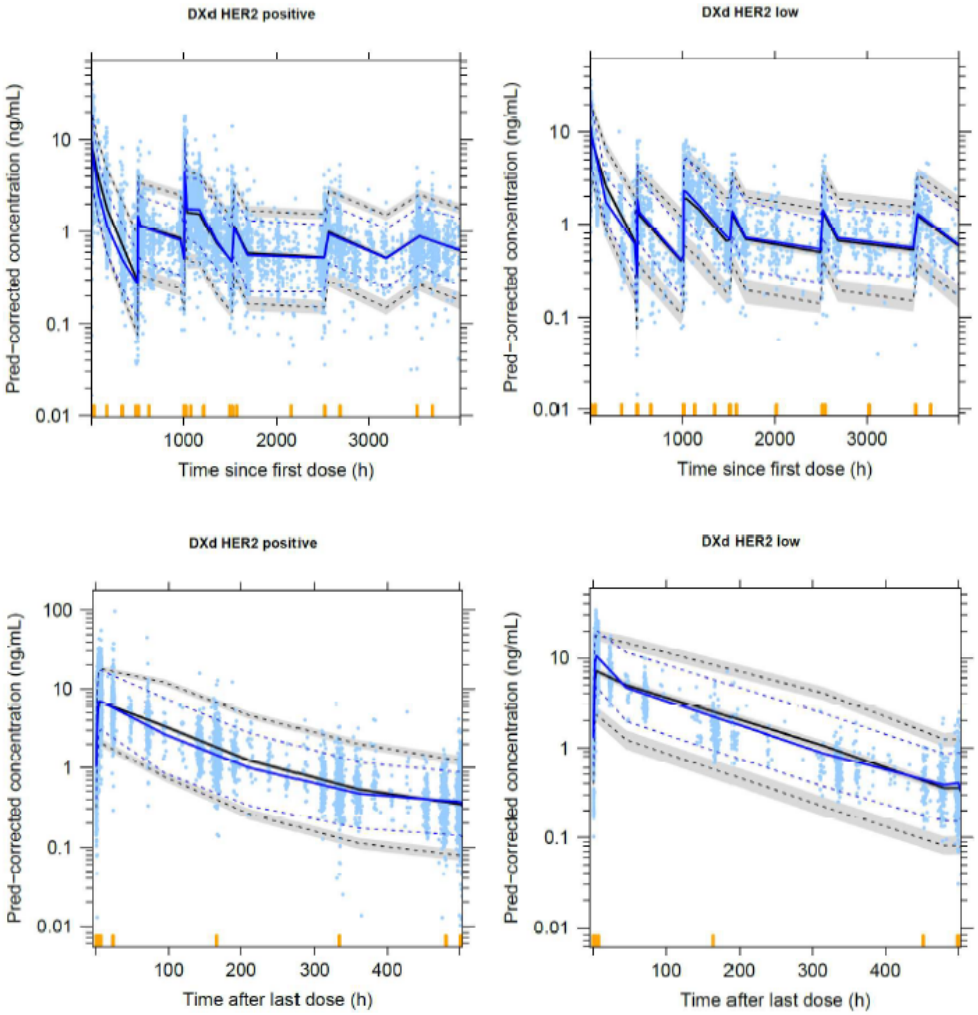


Abbreviations: HER2 = human epidermal growth factor receptor 2; PopPK = population pharmacokinetics; pred-corr = prediction-corrected; VPC = visual predictive check.

Note: Blue dots are prediction-corrected observed concentrations; blue lines are 50th (solid), 5th (dashed), and 95th (dashed) percentiles of observed concentrations; and black lines are 50th (solid), 5th (dashed), and 95th (dashed) percentiles of simulations. Gray bands are 95% prediction interval for corresponding black lines based on 500 simulations. Short yellow lines indicate bin intervals.

Source: VPC-TIME-both-HER2-034.pdf, VPC-TAD-both-HER2-034.pdf, 2022-02-23-ds8201-303-gof.R

Figure 4 Prediction-corrected VPC for the final DXd PopPK model (run034), stratified by HER2 status



Abbreviations: HER2 = human epidermal growth factor receptor 2; PopPK = population pharmacokinetics; pred-corr = prediction-corrected; VPC = visual predictive check.
Note: Blue dots are prediction-corrected observed concentrations; blue lines are 50th (solid), 5th (dashed), and 95th (dashed) percentiles of observed concentrations; and black lines are 50th (solid), 5th (dashed), and 95th (dashed) percentiles of simulations. Gray bands are 95% prediction interval for corresponding black lines based on 500 simulations. Short yellow lines indicate bin intervals.
Source: VPC-TIME-both-HER2-034.pdf, VPC-TAD-both-HER2-034.pdf, 2022-02-23-ds8201-303-gof.R

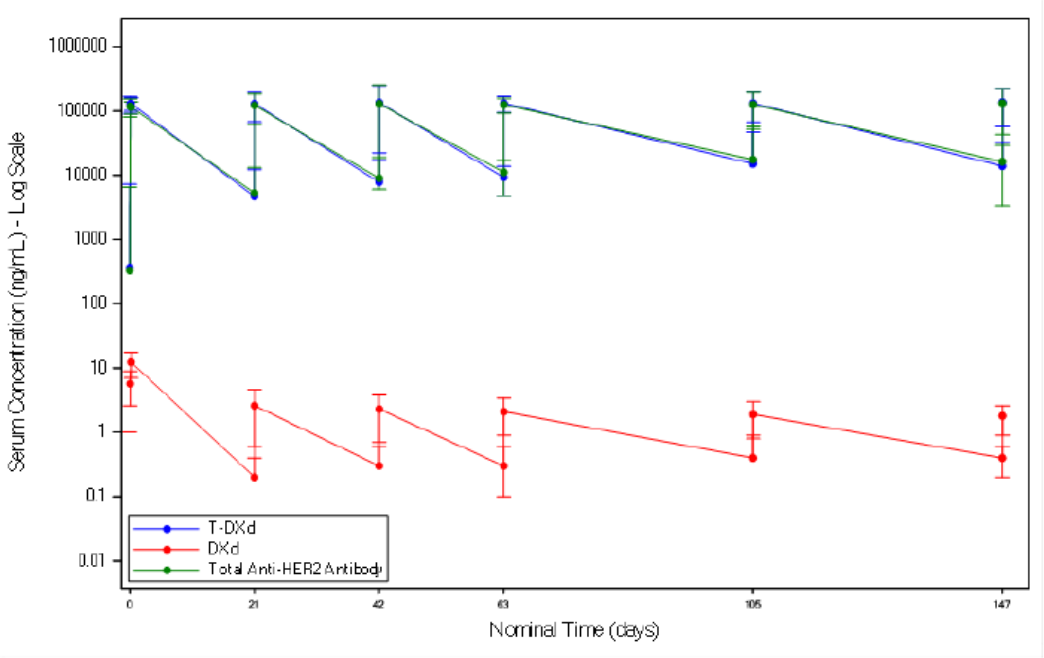
A sensitivity analysis of the final DXd PopPK model showed no impact of removing CWRES≥5 T-DXd and DXd outliers from Study U303 (run034s). A second sensitivity analysis showed no impact of including additional 211 (of which 30 were BLQ) DXd samples (run034ss), that were re-analysed after primary DCO.

ADME characteristics

The absorption, distribution, metabolism, and excretion of T-DXd, total anti-HER2 antibody and DXd was well-characterised and described in the initial BC application (see initial EPAR).

Mean observed exposure profiles of T-DXd, Total Anti-HER2 Antibody and DXd following 5.4 mg/kg Q3W are shown in Figure 5.

Figure 5 Time Course of Mean (+/- SD) Serum Concentrations of T-DXd, Total Anti-HER2 Antibody and DXd Concentrations- Semi-logarithmic Scale (PK Analysis Set)



DXd = released drug; HER2 = human epidermal growth factor receptor 2; PK = pharmacokinetic; Std Dev = standard deviation; T-DXd = trastuzumab deruxtecan
Data cut-off: 11 Jan 2022
Source: Figure 14.4.1.2

Exposure parameters for HER2-low subjects in Study U303 were predicted using the final Pop PK model for DXd (run 0034). T-DXd and DXd exposure were comparable between HER2-positive and HER2-low BC at the same dose. PK parameters for T-DXd and DXd based on the non-compartmental analysis of Cycle 1 PK data for HER2-positive or HER2-low patients following 5.4 or 6.4 mg/kg doses are displayed in Tables 6 and 7, respectively.

Table 6 Summary of T-DXd PK Parameters: Integrated Analysis of Cycle 1 PK Data in Subjects with Breast Cancer

Dose	PK Parameter (Unit)				
	Cmax (µg/mL)	Tmax (h) [a]	AUClast (µg*d/mL)	AUC21d (µg*d/mL)	Ctrough (µg/mL)
5.4 mg/kg (BC HER2-Positive)					
N	232	232	232	190	215
Mean [a]	124.15	2.167	544.68	572.6	5.5
Std Dev	32.608	–	163.415	167.08	5.13
Min/Max	–	0.02/166.73	–	–	–
6.4 mg/kg (BC HER2-Positive)					
N	122	122	122	115	116
Mean [a]	165.23	2.073	740.9	756.5	9.2455
Std Dev	50.955	–	212.27	205.10	20.02356
Min/Max	–	0.02/7.05	–	–	–
5.4 mg/kg (BC HER2-Low)					
N	21	21	21	20	21
Mean [a]	133.37	2.117	581.6	555.1	9.7
Std Dev	17.886	–	175.73	122.10	26.07
Min/Max	–	1.50/7.07	–	–	–
6.4 mg/kg (BC HER2-Low)					
N	79	79	79	79	78
Mean [a]	171.73	2.067	680.1	680.9	7.3
Std Dev	91.525	–	149.38	147.49	10.44
Min/Max	–	1.50, 7.23	–	–	–

AUC21d = area under the concentration-time curve from time zero to Day 21; AUClast = area under the serum concentration-time curve from time zero to the time of the last quantifiable serum concentration; BC = breast cancer; Cmax = maximum observed serum concentration; Ctrough = trough serum concentration; HER2 = human epidermal growth factor receptor 2; max = maximum; min = minimum; N = number of subjects; PK = pharmacokinetic; Std Dev = standard deviation; T-DXd = trastuzumab deruxtecan; Tmax = time of Cmax.

[a] Mean (Std Dev) values are presented for all parameters except Tmax, for which median (range) is presented.

Source: Module 5.3.5.3 Integrated PK Analysis, Table 14.2.3.1

Table 7 Summary of DXd PK Parameters: Integrated Analysis of Cycle 1 in Subjects with Breast Cancer

Dose	PK Parameter (Unit)				
	Cmax (µg/mL)	Tmax (h) [a]	AUClast (µg*d/mL)	AUC21d (µg*d/mL)	Ctrough (µg/mL)
5.4 mg/kg (BC HER2-Positive)					
N	232	232	232	109	226
Mean [a]	8.1871	6.792	31.729	33.334	0.26349
Std Dev	5.72156	–	17.6583	16.5512	0.249939
Min/Max	–	0.24/166.51	–	–	–
6.4 mg/kg (BC HER2-Positive)					
N	122	122	122	103	115
Mean [a]	10.453	6.840	43.69	43.61	0.35105
Std Dev	9.3428	–	32.364	31.395	0.244394
Min/Max	–	0.34/191.47	–	–	–
5.4 mg/kg (BC HER2-Low)					
N	21	21	21	20	21
Mean [a]	10.689	4.100	41.57	41.41	0.39816
Std Dev	5.2101	–	17.830	18.107	0.448617
Min/Max	–	2.05/23.48	–	–	–
6.4 mg/kg (BC HER2-Low)					
N	79	79	79	76	78
Mean [a]	13.399	6.767	40.82	40.64	0.32806
Std Dev	4.3519	–	11.787	11.938	0.201258
Min/Max	–	3.83/7.25	–	–	–

AUC21d = area under the concentration-time curve from time zero to Day 21; AUClast = area under the serum concentration-time curve from time zero to the time of the last quantifiable serum concentration; BC = breast cancer; Cmax = maximum observed serum concentration; Ctrough = trough serum concentration; DXd = released payload (MAAA-1181a); HER2 = human epidermal growth factor receptor 2; max = maximum; min = minimum; N = number of subjects; PK = pharmacokinetic; Std Dev = standard deviation; Tmax = time of Cmax.

[a] Mean (Std Dev) values are presented for all parameters except Tmax, for which median (range) is presented.

Source: Module 5.3.5.3 Integrated PK Analysis Table 14.2.3.3

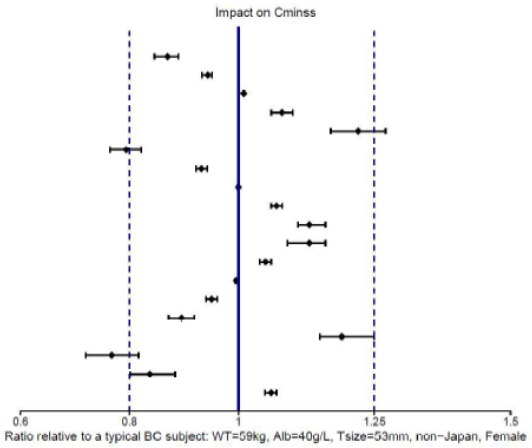
Special populations

In the Pop PK population, there were 571 Asian subjects from Japan, 337 Asian subjects not from Japan, and 767 non-Asian subjects. Subjects were aged 20 to 96 years, weighing 27.3 to 125 kg, with BSA ranging 1.06 to 2.45 m^2, albumin ranging 22 to 55 g/L, total bilirubin ranging 1 to 57.1 U/L, ALT ranging 2.00 to 202 U/L, LDH ranging 99.0 to 6850 U/L, ALP ranging 24.0 to 2650 U/L and CrCL ranging 25.3 to 264 mL/min. Of the 1675 subjects, 962 (58%) subjects received prior HER2 therapy.

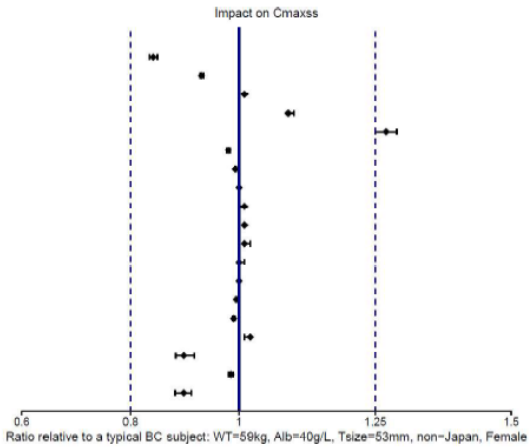
The clinical relevance of covariate effects included in the final Pop PK model was evaluated using Forest plots (Figures 6 and 7). For TDXd, subjects with low albumin (31 g/L; 5th percentile) had an approximately 21% lower steady state Cmin when compared to a typical BC subject with an albumin of 40 g/L. Subjects with extreme values of body weight (90kg; 95th percentile) had an approximately 27% higher Cmax and a 30% higher AUC relative to a typical BC subject of body weight 59 kg.

Figure 6 Forest plot of covariate effects on T-DXd exposure

Covariate	Percentile	Value	Ratio [90% CI]
Body weight (kg)	5th	44	0.87 [0.846, 0.89]
	25th	52	0.944 [0.933, 0.952]
	50th	60	1.01 [1, 1.01]
	75th	69	1.08 [1.06, 1.1]
	95th	90	1.22 [1.17, 1.27]
Baseline albumin (g/L)	5th	31	0.794 [0.765, 0.822]
	25th	37	0.932 [0.922, 0.943]
	50th	40	1 [0.998, 1]
	75th	43	1.07 [1.06, 1.08]
	95th	46	1.13 [1.11, 1.16]
Baseline tumor size (mm)	5th	16	1.13 [1.09, 1.16]
	25th	33	1.05 [1.04, 1.06]
	50th	55	0.996 [0.994, 0.999]
	75th	87	0.951 [0.941, 0.962]
	95th	157	0.896 [0.872, 0.919]
Race–Country		Japan	1.19 [1.15, 1.25]
Cancer type		Gastric cancer	0.768 [0.72, 0.817]
		NSCLC & other cancer	0.030 [0.001, 0.004]
Sex		Male	1.06 [1.05, 1.07]



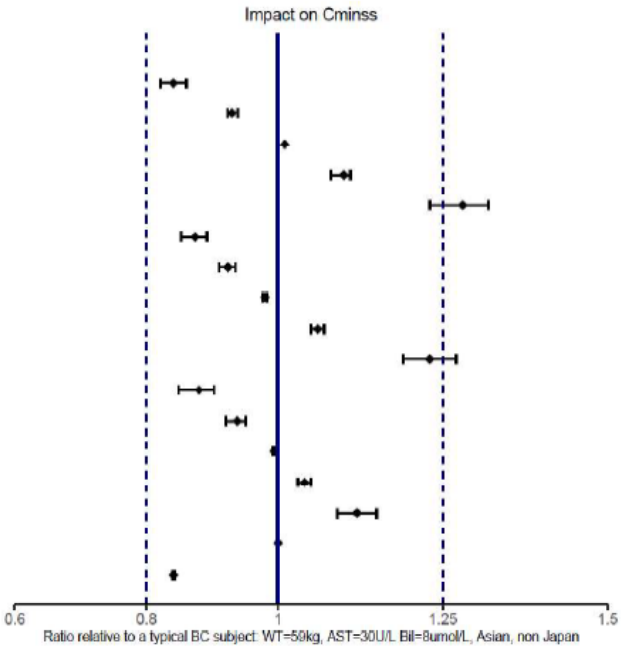
Covariate	Percentile	Value	Ratio [90% CI]
Body weight (kg)	5th	44	0.842 [0.835, 0.85]
	25th	52	0.931 [0.929, 0.935]
	50th	60	1.01 [1.01, 1.01]
	75th	69	1.09 [1.09, 1.1]
	95th	90	1.27 [1.25, 1.29]
Baseline albumin (g/L)	5th	31	0.98 [0.977, 0.983]
	25th	37	0.993 [0.992, 0.995]
	50th	40	1 [0.999, 1]
	75th	43	1.01 [1, 1.01]
	95th	46	1.01 [1.01, 1.01]
Baseline tumor size (mm)	5th	16	1.01 [1.01, 1.02]
	25th	33	1 [1, 1.01]
	50th	55	1 [0.999, 1]
	75th	87	0.995 [0.994, 0.996]
	95th	157	0.99 [0.988, 0.992]
Race–Country		Japan	1.02 [1.01, 1.02]
Cancer type		Gastric cancer	0.898 [0.883, 0.918]
		NSCLC & other cancer	0.985 [0.981, 0.989]
Sex		Male	0.898 [0.882, 0.912]



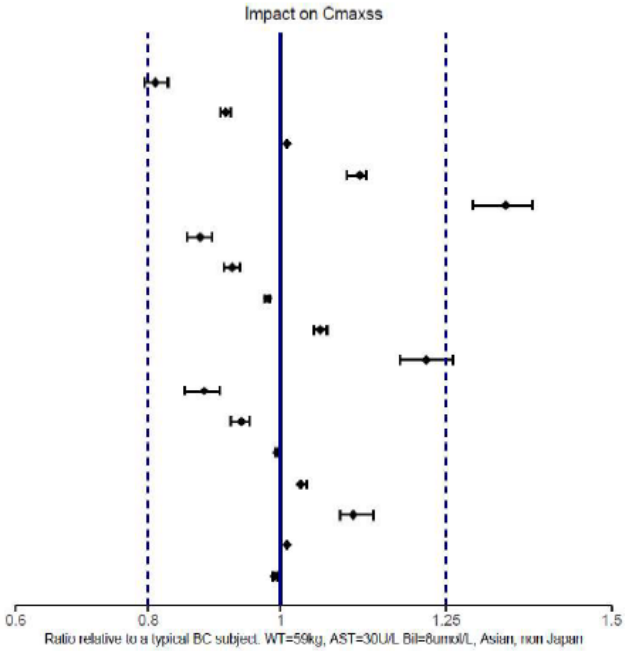
For DXd, subjects with extreme values of body weight (90 kg; 95th percentile) had an approximately 28% higher steady state Cmin, 34% higher Cmax, and a 36% higher AUC relative to a typical BC subject with body weight of 59 kg.

Figure 7 Forest plot of covariate effects on DXd exposure

Covariate	Percentile	Value	Ratio [90% CI]
Body weight (kg)	5th	44	0.841 [0.822, 0.861]
	25th	52	0.93 [0.923, 0.939]
	50th	60	1.01 [1.01, 1.01]
	75th	69	1.1 [1.08, 1.11]
	95th	90	1.28 [1.23, 1.32]
AST (U/L)	5th	15	0.874 [0.853, 0.892]
	25th	20	0.924 [0.911, 0.935]
	50th	27	0.98 [0.976, 0.983]
	75th	41	1.06 [1.05, 1.07]
	95th	86	1.23 [1.19, 1.27]
Total bilirubin (umol/L)	5th	3	0.88 [0.849, 0.903]
	25th	5	0.938 [0.921, 0.951]
	50th	8	0.994 [0.992, 0.996]
	75th	10	1.04 [1.03, 1.05]
	95th	17	1.12 [1.09, 1.15]
Race-country		Non-Asian	1 [0.998, 1]
Cancer type		NSCLC	0.841 [0.84, 0.843]

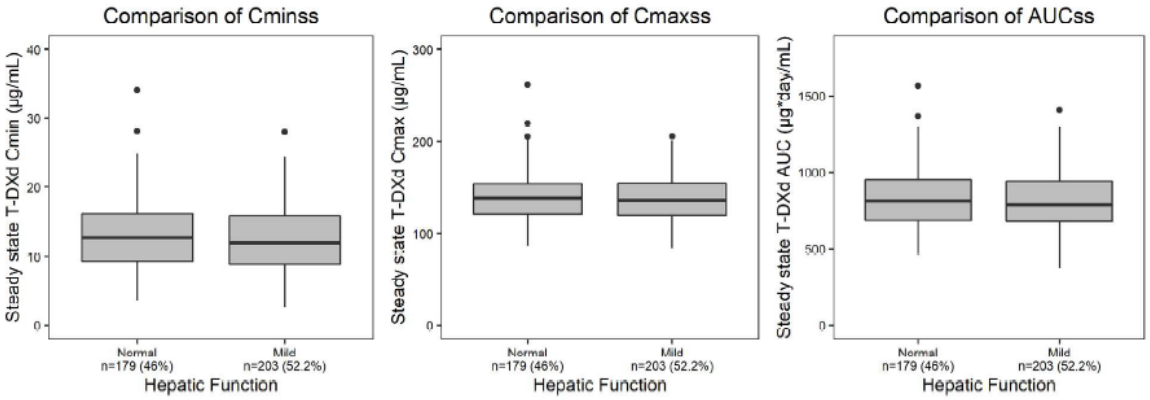


Covariate	Percentile	Value	Ratio [90% CI]
Body weight (kg)	5th	44	0.811 [0.794, 0.83]
	25th	52	0.917 [0.909, 0.925]
	50th	60	1.01 [1.01, 1.01]
	75th	69	1.12 [1.1, 1.13]
	95th	90	1.34 [1.29, 1.38]
AST (U/L)	5th	15	0.879 [0.859, 0.897]
	25th	20	0.927 [0.915, 0.939]
	50th	27	0.981 [0.977, 0.984]
	75th	41	1.06 [1.05, 1.07]
	95th	86	1.22 [1.18, 1.26]
Total bilirubin (umol/L)	5th	3	0.885 [0.855, 0.908]
	25th	5	0.941 [0.925, 0.953]
	50th	8	0.995 [0.992, 0.997]
	75th	10	1.03 [1.03, 1.04]
	95th	17	1.11 [1.09, 1.14]
Race-country		Non-Asian	1.01 [1.01, 1.01]
Cancer type		NSCLC	0.991 [0.988, 0.996]



Boxplots of exposure metrics by hepatic function and by renal function are displayed in Figures 8, 9, 10 and 11.

Figure 8 Boxplots of post hoc steady state T-DXd exposures in HER2-low BC subjects receiving 5.4 mg/kg Q3W by hepatic function

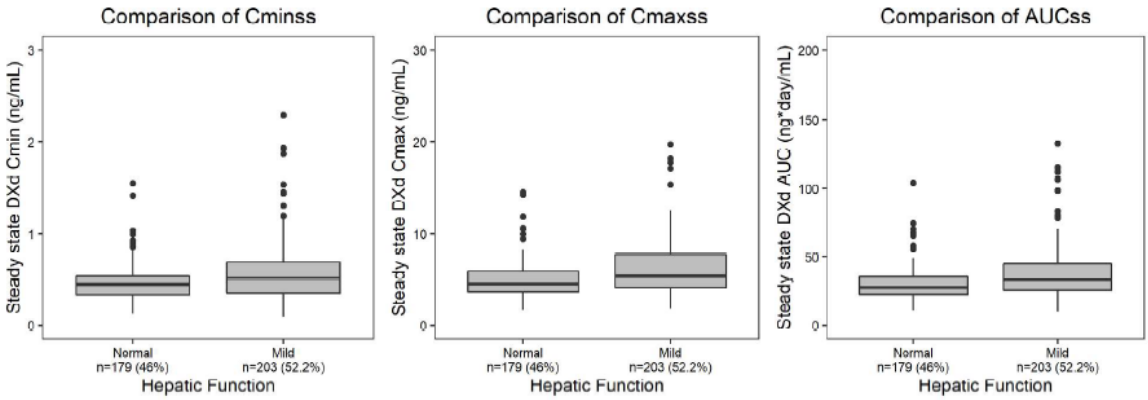


Abbreviations: AUC = area under the concentration-time curve; BC = breast cancer; Cmax = maximum concentration; Cmin = minimum concentration; HER2 = human epidermal growth factor receptor 2; n = number of subjects; Q3W = every 3 weeks; ss = steady state.

Notes: Boxes show the median and interquartile range of data. Whiskers represent the extent of data within 1.5 times the interquartile range. Points represent data outside the whiskers. Hepatic function was categorized using the NCI ODWG criteria [12].

Source: ds8201-intact-boxplots.docx, 2022-03-ds8201a-303-intact.r.

Figure 9 Boxplots of post hoc steady state DXd exposures in HER2-low BC subjects receiving 5.4 mg/kg Q3W by hepatic function

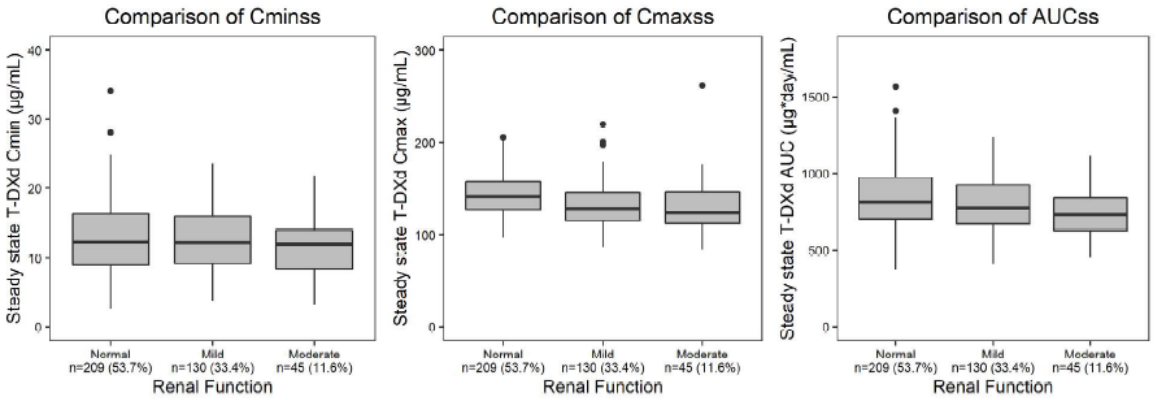


Abbreviations: AUC = area under the concentration-time curve; BC = breast cancer; Cmax = maximum concentration; Cmin = minimum concentration; HER2 = human epidermal growth factor receptor 2; n = number of subjects; Q3W = every 3 weeks; ss = steady state.

Notes: Boxes show the median and interquartile range of data. Whiskers represent the extent of data within 1.5 times the interquartile range. Points represent data outside the whiskers. Hepatic function was categorized using the NCI ODWG criteria [12].

Source: ds8201-payload-boxplots.docx, 2022-03-ds8201a-303-payload.r.

Figure 10 Boxplots of post hoc steady state T-DXd exposures in HER2-low BC subjects receiving 5.4 mg/kg Q3W by renal function

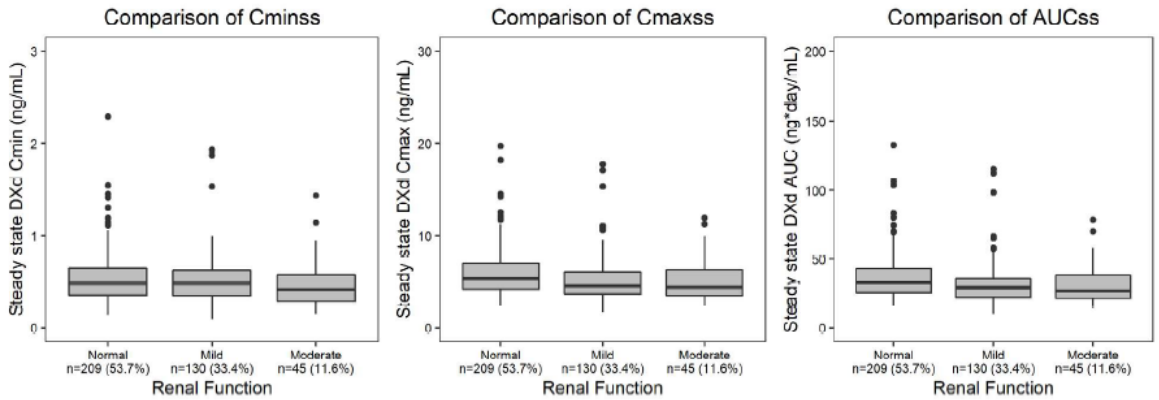


Abbreviations: AUC = area under the concentration-time curve; BC = breast cancer; Cmax = maximum concentration; Cmin = minimum concentration; CrCL = creatinine clearance; FDA = Food and Drug Administration; HER2 = human epidermal growth factor receptor 2; n = number of subjects; Q3W = every 3 weeks; ss = steady state.

Notes: Boxes show the median and interquartile range of data. Whiskers represent the extent of data within 1.5 times the interquartile range. Points represent data outside the whiskers. Renal function was categorized using the 2010 FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function [13]. Normal function, mild impairment, moderate impairment, and severe impairment were defined as CrCL (using Cockcroft and Gault equation) of ≥90, 60 to 89, 30 to 59, and 15 to 29 mL/min, respectively. One (1) subject with severe renal impairment is not displayed.

Source: ds8201-intact-boxplots.docx, 2022-03-ds8201a-303-intact.r.

Figure 11 Boxplots of post hoc steady state DXd exposures in HER2-low BC subjects receiving 5.4 mg/kg Q3W by renal function



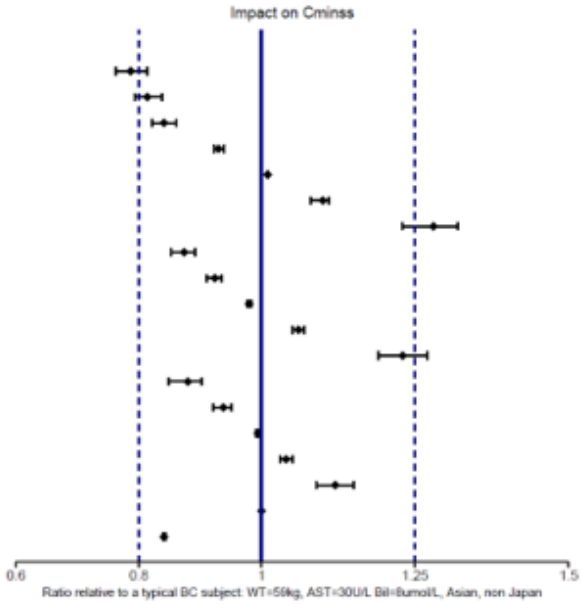
Abbreviations: AUC = area under the concentration-time curve; BC = breast cancer; Cmax = maximum concentration; Cmin = minimum concentration; CrCL = creatinine clearance; CrCL = creatinine clearance; FDA = Food and Drug Administration; HER2 = human epidermal growth factor receptor 2; n = number of subjects; Q3W = every 3 weeks; ss = steady state.

Notes: Boxes show the median and interquartile range of data. Whiskers represent the extent of data within 1.5 times the interquartile range. Points represent data outside the whiskers. Renal function was categorized using the 2010 FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function [13]. Normal function, mild impairment, moderate impairment, and severe impairment were defined as CrCL (using

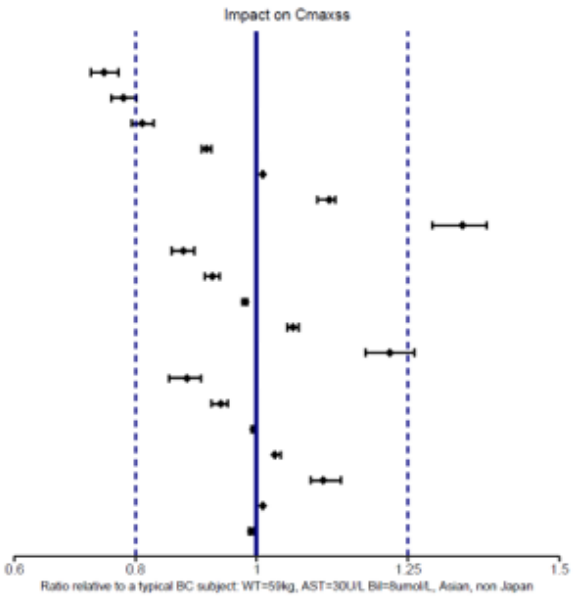
Forest plots updated with effects of body weight at the 1st and 2.5th percentiles are shown in Figure 12 below for DXd exposure metrics.

Figure 12 Forest plots of covariate effects of body weight at the 1st and 2.5th percentiles

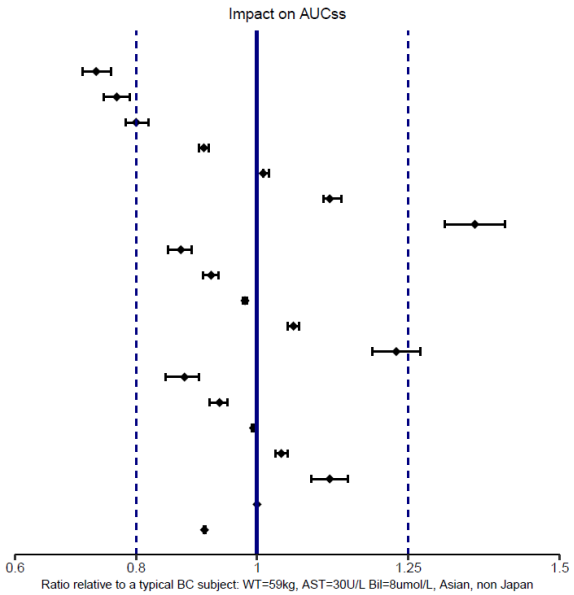
Covariate	Percentile	Value	Ratio [90% CI]
Body weight (kg)	1st	39	0.787 [0.762, 0.814]
	2.5th	41	0.814 [0.793, 0.838]
	5th	44	0.841 [0.822, 0.861]
	25th	52	0.93 [0.923, 0.939]
	50th	60	1.01 [1.01, 1.01]
	75th	69	1.1 [1.08, 1.11]
	95th	90	1.28 [1.23, 1.32]
AST (U/L)	5th	15	0.874 [0.853, 0.892]
	25th	20	0.924 [0.911, 0.935]
	50th	27	0.98 [0.976, 0.983]
	75th	41	1.06 [1.05, 1.07]
	95th	86	1.23 [1.19, 1.27]
Total bilirubin (umol/L)	5th	3	0.88 [0.849, 0.903]
	25th	5	0.938 [0.921, 0.951]
	50th	8	0.994 [0.992, 0.996]
	75th	10	1.04 [1.03, 1.05]
	95th	17	1.12 [1.09, 1.15]
Race−country		Non−Asian	1 [0.998, 1]
Cancer type		NSCLC	0.841 [0.84, 0.843]



Covariate	Percentile	Value	Ratio [90% CI]
Body weight (kg)	1st	39	0.748 [0.726, 0.772]
	2.5th	41	0.78 [0.76, 0.802]
	5th	44	0.811 [0.794, 0.83]
	25th	52	0.917 [0.909, 0.925]
	50th	60	1.01 [1.01, 1.01]
	75th	69	1.12 [1.1, 1.13]
	95th	90	1.34 [1.29, 1.38]
AST (U/L)	5th	15	0.879 [0.859, 0.897]
	25th	20	0.927 [0.915, 0.939]
	50th	27	0.981 [0.977, 0.984]
	75th	41	1.06 [1.05, 1.07]
	95th	86	1.22 [1.18, 1.26]
Total bilirubin (umol/L)	5th	3	0.885 [0.855, 0.908]
	25th	5	0.941 [0.925, 0.953]
	50th	8	0.995 [0.992, 0.997]
	75th	10	1.03 [1.03, 1.04]
	95th	17	1.11 [1.09, 1.14]
Race−country		Non−Asian	1.01 [1.01, 1.01]
Cancer type		NSCLC	0.991 [0.988, 0.996]



Covariate	Percentile	Value	Ratio [90% CI]
Body weight (kg)	1st	39	0.734 [0.711, 0.759]
	2.5th	41	0.768 [0.747, 0.79]
	5th	44	0.8 [0.783, 0.82]
	25th	52	0.912 [0.904, 0.92]
	50th	60	1.01 [1.01, 1.02]
	75th	69	1.12 [1.11, 1.14]
	95th	90	1.36 [1.31, 1.41]
AST (U/L)	5th	15	0.874 [0.853, 0.892]
	25th	20	0.924 [0.911, 0.936]
	50th	27	0.98 [0.976, 0.983]
	75th	41	1.06 [1.05, 1.07]
	95th	86	1.23 [1.19, 1.27]
Total bilirubin (umol/L)	5th	3	0.88 [0.849, 0.904]
	25th	5	0.938 [0.921, 0.951]
	50th	8	0.994 [0.992, 0.996]
	75th	10	1.04 [1.03, 1.05]
	95th	17	1.12 [1.09, 1.15]
Race−country		Non−Asian	1 [0.998, 1]
Cancer type		NSCLC	0.913 [0.912, 0.915]



2.3.3. Pharmacodynamics

Primary and secondary pharmacology is described in the initial BC application (see initial EPAR).

Immunogenicity

In Study U303, the treatment-emergent incidence of ADAs against T-DXd was 2.0% (7 of 357 subjects). The data available indicated no association between ADA status and allergic-type reactions. The incidence of NAbs against T-DXd was 0.1% across all studies (1 of 1668 subjects). The timepoints of immunogenicity samples in Study U303 are shown in Table 8. A summary of the available immunogenicity data is shown in Table 9.

Table 8 Immunogenicity sampling strategy for Study U303

Protocol	Anti-Drug Antibody Sampling Points						
	C1D1 BI	C1D8	C2D1 BI		Cycle 4 and Later Cycles BI	EOT	Follow-Up Visits
U303	X		X		X		D40 and long-term survival follow-up

ADA = anti-drug antibody; BI = before infusion; C = Cycle; D = Day; EOT = end of treatment.
Note: ADA samples were taken within 8 hours BI on Day 1 in Cycles 1, 2, and 4, and then every 4 cycles (Cycles 8, 12, 16, etc); from Cycle 2 onward, samples were taken on Day 1 ±2 days. If positive ADA at the 40-day (+7 days) Follow-up Visit, samples were collected every 3 months (±1 month) up to 1 year after the last dose, or until the ADA became negative, or until the ADA titer became less than baseline (applicable when pre-existing ADA was observed), or start of new anticancer therapy, or subject withdrew consent from the study (whichever occurred first).
Source: Module 5.3.5.1 DS8201-A-U303 CSR, Table 6.4

Table 9 Summary of clinical immunogenicity data

Statistic	Prior Clinical Studies (N = 1130)	U303 (N = 371)	Overall (N = 1701)
Baseline assessment			
Subjects with Baseline Data, n (%)	1310 (98.5)	352 (94.9)	1662 (97.7)
ADA Positive at Baseline, n (%) [a]	70 (5.3)	20 (5.7)	90 (5.4)
NAb Positive at Baseline, n (%) [a]	2 (0.2)	1 (0.3)	3 (0.2)
Post-baseline assessment			
Subjects with Post-Baseline Data, n (%)	1311 (98.6)	357 (96.2)	1668 (98.1)
ADA Positive Post-Baseline, n (%) [b]	36 (2.7)	13 (3.6)	49 (2.9)
NAb Positive Post-Baseline, n (%) [b]	1 (0.1)	1 (0.3)	2 (0.1)
ADA Positive at Baseline and Post-Baseline, n (%) [c]	12 (0.9)	6 (1.8)	18 (1.1)
NAb Positive at Baseline and Post-Baseline, n (%) [c]	0	0	0
Treatment-Emergent ADA Positive, n (%) [b, d]	27 (2.1)	7 (2.0)	34 (2.0)
Treatment-Induced ADA Positive, n (%) [b, e]	24 (1.8)	7 (2.0)	31 (1.9)
Treatment-Boosted ADA Positive, n (%) [b, f]	3 (0.2)	0	3 (0.2)
Treatment-Emergent NAb Positive, n (%) [b, g]	1 (0.1)	0	1 (0.1)

ADA = anti-drug antibody; n = number of subjects; N = total number subjects; NAb = neutralizing antibody; T-DXd = trastuzumab deruxtecan.
Note: The "prior clinical studies" were the following nine studies: J101, J102, A103, A104, U201, J202, U204, U205, and U302.
[a] Denominator for percentages is the number of subjects with baseline immunogenicity data.
[b] Denominator for percentages is the number of subjects with post-baseline immunogenicity data.
[c] Denominator for percentages is the number of subjects with baseline and post-baseline immunogenicity data.
[d] Treatment-emergent ADA positive: positive post-baseline after negative or missing baseline result, or titer increased after positive baseline result.
[e] Treatment-induced ADA positive: positive post-baseline result where baseline result was negative or missing.
[f] Treatment-boosted ADA positive: ADA titer increased following positive baseline result.
[g] Treatment-emergent NAb positive: NAb-positive subjects among treatment-emergent ADA-positive subjects.
Source: Module 5.3.5.3 SCP TFLs, Table 2.1.1.

2.3.4. PK/PD modelling

Exposure-response (ER) analyses

R (version 4.0.5) was used for exposure-efficacy modelling, data explorations prior to and/or after modelling, and simulations based on exposure-efficacy models.

Exposure metrics were generated from the final PopPK model using individual post hoc Bayes estimates. Binary variables were explored using boxplots, logistic regression plots or exposure-event tables. For time-to-event variables, Kaplan-Meier survival curves were plotted by exposure quartile. Cox regression models were fit to the endpoints. Covariates were tested on the intercept and the slope of logistic ER relationships or on the intercept of Cox regression models. Covariates were tested using a forward search at $p<0.05$ followed by a backward search at $p<0.01$ using the likelihood ratio test. Exposure was included in the backward search process, except for logistic regression safety endpoints.

Exposure-efficacy relations

All subjects with HER2-positive BC from Study U303 who were treated with T-DXd and had individual estimated exposures were included in the exposure-efficacy population. Efficacy data from Study U303 and Study J101 were not pooled due to the differences in subject population and study design. Thus, a total of 362 HER2-low subjects were included in the exposure-efficacy analyses of PFS, OS and ORR, of which 324 were HR-positive.

For PFS, Cox-regression showed a significant correlation (using a z-test) to T-DXd AUC in Cycle 1 for all subjects (p=0.038), but not in HR-positive (p=0.112) subjects. Because exposure was not present in the final model for PFS in all subjects or for PFS in HR positive subjects, no PFS simulations were performed. PFS final model parameters are shown in Table 10.

Table 10 PFS final model parameters in all subjects

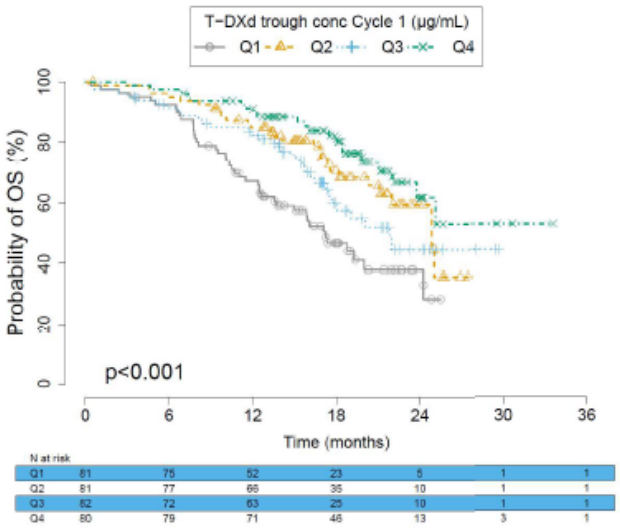
Exposure-Response Model		Parameter	Estimate	Standard Error	RSE (%)
Exposure Metric	Endpoint				
None	PFS in all subjects	AST	0.00565	0.00207	37

Abbreviations: AST = aspartate aminotransferase; PFS = progression free survival; RSE = relative standard error.
Source: ee.analysis.r

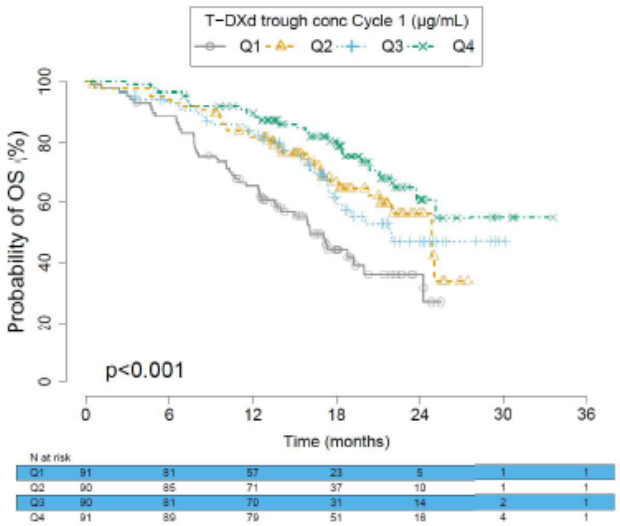
For OS, T-DXd Cmin in Cycle 1 (Cmin1) were selected for all subjects and for HR-positive subjects because it had the smallest p-value (p<0.001) by log-rank test and a negative effect on the OS hazard ratio in the univariate Cox-regression analysis. T-DXd AUC1, T-DXd AUCSS, and T-DXd CminSS had also significant effect on OS for all subjects. A significant ER relationship was detected for OS in all subjects which was confirmed by model-based analysis using multivariate Cox-regression that showed significant effect of T-DXd Cmin1. Other covariates that were detected included ECOG, AST, prior chemotherapy lines in the metastatic setting and race-country. See figure 13 and Table 11.

Figure 13 Kaplan-Meier curves for OS by exposure quartiles

(A) HR-positive subjects (N=324)



(B) All subjects (N=362)



Abbreviations: HR = hormone-receptor; OS = overall survival; CI = confidence interval; N = number of subjects; Q = exposure quartile.

Note: Curves are Kaplan Meier curves stratified by exposure quartiles. Points are censor times. P-value is for the log-rank test.

Source: ee.analysis.r

Table 11 OS final model parameters in all subjects

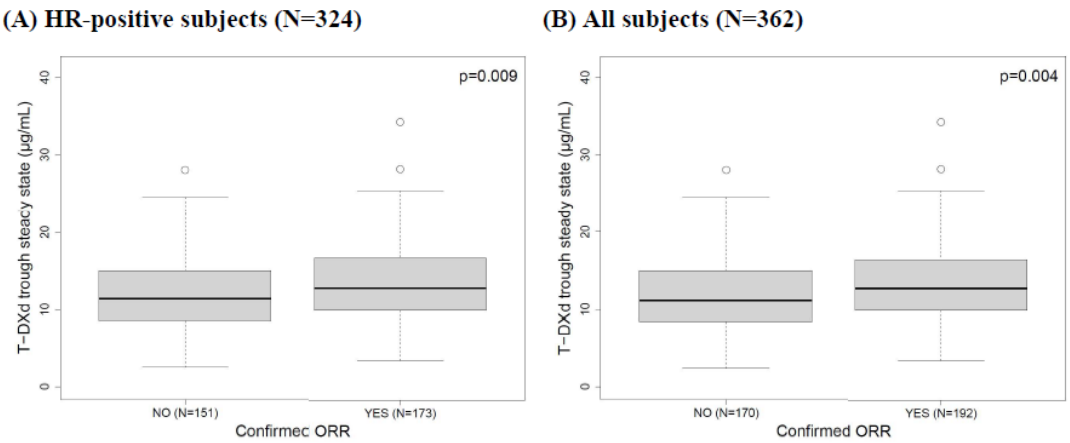
Exposure-Response Model		Parameter	Estimate	Standard Error	RSE (%)
Exposure Metric	Endpoint				
T-DXd Cmin Cycle 1 (µg/mL)	OS in all subjects	Slope	-0.154	0.0441	29
		ECOG ≥ 1	0.607	0.173	29
		AST (U/L)	0.00976	0.00256	26
		Prior chemotherapy lines metastatic ≥ 2	0.451	0.17	38
		Asian from Japan	0.0851	0.235	276
		Asian not from Japan	-0.682	0.227	33

Abbreviations: ECOG = Eastern Cooperative Oncology Group performance status; OS = overall survival; RSE = relative standard error.
Source: ee.analysis.r

The exposure-response of OS showed a shallow relationship across all covariates. Day 360 OS probabilities at the 5th, 50th and 95th percentiles of exposure were 0.815, 0.877, and 0.929 respectively. The difference between Day 360 OS probability at the extremes of exposure in U303 were within 6% of the Day 360 OS probability at the median exposure.

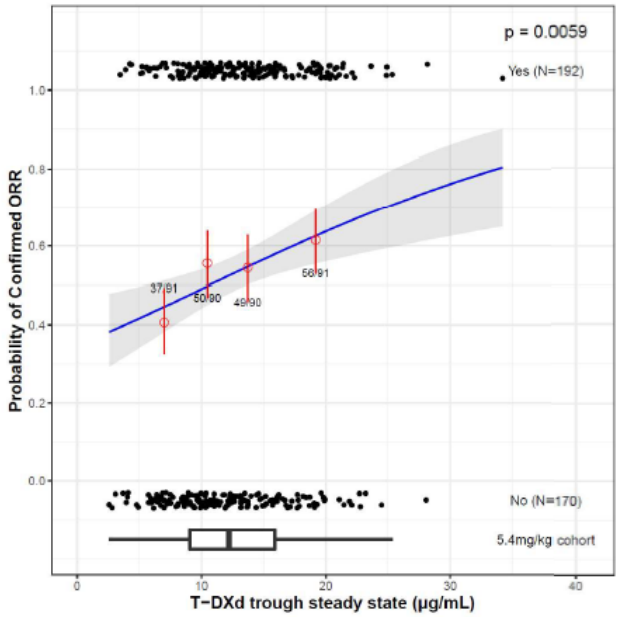
For ORR in all subjects and in HR-positive subjects, CminSS was selected because it had the smallest p-values (p=0.004 and p=0.009) by Kruskal-Wallis test. ORR in HR-positive subjects was not modelled. See Figures 14, 15 and Table 12 for ORR.

Figure 14 Boxplot of T-DXd CminSS grouped by ORR status



Abbreviations: $Cmin_{SS}$ = trough concentration at steady state; ORR = confirmed objective response rate by blinded independent central review.
Note: Thick horizontal line represents median, box ends show the upper and lower quartiles of the data, whiskers show the range of points within 1.5 times the interquartile range, and points are data that lie outside the whiskers (circles). The p-value is for a Kruskal-Wallis test of difference between distributions.
Source: ee.analysis.r

Figure 15 ORR in all subjects versus T-DXd CminSS



Abbreviations: $Cmin_{SS}$ = T-DXd trough concentration at steady-state; CI = confidence interval; N = number of subjects; ORR = confirmed objective response rate by blinded independent central review.

Note: Yes and No refer to if subjects experienced or did not experience confirmed objective response. Subjects are stratified into exposure quartiles. Red points are ORR per exposure quartile plotted at the median exposure per quartile. Vertical red bars are 90% CIs of the confirmed ORR. Gray band represents the 5th to 95th percentile CI of a linear logistic regression fit. The p-value is the significance level of the slope of the logistic regression fit using a z-test. Horizontal boxplot below shows the exposure distribution for the 5.4 mg/kg dose group; the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.

Source: ee.analysis.r

Table 12 Summary of ORR final model parameters

Exposure-Response Model		Parameter	Estimate	Standard Error	RSE (%)
Exposure Metric	**Efficacy Endpoint**				
T-DXd $Cmin_{SS}$ (µg/mL)	ORR in all subjects	Intercept	-0.636	0.293	-
		Slope	0.060	0.022	36

Abbreviations: $Cmin_{SS}$ = trough concentration at steady-state; ORR = confirmed objective response rate by independent central review; RSE = relative standard error.

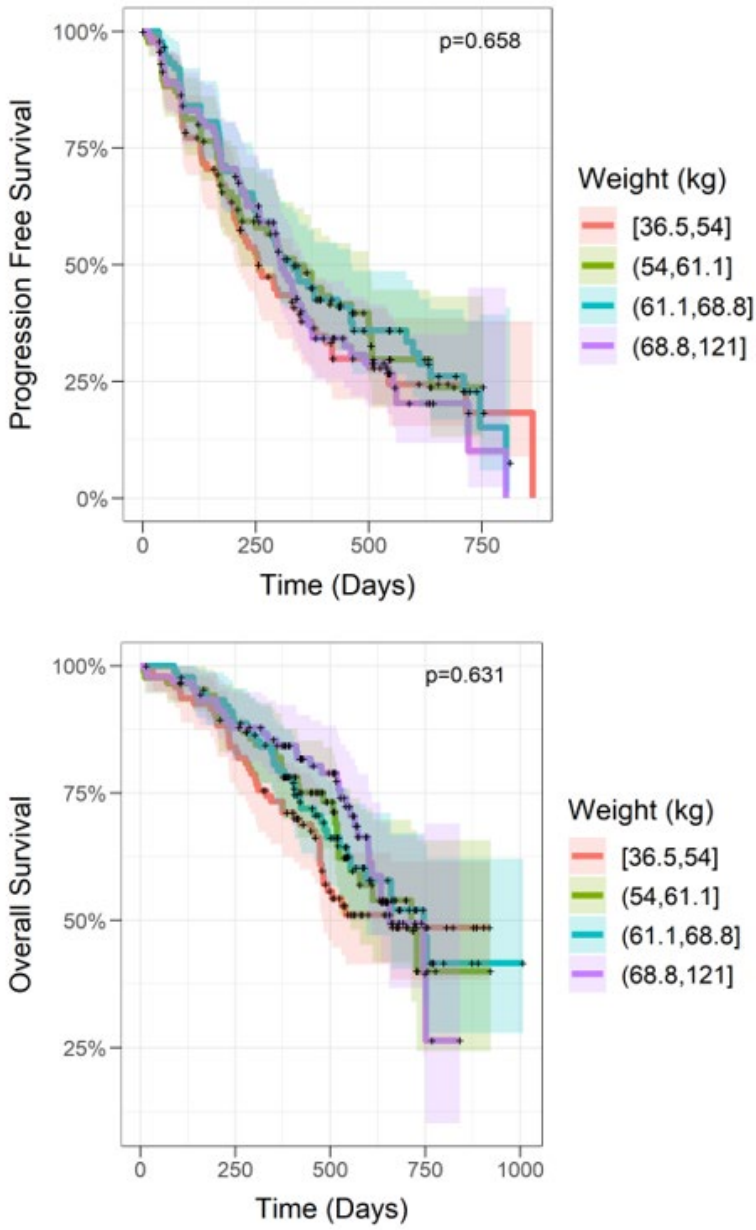
Note: RSE value not reported for the intercept term, because not relevant for logistic regression.

Source: ee.analysis.r

There was a significant ER relationship between T-DXd CminSS and increasing ORR in all subjects. No other covariates were detected in the multivariate logistic regression analysis.

Kaplan-Meier Plots for PFS and OS data stratified for weight quartiles in Study U303 are shown in Figure 16.

Figure 16 Kaplan-Meier Plots for PFS and OS data stratified by baseline body weight for weight quartiles in Study U303



Exposure-safety relations

The previous exposure-safety analyses were based on data from Studies J101, J102, A103, A104, U201, J202, U204, U205, U302 and updated with data from Study U303. A total of 1675 subjects were included, of whom 1328 (79%) were female and 347 (21%) were male, 569 (34%) were Asians from Japan, 337 (20%) were Asians from countries other than Japan, and 769 (46%) were non-Asians. The median age was 58 years, and the median body weight was 60.0 kg. Most subjects had BC (67%) and were HER2-positive (55%) and 22% were HER2-low.

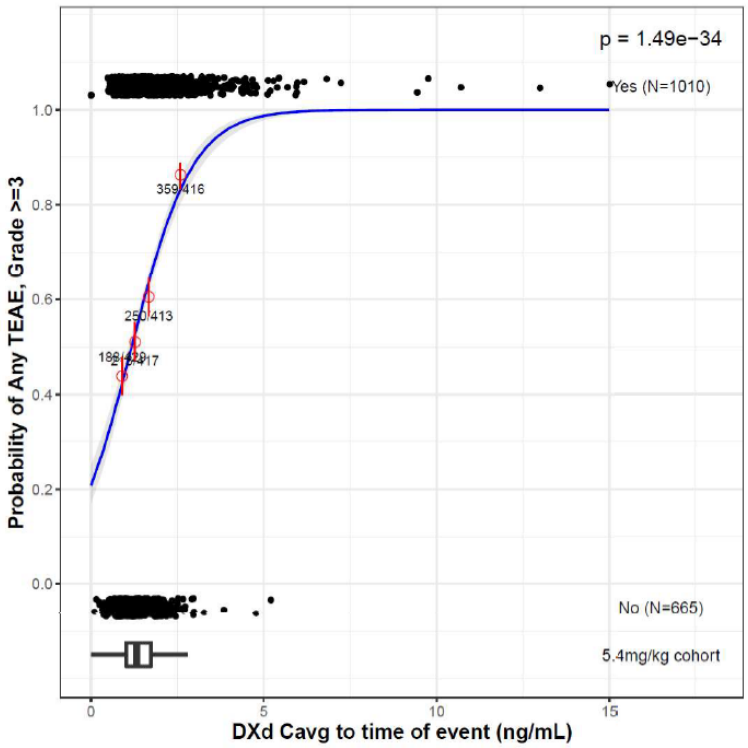
The evaluated endpoints were: Grade 3 TEAEs, Grade 3 anaemia, Grade 3 neutrophil count decreased, Grade 3 platelet count decreased, Any Grade drug-related adjudicated interstitial lung disease (ILD), Grade 3 adjudicated ILD, and Grade 2 laboratory defined left-ventricular ejection fraction (LVEF)

decreased by echocardiogram/multigated acquisition scan (ECHO/MUGA). Additional safety endpoints were included in explorative analyses.

Per modeled safety endpoint, the prior model was fit to the updated exposure-safety analysis set and model parameters and covariate effects were re-estimated. Any covariates that were not significant (p>0.05 using z-test) were removed and re-evaluated using forward and backward covariate analysis. See Figure 5-12 and Table 5-20 for Grade ≥3 TEAEs, Figure 5-18 and Table 5-25 for Grade ≥3 anemia; Figure 5-24 and Table 5-30 for Grade ≥3 neutropenia; Figure 5-30 and Table 5-35 for Grade ≥3 thrombocytopenia; Figure 5-36 and Table 5-40 for Grade ≥2 LVEF decrease and Figures 5-42, 5-43 and Table 5-46, 5-47 for Any Grade ILD.

Figure 17 Probability of Grade ≥3 TEAEs versus exposure

Figure 5-12: Probability of Grade ≥3 TEAEs versus exposure



Abbreviations: Cavg = average concentration; CI = confidence interval; N = number of subjects; TEAE = treatment emergent adverse event.

Note: Plot shows probability of AE versus exposure. Yes and No refer to if subjects experienced or did not experience Grade ≥3 TEAEs. Subjects are stratified into exposure quartiles. Red points are AE rates per exposure quartile plotted at the median exposure of the quartile. Vertical red bars are 90% CIs of the AE rate. Blue line is the linear logistic regression fit. Gray band represents the 5th to 95th percentile CI of the fit. The p-value is the significance level of the slope of the logistic regression fit using a z-test. The plot shows data for all dose groups. Horizontal boxplot below shows the exposure distribution for the 5.4 mg/kg dose group; the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.

Source: es.analysis.r

Table 13 Grade ≥3 TEAE final model parameters

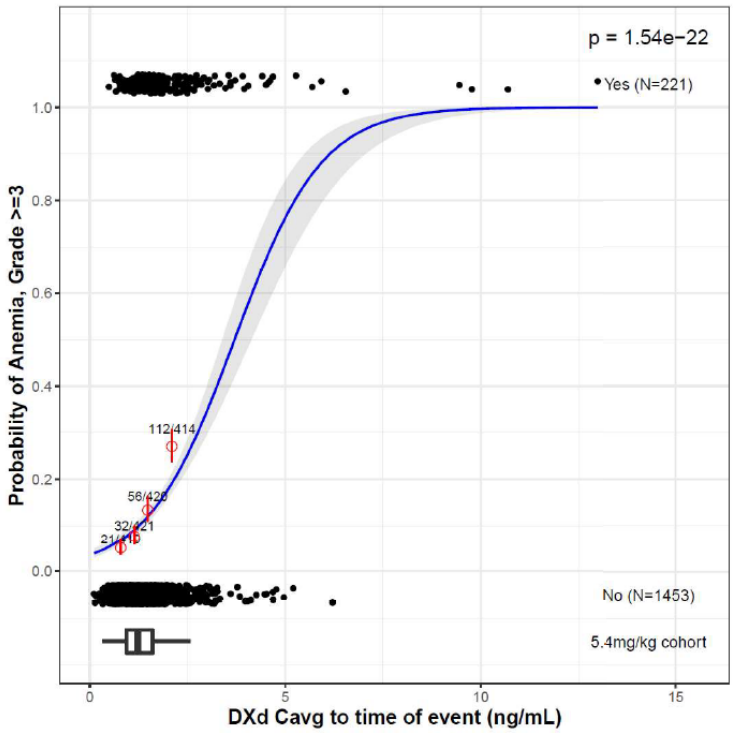
Exposure-Response Model		Parameter	Estimate	Standard Error	RSE (%)
Exposure Metric	Endpoint				
DXd Cavg to time of event (ng/mL)	Grade ≥3 TEAE	Intercept	-1.23	0.209	--
		Slope	0.999	0.117	12
		Albumin (g/L)	-0.0668	0.0132	20
		Gastric cancer	-1.26	0.479	38
		NSCLC (HER2 mutant)	-1.51	0.792	52
		NSCLC (HER2 overexpressing)	-1.92	0.827	43
		Other tumor type	-0.37	0.857	232
		Prior CDK46 Inhibitor	-0.249	0.182	73
		CDK46 Missing	0.238	0.141	59
		Gastric cancer on slope	0.801	0.299	37
		NSCLC (HER2 mutant) on slope	1.56	0.621	40
		NSCLC (HER2 overexpressing) on slope	1.18	0.524	44
		Other tumor type on slope	0.0806	0.489	607
		Weight (kg) on slope	-0.00876	0.00233	27

Abbreviations: AE = adverse event; Cavg= average concentration; CDK46 = cyclin-dependent kinase 4 or 6; HER2 = human epidermal growth factor receptor 2; NSCLC = non-small cell lung cancer; RSE = relative standard error; TEAE = treatment-emergent adverse event.

Note: RSE value not reported for the intercept term, because not relevant for logistic regression. The large RSE for some categories of tumor type may reflect that this category is not significantly different from the BC category, or it may reflect a small sample size. Overall, tumor type is still significant as a categorical variable.

Source: es.analysis.r

Figure 18 Probability of Grade ≥3 anemia versus exposure



Abbreviations: AE = adverse event; Cavg = average concentration; CI = confidence interval; N = number of subjects.

Note: Plot shows probability of AE versus exposure. Yes and No refer to if subjects experienced or did not experience anemia (laboratory-based). Subjects are stratified into exposure quartiles. Red points are AE rates per exposure quartile plotted at the median exposure of the quartile. Vertical red bars are 90% CIs of the AE rate. Blue line is the linear logistic regression fit. Gray band represents the 5th to 95th percentile CI of the fit. The p-value is the significance level of the slope of the logistic regression fit using a z-test. The plot shows data for all dose groups. Horizontal boxplot below the graph shows the exposure distribution for the 5.4 mg/kg dose group; the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.

Source: es.analysis.r

Table 14 Grade ≥3 lab-based anemia final model parameters

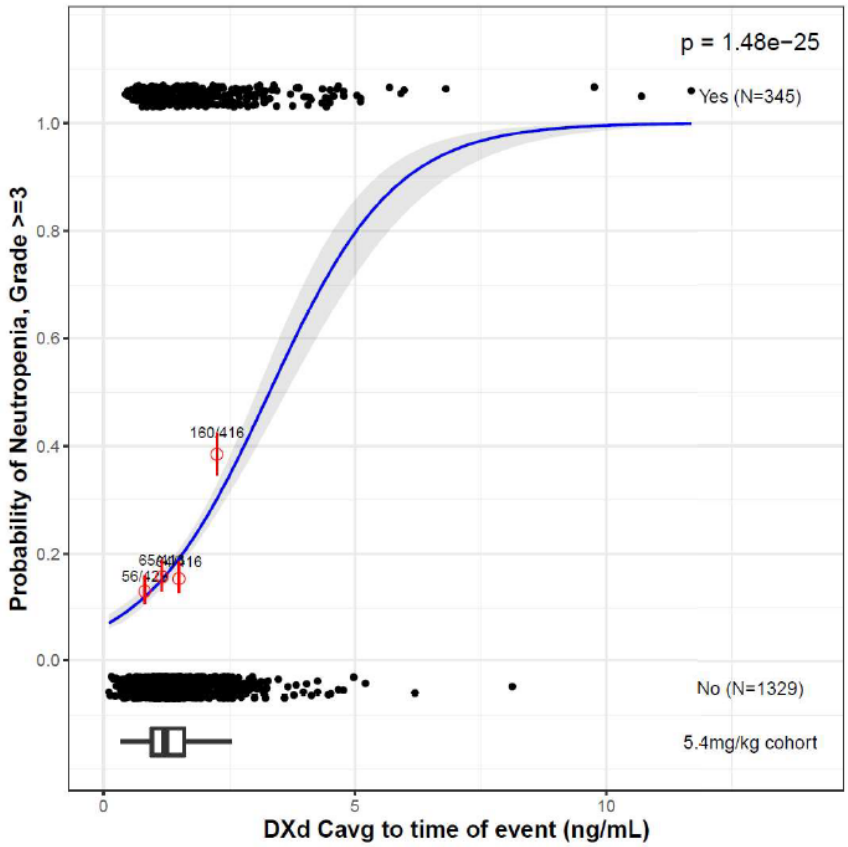
Exposure-Response Model		Parameter	Estimate	Standard Error	RSE (%)
Exposure Metric	Safety Endpoint				
DXd Cavg to time of event (ng/mL)	Grade ≥3 lab-based anemia	Intercept	-3.67	0.283	--
		Slope	1.54	0.169	11
		Hemoglobin (g/L)	-0.0663	0.00650	10
		Weight (kg)	0.0232	0.00837	36
		Prior CDK46 Inhibitor	-1.10	0.350	32
		CDK46 Missing	-0.574	0.206	36
		Gastric cancer type on slope	0.122	0.125	102
		NSCLC (HER2 mutant) on slope	-0.0467	0.274	587
		NSCLC (HER2 overexpressing) on slope	-1.15	0.442	38
		Other tumor type on slope	-0.382	0.217	57
		Creatinine clearance (mL/min) on slope	-0.00794	0.0019	24
		Total bilirubin (µmol/L) on slope	-0.0293	0.0105	36
		Non-Asian on slope	-0.754	0.140	19
		Asian not from Japan on slope	-0.238	0.134	56

Abbreviations: Cavg = average concentration; CDK46 = cyclin-dependent kinase 4 or 6; HER2 = human epidermal growth factor receptor 2; NSCLC = non-small cell lung cancer; RSE = relative standard error.

Note: RSE value not reported for the intercept term, because not relevant for logistic regression. The large RSE for Asian not from Japan indicates that this race-country category is not significantly different from Asian from Japan for Grade ≥3 anemia. Overall race-country category was still significant as a categorical variable. The large RSE for gastric cancer and NSCLC HER2 mutant indicates that these tumor types are not significantly different from BC for Grade ≥3 anemia. Overall, tumor type was still significant as a categorical variable.

Source: es.analysis.r

Figure 19 Probability of Grade ≥3 neutropenia versus Dxd exposure



Abbreviations: AE = adverse event; Cavg = average concentration; CI = confidence interval; N = number of subjects.

Note: Plot shows probability of AE versus exposure. Yes and No refer to if subjects experienced or did not experience neutropenia (laboratory-based). Subjects are stratified into exposure quartiles. Red points are AE rates per exposure quartile plotted at the median exposure of the quartile. Vertical red bars are 90% CIs of the AE rate. Blue line is the linear logistic regression fit. Gray band represents the 5th to 95th percentile CI of the fit. The p-value is the significance level of the slope of the logistic regression fit using a z-test. The plot shows data for all dose groups. Horizontal boxplot below the graph shows the exposure distribution for the 5.4 mg/kg dose group. The box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.

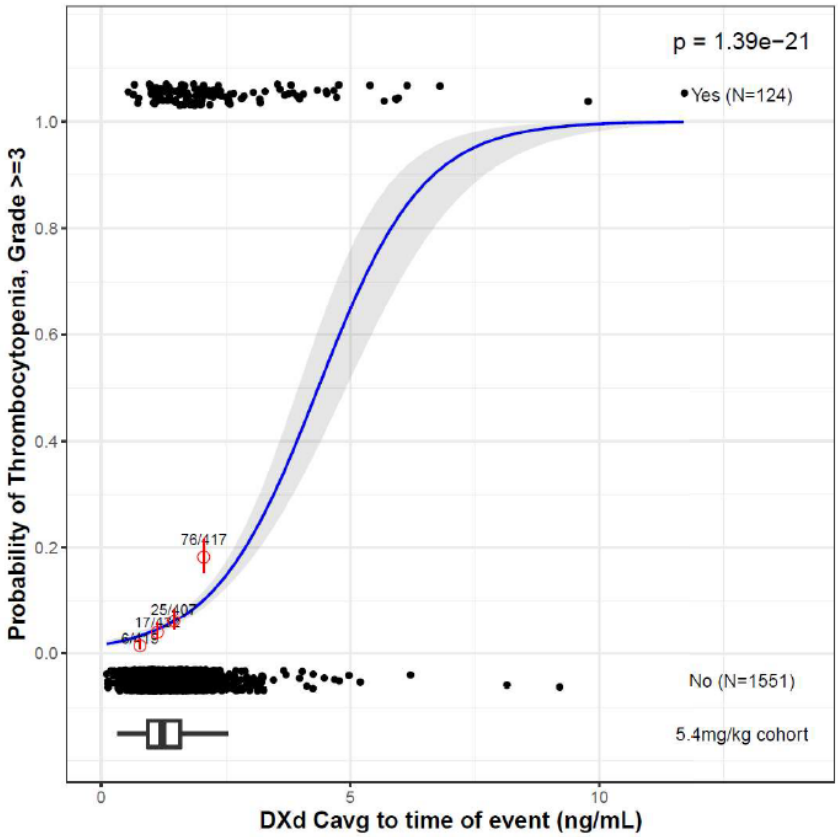
Source: es.analysis.r

Table 15 Grade ≥3 neutropenia final model parameters

Exposure-Response Model		Parameter	Estimate	Standard Error	RSE (%)
Exposure Metric	Safety Endpoint				
DXd Cavg to time of event (ng/mL)	Grade ≥3 neutropenia	Intercept	-3.36	0.293	--
		Slope	1.40	0.163	12
		Neutrophils (10^9/L)	-0.785	0.105	13
		Non-Asian	0.558	0.377	68
		Asian not from Japan	1.57	0.416	26
		Prior checkpoint inhibitor on slope	0.460	0.169	37
		Albumin (g/L) on slope	-0.0339	0.00914	27
		Non-Asian on slope	-1.02	0.211	21
		Asian not from Japan on slope	-1.11	0.243	22
		Neutrophils (10^9/L) on slope	0.228	0.0434	19

Abbreviations: Cavg = average concentration; RSE = relative standard error.
Note: RSE value not reported for the intercept term, because not relevant for logistic regression.
Source: es.analysis.r

Figure 20 Probability of Grade ≥3 thrombocytopenia versus exposure



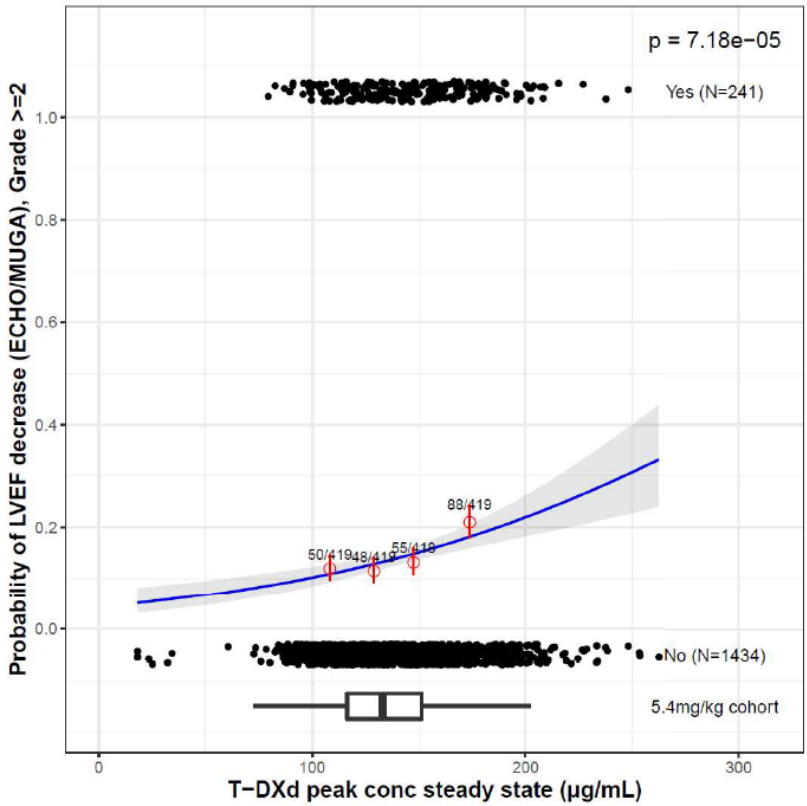
Abbreviations: AE = adverse event; Cavg = average concentration; CI = confidence interval; N = number of subjects.
Note: Plot shows probability of AE versus exposure. Yes and No refer to if subjects experienced or did not experience thrombocytopenia (laboratory-based). Subjects are stratified into exposure quartiles. Red points are AE rates per exposure quartile plotted at the median exposure of the quartile. Vertical red bars are 90% CIs of the AE rate. Blue line is the linear logistic regression fit. Gray band represents the 5th to 95th percentile CI of the fit. The p-value is the significance level of the slope of the logistic regression fit using a z-test. The plot shows data for all dose groups. Horizontal boxplot below shows the exposure distribution for the 5.4 mg/kg dose group; the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.
Source: es.analysis.r

Table 16 Grade ≥3 thrombocytopenia final model parameters

Exposure-Response Model		Parameter	Estimate	Standard Error	RSE (%)
Exposure Metric	Safety Endpoint				
DXd Cavg to time of event (ng/mL)	Grade ≥3 thrombocytopenia	Intercept	-4.26	0.226	--
		Slope	1.21	0.119	10
		Creatinine clearance (mL/min)	0.00941	0.0034	36
		Platelets (10^9/L) on slope	-0.00331	0.000543	16
		Non-Asian on slope	-0.788	0.13	16
		Asian not from Japan on slope	0.0486	0.131	270

Abbreviations: Cavg = average concentration; RSE = relative standard error.
Note: RSE value not reported for the intercept term, because not relevant for logistic regression. The large RSE for Asian not from Japan indicates this race-country category is similar to the Asian from Japan reference group. Overall, race-country was still significant as a categorical variable.
Source: es.analysis.r

Figure 21 Probability of Grade ≥ 2 LVEF decreases (ECHO/MUGA) versus exposure



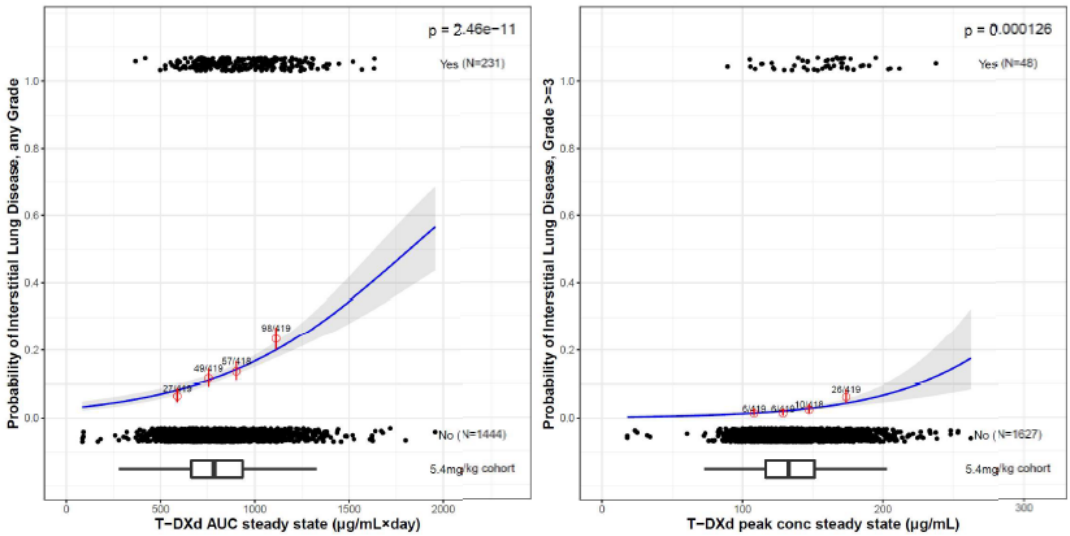
Abbreviations: AE = adverse event; CI = confidence interval; conc = concentration; ECHO = echocardiogram-based; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition scan; N = number of subjects.
Note: Plot shows probability of AE versus exposure. Yes and No refer to if subjects experienced or did not experience LVEF decrease (ECHO/MUGA). Subjects are stratified into exposure quartiles. Red points are AE rates per exposure quartile plotted at the median exposure of the quartile. Vertical red bars are 90% CIs of the AE rate. Blue line is the linear logistic regression fit. Gray band represents the 5th to 95th percentile CI of the fit. The p-value is the significance level of the slope of the logistic regression fit using a z-test. The plot shows data for all dose groups. Horizontal boxplot below the graph shows the exposure distribution for the 5.4 mg/kg dose group; the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.
Source: es.analysis.r

Table 17 Grade ≥ 2 LVEF decreases (ECHO/MUGA) final model parameters

Exposure-Response Model		Parameter	Estimate	Standard Error	RSE (%)
Exposure Metric	Safety Endpoint				
T-DXd peak conc steady state (µg/mL)	Grade ≥2 LVEF decrease (ECHO/MUGA)	Intercept	-2.62	0.353	--
		Slope	0.00896	0.00235	26
		Sex Male	-0.799	0.209	26
		Non-Asian	-0.381	0.157	41
		Asian not from Japan	-0.778	0.221	28

Abbreviations: conc = concentration; ECHO = echocardiogram-based; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition scan; RSE = relative standard error.
Note: RSE value not reported for the intercept term, because not relevant for logistic regression.
Source: es.analysis.r

Figure 22 Rate of Any Grade and Grade ≥3 ILD versus exposure



Abbreviations: AE = adverse event; AUC = area under the concentration-time curve; CI = confidence interval; conc = concentration; ILD = interstitial lung disease; N = number of subjects.
Note: Yes and No refer to if subjects experienced or did not experience ILD. Subjects are stratified into exposure quartiles. Red points are AE rates per exposure quartile plotted at the median exposure of the quartile. Vertical red bars are 90% CIs of the AE rate. Blue line is the linear logistic regression fit. Gray band represents the 5th to 95th percentile CI of the fit. The p-value is the significance level of the slope of the logistic regression fit using a z-test. The plot shows data for all dose groups. Horizontal boxplot below shows the exposure distribution for the 5.4 mg/kg dose group; the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.
Source: es.analysis.r

Figure 23 Kaplan-Meier curves with univariate Cox regression fit for Any Grade ILD for AUC exposure quartiles

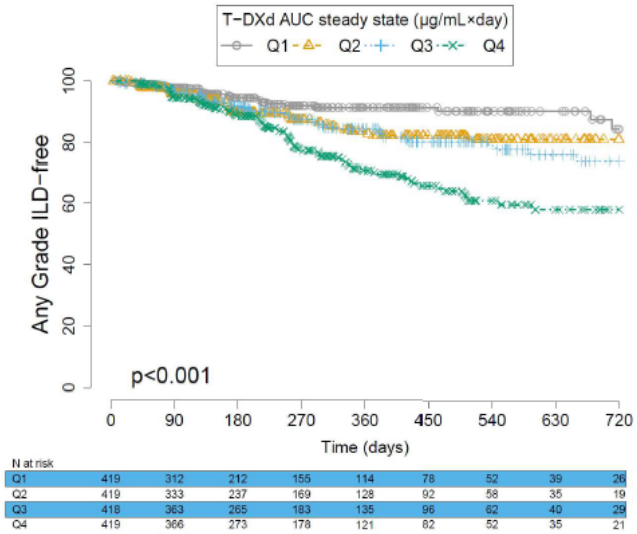


Table 18 Any Grade ILD final model parameters

Exposure-Response Model		Parameter	Estimate	Standard Error	RSE (%)
Exposure Metric	Safety Endpoint				
T-DXd AUC steady state (µg/mL×day)	Any Grade ILD	Slope	0.00148	0.000264	18
		Creatinine clearance (mL/min)	-0.00989	0.00241	24
		Non-Asian	-0.609	0.14	23
		Asian not from Japan	-1.12	0.227	20
		Oxygen saturation (%)	-0.0971	0.0398	41

Abbreviations: AUC = area under the concentration-time curve; ILD = interstitial lung disease; RSE = relative standard error.
Source: es.analysis.r

Table 5-47: Grade ≥3 ILD final model parameters

Exposure-Response Model		Parameter	Estimate	Standard Error	RSE (%)
Exposure Metric	Safety Endpoint				
T-DXd peak conc steady state (µg/mL)	Grade ≥3 ILD	Slope	0.0192	0.00448	23
		ECOG ≥ 1	0.96	0.319	33
		Oxygen saturation (%)	-0.17	0.051	30
		Albumin (g/L)	-0.079	0.0317	40

Abbreviations: conc = concentration; ECOG = Eastern Cooperative Oncology Group Performance Status; ILD = interstitial lung disease; RSE = relative standard error.
Source: es.analysis.r

Predicted incidence rate for all safety end-points are summarised in Table 19 and 20.

Table 19 Incidence Rate of Adverse Events in Subjects with Breast Cancer (at 5.4 mg/kg Q3W T-DXd), Predicted in the Final Model (by HER2 Status, Region, and Race-Country)

	N	Model-Predicted Rate, % Estimate (90% CI)				
		Grade ≥3 TEAE	Grade ≥3 Anemia	Grade ≥3 Neutropenia	Grade ≥3 Thrombocyt	Grade ≥2 LVEF Decrease
HER2 Status						
HER2-Positive	645	56.5 (51.8, 61.1)	9.8 (7.2, 13.2)	17.5 (13.9, 21.9)	6.3 (4.6, 8.5)	14.4 (12.0, 17.4)
HER2-Low	362	51.5 (45.4, 57.3)	7.3 (4.8, 11.3)	15.7 (12.2, 19.9)	6.1 (4.3, 8.4)	14.5 (12.1, 17.4)
Region						
Asia	560	57.6 (52.6, 62.3)	11.7 (8.5, 15.5)	23.7 (19.4, 29.0)	8.9 (6.6, 11.5)	14.6 (11.9, 18.1)
Europe	284	53.1 (47.5, 58.2)	4.8 (3.0, 7.6)	10.6 (8.0, 14.0)	3.0 (2.0, 4.5)	14.8 (12.6, 17.8)
North America	234	54.2 (48.4, 59.6)	10.7 (7.2, 15.0)	12.0 (9.1, 16.0)	4.6 (3.1, 6.5)	14.5 (12.1, 17.4)
ROW	50	52.4 (46.0, 58.3)	5.2 (3.2, 8.4)	11.8 (8.6, 16.1)	3.7 (2.2, 6.1)	16.5 (13.5, 20.2)
Race-Country						
Non-Asian	542	53.3 (47.8, 58.7)	6.8 (4.6, 9.8)	10.9 (8.4, 14.1)	3.4 (2.2, 5.0)	15.1 (12.7, 18.1)
Asian-Japan	303	60.1 (54.9, 65.1)	13.5 (10.0, 17.7)	25.4 (21.3, 30.3)	8.7 (6.5, 11.0)	18.6 (15.8, 22.4)
Asian Non-Japan	283	55.4 (50.3, 60.3)	10.7 (7.3, 14.9)	22.5 (17.9, 28.4)	10.0 (7.2, 13.4)	9.8 (7.4, 13.1)

BC = breast cancer; CI = confidence interval; HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; N = number of subjects; T-DXd = trastuzumab deruxtecan; Thrombocyt = thrombocytopenia; ROW = rest of the world; TEAE = treatment-emergent adverse event; Q3W = every 3 weeks.
Note: Modeled safety endpoint rates use BC subjects from all dose groups in indicated group. Exposures are dose-normalized to a 5.4 mg/kg T-DXd dose.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx020, Table 5-60, Table 5-61, and Table 5-62

Table 20 Incidence Rate of Interstitial Lung Disease in Subjects with Breast Cancer (at 5.4 mg/kg Q3W T-DXd), Predicted in the Final Model (by HER2 Status, Region, and Race-Country)

	N	Model-Predicted Rate, % Estimate (90% CI)			
		ILD Any Grade		ILD Grade ≥3	
		Day 180	Day 360	Day 180	Day 360
HER2 Status					
HER2-Positive	645	7.4 (6.2, 8.7)	15.6 (13.5, 17.6)	1.6 (1.1, 2.2)	3.2 (2.3, 4.1)
HER2-Low	362	6.9 (5.8, 8.2)	14.5 (12.6, 16.7)	2.0 (1.4, 2.8)	3.8 (2.7, 5.0)
Region					
Asia	560	8.4 (7.1, 9.9)	17.4 (15.0, 20.0)	1.4 (0.9, 1.9)	2.7 (1.9, 3.7)
Europe	284	6.9 (5.5, 8.5)	14.4 (12.0, 17.0)	2.0 (1.3, 3.0)	3.7 (2.7, 5.1)
North America	234	6.6 (5.4, 8.0)	14.0 (11.8, 16.5)	1.9 (1.3, 2.7)	3.8 (2.7, 5.0)
ROW	50	6.6 (5.2, 8.1)	14.0 (11.3, 16.8)	2.6 (1.6, 4.1)	5.1 (3.4, 7.6)
Race-Country					
Non-Asian	542	6.8 (5.5, 8.4)	14.5 (12.0, 16.9)	2.1 (1.5, 2.9)	4.0 (3.0, 5.2)
Asian-Japan	303	12.1 (10.1, 14.2)	24.8 (21.4, 28.6)	1.3 (0.9, 1.9)	2.6 (1.8, 3.5)
Asian Non-Japan	283	3.9 (2.5, 5.3)	8.4 (5.7, 11.4)	1.5 (1.0, 2.1)	2.9 (2.0, 4.1)

BC = breast cancer; CI = confidence interval; HER2 = human epidermal growth factor receptor 2; N = number of subjects; Q3W = every 3 weeks; T-DXd = trastuzumab deruxtecan; ROW = rest of the world; TEAE = treatment-emergent adverse event.
Note: Simulations were based on subjects in the specified population and race-country category using subject-specific exposures and covariates. Simulated number of subjects includes all BC subjects in the indicated category. The 90% CI was based on model uncertainty and covariate variability.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx020, Tables 5-50 and 5-51

2.3.5. Discussion on clinical pharmacology

The clinical pharmacology package included in the current application is based on data from a Phase 3 study in subjects with HER2-low BC (Study U303) plus data from nine prior studies. The T-DXd PK was described by a two-compartment model with linear elimination, and DXd PK was described by a one-compartment model, with time-varying release of drug from T-DXd. The previous Pop PK model for BC was updated with data from Study U303 in a sequential way with T-DXd data first. In the Pop PK population, 919 subjects (55%) were HER2-positive, and 468 subjects (28%) were HER2-low. No new covariates were identified. The final Pop PK model (run034) could adequately describe the data from BC patients independent of HER2 status (positive or low).

The absorption, distribution, metabolism, and excretion of T-DXd, total anti-HER2 antibody and DXd is considered well-characterised and described in the initial BC application. The recommended 5.4 mg/kg Q3W dose regimen for HER2-low BC patients applied in Study U303 resulted in comparable exposures to the approved regimen of T-DXd for subjects with unresectable or metastatic HER2-positive BC. The recommended dose regimen is weight-based and resulted in increased Cmax and AUC with increasing body weight. Extended Forest plots indicated that subjects of lower body weight (<41 kg, corresponding to the 2.5th body weight percentile) experienced T-Dxd and Dxd exposures at steady-state, below the 0.8 exposure ratio relative to a typical Asian female BC subject of 59 kg. The impact was largest on Cmax,ss and AUC,ss and less pronounced on Cmin,ss. For subjects with body weights above 90 kg, the steady-state exposure for T-Dxd and Dxd were predicted to be above the upper 1.25 exposure ratio.

Steady-state exposures of T-DXd and DXd were comparable between HER2-low subjects with normal hepatic function (n=179) and mild hepatic impairment (n=203) and between HER2-low subjects with normal renal function (n=209), mild (n=130) or moderate renal impairment (n=45). The incidence of post-baseline ADAs and NAbs in Study U303 was low, 3.6% and 0.3%, respectively.

The exposure-efficacy relationship was evaluated in Study U303 HER2-low subjects (n=362) for PFS, OS and ORR. For OS and ORR, a significant ER relationship was detected in all subjects, however, the effect was not deemed clinically relevant for ORR. As weight had great impact on exposure, a subgroup analysis of efficacy measures per weight quartiles displayed by Kaplan Meier plots was requested and indicated some effect on OS for the lowest weight quartile which included weights up to 54 kg.

The previous exposure-safety analyses were updated with the data from Study U303 (total n=1675). The E-R relationships were consistent with those detected previously. T-DXd steady-state Cmax was correlated with Grade ≥2 LVEF and Grade ≥3 ILD. T-DXd steady-state AUC was correlated with Any Grade ILD. DXd CavgTOE was correlated with Grade ≥3 TEAE and laboratory-based Grade ≥3 anemia, neutropenia and thrombocytopenia. Across all evaluated safety endpoints, the model-predicted incidence rates were comparable between HER2-positive and HER2-low BC subjects.

The magnitude of effect on ORR at the extremes of exposure in Study U303 is not deemed clinically meaningful relative to ORR at the median exposure. No relationships between increasing DXd exposures and decreasing PFS/OS hazard or increasing ORR probability were detected in the exposure-efficacy analysis. Also, no effect of HER2 status (positive versus low) was detected in this analysis.

Treatment benefit of HER2-low BC patients with very low body weight was further discussed. In the HER2-low BC population in Study U303, 13 subjects had a body weight below 44 kg (cut-off close to the 5th percentile of body weight in the 'all BC population'). Of these, 8 subjects discontinued due to progressive disease. This subgroup of patients seemed to have worse prognosis in terms of ECOG

status, renal function, old age, prior lines of treatment and disease burden. Comparison of simulated T-DXd and DXd exposures at T-DXd doses of 5.4 and 6.4 mg/kg in subjects with a body weight ≤44 kg, indicated the higher dose would result in approximate 20% exposure increase at Cycle 1 and at steady-state. A multi-variate E-R analysis indicated that the predicted OS probability at Day 360 for subjects with a body weight ≤44 kg would be similar at both T-DXd doses. Comparing the safety profiles stratified for body weight in the 'all BC population', the 6.4 mg/kg dose seemed to result in a worse safety profile compared to 5.4 mg/kg in the ≤44 kg subgroup of patients. Thus, the recommendation for the 5.4 mg/kg dose independent of body weight is supported.

2.3.6. Conclusions on clinical pharmacology

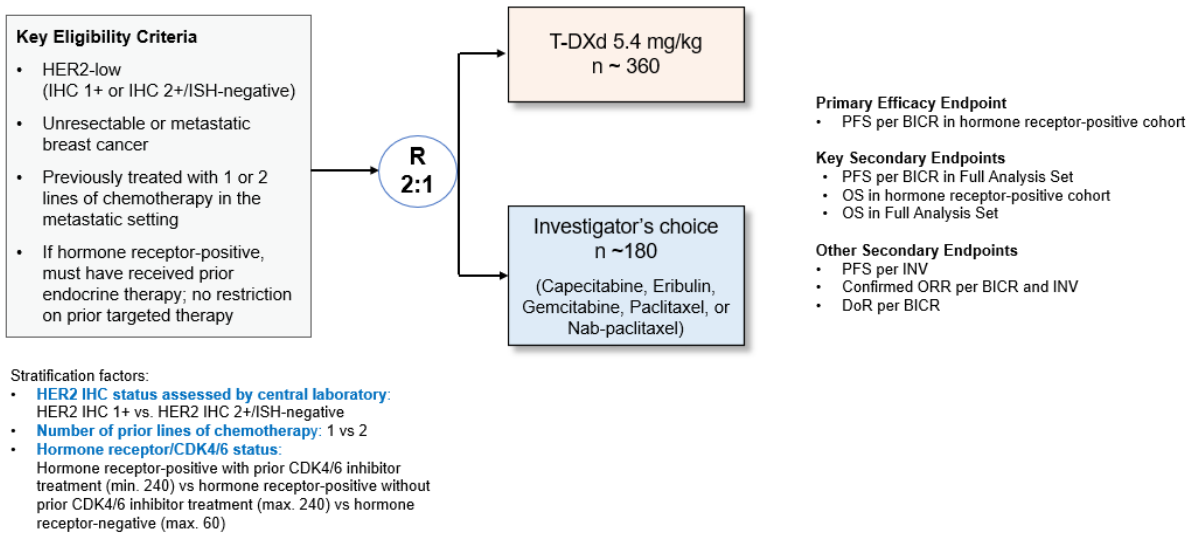
Overall, the clinical pharmacology is considered adequately described for treatment of HER2-low BC subjects with T-DXd at the recommended dose 5.4 mg/kg Q3W. The final bioanalytical reports for Study U303 will be submitted within 6 months of study closure (PAM-REC).

2.4. Clinical efficacy

2.4.1. Main study

Destiny Breast04 – Study U303: A randomized, Phase III, open-label, multi-centre study to compare the safety and efficacy of trastuzumab deruxtecan versus the physician's choice in HER2-low, unresectable and/or metastatic breast cancer

Figure 24 Study U303 (DESTINY-Breast04) Design



BICR = blinded independent central review; CDK = cyclin-dependent kinase; DoR = duration of response; FAS = Full Analysis Set; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; IHC = immunohistochemistry; INV = investigator; ISH = in situ hybridization; max = maximum; min = minimum; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; R = randomization; T-DXd = trastuzumab deruxtecan; vs = versus

Methods

Study participants

Inclusion Criteria

Subjects had to satisfy all of the criteria shown below to be included in the study. For subjects randomized to the TPC arm, the investigator followed the label approved in the country of drug administration for eligibility criteria for the individual treatment options (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel).

1. Competent and able to comprehend, sign, and date an IRB- or IEC-approved ICF before performance of any study-specific procedures or tests.

2. Men or women ≥18 years of age.

3. Pathologically documented BC that:

a. Was unresectable or metastatic.

b. Had a history of low HER2 expression, defined as IHC 2+/ISH-negative or IHC 1+ (ISH-negative or untested).

c. Was assessed as low HER2 expression, defined as IHC 2+/ISH-negative or IHC 1+ according to ASCO-CAP 2018 HER2 testing guidelines, adapted by Daiichi Sankyo Inc. and Ventana Medical Systems, Inc., evaluated at a central laboratory.

d. Was hormone receptor-positive or hormone receptor-negative. Approximately 60 subjects with hormone receptor-negative BC were to be enrolled; the remaining subjects were to be hormone receptor-positive (positive for estrogen receptor or progesterone receptor if finding of ≥1% immunoreactive tumor cell nuclei).

e. If the BC was hormone receptor-positive, it was documented as refractory to ET, defined as having progressed on at least 1 endocrine therapy and determined by the investigator that the subject would no longer benefit from further treatment with ET.

f. If the BC was hormone receptor-positive, had or had not been treated with a CDK4/6 inhibitor. No more than 240 subjects with hormone receptor-positive BC who had no prior therapy with a CDK4/6 inhibitor and at least 240 subjects with hormone receptor-positive BC who had prior therapy with a CDK4/6 inhibitor were to be enrolled.

g. Had been treated with at least 1 and no more than 2 prior lines of chemotherapy in the recurrent or metastatic setting.

• If recurrence occurred within 6 months of (neo)adjuvant chemotherapy, (neo)adjuvant therapy would count as 1 line of chemotherapy.

• Targeted agents (such as mammalian target of rapamycin [mTOR] inhibitors, poly adenosine diphosphate ribose polymerase [PARP] inhibitors, programmed cell death ligand [PD-L] inhibitors, programmed cell death ligand 1 [PD-L1] inhibitors, histone deacetylase inhibitors, or CDK4/6 inhibitors) and endocrine therapies on their own did not contribute to the count of prior lines of chemotherapy, although regimens with such agents in combination with chemotherapy still counted as 1 line of chemotherapy.

h. Was never previously HER2-positive (IHC 3+ or IHC 2+/ISH-positive) on prior pathology testing (per ASCO-CAP guidelines) or was historically HER2 IHC 0 only.

i. Was never previously treated with anti-HER2 therapy.

4. Had documented radiologic progression (during or after most recent treatment).

5. An adequate archival tumor tissue sample was available for assessment of HER2 status by central laboratory (based on most recent available tumor tissue sample obtained either prior to or after the last treatment regimen). If archival tumor tissue was not available, a fresh tumor tissue biopsy was required.

6. Had a recent tumor tissue sample after the most recent treatment regimen or subject agreed to undergo a tissue biopsy prior to randomization for exploratory biomarker analysis.

7. Presence of at least 1 measurable lesion based on CT or MRI per modified Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).26

• Brain lesions were considered as non-target lesions only.

8. Had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.

9. Had left ventricular ejection fraction (LVEF) ≥50% within 28 days prior to randomization.

10. Had adequate bone marrow function within 14 days before randomization, defined as:

a. Platelet count ≥100,000/mm3 (platelet transfusion was not allowed within 1 week prior to Screening assessment).

b. Hemoglobin level ≥9.0 g/dL (red blood cell transfusion was not allowed within 1 week prior to Screening assessment).

c. Absolute neutrophil count ≥1500/mm3 (granulocyte colony-stimulating factor [G-CSF] administration was not allowed within 1 week prior to Screening assessment).

11. Had adequate renal function within 14 days before randomization, defined as:

• Creatinine clearance ≥30 mL/min, as calculated using the Cockcroft-Gault equation: CrCl (mL/min) = [140 - age (years)] × weight (kg) 72 × serum creatinine (mg/dL) {× 0.85 for females}.

12. Had adequate hepatic function within 14 days before randomization, defined as:

• Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤5 × upper limit of normal (ULN).

• Total bilirubin ≤1.5 × ULN if no liver metastases or <3 × ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline.

13. Had adequate blood clotting function within 14 days before randomization, defined as:

• International normalized ratio/prothrombin time ≤1.5 × ULN and either partial thromboplastin or activated partial thromboplastin time.

14. Male and female subjects of reproductive/childbearing potential were required to agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and after the last dose of T-DXd for at least 7 months for females or 4.5 months for males or according to the label approved in the country of drug administration for the TPCs. Male subjects were required to agree to inform all female partners that they were participating in a clinical study that could cause birth defects.

15. Male subjects were not allowed to freeze or donate sperm starting at Screening and throughout the study period, and at least 4.5 months after the final study drug administration or according to the label

approved in the country of drug administration for the TPCs. Preservation of sperm was to be considered prior to enrollment in this study.

16. Female subjects were not allowed to donate ova, or retrieve for their own use, from the time of Screening and throughout the study drug period, and for at least 7 months after the final study drug administration or according to the label approved in the country of drug administration for the TPCs.

17. Had adequate treatment washout period before randomization/enrollment, defined as chloroquine /hydroxychloroquine >14 days.

Exclusion Criteria

The investigator was instructed to follow the label approved in the country of drug administration for the individual treatment options for eligibility criteria if the subject was randomized to the TPC arm.

Subjects with any of the following were disqualified from entering the study:

1. Ineligibility for the declared TPC comparator because of previous treatment with the same comparator in the metastatic setting or the comparator was contraindicated. Subjects were eligible to be treated with a comparator with which they had not previously been treated.

2. Prior treatment with an ADC consisting of an exatecan derivative that is a topoisomerase I inhibitor, including prior participation in a study involving an ADC produced by Daiichi Sankyo Inc. and/or AstraZeneca.

3. Uncontrolled or significant cardiovascular disease, including any of the following:

a. History of myocardial infarction within 6 months before randomization, or troponin levels consistent with myocardial infarction (as defined according to the manufacturer) 28 days prior to randomization.

b. History of symptomatic congestive heart failure (New York Heart Association Class II to IV).

c. Corrected QT interval (QTc) prolongation to >470 ms (females) or >450 ms (males) based on average of Screening triplicate 12-lead electrocardiograms (ECGs).

4. History of (noninfectious) ILD/pneumonitis that required steroids, current ILD/pneumonitis, or suspected ILD/pneumonitis that could not be ruled out by imaging at Screening.

5. Spinal cord compression or clinically active central nervous system metastases, defined as untreated or symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms.

• Subjects with treated brain metastases that were no longer symptomatic and who required no treatment with corticosteroids or anticonvulsants could be included in the study if they had recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and study enrollment.

6. Multiple primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in situ disease, or contralateral BC.

7. History of severe hypersensitivity reactions to either the drug substances or inactive ingredients in the drug product.

8. History of severe hypersensitivity reactions to other monoclonal antibodies.

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

10. Substance abuse or medical conditions such as clinically significant cardiac or pulmonary diseases or psychological conditions, that could, in the opinion of the investigator, interfere with the subject's participation in the clinical study or evaluation of the clinical study results.

11. Social, familial, or geographical factors that could interfere with study participation or follow-up.

12. Known human immunodeficiency virus (HIV) infection or active hepatitis B or C infection. Subjects positive for hepatitis C antibody were eligible only if polymerase chain reaction was negative for hepatitis C ribonucleic acid (RNA). Subjects were to be tested for HIV prior to randomization if required by local regulations or IRB/IEC.

13. Unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤1 or baseline. Subjects with chronic Grade 2 toxicities could be eligible at the discretion of the investigator after consultation with the Sponsor Medical Monitor or designee (e.g., Grade 2 chemotherapy-induced neuropathy).

14. Therapeutic radiation therapy or major surgery within 4 weeks before study drug or palliative stereotactic radiation therapy within 2 weeks before study drug.

15. Systemic treatment with anticancer therapy (immunotherapy [non-antibody-based therapy], retinoid therapy) or hormonal therapy within 3 weeks before study drug; antibody-based-anticancer-therapy within 4 weeks before randomization; or treatment with nitrosoureas or mitomycin C within 6 weeks before study drug; or treatment with small-molecule targeted agents within 2 weeks, or 5 half-lives, whichever was longer.

16. Participation in a therapeutic clinical study within 3 weeks before study drug (for small-molecule targeted agents, this nonparticipation period was 2 weeks or 5 half-lives, whichever was longer), current participation in other therapeutic investigational procedures, or prior participation in this investigational study.

17. Pregnancy, breastfeeding, or a plan to become pregnant.

18. Subject could not be study site personnel or Sponsor employee directly involved in the clinical study, or an immediate family member of someone directly involved.

19. Otherwise considered inappropriate for the study by the investigator.

20. Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (i.e., pulmonary emboli within 3 months of the study enrollment, severe asthma, severe chronic obstructive pulmonary disease [COPD], restrictive lung disease, pleural effusion, etc.), and any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (i.e., rheumatoid arthritis, Sjögren's, sarcoidosis, etc.), or prior pneumonectomy.

Treatments

T-DXd was given intravenously (IV) at a dose of 5.4 mg/kg every 3 weeks (Q3W) (21-day cycle) until disease progression or unacceptable toxicity.

Table 21 Treatment per Physician's choice in the control arm

Comparator	Dosing Regimen
Capecitabine	1000-1250 mg/m² PO twice daily on Days 1-14; cycled every 21 days
Eribulin	1.4 mg[a]/m² IV on Days 1 and 8; cycled every 21 days
Gemcitabine	Option 1: 800-1200 mg/m² IV on Days 1 and 8; cycled every 21 days Option 2: 800-1200 mg/m² IV on Days 1, 8, and 15; cycled every 28 days
Paclitaxel	Option 1: 175 mg/m² IV on Day 1; cycled every 21 days Option 2: 80 mg/m² IV on Day 1 weekly
Nab-paclitaxel	Option 1: 260 mg/m² IV; cycled every 21 days Option 2: 100 mg/m² or 125 mg/m² IV on Days 1, 8, and 15; cycled every 28 days

NCCN = National Comprehensive Cancer Network; IV = intravenously; PO = orally
[a] Refers to eribulin mesylate (1.23 mg eribulin base = 1.4 mg eribulin mesylate)

In both treatment arms, the study drug was continued according until discontinuation criteria were met, which included progressive disease, unacceptable toxicity, or withdrawal of consent by subject.

Objectives

Primary Objective

The primary objective was to compare the PFS benefit of T-DXd to TPC in the cohort of subjects with HER2-low, hormone receptor-positive BC (i.e., the hormone receptor-positive cohort of the Full Analysis Set [FAS]), based on BICR.

Key Secondary Objectives

The key secondary objectives were as follows:

• To compare the PFS benefit of T-DXd to TPC in all randomized subjects regardless of hormone-receptor status (i.e., the FAS), based on BICR

• To compare the OS benefit of T-DXd to TPC in subjects with HER2-low hormone receptor-positive BC

• To compare the OS benefit of T-DXd to TPC in the FAS.

Other Secondary Objectives

Other secondary objectives were as follows:

• To investigate the efficacy of T-DXd compared to TPC on the following parameters:

– PFS in subjects with HER2-low hormone receptor-positive BC, based on investigator assessment

– Confirmed ORR, based on BICR and investigator assessment in subjects with HER2-low hormone receptor-positive BC

– DoR, based on BICR in subjects with HER2-low hormone receptor-positive BC

– Confirmed ORR and DoR in the FAS

• To determine pharmacokinetics (PK) of T-DXd

• To evaluate the safety of T-DXd compared to TPC

• To evaluate Health Economics and Outcomes Research (HEOR) endpoints for T-DXd compared to TPC.

Exploratory Objectives

The exploratory objectives were to evaluate the following:

• Clinical benefit rate (CBR; the proportion of complete response [CR], partial response [PR], and ≥6 months' stable disease [SD]), based on BICR in subjects with hormone receptor-positive BC and in the FAS

• Disease control rate (DCR), based on BICR in subjects with hormone receptor positive BC and in the FAS

• Time to response (TTR) based on BICR in subjects with hormone receptor-positive BC and in the FAS

• PFS on the next line of therapy (PFS2)

• Potential biomarkers of response/resistance

• Exposure-response relationships for efficacy and safety endpoints

• PFS, OS, confirmed ORR, and DoR in subjects with HER2-low hormone receptor negative BC.

Outcomes/endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was PFS based on BICR in the hormone receptor-positive cohort. PFS was defined as the time from the date of randomization to the earliest date of first objective documentation of radiographic disease progression according to RECIST v1.1 or death due to any cause. If a subject had not progressed or died at the analysis DCO date, PFS was censored at the last adequate tumor evaluation date before the DCO date. Discontinuation associated with disease progression without supporting objective evidence satisfying progression criteria per RECIST v1.1 was not considered to be a PFS event.

Key Secondary Efficacy Endpoints

- PFS based on BICR in all randomized subjects (i.e., regardless of hormone receptor status)
- OS in the hormone receptor-positive cohort
- OS in all randomized subjects

OS was defined as the time from the date of randomization to the date of death from any cause. If there was no death reported for a subject before the DCO for OS analysis, OS was censored at the last contact date at which the subject was known to be alive.

Other Secondary Efficacy Endpoints

- PFS based on investigator assessment (INV).
- Confirmed ORR based on BICR and INV. Confirmed ORR was defined as the proportion of subjects with best overall response of complete response (CR) or partial response (PR) that was confirmed by a second assessment.
- DoR based on BICR. DoR was defined as the time from the date of the first documentation of objective response (confirmed CR or PR) to the date of the first documentation of disease progression

or death. Subjects who were progression-free at the time of the DCO were censored at the date of the last evaluable tumor assessment.

Exploratory Efficacy Endpoints

- Clinical benefit rate (CBR) based on BICR: CBR was defined as the sum of CR rate, PR rate, and the rate of stable disease (SD) lasting more than 6 months.
- Disease control rate (DCR) based on BICR and INV: DCR was defined as the sum of CR rate, PR rate, and SD rate.
- Time to response (TTR) based on BICR: TTR was defined as the time from the date of randomization to the date of first documentation of objective response (confirmed CR or PR) for responding subjects.
- PFS on next-line therapy (PFS2) based on INV: PFS2 was defined as the time from the date of randomization to the first documented progression on next-line therapy or death due to any cause, whichever came first.
- PFS, OS, confirmed ORR, and DoR based on BICR in the hormone receptor-negative cohort.
- Best percent change in the sum of diameters (SoD) of measurable tumors based on BICR.

Health Economics and Outcome Research Endpoints

Health Economics and Outcome Research (HEOR) endpoints derived using the QLQ-C30, QLQ-BR45 (BR23), and EQ-5D-5L questionnaires, and hospitalization-related endpoints. The primary patient reported outcome (PRO) variable of interest was the global health status/global quality-of-life (QoL) scale score of the QLQ C30. Secondary PRO variables of interest were physical functioning, emotional functioning, and social functioning subscale scores of the QLQ C30, the BC symptom scale of the QLQ-BR45, and the index score of the EQ 5D-5L. Because the QLQ-BR45 was still undergoing validation at the time of the analysis, these analyses were performed using the QLQ-BR23 scoring guidelines and are presented in the results as QLQ-BR45/BR23.

Sample size

Approximately 480 subjects with hormone receptor-positive BC were planned to be randomized (approximately 320 T-DXd and 160 TPC). In addition, approximately 60 subjects with hormone receptor-negative BC (approximately 40 T-DXd and 20 TPC) were planned to be enrolled for exploratory purposes.

Assuming a true hazard ratio of 0.68 (corresponding an improvement in median PFS from the physician's choice arm of 4.2 months [NCT00337103] to a median PFS in T-DXd arm of 6.2 months), a total of 318 PFS events per BICR in HR-positive cohort was needed to ensure at least 90% power of log-rank test to reject the null hypothesis of no difference in PFS distributions at 2-sided alpha of 0.05 in HR-positive cohort (primary analysis). A total of ~480 HR-positive subjects (~320 T-DXd and ~160 physician's choice) and ~60 HR-negative subjects (~40 T-DXd and ~20 physician's choice) would be randomized, for a total enrollment of ~540 subjects (~360 T-DXd and ~180 physician's choice).

The primary efficacy analyses was to be event driven, and the primary analyses for PFS was to be performed when approximately 318 PFS events per BICR have been observed in the HR-positive population. The expected data cut-off dates for the final analyses of PFS was to be approximately 28.3 months after the first subject is randomized, based on updated enrolment rates.

The key secondary endpoint of OS was to be compared between the 2 treatment groups, provided that the log-rank tests for comparison of PFS in both the HR-positive cohort and the FAS demonstrate statistical significance. Assuming a median OS of 15 months in the control arm and a hazard ratio of 0.72, a total of 333 OS events was needed to ensure 80% power of a log-rank test to reject a null hypothesis of no difference in OS distributions at an overall 2-sided significance level of 0.05 under a 3-look group sequential design using Lan-DeMets alpha spending function with O'Brien-Fleming type superiority stopping boundary provided PFS is statistically significant. Final OS analysis was projected approximately 49.3 months from the date of first subject randomized when 333 OS events were documented in the HR-positive cohort. Approximately 162 (49%) and 233 (70%) out of the target total OS events were projected at the first and the second OS interim analyses in the HR positive cohort.

The sample size computation was performed using the EAST 6.4.

Randomisation

Subjects will be randomized into 1 of the 2 treatment arms (T-DXd versus physician's choice) in a 2:1 ratio. The randomization was to be stratified by:

- HER2 IHC status of tissue samples assessed by a central laboratory: HER2 IHC 1+ vs. HER2 IHC 2+/ISH-

- Number of prior lines of chemotherapy: 1 vs. 2

- HR/CDK status: HR-positive with prior CDK4/6 inhibitor treatment vs.HR-positive without prior CDK4/6 inhibitor treatment vs.HR-negative.

Randomization was to be managed through an Interactive Web/Voice Response System (IXRS) for subjects meeting all eligibility criteria.

All subjects were to have physician's choice treatment declared and recorded in the IXRS prior to randomization.

Blinding (masking)

The study was open-label.

Statistical methods

Full Analysis Set (FAS)

The FAS included all subjects randomized into the study, including those who did not receive a dose of study treatment. Subjects were to be analysed according to the treatments and strata assigned at randomization.

The hormone receptor positive cohort of FAS, according to baseline hormone receptor status per IXRS, was to be the primary analysis set for efficacy analyses.

Per-Protocol Analysis Set (PPS)

The PPS included all subjects in the hormone receptor positive cohort who complied sufficiently with the protocol with respect to exposure to study treatment, availability of tumor assessment, and absence of major protocol violations likely to impact efficacy outcome.

Primary efficacy endpoint: PFS based on BICR

The primary efficacy analysis was to be the comparison of the distribution of PFS per BICR in hormone receptor positive cohort between the two treatment groups using stratified log-rank test, with stratification factors from IXRS, at two-sided significance level of 0.05.

The distribution of PFS was to be estimated using the Kaplan-Meier (K-M) method for each treatment arm, and the results were to be presented graphically by treatment group.

The median PFS and the two-sided 95% confidence intervals (CIs) using Brookmeyer and Crowley method was to be provided for each treatment group. In addition, PFS rates at fixed time points (e.g., 3, 6, 9, 12 months) and the two-sided 95% CIs will be provided for each treatment group.

The hazard ratio of PFS and its two-sided 95% CI were estimated using stratified Cox proportional hazards regression model with treatment group as model factor and the stratification factors from IXRS as strata.

Table 22 Censoring rules for PFS

Case Scenario	Event/Censor (Event or Censoring Description)	Event or Censoring Date
No baseline evaluable tumor assessment	Censored (no baseline tumor assessment)	Date of randomization
No post-baseline tumor assessment	Censored (no post-baseline assessment)	Date of randomization
Early death (within 14 weeks of randomization) without baseline or postbaseline tumor assessment	Event (death)	Date of death
Radiographic disease progression or death without missing two or more consecutive tumor assessments immediately preceding the event	Event (progression or death)	Date of progressive disease assessment or date of death
Disease progression or death after missing ≥ 2 consecutive scheduled tumor assessments (i.e., more than 14 weeks)	Censor (event after missing 2 or more consecutive tumor assessments)	Date of last evaluable tumor assessment (prior to earliest of death/progression date and analysis cut-off date)
At least one post-baseline response assessment, subject with no death or objective documentation of radiographic disease progression (progression-free)	Censor (lost to follow-up; withdraw consent; ongoing without event; adequate tumor assessment no longer available*)	Date of last evaluable tumor assessment (prior to analysis cut-off date, NOT coded as "inevaluable")
Anti-cancer therapy started prior to disease progression, death or analysis cut-off date (**)	Censor (anti-cancer therapy)	Date of last evaluable tumor assessment prior to anti-cancer therapy (other than study drug)

* Censoring reason will be lost to follow-up if date of lost to follow-up from end of treatment page or post-treatment follow-up page is within 2 consecutive tumor assessments from last adequate tumor assessment; Censoring reason will be withdrew consent if date of withdraw of consent from study is within 2 consecutive tumor assessments from last adequate tumor assessment; Censoring reason will be ongoing without progression if cutoff date is within 2 consecutive tumor assessments from last adequate tumor assessment; Otherwise censoring reason will be adequate assessment no longer available.

** This censoring rule will be used for sensitivity analysis

Source SAP v 2.0, page 57/152

Supportive and Sensitivity Analyses

As a sensitivity analysis to assess the impact of stratification on primary efficacy analysis, the two treatment groups were to be compared using an unstratified log-rank test. The same censoring rules used for the primary efficacy analysis were to be applied.

The primary efficacy analyses were to be repeated for FAS and PPS if the PPS and the full analysis sets differed.

A stratified Cox regression model with strata collected through IXRS as stratification factor was to be fitted to evaluate the effect of other baseline demographic or disease characteristics on the estimated hazard ratio. This model included the following key prognostic factors as covariates: ECOG performance status (0, 1), lines of endocrine therapy received in the metastatic setting (0, 1, >=1), history CNS metastases (yes, no), and age (<65, ≥65 years old).

In addition to the above, the sensitivity analyses of the primary efficacy endpoint were to be performed to assess the impact of censoring rules used for the primary efficacy analysis. Sensitivity analyses included the following:

• Using the BICR-assessed PFS data on the hormone receptor positive cohort, and including PFS events whenever they occurred, i.e. not censoring for missing 2 consecutive tumor assessments

• Using the BICR PFS data on the hormone receptor positive cohort, but censoring for new anticancer therapy

• Backdating PFS analysis: repeat BICR PFS analysis not censoring for missing tumor assessment, but backdate PFS event time in the case that PFS event occurred after missing one or more tumor assessments. In such cases, the PFS event date would be considered to be 6 weeks after last evaluable tumor assessment occurring prior to progression/death.

Additional supportive analyses included:

• Number of subjects and number of events by treatment arm within each stratum to be presented along with hazard ratio obtained using unstratified cox regression model, provided enough events are observed within each stratum. No formal statistical comparison to be carried out within stratum.

If there is ≥10% discrepancy between strata constructed through the eCRF data and those obtained through IXRS, a sensitivity analysis may be performed where the stratum is based on the eCRF data.

If the number of BICR PFS events by the data cutoff date is more than 328 (3% over the target number of PFS events), a sensitivity analysis using the data up to the target 318 BICR PFS events was to be carried out following the primary analysis approach.

Sensitivity analyses due to COVID-19

Sensitivity analysis of primary analysis of PFS may have been performed if there was a considerable number of subjects who may have been impacted by COVID-19 and had delayed or missing tumor scan assessments by either excluding data from these subjects or not applying the censoring rule of missing 2 or more consecutive tumor assessments due to COVID-19 for PFS. No P-value was to be presented for these sensitivity analyses.

Key Secondary endpoint: OS

Overall survival was to be compared between the 2 treatment groups, using a stratified log-rank test stratified by the randomization stratification factors as recorded by IXRS, at 2-sided significance level adjusting for alpha spending, provided superiority in PFS per BICR is demonstrated in both hormone receptor positive cohort and FAS. The survival distribution of OS was to be estimated by Kaplan-Meier method and results will be presented graphically. The median survival time and the 2-sided 95% CI for the median were to be provided using Brookmeyer and Crowley method for each treatment group.

The treatment effect hazard ratio and its 95% CI were estimated, using stratified Cox proportional hazards regression model stratified by the randomization stratification factors as recorded by the IXRS.

Censoring rules for OS

If there was no death reported for a subject before the data cutoff for OS analysis, OS was to be censored at the last contact date at which the subject was known to be alive.

Supportive Analyses for OS

If the analysis of OS was significant, a Cox regression model stratified by the IXRS stratification factors was to fitted to evaluate the effect of the same prognostic factors as specified earlier for the Cox regression analysis for PFS.

Other secondary efficacy endpoint: Confirmed Objective Response Rate

ORR was summarized by treatment group along with the two-sided 95% CIs using the Clopper-Pearson method. The difference of ORR between the two treatment groups was summarized and the 95% CI calculated using continuity correction. The Cochran-Mantel-Haenszel test stratified by the randomization stratification factors per IXRS was used to compare ORR at two-sided significance level of 0.05.

Subjects with only non-measurable disease at baseline were included in the numerator only if a complete response was observed.

Interim Analyses and Data Monitoring

No formal interim analysis was planned for PFS.

Up to three analyses of OS were planned:

• First interim analysis at the time of the final analysis for PFS (provided PFS is significant in both hormone receptor positive cohort and FAS), at which point a total of 162 OS events (49% information fraction) in hormone receptor positive cohort are expected.

• If the first OS interim analysis was not significant, a second interim analysis for OS was planned when approximately 233 OS events (70% information fraction) in hormone receptor positive cohort had been documented.

• If the second OS interim analysis was not significant, a final analysis for OS after approximately 333 OS events in hormone receptor positive cohort had been documented.

OS was to be compared between the 2 treatment groups at either interim or final analysis, provided superiority in PFS was demonstrated for both the hormone receptor positive cohort and the FAS. A hierarchical testing procedure was adopted as described below.

A group sequential design, utilizing 3-look Lan-DeMets alpha spending function with O'Brien-Fleming type stop boundary was used to construct the efficacy stopping boundaries with an overall 2-sided significance level of 0.05. The trial allowed for the early stopping of the study for a superior OS, provided the log-rank test for PFS had demonstrated statistical significance in both hormone receptor positive cohort and FAS. The same interim efficacy stopping boundaries was used for OS hypotheses testing with hormone receptor positive cohort and FAS. If the study continues to final analysis, the efficacy stopping boundaries at the final OS analysis to control the 2-sided significance level of the repeated testing at 0.05 was to derived separately for hormone receptor positive cohort and FAS based on the actual number of OS events documented at the cut-off date, and the actual information fractions and the alpha already spent at the interim analyses. This was to ensure the overall significance level at 0.05 (2-sided) across the 2 OS hypotheses testing with hormone receptor positive cohort and FAS, and the repeated testing of the OS hypotheses at the interim and the final analyses,

provided the log-rank test for PFS had demonstrated statistical significance in both hormone receptor positive cohort and FAS.

It was recognized that the information fractions at the interim analyses may not be as planned. The stopping boundary was to be updated based on the actual information fraction at the interim analyses.

Multiple Comparisons/Multiplicity

The primary efficacy endpoint, and the key secondary efficacy endpoints were to be tested hierarchically to maintain the overall two-sided type-I error rate to 0.05 or less, in the order below:

1. PFS based on BICR in the hormone receptor positive cohort

2. PFS based on BICR in the FAS

3. OS in the hormone receptor positive cohort (up to 3 analyses)

4. OS in the FAS (up to 3 analyses)

The statistical testing for a key secondary endpoint was to be performed only when the analyses in the hierarchy above the current endpoint had demonstrated statistical significance.

Table 23 Changes to the SAP and to the planned analyses specified in protocol

Protocol Version	Approval Date	Salient Changes, if any*
1.0	Nov 11, 2020	NA
1.1	Oct 10, 2021	• Refine the safety analyses • Add summary for ORR and DoR for HR-negative cohort (exploratory objective, but no analyses were specified in SAP v1.0) • Provide algorithm for TPC duration of exposure • Specify algorithm for prior lines of chemotherapy and lines of endocrine therapy • Update PRO section • Add death date imputation rule • Refine the algorithm for time windows for ECOG and PRO • Clarify HR positive cohorts and HR negative cohort of FAS, is based on baseline HR status • Add censoring rules for PFS2

Source SAP v2.0 page 74/152

Four changes made to the analytic conventions after the finalization of SAP v2.0 on 04 Jan 2022 (before database lock date of 08 Feb 2022) were implemented without a SAP addendum: as summarized below.

1. Added subject disposition for HR-positive cohort and HR-negative cohort.

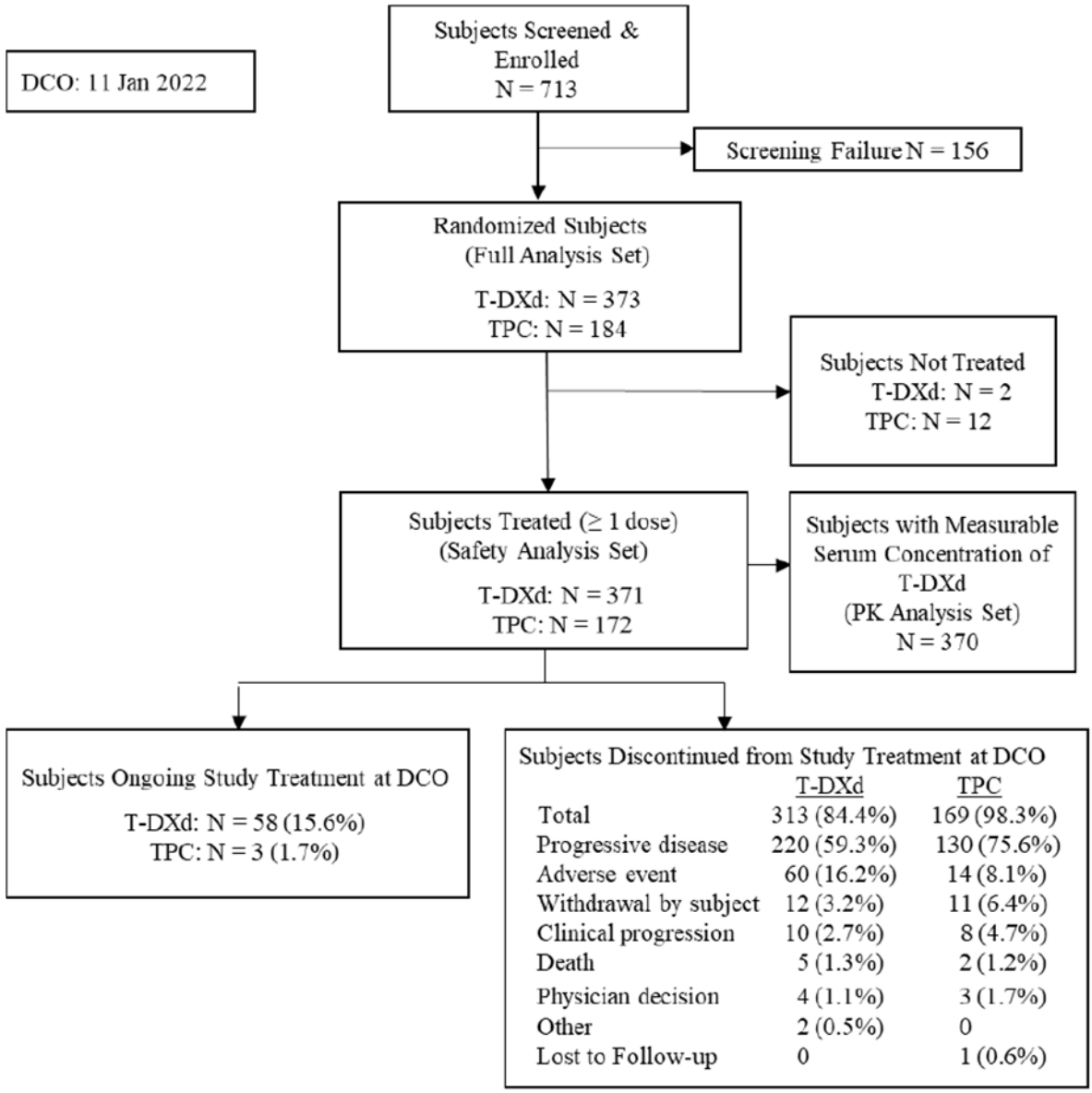
2. Added summary of major protocol deviation for HR-positive cohort.

3. PFS follow-up (time from the PFS end date to DCO in weeks) and OS follow-up (time from the OS end date to DCO in months) were to be summarized for total patients, instead of "by treatment arm".

4. Added subgroup analysis for selected TEAE and grouped terms.

Results

Figure 25 Participant flow in Study U303



DCO = data cut-off; N = number of subjects; PK = pharmacokinetic; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice
Data cut-off: 11 Jan 2022
Source: Table 14.1.1.1.1

Table 24 Main Reasons for Screen Failures in Study U303

Reason for Screen Failure	Number of Subjects
Subject did not satisfy inclusion/exclusion criteria[a]	135
Inclusion 3: pathologically documented breast cancer	26
Inclusion 6: have a recent tumour tissue sample after the most recent treatment regimen or agree to undergo biopsy prior to randomisation	19
Inclusion 8: ECOG PS 0 or 1	11

Reason for Screen Failure	Number of Subjects
Inclusion 10: adequate bone marrow function within 14 days before randomisation	10
Inclusion 12: adequate hepatic function within 14 days before randomisation	19
Exclusion 3: uncontrolled or significant cardiovascular disease	11
Exclusion 5: has spinal cord compression or clinically active CNS metastases	52
Other[b]	43
Physician decision	8
Withdrawal by subject	7
Other:	5
Study closed to enrolment before subject completed screening	1
Death	2
Subject admitted to hospice due to worsening condition	1
Screening for the impact of new crown pneumonia failed	1
Adverse event	1

CNS = central nervous system; EC = exclusion criteria; ECOG PS = Eastern Cooperative Group Performance Score; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus IC = inclusion criteria.
a Refer to section 4.1 and Section 4.2 of the protocol for full details of inclusion and exclusion criteria, respectively. Subjects may be counted more than once (ie, Did not meet multiple exclusion and/or inclusion criteria).
b IC 1 (n=2), IC 2 (n=1), IC 4 (n=4), IC 5 (n=2), IC 7 (n=9), IC 9 (n=4), IC 11 (n=2), EC 4 (n=3), EC 6 (n=1), EC 7 (n=1), EC 9 (n=1), EC 10 (n=1), EC 12 (n=3), EC 14 (n=1), EC 15 (n=4), EC 16 (n=1), EC 20 (n=5), EC 21 (n=2)
Source: Module 5.3.5.1 DS-8201-A-U303 CSR Listing 16.2.1.1 and 16.2.2.1.

Recruitment

From 21 Dec 2018 to the DCO of 11 Jan 2022, 557 patients were enrolled from study sites in the United States (27), Japan (18), France (16), China (15), Italy (13), Spain (12), Greece (8), Portugal (8), Republic of Korea (8), Israel (6), Switzerland (6), Austria (4), Belgium (4), Russia (3), Sweden (3), Taiwan (3), United Kingdom (3), Canada (2), and Hungary (2). Median duration of follow (study duration) as of DCO: 16.1 months in the T-DXd arm and 13.5 months in the TPC arm.

Conduct of the study

After the initial release (Version 1.0, 23 Aug 2018), the study protocol was amended 4 times. Key changes in each amendment were as follows:

Amendment 1 (Version 2.0) - 23 Nov 2018, Before the First Subject Signed an ICF

The primary changes made by Amendment 1 were as follows:

• Added information on T-DXd dosing (starting dose, infusion time for initial dose, and dose modifications)

• Updated text regarding Screening to be within 14 days of randomization

• Clarified prohibited medications and treatments for T-DXd and TPC

• Updated CBR to include at least 6 months' SD

• Clarified inclusion/exclusion criteria

• Added HEOR questionnaires at Cycle 2 Day 1

• Updated AESI wording to reflect the latest T-DXd safety profile

• Clarified the EOT visit timing and updated the 40-day Follow-up and Long-term/Survival Follow-up visits to allow for a window of ±7 days.

Amendment 2 (Protocol Version 3.0) - 24 Apr 2019, During the Course of the Study

The primary changes made by Amendment 2 were as follows:

• Clarified tissue biopsy text regarding archival and fresh sample requirements

• Increased the number of study centers to approximately 255 sites

• Clarified the number of hormone receptor-positive and hormone receptor-negative subjects with and without prior therapy with a CDK4/6 inhibitor to be enrolled in the study

• Added statement that the investigator should follow the locally approved label for the individual treatment options for subjects randomized to the TPC arm

• Updated the inclusion criterion related to hormone receptor-positive subjects

• Updated the criterion for recalculating a subject's dose based on a change in body weight

• Updated the inclusion criterion related to male and female subjects of reproductive/childbearing potential

• Amended the ILD monitoring/management instructions.

Amendment 3 (Protocol Version 4.0) - 23 Apr 2020, During the Course of the Study

The primary changes made by Amendment 3 were the clarification that tumor assessments were to be conducted every 6 weeks from randomization and clarification regarding the TPC dose regimens.

Amendment 4 (Version 5.0) - 12 Oct 2020, During the Course of the Study

The primary changes made by Amendment 4 were as follows:

• Added new timepoints for OS analyses. The study was originally designed to perform OS analysis at the same time as the final PFS analysis. This early analysis would not have provided adequate follow-up and statistical power to detect a statistically significant difference in OS. Therefore, the protocol was amended to include OS as a key secondary endpoint with adequate follow-up to provide statistical power to detect meaningful improvement in OS between the 2 treatment arms.

• Added PFS2 as an exploratory objective and endpoint.

• To evaluate the impact of the global pandemic caused by COVID-19, added an analysis to identify subjects affected by COVID-19, and updated the analysis plan to identify the impact of COVID-19 on study conduct, efficacy, and safety.

Contingency Measures Implemented to the Conduct of the Study as a Result of the COVID-19 Pandemic

Changes in Collection of Data

Because of site closures and travel restrictions, 4 subjects were transferred to another existing study site or satellite site that was different from the site at which the subject originally enrolled. In such cases, the transfer was initiated by the investigator. Study activities, including drug dispensing and

dosing for each subject, were performed per protocol at the transfer site. Modification of study procedures as a result of the COVID-19 pandemic was not necessary.

Changes in Monitoring/Oversight

Risk-based/remote monitoring activities were initiated at the beginning of the study. During the COVID-19 pandemic, based on site and/or country policy, on-site monitoring visits were not conducted if sites could not accept visitors. During this time, on-site monitoring visits were replaced with remote visits/more frequent remote monitoring and telephone contacts were made where permissible by local regulations. Monitors used virtual monitoring visits to reinforce AE reporting and timely data entry.

Targeted source data verification was the primary task during these on-site visits, focusing on primary efficacy and key safety data points. At the time of the primary analysis database lock, targeted source data verification could not be completed for some sites due to site access limitations as a result of the COVID-19 pandemic. The risk to data quality was considered minimal, as alternative methods of risk-based monitoring/central monitoring of data review and data cleaning activities were conducted over the course of the study.

Table 25 Major Protocol Deviations in the Hormone Receptor-positive Cohort and the Full Analysis Set

Deviation Category	Number (%) of Subjects			
	Hormone Receptor-positive Cohort		Full Analysis Set	
	T-DXd (N = 331)	TPC (N = 163)	T-DXd (N = 373)	TPC (N = 184)
Subjects with any major protocol deviation	36 (10.9)	30 (18.4)	42 (11.3)	35 (19.0)
Related to COVID-19	3 (0.9)	0	3 (0.8)	0
Serious adverse event reporting	8 (2.4)	6 (3.7)	9 (2.4)	7 (3.8)
Informed consent	8 (2.4)	2 (1.2)	8 (2.1)	2 (1.1)
Eligibility criteria	8 (2.4)	10 (6.1)	11 (2.9)	10 (5.4)
Study procedures	8 (2.4)	1 (0.6)	8 (2.1)	3 (1.6)
Related to COVID-19	2 (0.6)	0	2 (0.5)	0
Investigational product	6 (1.8)	12 (7.4)	7 (1.9)	13 (7.1)
Related to COVID-19	1 (0.3)	0	1 (0.3)	0
Concomitant and prohibited medications or non-drug therapy	4 (1.2)	0	4 (1.1)	0
Laboratory assessment criteria	1 (0.3)	2 (1.2)	3 (0.8)	3 (1.6)

COVID-19 = coronavirus disease 2019; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice
For each category and deviation, subjects who experienced multiple events in that category or deviation were counted only once.
Percentages were calculated using the number of subjects in the column heading as the denominator.
Data cut-off: 11 Jan 2022
Source: Table 14.1.1.2.1, 14.1.1.2.2

Baseline data

Table 26 Demographic and Baseline Disease Characteristics in the Hormone Receptor-positive Cohort and the Full Analysis Set (Study U303)

Parameter	Hormone Receptor-positive Cohort		Full Analysis Set	
	T-DXd (N = 331)	TPC (N = 163)	T-DXd (N = 373)	TPC (N = 184)
Age (years)				
Mean (Std Dev)	56.3 (10.57)	56.3 (11.39)	56.5 (10.58)	56.5 (11.51)
Median	56.8	55.7	57.5	55.9
Min, Max	31.5, 80.2	28.4, 80.0	31.5, 80.2	28.4, 80.5
Age group (years), n (%)				
<65	260 (78.5)	120 (73.6)	290 (77.7)	136 (73.9)
≥65	71 (21.5)	43 (26.4)	83 (22.3)	48 (26.1)
<75	320 (96.7)	157 (96.3)	359 (96.2)	175 (95.1)
≥75	11 (3.3)	6 (3.7)	14 (3.8)	9 (4.9)
Sex, n (%)				
Female	329 (99.4)	163 (100.0)	371 (99.5)	184 (100.0)
Male	2 (0.6)	0	2 (0.5)	0
Region,[a] n (%)				
Asia	128 (38.7)	60 (36.8)	147 (39.4)	66 (35.9)
North America	54 (16.3)	30 (18.4)	60 (16.1)	33 (17.9)
Europe + Israel	149 (45.0)	73 (44.8)	166 (44.5)	85 (46.2)
Race, n (%)				
White	156 (47.1)	78 (47.9)	176 (47.2)	91 (49.5)
Black or African American	7 (2.1)	2 (1.2)	7 (1.9)	3 (1.6)
Asian	131 (39.6)	66 (40.5)	151 (40.5)	72 (39.1)
American Indian or Alaska Native	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	1 (0.3)	0
Other	37 (11.2)	16 (9.8)	38 (10.2)	17 (9.2)
Missing	0	1 (0.6)	0	1 (0.5)
Stratification factors per IXRS				
HER2 status, n (%)				
IHC 1+	193 (58.3)	95 (58.3)	215 (57.6)	106 (57.6)
IHC 2+/ISH-negative	138 (41.7)	68 (41.7)	158 (42.4)	78 (42.4)
Number of prior lines of chemotherapy, n (%)				
1	197 (59.5)	96 (58.9)	212 (56.8)	103 (56.0)

Parameter	Hormone Receptor-positive Cohort		Full Analysis Set	
	T-DXd (N = 331)	TPC (N = 163)	T-DXd (N = 373)	TPC (N = 184)
2	134 (40.5)	67 (41.1)	161 (43.2)	81 (44.0)
Hormone receptor/CDK status, n (%)				
Hormone receptor-positive with prior CDK4/6 inhibitor	233 (70.4)	115 (70.6)	233 (62.5)	115 (62.5)
Hormone receptor-positive without prior CDK4/6 inhibitor	98 (29.6)	48 (29.4)	98 (26.3)	48 (26.1)
Hormone receptor-negative	-	-	42 (11.3)	21 (11.4)
Subgroups				
Lines of prior ET in any setting, n (%)				
0	1 (0.3)	3 (1.8)	26 (7.0)	19 (10.3)
1	65 (19.6)	34 (20.9)	74 (19.8)	35 (19.0)
2	112 (33.8)	46 (28.2)	117 (31.4)	49 (26.6)
≥3	153 (46.2)	80 (49.1)	156 (41.8)	81 (44.0)
Lines of prior ET in the metastatic setting - derived, n (%)				
0	28 (8.5)	17 (10.4)	60 (16.1)	34 (18.5)
1	105 (31.7)	49 (30.1)	108 (29.0)	51 (27.7)
2	110 (33.2)	53 (32.5)	115 (30.8)	54 (29.3)
≥3	88 (26.6)	44 (27.0)	90 (24.1)	45 (24.5)
Reported history of CNS metastases at baseline, n (%)				
Yes	30 (9.1)	13 (8.0)	37 (9.9)	15 (8.2)
No	301 (90.9)	150 (92.0)	336 (90.1)	169 (91.8)
Renal function at baseline,[b] n (%)				
Within normal range	185 (55.9)	79 (48.5)	202 (54.2)	87 (47.3)
Mild impairment	104 (31.4)	61 (37.4)	123 (33.0)	69 (37.5)
Moderate impairment	37 (11.2)	18 (11.0)	41 (11.0)	23 (12.5)
Severe impairment	0	0	1 (0.3)	0
End-stage renal disease	0	0	0	0
Missing	5 (1.5)	5 (3.1)	6 (1.6)	5 (2.7)
Hepatic function at baseline,[b] n (%)				
Normal hepatic function	149 (45.0)	83 (50.9)	170 (45.6)	98 (53.3)
Mild impairment	176 (53.2)	78 (47.9)	195 (52.3)	84 (45.7)
Moderate impairment	2 (0.6)	0	3 (0.8)	0
Severe impairment	0	0	0	0
Missing	4 (1.2)	2 (1.2)	5 (1.3)	2 (1.1)
Baseline visceral disease,[c] n (%)				

Parameter	Hormone Receptor-positive Cohort		Full Analysis Set	
	T-DXd (N = 331)	TPC (N = 163)	T-DXd (N = 373)	TPC (N = 184)
Yes	298 (90.0)	146 (89.6)	332 (89.0)	157 (85.3)
No	33 (10.0)	17 (10.4)	41 (11.0)	27 (14.7)
Baseline CNS metastases, n (%)				
Yes	18 (5.4)	7 (4.3)	24 (6.4)	8 (4.3)
No	313 (94.6)	156 (95.7)	349 (93.6)	176 (95.7)
ECOG PS, n (%)				
0	187 (56.5)	95 (58.3)	200 (53.6)	105 (57.1)
1	144 (43.5)	68 (41.7)	173 (46.4)	79 (42.9)
2	0	0	0	0
>2	0	0	0	0

CDK = cyclin-dependent kinase; CNS = central nervous system; CSR = clinical study report; ECOG PS = Eastern Cooperative Oncology Group performance status; ET = endocrine therapy; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; IXRS = interactive web/voice response system; ISH = in situ hybridization; Max = maximum; Min = minimum; SAP = statistical analysis plan; Std Dev = standard deviation; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice

[a] Asia = China, Japan, Republic of Korea, Taiwan; Europe + Israel = Austria, Belgium, France, Greece, Hungary, Israel, Italy, Portugal, Russia, Spain, Sweden, Switzerland, United Kingdom; North America = US, Canada. In this study, Israel was combined with Europe geographic subgroup.

[b] Definitions for hepatic and renal function at baseline are specified in DS8201-A-U303 CSR Appendix 16.1.9.1 SAP Version 2.0 Section 7.2.1.5.

[c] Visceral disease is defined in SAP Appendix 11.3 see (DS8201-A-U303 CSR Appendix 16.1.9.1 SAP Version 2.0 Section 7.2.1.5).

Source: DS8201-A-U303 CSR Tables 14.1.2.1.1.1, 14.1.2.1.4.1, 14.1.3.2.1, and 14.1.3.2.2

Table 27 Baseline Disease Characteristics in the Hormone Receptor-positive Cohort and the Full Analysis Set (Study U303)

Parameter	Number (%) of Subjects			
	Hormone Receptor-positive Cohort		Full Analysis Set	
	T-DXd (N = 331)	TPC (N = 163)	T-DXd (N = 373)	TPC (N = 184)
Stratification factor: HER2 IHC status per IXRS				
HER2 IHC 1+	193 (58.3)	95 (58.3)	215 (57.6)	106 (57.6)
HER2 IHC 2+/ISH negative	138 (41.7)	68 (41.7)	158 (42.4)	78 (42.4)
Stratification factor: Number of prior lines of chemotherapy per IXRS				
1	197 (59.5)	96 (58.9)	212 (56.8)	103 (56.0)
2	134 (40.5)	67 (41.1)	161 (43.2)	81 (44.0)
Stratification factor: Hormone receptor/CDK status per IXRS				
Hormone receptor-positive with prior CDK4/6	233 (70.4)	115 (70.6)	233 (62.5)	115 (62.5)
Hormone receptor-positive without prior CDK4/6	98 (29.6)	48 (29.4)	98 (26.3)	48 (26.1)
Hormone receptor-negative	0	0	42 (11.3)	21 (11.4)
Hormone receptor – derived[a]				
Positive	328 (99.1)	162 (99.4)	333 (89.3)	166 (90.2)
Negative	3 (0.9)	1 (0.6)	40 (10.7)	18 (9.8)
Reported history of CNS metastases	30 (9.1)	13 (8.0)	37 (9.9)	15 (8.2)
Baseline CNS metastases	18 (5.4)	7 (4.3)	24 (6.4)	8 (4.3)
Renal function[b]				
Within normal range	185 (55.9)	79 (48.5)	202 (54.2)	87 (47.3)
Mild impairment	104 (31.4)	61 (37.4)	123 (33.0)	69 (37.5)
Moderate impairment	37 (11.2)	18 (11.0)	41 (11.0)	23 (12.5)
Severe impairment	0	0	1 (0.3)[c]	0
Missing[d]	5 (1.5)	5 (3.1)	6 (1.6)	5 (2.7)
Hepatic function[e]				
Within normal range	149 (45.0)	83 (50.9)	170 (45.6)	98 (53.3)
Mild impairment	176 (53.2)	78 (47.9)	195 (52.3)	84 (45.7)
Moderate impairment	2 (0.6)	0	3 (0.8)	0
Missing[d]	4 (1.2)	2 (1.2)	5 (1.3)	2 (1.1)
Presence of baseline lung metastases	98 (29.6)	58 (35.6)	120 (32.2)	63 (34.2)
Presence of baseline liver metastases	247 (74.6)	116 (71.2)	266 (71.3)	123 (66.8)
Presence of baseline visceral disease[f]	298 (90.0)	146 (89.6)	332 (89.0)	157 (85.3)
ECOG performance status				
0	187 (56.5)	95 (58.3)	200 (53.6)	105 (57.1)
1	144 (43.5)	68 (41.7)	173 (46.4)	79 (42.9)

AST = aspartate aminotransferase; CDK = cyclin-dependent kinase; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; EDC = electronic data capture; HER2 = human epidermal growth factor receptor 2; IHC = immunochemistry; ISH = in situ hybridization; IXRS = interactive web/voice response system; T-DXd = trastuzumab deruxtecan; TBL = total bilirubin; TPC = treatment of physician's choice; ULN = upper limit of normal

Percentages were calculated using the number of subjects in the column heading as the denominator.

[a] Hormone receptor (based on factors from EDC):
Positive = estrogen receptors negative and progesterone receptors positive; estrogen receptors positive and progesterone receptors negative; estrogen receptors positive and progesterone receptors positive; estrogen receptors positive and progesterone receptors indeterminate; estrogen receptors indeterminate and progesterone receptors positive
Negative = estrogen receptors negative and progesterone receptors negative
Indeterminate = estrogen receptors negative and progesterone receptors indeterminate; estrogen receptors indeterminate and progesterone receptors negative; estrogen receptors indeterminate and progesterone-receptors indeterminate
Data presented here are based on EDC. Data from IXRS could not be modified. The derived data in EDC captured the correct status. Further details are provided in Table 14.1.2.2.

[b] Renal function:
- normal function = creatinine clearance ≥90 mL/min
- mild impairment = creatinine clearance ≥60, <90 mL/min
- moderate impairment = creatinine clearance ≥30, <60 mL/min
- severe impairment = creatinine clearance ≥15, <30 mL/min
- end stage renal disease = creatinine clearance <15 mL/min

[c] A protocol deviation was captured for this subject. The site mistakenly used the male parameters to calculate the creatinine clearance and the investigator overlooked this while reviewing eligibility criteria.

[d] Sites switched from using a central laboratory to local laboratory on 17 Apr 2019 (ie, after enrollment had started). Sites were instructed to obtain local laboratory data (including baseline) for all subjects. There were some sites that collected central baseline data and the data were not captured into the EDC; as a result, the central data appeared as missing data for these subjects. For all subjects denoted as "missing" except the 3 subjects detailed below, the baseline data are captured in the central laboratory database and the subject's values were within normal range. For the other 3 subjects, 1 subject was randomized and never treated and the other 2 subjects were confirmed to have met the criteria via site query; no protocol deviations were captured for these 3 subjects.

[e] Hepatic function:
- normal function = TBL ≤ULN and (AST ≤ULN) without Gilbert's syndrome, TBL ≤3.0 × ULN and (AST ULN) with Gilbert's syndrome
- mild impairment = TBL >ULN, ≤1.5 × ULN and any AST without Gilbert's syndrome, TBL >ULN, ≤3.0 × ULN and (AST >ULN) with Gilbert's syndrome, TBL ≤ULN and (AST >ULN) regardless of Gilbert's syndrome
- moderate impairment = TBL >1.5 × ULN, ≤3.0 × ULN and any AST without Gilbert's syndrome
- severe impairment = TBL >3.0 × ULN and any AST regardless of Gilbert's syndrome.

[f] Baseline visceral disease was determined with any target or non-target tumor in the lesion locations specified in Section 7.2.1.5 of the Statistical Analysis Plan (Appendix 16.1.9)

Data cut-off: 11 Jan 2022

Source: Tables 14.1.2.1.1.1, 14.1.2.1.4.1

In most patients, HER2 status was determined based on archival tissue (about 86%) and about 14% had a fresh biopsy taken.

Table 28 Breast Cancer History in the Hormone Receptor-positive Cohort and the Full Analysis Set

Parameter	Number (%) of Subjects			
	Hormone Receptor-positive Cohort		Full Analysis Set	
	T-DXd (N = 331)	TPC (N = 163)	T-DXd (N = 373)	TPC (N = 184)
Time from initial histological diagnosis to study drug (months)				
n	329	152	371	172
Mean (Std Dev)	103.8 (79.62)	95.4 (81.70)	100.5 (78.36)	88.7 (79.44)
Median	80.1	71.4	75.4	64.0
Minimum, maximum	5, 445	4, 358	5, 445	4, 358
Histology				
Adenocarcinoma	217 (65.6)	107 (65.6)	243 (65.1)	123 (66.8)
Inflammatory	4 (1.2)	1 (0.6)	5 (1.3)	1 (0.5)
Other	110 (33.2)	55 (33.7)	125 (33.5)	60 (32.6)
Grade				
Well differentiated	20 (6.0)	9 (5.5)	25 (6.7)	11 (6.0)
Moderately differentiated	81 (24.5)	48 (29.4)	90 (24.1)	52 (28.3)
Poorly differentiated	83 (25.1)	35 (21.5)	99 (26.5)	42 (22.8)
Undifferentiated	1 (0.3)	1 (0.6)	1 (0.3)	1 (0.5)
Unknown	146 (44.1)	70 (42.9)	158 (42.4)	78 (42.4)
HER2 expression (IHC) local [a]				
0	2 (0.6)	0	2 (0.5)	0
1+	171 (51.7)	93 (57.1)	194 (52.0)	102 (55.4)
2+	155 (46.8)	70 (42.9)	174 (46.6)	81 (44.0)
Not evaluable	1 (0.3)	0	1 (0.3)	0
Not examined	2 (0.6)	0	2 (0.5)	1 (0.5)
HER2 gene amplification (ISH) local				
Amplified (positive)	0	0	0	0
Equivocal	13 (3.9)	7 (4.3)	16 (4.3)	7 (3.8)
Non-amplified (negative)	173 (52.3)	84 (51.5)	196 (52.5)	97 (52.7)
Examined but not evaluable	9 (2.7)	3 (1.8)	9 (2.4)	3 (1.6)
Missing	136 (41.1)	69 (42.3)	152 (40.8)	77 (41.8)
BRCA1				
Positive (mutated)	3 (0.9)	2 (1.2)	3 (0.8)	2 (1.1)
Negative (wild type)	93 (28.1)	56 (34.4)	112 (30.0)	65 (35.3)
Indeterminate	3 (0.9)	1 (0.6)	3 (0.8)	1 (0.5)
Invalid	0	1 (0.6)	0	1 (0.5)
Missing	232 (70.1)	103 (63.2)	255 (68.4)	115 (62.5)
BRCA2				
Positive (mutated)	11 (3.3)	8 (4.9)	15 (4.0)	8 (4.3)
Negative (wild type)	87 (26.3)	50 (30.7)	103 (27.6)	59 (32.1)
Indeterminate	3 (0.9)	2 (1.2)	3 (0.8)	2 (1.1)
Invalid	0	1 (0.6)	0	1 (0.5)
Missing	230 (69.5)	102 (62.6)	252 (67.6)	114 (62.0)

BRCA1 = breast cancer gene 1; BRCA2 = breast cancer gene 2; HER2 = human epidermal growth factor receptor 2; IHC = immunochemistry; ISH = in situ hybridization; Std Dev = standard deviation; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice

Percentages were calculated using the number of subjects in the column heading as the denominator.

[a] From most recent tissue sample

Data cut-off: 11 Jan 2022

Source: Tables 14.1.3.1.1, 14.1.3.1.2

Prior anticancer therapies

Table 29 Prior Lines of Breast Cancer Systemic Therapy in the Hormone Receptor positive Cohort and the Full Analysis Set

Parameter	Number (%) of Subjects			
	Hormone Receptor-positive Cohort		Full Analysis Set	
	T-DXd (N = 331)	TPC (N = 163)	T-DXd (N = 373)	TPC (N = 184)
Lines of prior systemic therapy in any setting				
1	2 (0.6)	3 (1.8)	5 (1.3)	4 (2.2)
2	37 (11.2)	24 (14.7)	48 (12.9)	33 (17.9)
≥3	292 (88.2)	136 (83.4)	320 (85.8)	147 (79.9)
n	331	163	373	184
Mean (Std Dev)	4.3 (1.70)	4.4 (1.97)	4.2 (1.71)	4.2 (1.95)
Median	4.0	4.0	4.0	4.0
Minimum, Maximum	1, 13	1, 12	1, 13	1, 12
Lines of prior systemic therapy in metastatic setting - derived				
1	23 (6.9)	14 (8.6)	39 (10.5)	19 (10.3)
2	85 (25.7)	41 (25.2)	100 (26.8)	53 (28.8)
≥3	223 (67.4)	108 (66.3)	234 (62.7)	112 (60.9)
n	331	163	373	184
Mean (Std Dev)	3.3 (1.49)	3.3 (1.45)	3.2 (1.52)	3.1 (1.45)
Median	3.0	3.0	3.0	3.0
Minimum, Maximum	1, 9	1, 8	1, 9	1, 8

Lines of prior endocrine therapy				
0	1 (0.3)	3 (1.8)	26 (7.0)	19 (10.3)
1	65 (19.6)	34 (20.9)	74 (19.8)	35 (19.0)
2	112 (33.8)	46 (28.2)	117 (31.4)	49 (26.6)
≥3	153 (46.2)	80 (49.1)	156 (41.8)	81 (44.0)
n	331	163	373	184
Mean (Std Dev)	2.6 (1.26)	2.6 (1.37)	2.4 (1.37)	2.3 (1.48)
Median	2.0	2.0	2.0	2.0
Minimum, Maximum	0, 9	0, 8	0, 9	0, 8
Lines of prior endocrine therapy in metastatic setting - derived				
0	28 (8.5)	17 (10.4)	60 (16.1)	34 (18.5)
1	105 (31.7)	49 (30.1)	108 (29.0)	51 (27.7)
2	110 (33.2)	53 (32.5)	115 (30.8)	54 (29.3)
≥3	88 (26.6)	44 (27.0)	90 (24.1)	45 (24.5)
n	331	163	373	184
Mean (Std Dev)	1.9 (1.20)	1.9 (1.17)	1.8 (1.27)	1.7 (1.23)
Median	2.0	2.0	2.0	2.0
Minimum, Maximum	0, 7	0, 6	0, 7	0, 6
Lines of prior chemotherapy				
0	0	1 (0.6) [a]	0	1 (0.5) [a]
1	89 (26.9)	49 (30.1)	93 (24.9)	52 (28.3)
2	155 (46.8)	61 (37.4)	176 (47.2)	71 (38.6)
≥3	87 (26.3)	52 (31.9)	104 (27.9)	60 (32.6)
n	331	163	373	184
Mean (Std Dev)	2.0 (0.81)	2.1 (0.93)	2.1 (0.81)	2.1 (0.95)
Median	2.0	2.0	2.0	2.0
Minimum, Maximum	1, 5	0, 5	1, 5	0, 5
Lines of prior chemotherapy in metastatic setting-derived [b]				
0	1 (0.3)	1 (0.6)	1 (0.3)	1 (0.5)

1	203 (61.3)	93 (57.1)	221 (59.2)	100 (54.3)
2	124 (37.5)	69 (42.3)	145 (38.9)	83 (45.1)
≥3	3 (0.9)	0	6 (1.6)	0
n	331	163	373	184
Mean (Std Dev)	1.4 (0.51)	1.4 (0.51)	1.4 (0.53)	1.4 (0.51)
Median	1.0	1.0	1.0	1.0
Minimum, Maximum	0, 3	0, 2	0, 3	0, 2
Intent of any prior breast cancer therapy [c]				
Metastatic	330 (99.7)	162 (99.4)	371 (99.5)	182 (98.9)
Adjuvant	212 (64.0)	99 (60.7)	229 (61.4)	109 (59.2)
Neo-adjuvant	61 (18.4)	38 (23.3)	75 (20.1)	45 (24.5)
Maintenance	23 (6.9)	10 (6.1)	24 (6.4)	11 (6.0)
Locally advanced	11 (3.3)	4 (2.5)	13 (3.5)	5 (2.7)
Preventive	2 (0.6)	1 (0.6)	2 (0.5)	2 (1.1)
Other	2 (0.6)	2 (1.2)	2 (0.5)	2 (1.1)

Std Dev = standard deviation; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice
Percentages were calculated using the number of subjects in the column heading as the denominator.
Results are presented in descending order of subjects within the T-DXd arm of Study U303 within the hormone receptor-positive cohort.
[a] A protocol deviation was captured for this subject.
[b] If recurrence occured within 6 months of (neo)adjuvant chemotherapy, (neo)adjuvant therapy was counted as 1 line of chemotherapy in the advanced disease setting. Subjects with 0 and 3 prior lines of chemotherapy represent protocol deviations.
[c] Subjects may have been treated with more than 1 type of therapy.
Data cut-off: 11 Jan 2022
Source: Tables 14.1.3.2.1, 14.1.3.2.2

Table 30 Most Common Prior Breast Cancer Systemic Therapy Administered in the Hormone Receptor-positive Cohort and the Full Analysis Set

Parameter	Number (%) of Subjects			
	Hormone Receptor-positive Cohort		Full Analysis Set	
	T-DXd (N = 331)	TPC (N = 163)	T-DXd (N = 373)	TPC (N = 184)
Any prior systemic cancer therapy [a]				
Targeted Therapy	259 (78.2)	132 (81.0)	279 (74.8)	140 (76.1)
CDK4/6 inhibitor	233 (70.4)	115 (70.6)	239 (64.1)	119 (64.7)
Palbociclib	197 (59.5)	100 (61.3)	203 (54.4)	104 (56.5)
Abemaciclib	29 (8.8)	10 (6.1)	30 (8.0)	10 (5.4)
Ribociclib	16 (4.8)	13 (8.0)	16 (4.3)	13 (7.1)
Investigational antineoplastic drugs	3 (0.9)	2 (1.2)	3 (0.8)	2 (1.1)
Ribociclib succinate	1 (0.3)	0	1 (0.3)	0
Immunotherapy	10 (3.0)	8 (4.9)	20 (5.4)	12 (6.5)
Pembrolizumab	3 (0.9)	1 (0.6)	3 (0.8)	2 (1.1)
Durvalumab	3 (0.9)	0	3 (0.8)	0
Atezolizumab	2 (0.6)	2 (1.2)	12 (3.2)	5 (2.7)
Avelumab	1 (0.3)	1 (0.6)	1 (0.3)	1 (0.5)
Durvalumab; tremelimumab	1 (0.3)	0	1 (0.3)	0
Others	128 (38.7)	70 (42.9)	140 (37.5)	76 (41.3)
Everolimus	79 (23.9)	44 (27.0)	84 (22.5)	45 (24.5)
Bevacizumab	29 (8.8)	16 (9.8)	31 (8.3)	19 (10.3)
Alpelisib	11 (3.3)	8 (4.9)	12 (3.2)	8 (4.3)
Talazoparib	5 (1.5)	3 (1.8)	5 (1.3)	3 (1.6)
Olaparib	3 (0.9)	2 (1.2)	5 (1.3)	3 (1.6)
Endocrine therapy	330 (99.7)	160 (98.2)	347 (93.0)	165 (89.7)
Letrozole	212 (64.0)	108 (66.3)	222 (59.5)	113 (61.4)
Fulvestrant	211 (63.7)	107 (65.6)	217 (58.2)	110 (59.8)
Tamoxifen	160 (48.3)	81 (49.7)	166 (44.5)	82 (44.6)
Exemestane	133 (40.2)	64 (39.3)	138 (37.0)	65 (35.3)
Anastrozole	103 (31.1)	46 (28.2)	106 (28.4)	46 (25.0)
Chemotherapy	331 (100.0)	162 (99.4)	373 (100.0)	183 (99.5)

Cyclophosphamide	182 (55.0)	85 (52.1)	207 (55.5)	93 (50.5)
Capecitabine	177 (53.5)	83 (50.9)	191 (51.2)	95 (51.6)
Paclitaxel	161 (48.6)	82 (50.3)	187 (50.1)	93 (50.5)
Docetaxel	109 (32.9)	62 (38.0)	126 (33.8)	68 (37.0)
Epirubicin	68 (20.5)	38 (23.3)	81 (21.7)	42 (22.8)
Supportive Therapy	79 (23.9)	37 (22.7)	85 (22.8)	39 (21.2)
Goserelin acetate	32 (9.7)	13 (8.0)	35 (9.4)	13 (7.1)
Leuprorelin acetate	19 (5.7)	8 (4.9)	21 (5.6)	9 (4.9)
Goserelin	18 (5.4)	8 (4.9)	18 (4.8)	8 (4.3)
Leuprorelin	4 (1.2)	1 (0.6)	4 (1.1)	1 (0.5)
Triptorelin	4 (1.2)	0	4 (1.1)	0
Other	8 (2.4)	3 (1.8)	8 (2.1)	4 (2.2)
Investigational antineoplastic drugs	6 (1.8)	1 (0.6)	6 (1.6)	1 (0.5)
Placebo	1 (0.3)	1 (0.6)	1 (0.3)	1 (0.5)
Ipatasertib	1 (0.3)	0	1 (0.3)	1 (0.5)
Investigational drug	0	1 (0.6)	0	1 (0.5)

CDK = cyclin-dependent kinase; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice
Percentages were calculated using the number of subjects in the column heading as the denominator.
[a] Results were presented in descending order of subjects within the T-DXd arm of Study U303 within the hormone receptor-positive cohort.
Data cut-off: 11 Jan 2022
Source: Tables 14.1.3.2.1, 14.1.3.2.2

Table 31 Proportion of anthracycline pretreated subjects HR+ and FAS

	HR+		FAS	
	T-DXd (N=331)	**TPC (N=163)**	**T-DXd (N=373)**	**TPC (N=184)**
Prior anthracyclines use[a,b]	210 (63.4)	102 (62.6)	239 (64.1)	113 (61.4)
Adjuvant/neoadjuvant[c]	155 (46.8)	72 (44.2)	178 (47.7)	80 (43.5)
Locally advanced/metastatic[d]	63 (19.0)	34 (20.9)	71 (19.0)	37 (20.1)

FAS = full analysis set; HR+ = hormone receptor positive; IXRS = Interactive Web/Voice Response System; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice.
[a] A subject may receive multiple therapies intended for different purposes.
[b] Prior anthracyclines is defined as prior anticancer therapy of 'anthracyclines', 'doxorubicin', 'epirubicin', 'daunorubicin', or 'idarubicin' in CMDECOD and CMTRT in ADCM.
[c] Adjuvant/neoadjuvant: subject with prior anthracycline therapy intended for adjuvant and/or neoadjuvant.
[d] Locally advanced/metastatic: subject with prior anthracycline therapy intended for locally advanced and/or metastatic.
HR+ status based on IXRS.

Numbers analysed

Table 32 Data sets analysed (Study U303)

Analysis Set	Number (%) of Subjects		
	T-DXd (N = 373)	TPC (N = 184)	Total (N = 557)
Full Analysis Set	373 (100.0)	184 (100.0)	557 (100.0)
Safety Analysis Set	371 (99.5)	172 (93.5)	543 (97.5)
Per-protocol Analysis Set	361 (96.8)	164 (89.1)	525 (94.3)
Pharmacokinetic Analysis Set	370 (99.2)	0	370 (66.4)

T-DXd=trastuzumab deruxtecan; TPC = treatment of physician's choice
Data cut-off: 11 Jan 2022
Source: Table 14.1.1.1.1

Outcomes and estimation

The data cut-off for the presented results was 11 January 2022.

Primary endpoint - PFS by BIRC

Table 33 Progression-free Survival per Blinded Independent Central Review in the Hormone Receptor-positive Cohort and Full Analysis Set (Study U303)

Parameter	Hormone Receptor-positive Cohort		Full Analysis Set	
	T-DXd (N = 331)	TPC (N = 163)	T-DXd (N = 373)	TPC (N = 184)
Subjects (%) with events	211 (63.7)	110 (67.5)	243 (65.1)	127 (69.0)
Progressive disease	180 (54.4)	101 (62.0)	208 (55.8)	117 (63.6)
Death	31 (9.4)	9 (5.5)	35 (9.4)	10 (5.4)
Subjects (%) without events (censored)	120 (36.3)	53 (32.5)	130 (34.9)	57 (31.0)
No baseline evaluable tumor assessment	0	0	0	0
No post-baseline tumor assessment	3 (0.9)	14 (8.6)	3 (0.8)	15 (8.2)
Event after missing 2 consecutive assessments	28 (8.5)	15 (9.2)	31 (8.3)	17 (9.2)
Lost to follow-up	0	1 (0.6)	0	1 (0.5)
Withdrew consent	4 (1.2)	7 (4.3)	4 (1.1)	7 (3.8)
Ongoing without event	67 (20.2)	8 (4.9)	69 (18.5)	8 (4.3)
Adequate tumor assessment no longer available	18 (5.4)	8 (4.9)	23 (6.2)	9 (4.9)
Median PFS, months[a]	10.1	5.4	9.9	5.1
95% CI	9.5, 11.5	4.4, 7.1	9.0, 11.3	4.2, 6.8
Stratified log-rank test *P*-value (2-sided)[b]	<0.0001		<0.0001	
Stratified Cox proportional hazards model[b]				
Hazard ratio	0.5085		0.5014	

Parameter	Hormone Receptor-positive Cohort		Full Analysis Set	
	T-DXd (N = 331)	TPC (N = 163)	T-DXd (N = 373)	TPC (N = 184)
95% CI	0.4012, 0.6444		0.4013, 0.6265	

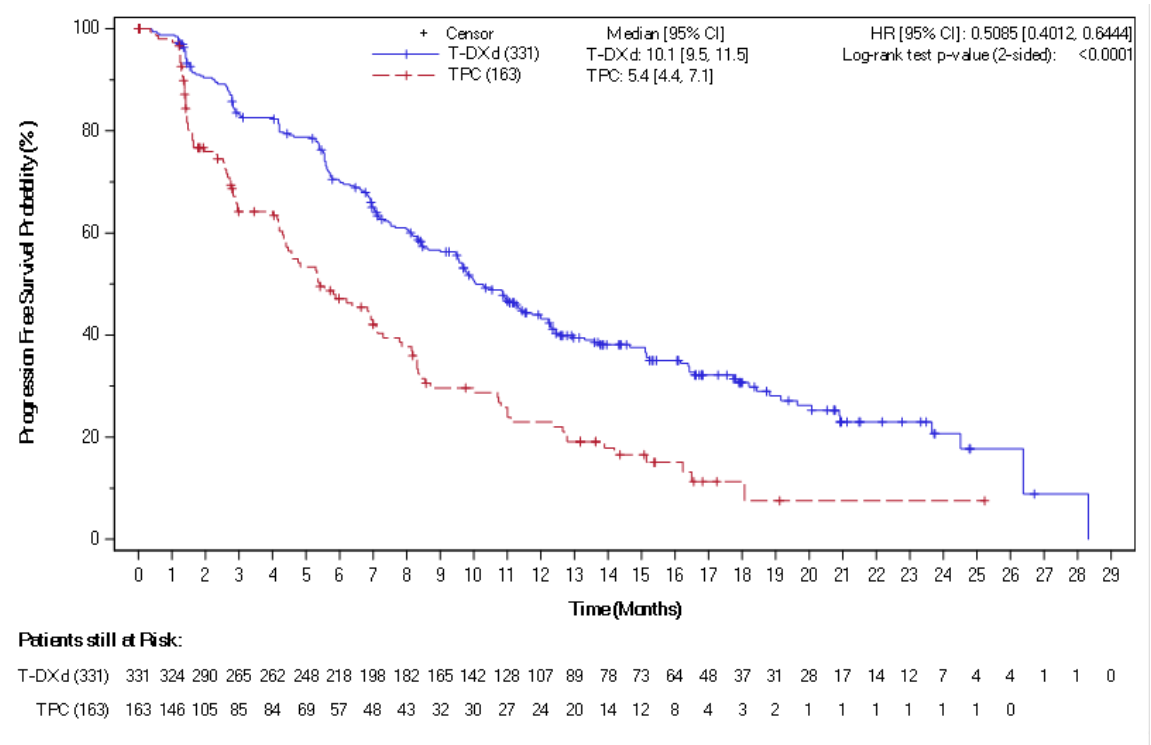
CDK = cyclin-dependent kinase; CI = confidence interval; CSR = clinical study report; HER2 = human epidermal growth factor receptor 2; IXRS = interactive web/voice response system; PFS = progression-free survival; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice

[a] Median PFS was from Kaplan-Meier analysis. CI for median was computed using the Brookmeyer-Crowley method.

[b] Two-sided *P*-value from stratified log-rank test and stratified Cox proportional hazards model with stratification factors: HER2 status, number of prior lines of chemotherapy, and hormone receptor/CDK status as defined by the IXRS.

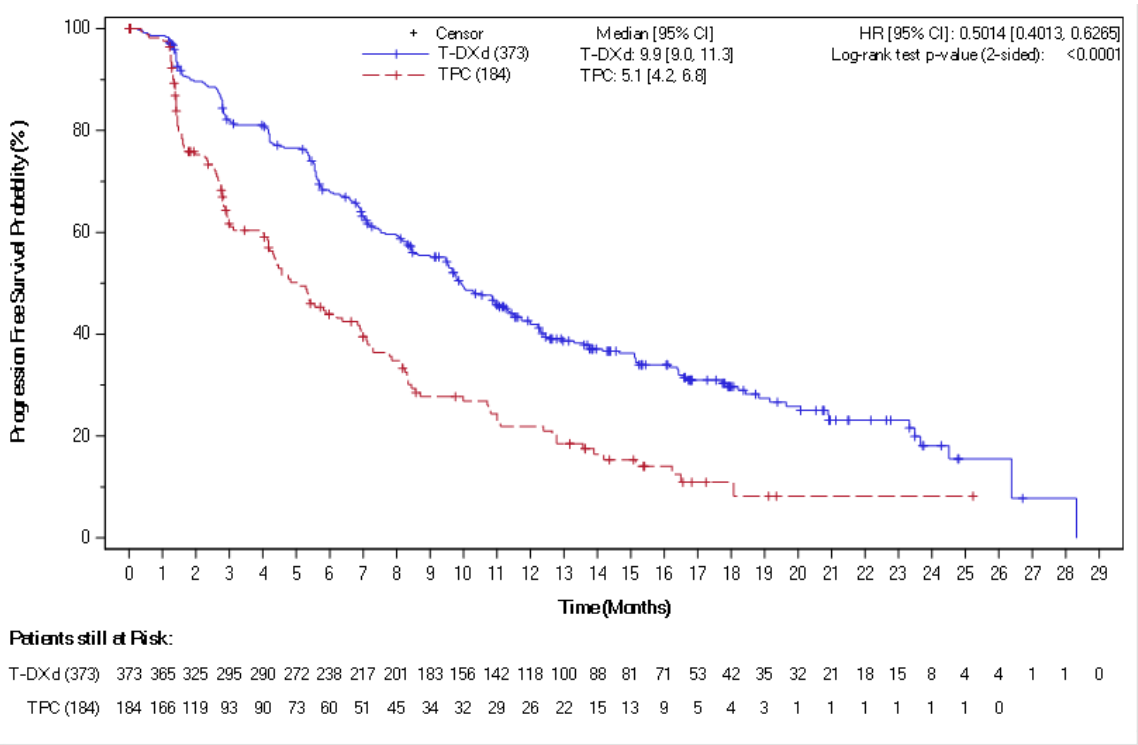
Data cut-off: 11 Jan 2022 Source: DS8201-A-U303 CSR Tables 14.2.1.1.1 and 14.2.1.1.2

Figure 26 Kaplan-Meier Plot of Progression-free Survival by Blinded Independent Central Review in Hormone Receptor-positive Cohort (Study U303)



CI = confidence interval; HR = hazard ratio; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice
Stratified Cox proportional hazards model for hazard ratio and stratified log-rank test for the *P*-value.
Data cut-off: 11 Jan 2022 Source: DS8201-A-U303 CSR Figure 14.2.1.1.1

Figure 27 Kaplan-Meier Plot of Progression-free Survival by Blinded Independent Central Review in the Full Analysis Set (Study U303)



CI = confidence interval; HR= hazard ratio; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice
Stratified Cox proportional hazards model for hazard ratio and stratified log-rank test for the *P*-value.
Data cut-off: 11 Jan 2022 Source: DS8201-A-U303 CSR Figure 14.2.1.1.2

Secondary endpoint – OS (analysis at the time of the final analysis for PFS)

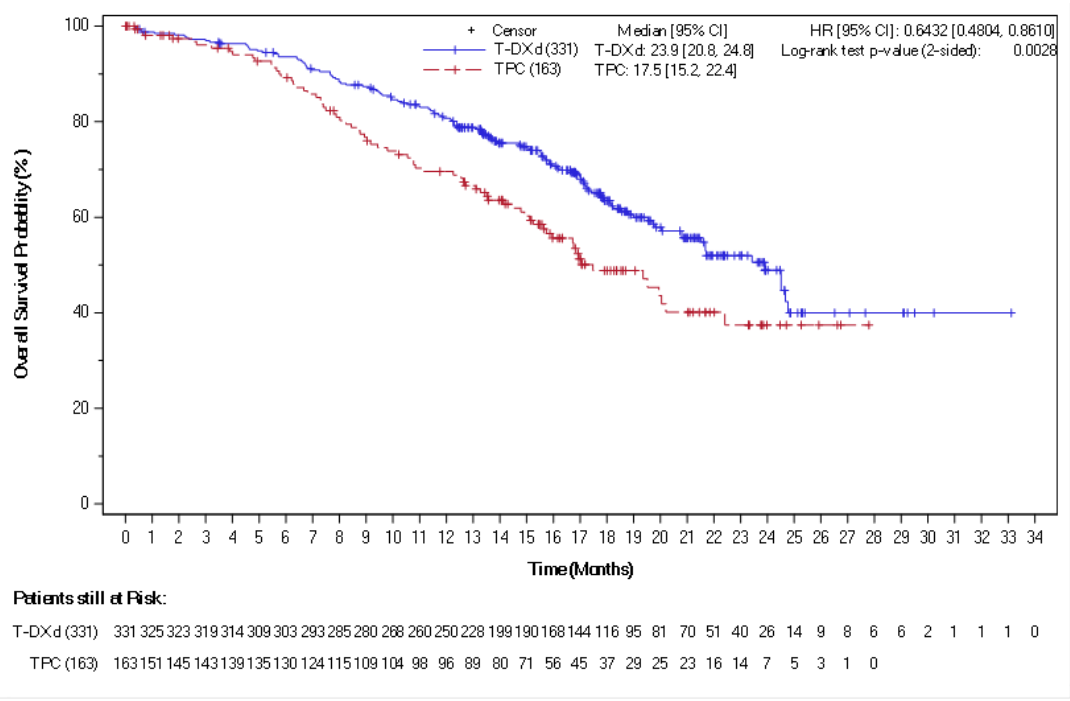
Table 34 Overall Survival in the Hormone Receptor-positive Cohort and Full Analysis Set (Study U303)

Parameter	Hormone Receptor-positive Cohort		Full Analysis Set	
	T-DXd (N = 331)	TPC (N = 163)	T-DXd (N = 373)	TPC (N = 184)
Subjects with events (deaths), n (%)	126 (38.1)	73 (44.8)	149 (39.9)	90 (48.9)
Subjects without event (censored), n (%)	205 (61.9)	90 (55.2)	224 (60.1)	94 (51.1)
Alive	183 (55.3)	67 (41.1)	201 (53.9)	70 (38.0)
Lost to follow-up	5 (1.5)	1 (0.6)	6 (1.6)	1 (0.5)
Withdrawal by Subject	16 (4.8)	22 (13.5)	16 (4.3)	23 (12.5)
Other	1 (0.3)	0	1 (0.3)	0
Median OS (months)[a]	23.9	17.5	23.4	16.8
95% CI	20.8, 24.8	15.2, 22.4	20.0, 24.8	14.5, 20.0
Stratified log-rank *P*-value[b]	0.0028		0.0010	
Stratified Cox regression hazards ratio[b]	0.6432		0.6408	
95% CI	0.4804, 0.8610		0.4903, 0.8375	

Parameter	Hormone Receptor-positive Cohort		Full Analysis Set	
	T-DXd (N = 331)	TPC (N = 163)	T-DXd (N = 373)	TPC (N = 184)
OS rate at 3 months[c] (95% CI)	97.0 (94.4, 98.4)	96.1 (91.5, 98.2)	96.2 (93.7, 97.8)	95.3 (90.9, 97.6)
OS rate at 6 months[c] (95% CI)	93.6 (90.3, 95.8)	89.2 (83.0, 93.3)	92.4 (89.2, 94.7)	88.1 (82.2, 92.2)
OS rate at 9 months[c] (95% CI)	87.4 (83.3, 90.6)	76.7 (68.9, 82.8)	85.3 (81.3, 88.5)	74.0 (66.6, 80.0)
OS rate at 12 months[c] (95% CI)	80.7 (76.0, 84.6)	69.6 (61.3, 76.4)	78.8 (74.3, 82.7)	66.5 (58.8, 73.2)
OS rate at 18 months[c] (95% CI)	63.5 (57.4, 69.0)	48.8 (39.5, 57.5)	61.7 (55.9, 66.9)	45.9 (37.5, 54.0)
OS rate at 24 months[c] (95% CI)	48.9 (40.9, 56.5)	37.4 (26.8, 48.0)	48.1 (40.8, 54.9)	32.0 (21.9, 42.4)

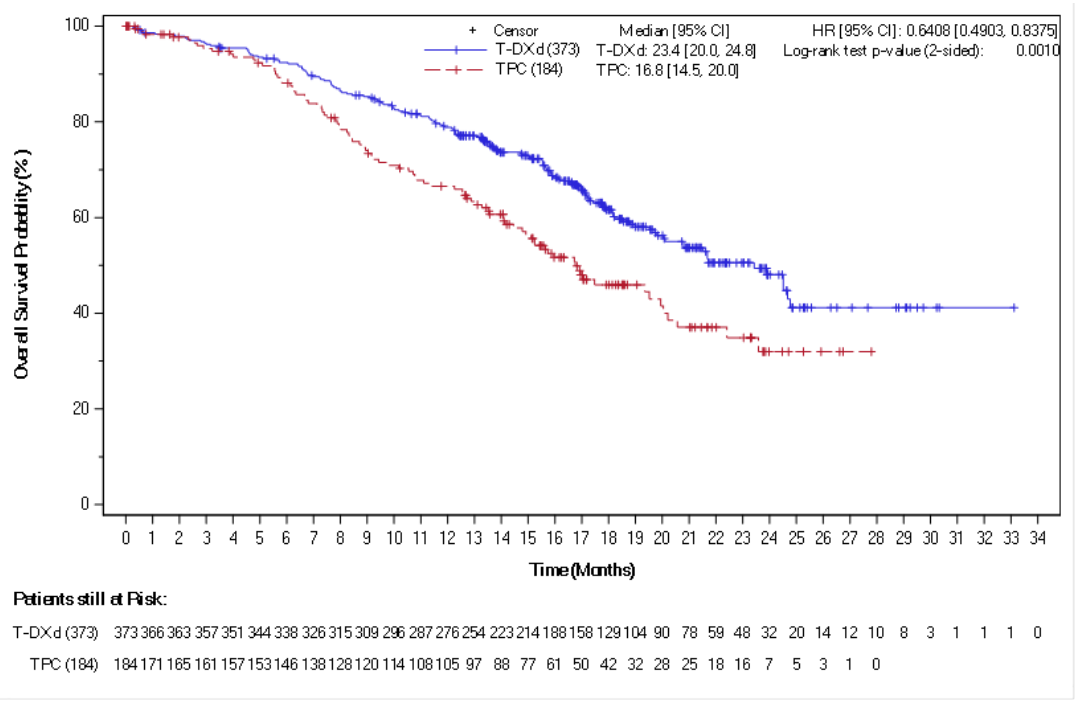
CDK = cyclin-dependent kinase; CI = confidence interval; HER2 = human epidermal growth factor receptor 2; IXRS = interactive web/voice response system; OS = overall survival; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice
OS was defined as the time from the date of randomization to the date of death from any cause. If there was no death reported for a subject before the data cutoff for the OS analysis, OS was censored at the last contact date at which the subject was known to be alive. [a]Median OS is from Kaplan-Meier analysis. CI for median was computed using the Brookmeyer-Crowley method. [b]Two-sided *P*-value from stratified log-rank test and stratified Cox proportional hazards model adjusted for IXRS stratification factors: HER2 status, number of prior lines of chemotherapy, hormone receptor/CDK status as defined by the IXRS. [c]Estimate and CI for OS rate at the specified time point are from Kaplan-Meier analysis. Data cut-off: 11 Jan 2022 Source: DS8201-A-U303 CSR Tables 14.2.2.1 and 14.2.2.2

Figure 28 Kaplan-Meier Plot of Overall Survival in Hormone Receptor-positive Cohort (Study U303)



Data cut-off: 11 Jan 2022 Source: DS8201-A-U303 CSR Figure 14.2.2.1.1

Figure 29 Kaplan-Meier Plot of Overall Survival in Full Analysis Set



Data cut-off: 11 Jan 2022 Source: DS8201-A-U303 CSR Figure 14.2.2.1.2

Other secondary endpoints – ORR and DOR

Table 35 Objective Response Rate and Clinical Benefit Rate Based on Blinded Independent Central Review in the Hormone Receptor-positive Cohort and Full Analysis Set (Study U303)

Parameter	Hormone Receptor-positive Cohort		Full Analysis Set	
	T-DXd (N = 331)	TPC (N = 163)	T-DXd (N = 373)	TPC (N = 184)
Best overall response, n (%)				
Complete response	12 (3.6)	1 (0.6)	13 (3.5)	2 (1.1)
Partial response	164 (49.5)	26 (16.0)	183 (49.1)	28 (15.2)
Stable disease	115 (34.7)	81 (49.7)	129 (34.6)	91 (49.5)
Progressive disease	26 (7.9)	34 (20.9)	31 (8.3)	41 (22.3)
Not evaluable	14 (4.2)	21 (12.9)	17 (4.6)	22 (12.0)
Confirmed ORR[a]				
n (%)	175 (52.9)[b]	27 (16.6)	195 (52.3)	30 (16.3)
95% CI[c]	47.3, 58.4	11.2, 23.2	47.1, 57.4	11.3, 22.5
P-value (stratified analysis)[d]	<0.0001		<0.0001	
Clinical benefit rate[e]				
n (%)	238 (71.9)	57 (35.0)	262 (70.2)	62 (33.7)

Parameter	Hormone Receptor-positive Cohort		Full Analysis Set	
	T-DXd (N = 331)	TPC (N = 163)	T-DXd (N = 373)	TPC (N = 184)
95% CI[c]	66.7, 76.7	27.7, 42.8	65.3, 74.8	26.9, 41.0
P-value (stratified analysis)[d]	<0.0001		<0.0001	

CI = confidence interval; CR = complete response; IXRS = interactive web/voice response system; ORR = objective response rate; PR = partial response; SD = stable disease; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice
[a] ORR = CR + PR; all responses are confirmed responses.
[b] One subject in the T-DXd arm who had a confirmed best overall response of complete or partial response had baseline scan done after randomization but before the first dose and thus was considered a non-responder in the calculation of confirmed ORR.
[c] Based on Clopper-Pearson method for single proportion and for the difference of 2 proportions with continuity correction
[d] Two-sided *P*-value based on the Cochran-Mantel-Haenszel test adjusted for stratification factors (hormone receptor status, prior treatment with pertuzumab, history of visceral disease) as defined by the IXRS
[e] defined as CR + PR + SD >6 months Data cut-off date: 11 Jan 2022 Source: DS8201-A-U303 CSR Tables 14.2.3.1.1 and 14.2.3.1.2

Table 36 Duration of Response Based on Blinded Independent Central Review in Hormone Receptor-positive Cohort and Full Analysis Set (Study U303)

Parameter	Hormone Receptor-positive Cohort		Full Analysis Set	
	T-DXd (N = 331)	TPC (N = 163)	T-DXd (N = 373)	TPC (N = 184)
Subjects with CR or PR, n	176	27	196	30
Subjects with subsequent events, n (%)	100 (56.8)	18 (66.7)	113 (57.7)	20 (66.7)
Progressive disease	87 (49.4)	16 (59.3)	99 (50.5)	18 (60.0)
Death	13 (7.4)	2 (7.4)	14 (7.1)	2 (6.7)
Subjects without subsequent events (censored), n (%)	76 (43.2)	9 (33.3)	83 (42.3)	10 (33.3)
Event after missing 2 consecutive assessments	13 (7.4)	2 (7.4)	15 (7.7)	3 (10.0)
Lost to follow-up	0	0	0	0
Withdrew consent	3 (1.7)	1 (3.7)	3 (1.5)	1 (3.3)
Ongoing without event	49 (27.8)	4 (14.8)	51 (26.0)	4 (13.3)
Adequate tumor assessment no longer available	11 (6.3)	2 (7.4)	14 (7.1)	2 (6.7)
Median confirmed DoR,[a] months	10.7	6.8	10.7	6.8
95% CI	8.5, 13.7	6.5, 9.9	8.5, 13.2	6.0, 9.9

CI = confidence interval; CR = complete response; DoR = duration of response; PR = partial response; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice
Responses were confirmed responses.
Percentage was calculated using number of subjects with CR/PR
[a] Median is from Kaplan-Meier estimate. Confidence interval for median is computed using the Brookmeyer-Crowley method.
Data cut-off date: 11 Jan 2022 Source: DS8201-A-U303 CSR Tables 14.2.3.2.1 and 14.2.3.2.2

Exploratory endpoint – PFS 2 (Progression-free Survival on Next Line of Treatment)

Table 37 Progression-free Survival on Next Line Therapy in the Hormone Receptor-positive Cohort and the Full Analysis Set Based on Investigator Assessment (Study U303)

Parameter	Hormone Receptor-positive Cohort		Full Analysis Set	
	T-DXd (N = 331)	TPC (N = 163)	T-DXd (N = 373)	TPC (N = 184)
Subjects with events, n (%)	172 (52.0)	96 (58.9)	199 (53.4)	112 (60.9)
Progression on next line of therapy	108 (32.6)	65 (39.9)	125 (33.5)	73 (39.7)
Death	64 (19.3)	31 (19.0)	74 (19.8)	39 (21.2)
Subjects (%) without events (censored)	159 (48.0)	67 (41.1)	174 (46.6)	72 (39.1)
No new anti-cancer therapy	86 (26.0)	25 (15.3)	89 (23.9)	26 (14.1)
No progression/death on next line of therapy	38 (11.5)	23 (14.1)	43 (11.5)	24 (13.0)
Second new anti-cancer therapy	35 (10.6)	19 (11.7)	42 (11.3)	22 (12.0)
Stratified Cox proportional hazards model[a]				
Hazard ratio	0.5424		0.5513	
95% CI	0.4206, 0.6995		0.4344, 0.6996	
Median PFS2 (months)[b]	15.5	10.5	15.4	10.5
95% CI	13.8, 17.5	8.4, 11.9	13.6, 17.3	8.3, 11.4

CDK = cyclin-dependent kinase: CI = confidence interval; HER2 = human epidermal growth factor receptor 2; IXRS = interactive web/voice response system; KM = Kaplan-Meier; PFS2 = progression-free survival on next line of treatment; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice

[a] Stratified Cox proportional hazards model with stratification factors: HER2 status, number of prior lines of chemotherapy, and hormone receptor/CDK status as defined by the IXRS.

[b] Median PFS2 was from Kaplan-Meier analysis; CI for median was computed using Brookmeyer-Crowley method.

Data cut-off: 11 Jan 2022 Source: DS8201-A-U303 CSR Tables 14.2.3.7 and 14.2.3.8

Table 38 Progression-free survival on subsequent line of therapy based on investigator assessment (HR- cohort of FAS)

T-DXd (N=40)			TPC (N=18)			
n	No of Events (%)	Median PFS2 (95% CI)[a] (months)	n	No of Events (%)	Median PFS2 (95% CI)[a] (months)	T-DXd vs. TPC Hazard Ratio (95% CI)[b]
40	25 (62.5)	12.9 (9.6, 18.2)	18	14 (77.8)	8.9 (5.0, 14.1)	0.7236 (0.3399, 1.5405)

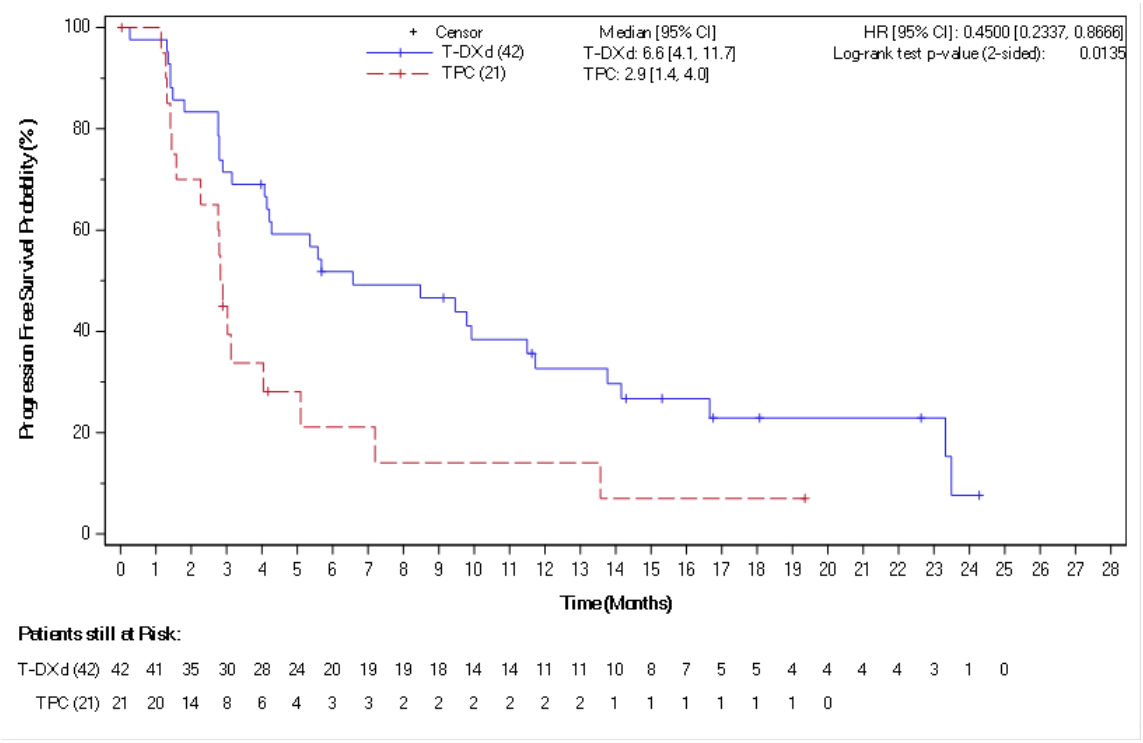
CDK = cyclin-dependent kinase; CI = confidence interval; EDC = electronic data capture system; FAS = full analysis set; HER2 = human epidermal growth factor receptor 2; HR+/− = hormone receptor positive/negative; IHC = immunohistochemistry; ISH = in situ hybridisation; IXRS = Interactive Web/Voice Response System; PFS2 = progression-free survival on next-line treatment; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice.

[a] Median PFS2 is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method.

[b] Hazard ratio and 95% CI from stratified Cox proportional hazards model with stratification factors: HER2 IHC status (1+ vs. 2+/ISH-), HR/CDK status (HR+ with prior CDK4/6 vs. HR+ without CDK4/6 vs. HR−), and number of prior lines of chemotherapy (1 vs. 2) as defined by the IXRS.
HR−: estrogen receptors negative and progesterone receptors negative based on factors reported from EDC.
PFS2 is defined as the time from the date of randomisation to the date of the first documented progression on next-line therapy based on investigator assessment or death due to any cause, whichever comes first.
Source: Appendix 1 Table 8.

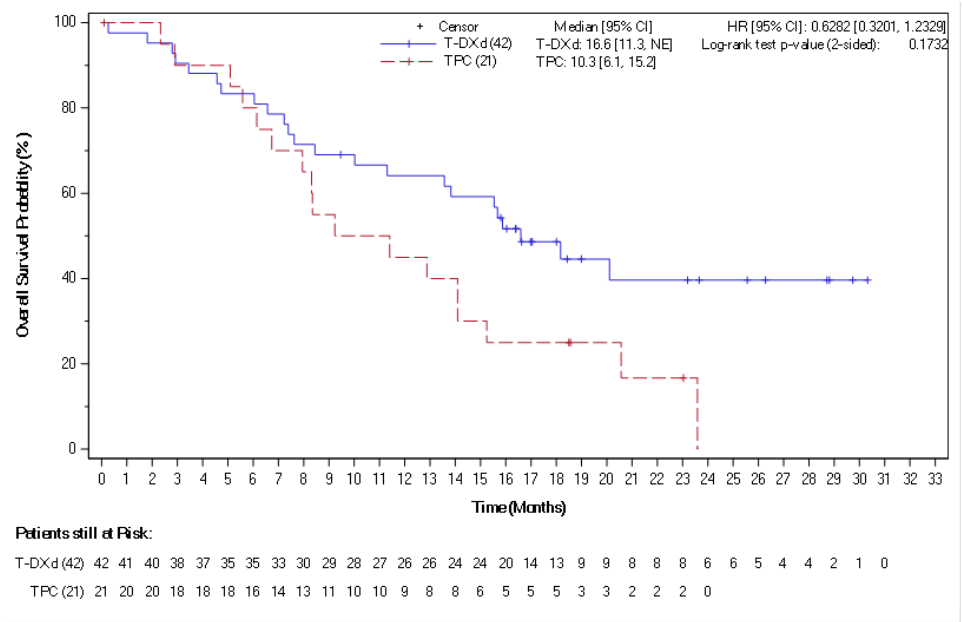
Exploratory endpoints – PFS and OS in the Hormone Receptor-negative Cohort

Figure 30 Kaplan-Meier Plot of Progression-free Survival by Blinded Independent Central Review in the Hormone Receptor-negative Cohort Based on IXRS (Study U303)



CI = confidence interval; HR = hazard ratio; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice
Stratified Cox proportional hazards model for HR and stratified log-rank test for the *P*-value.
Data in this figure are based on the 63 subjects with hormone receptor-negative disease per IXRS.
Data cut-off: 11 Jan 2022 Source: DS8201-A-U303 CSR Figure14.2.1.1.3

Figure 31 Kaplan-Meier Plot of Overall Survival in Hormone Receptor-negative Cohort Based on IXRS (Study U303)



Data cut-off: 11 Jan 2022 Source: DS8201-A-U303 CSR Figure 14.2.2.1.3

Exploratory endpoint – Patient-related outcomes (PRO)

In both arms, compliance for questionnaires was >92% at baseline and >80% for Cycle 2 through Cycle 27. Data from the QLQ-C30 questionnaire showed that all scales either remained stable or improved up to Cycle 33, after which the number of subjects became too small to allow for meaningful interpretation. The global health status/global QoL score of the QLQ-C30 (the primary PRO variable of interest) remained stable over time for subjects in both treatment arms up to and including Cycle 21, indicating that HRQoL was maintained throughout treatment.

There was a delay in TTDD by at least 10 points in the T-DXd arm compared with the TPC arm for the following:

- QLQ-C30 global health status scale: the median TTDD by at least 10 points in global health status/global QoL scale score was 7.6 months (95%CI: 5.8, 9.2) in the T-DXd arm vs 5.1 months (95% CI: 3.1, 6.9) in the TPC arm (stratified HR: 0.71 [95%CI: 0.56, 0.92]).
- QLQ-C30 pain symptom sub-scale: the median TTDD by at least 10 points in pain symptoms was 9.7 months (95%CI: 8.5, 11.1) in the T-DXd arm vs 4.4 months (95% CI: 2.8, 6.2) in the TPC arm (stratified HR: 0.51 [95%CI: 0.39, 0.65]).
- QLQ-C30 physical functioning sub-scale: the median TTDD by at least 10 points in physical functioning was 9.2 months (95%CI: 7.6, 11.3) in the T-DXd arm vs 4.9 months (95% CI: 4.0, 6.1) in the TPC arm (stratified HR: 0.54 [95%CI: 0.42, 0.70]).
- QLQ-C30 emotional functioning sub-scale: the median TTDD by at least 10 points in emotional functioning was 11.3 months (95%CI: 9.9, 13.8) in the T-DXd arm vs 6.3 months (95%CI: 5.7, 7.9) in the TPC arm (stratified HR: 0.64 [95%CI: 0.48, 0.85]).
- QLQ-C30 social functioning subscale: the median TTDD by at least 10 points in social functioning was 7.7 months (95% CI: 5.9, 9.2) in the T-DXd arm vs 4.4 months (95%CI: 2.8, 5.8) in the TPC arm (stratified HR: 0.67 [95%CI: 0.53, 0.86]).

- QLQ-BR45 (BR23) breast symptoms sub-scale: the median TTDD by at least 10 points in breast symptoms was 20.3 months (95%CI: 15.3, NE) in the T-DXd arm vs NE (95% CI: 10.5, NE) in the TPC arm (stratified HR: 0.71 [95%CI: 0.50, 1.01]).
- QLQ-BR45 (BR23) arm symptoms sub-scale: the median TTDD by at least 10 points in arm symptoms was 9.8 months (95%CI: 7.4, 11.2) in the T-DXd arm vs 5.4 months (95% CI: 3.3, 7.1) in the TPC arm (stratified HR: 0.67 [95%CI: 0.50, 0.88]).

VAS of the EQ-5D-5L: the median TTDD by at least 10 points in VAS was 8.8 months (95% CI: 7.1, 10.9) in the T-DXd arm vs 4.7 months (95%CI: 3.9, 6.1) in the TPC arm (stratified HR: 0.70 [95%CI: 0.54, 0.91]).

Ancillary analyses

Concordance analyses between Investigator and BICR

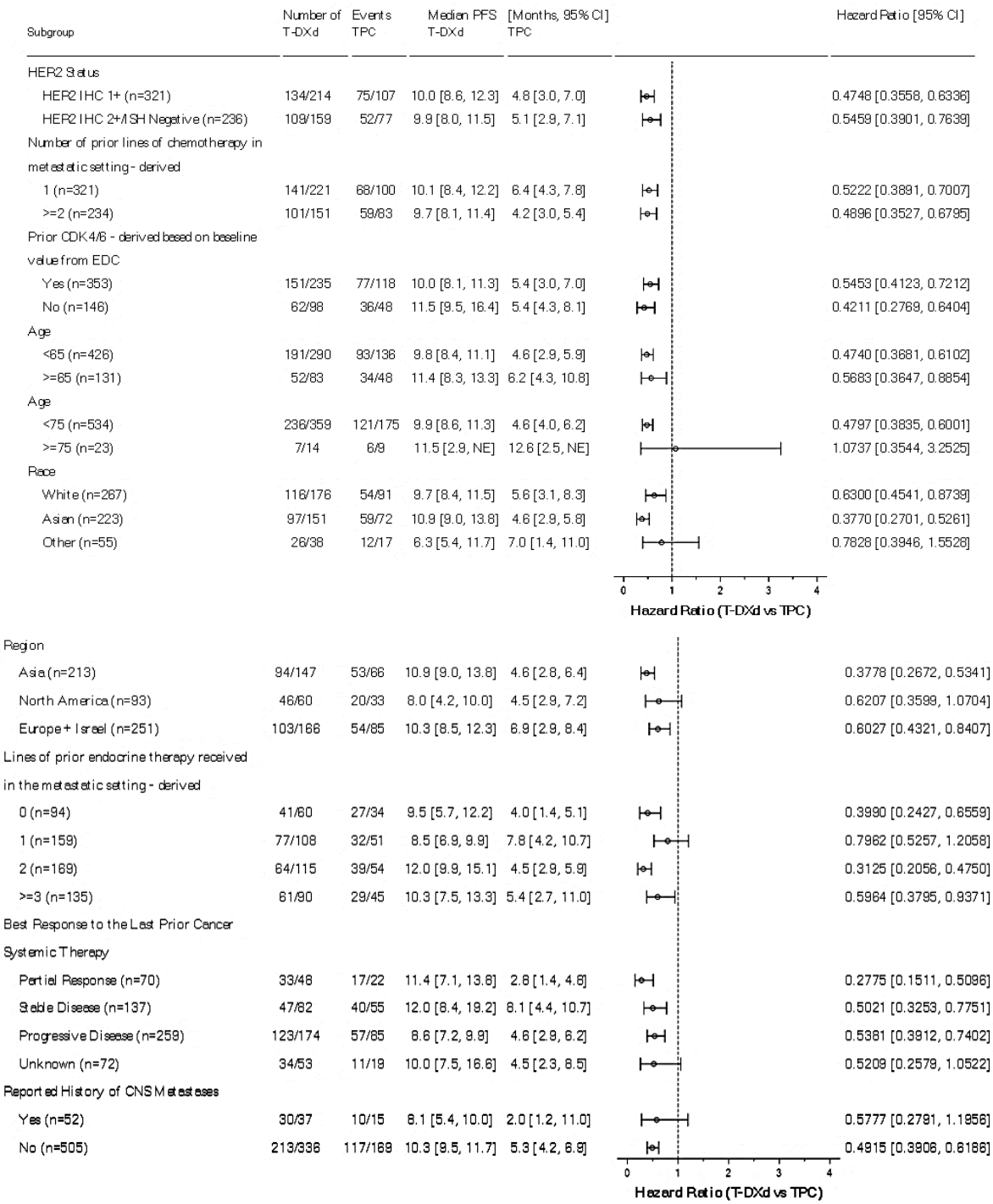
Table 39 Concordance Analysis of Progression-free Survival Between Investigator and Blinded Independent Central Review Assessments for the Full Analysis Set (Study U303)

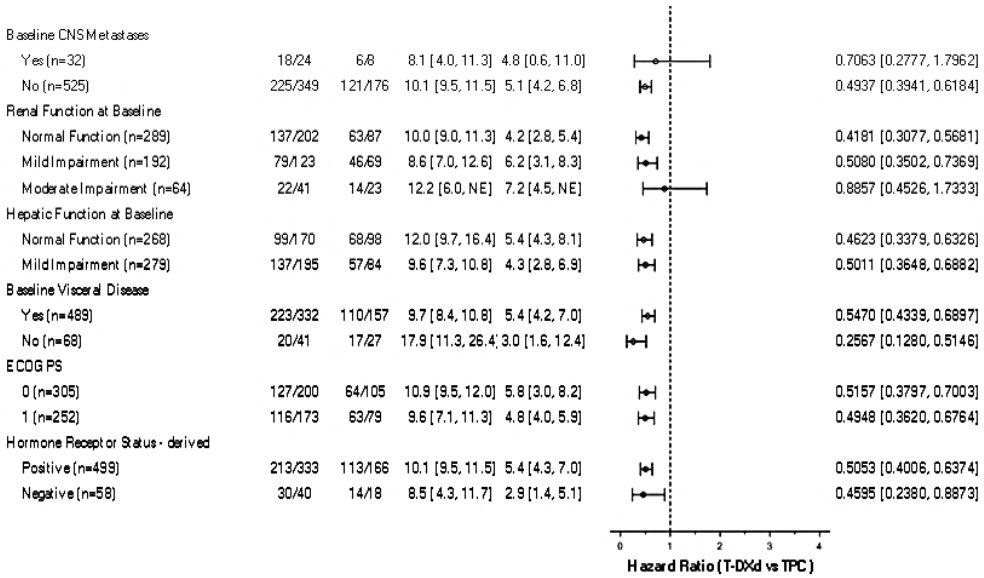
		BICR PFS Result n (%)				
Treatment Group	**INV PFS Result**	**Death**	**PD**	**Censored**	**Total**	**Concordance Rate**
T-DXd (N = 373)	Death	20 (87.0)	3 (13.0)	0	23	79.36%
	PD	15 (6.1)	180 (72.9)	52 (21.1)	247	
	Censored	0	25 (24.3)	78 (75.7)	103	
	Total	35	208	130	373	
TPC (N = 184)	Death	2 (40.0)	3 (60.0)	0	5	80.43%
	PD	7 (4.8)	109 (74.7)	30 (20.5)	146	
	Censored	1 (3.0)	5 (15.2)	27 (81.8)	33	
	Total	10	117	57	184	

BICR = blinded independent central review; INV = investigator; PD = progressive disease; PFS = progression-free survival; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice
Percentages are based on row total.
Data cut-off: 11 Jan 2022 Source: DS8201-A-U303 CSR Table 14.2.5.1.2

Subgroup analyses

Figure 32 Forest Plot of Treatment Comparison for Progression-free Survival by Blinded Independent Central Review in Subgroups in Full Analysis Set Based on Electronic Data Capture (Study U303)





CDK4/6 = cyclin-dependent kinase 4/6; CI = confidence interval; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status; EDC = electronic data capture; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ISH = in situ hybridization; NE = not estimable; PFS = progression-free survival; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice
Analyses were performed only for the category of the subgroup if there were at least 10 PFS events in the treatment arms combined.
Data presented in this figure are based on EDC instead of IXRS. Any data entry in IXRS could not be modified; the derived data in EDC captured the correct status for the stratification factors.
Data cut-off: 11 Jan 2022
Source: DS8201-A-U303 CSR Figure 14.2.1.3.2

Table 40 Progression-free Survival by Pretreated Status of Anthracyclines Based on BICR (FAS)

	T-DXd (N=373)			TPC (N=184)			
	n	**Number of Events (%)**	**Median (95% CI)[a] (months)**	**n**	**Number of Events (%)**	**Median (95% CI)[a] (months)**	**T-DXd vs. TPC Hazard Ratio (95% CI)[b]**
Anthracycline Pretreated							
Yes[c]	239	155 (64.9)	9.8 (8.5, 11.7)	113	81 (71.7)	5.3 (3.0, 7.9)	0.5298 (0.4034,0.6957)
No	134	88 (65.7)	10.0 (7.2, 12.5)	71	46 (64.8)	4.6 (3.0, 6.8)	0.4588 (0.3179,0.6622)

BICR = Blinded Independent Central Review; CI = confidence interval; FAS = full analysis set; HR+ = hormone receptor positive; IXRS = Interactive Web/Voice Response System; PFS = progression-free survival; SAP = statistical analysis plan; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice.
[a] Median PFS is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate.
[c] Pretreated anthracyclines use is defined as prior anticancer therapy of "anthracyclines," "doxorubicin," "epirubicin," "daunorubicin," or "idarubicin" in CMDECOD and CMTRT in ADCM.
PFS is defined as the time from the date of randomisation to the date of the first radiographic disease progression or death due to any cause, whichever comes first. See SAP for the handling of censored cases.
HR+ status based on IXRS.
Source: Appendix 1 Table 11.

Table 41 Overall Survival by Pretreated Status of Anthracyclines (FAS)

	T-DXd (N=373)			TPC (N=184)			
	n	**Number of Events (%)**	**Median (95% CI)[a] (months)**	**n**	**Number of Events (%)**	**Median (95% CI)[a] (months)**	**T-DXd vs. TPC Hazard Ratio (95% CI)[b]**
Anthracycline Pretreated							

	T-DXd (N=373)			TPC (N=184)			
	n	Number of Events (%)	Median (95% CI)[a] (months)	n	Number of Events (%)	Median (95% CI)[a] (months)	T-DXd vs. TPC Hazard Ratio (95% CI)[b]
Yes[c]	239	97 (40.6)	24.5 (18.5, NE)	113	54 (47.8)	17.0 (14.1, 20.2)	0.6587 (0.4717,0.9200)
No	134	52 (38.8)	23.4 (19.8, NE)	71	36 (50.7)	16.0 (12.6, 23.6)	0.5822 (0.3803,0.8912)

CI = confidence interval; FAS = full analysis set; HR+ = hormone receptor positive; IXRS = Interactive Web/Voice Response System; NE = not estimable; OS = overall survival; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice.

[a] Median OS is from Kaplan-Meier analysis. CI for median was computed using the Brookmeyer-Crowley method.

[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate.

[c] Pretreated anthracyclines use is defined as prior anticancer therapy of "anthracyclines," "doxorubicin," "epirubicin," "daunorubicin," or "idarubicin" in CMDECOD and CMTRT in ADCM.

OS is defined as the time from the date of randomisation to the date of death due to any cause, whichever comes first. If there is no death reported for a subject before the data cutoff for OS analysis, OS will be censored at the last contact date at which the subject is known to be alive.

HR+ status based on IXRS.

Source: Appendix 1 Table 12.

Table 42 Summary of Subjects with De Novo Metastatic Status

	Full Analysis Set		HR+ Cohort of Full Analysis Set		HR− Cohort of Full Analysis Set	
De Novo Metastatic Status	T-DXd (N=373) n(%)	TPC (N=184) n(%)	T-DXd (N=331) n(%)	TPC (N=163) n(%)	T-DXd (N=42) n(%)	TPC (N=21) n(%)
Yes	122 (32.7)	64 (34.8)	108 (32.6)	56 (34.4)	14 (33.3)	8 (38.1)
No	251 (67.3)	120 (65.2)	223 (67.4)	107 (65.6)	28 (66.7)	13 (61.9)

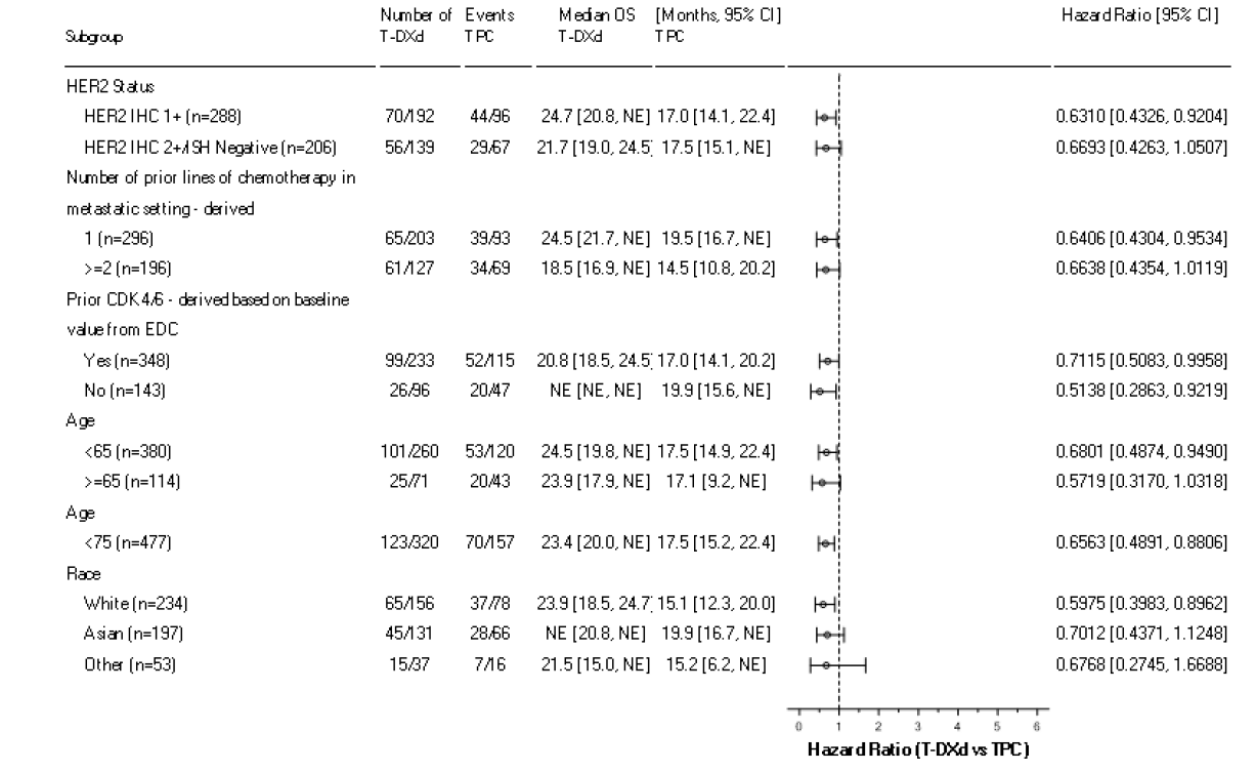
HR+/− = hormone receptor positive/negative; IXRS = Interactive Web/Voice Response System; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice.

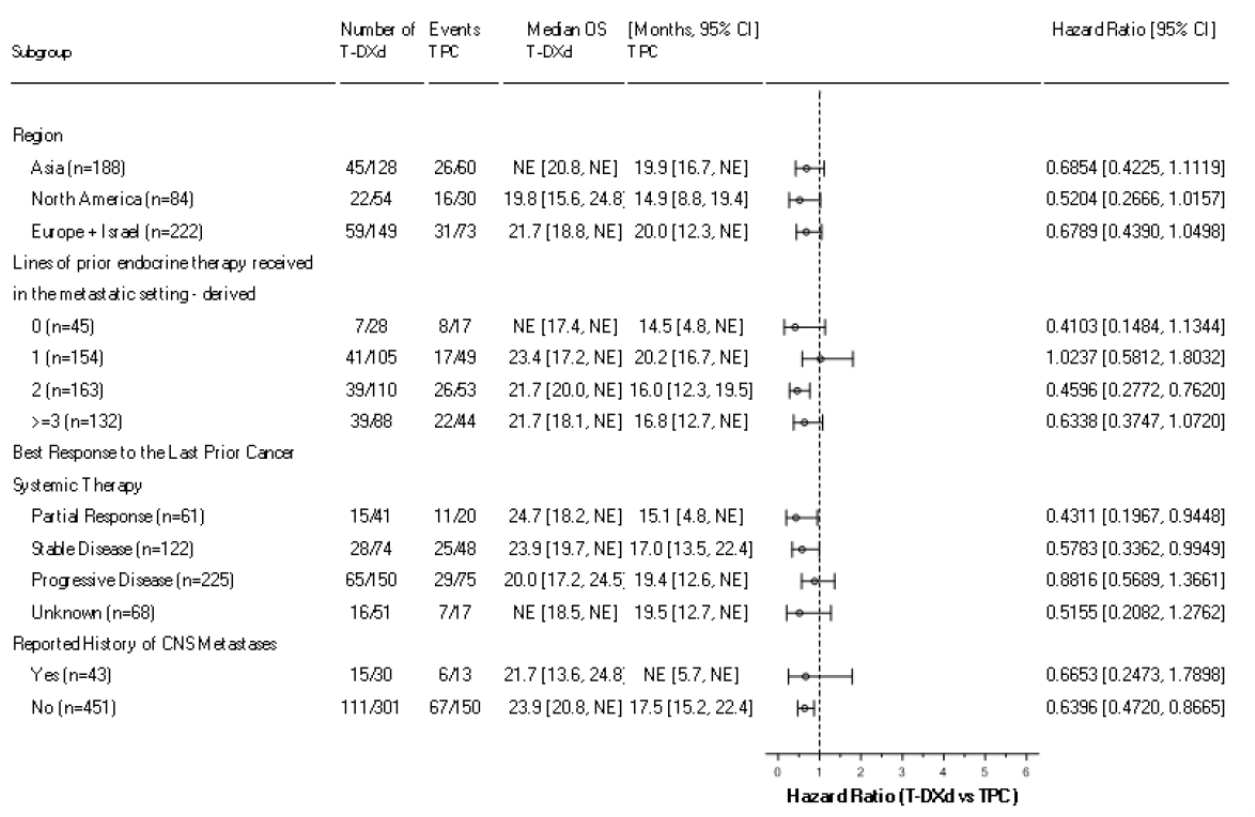
De novo metastatic is defined as subjects with the very first reported prior breast cancer therapy was intended for metastatic.

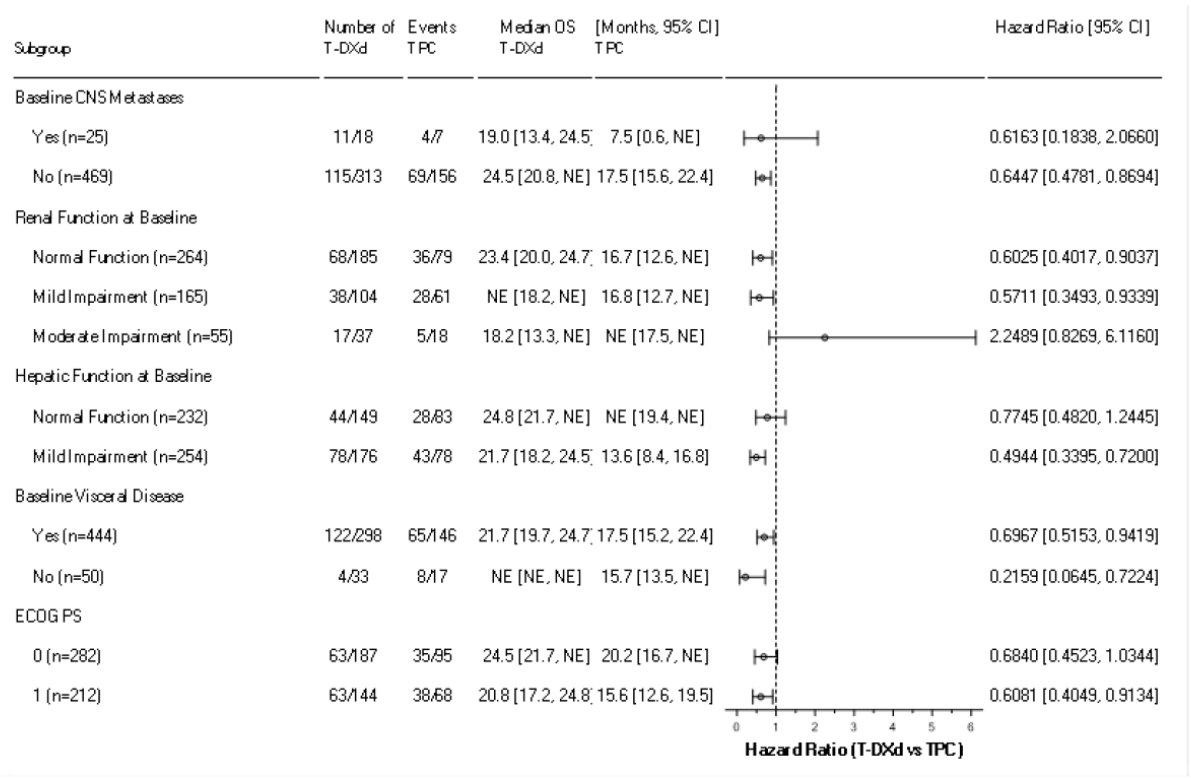
HR+ /−status is based on IXRS.

Source: Appendix 1 Table 13.

Figure 33 Forest Plot of Treatment Comparison for Overall Survival by Subgroup in the Hormone Receptor-positive Cohort Based on Electronic Data Capture







CDK = cyclin-dependent kinase; CI = confidence interval; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status; EDC = electronic data capture; HER2 = human epidermal growth factor receptor 2; IXRS = interactive web/voice response system; IHC = immunohistochemistry; ISH = in situ hybridization; NE = not estimable; OS = overall survival; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice
Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate.

Sensitivity analyses

Table 43 Sensitivity Analysis of Progression-Free Survival per Blinded Independent Central Review Analyses in Hormone Receptor-positive Cohort of the Per-protocol Analysis Set (Study U303)

Type of Analysis	Number (%) of Subjects with Events	Median PFS (95% CI) [a] months	Hazard Ratio (95% CI)[b]
Analysis using Per-protocol Analysis Set			
T-DXd	207 (64.5)	10.1 (9.5, 11.5)	0.5273 (0.4147, 0.6707)
TPC	106 (73.1)	5.6 (4.4, 7.3)	

CI = confidence interval; PFS = progression-free survival; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice
[a] Median PFS is from Kaplan-Meier analysis. Confidence interval for median is computed using the Brookmeyer-Crowley method.
[b] Based on stratified Cox proportional hazards model.
Data cut-off: 11 Jan 2022
Source: DS8201-A-U303 CSR Table 14.2.1.2.1.1

Table 44 Sensitivity Analyses of Progression-Free Survival per Blinded Independent Central Review in Hormone Receptor-positive Cohort (Study U303)

Type of Analysis	Number (%) of Subjects with Events	Median PFS (95% CI)[a] Months	Hazard Ratio (95% CI)[b]
Impact of stratification – Unstratified analysis			
T-DXd	211 (63.7)	10.1 (9.5, 11.5)	

Type of Analysis	Number (%) of Subjects with Events	Median PFS (95% CI)[a] Months	Hazard Ratio (95% CI)[b]
TPC	110 (67.5)	5.4 (4.4, 7.1)	0.5093 (0.4028, 0.6439)
Impact of censoring rule – Not censoring for missing 2 consecutive assessments			
T-DXd	239 (72.2)	10.3 (9.5, 11.5)	0.5099 (0.4083, 0.6367)
TPC	126 (77.3)	5.8 (4.5, 7.1)	
Impact of censoring rule – Censoring for new anti-cancer therapy[c]			
T-DXd	175 (52.9)	10.9 (9.6, 13.8)	0.4359 (0.3307, 0.5746)
TPC	84 (51.5)	5.4 (4.3, 6.9)	
Impact of censoring rule – Back-dating PFS[d]			
T-DXd	239 (72.2)	9.6 (8.3, 10.5)	0.5012 (0.4015, 0.6257)
TPC	126 (77.3)	5.3 (4.0, 6.2)	

CI = confidence interval; PFS = progression-free survival; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice
[a] Median PFS is from Kaplan-Meier analysis. Confidence interval for median is computed using the Brookmeyer-Crowley method.
[b] Based on stratified (or unstratified for impact on stratification) Cox proportional hazards model.
[c] Subjects were censored at the last tumor assessment date before starting the new anti-cancer therapy.
[d] Primary PFS analysis was repeated not censoring for missing 1 or more tumor assessments. In such cases, the PFS event date was considered to be 6 weeks after the last evaluable tumor assessment occurring prior to progression or death.
Data cut-off: 11 Jan 2022
Source: DS8201-A-U303 CSR Tables 14.2.1.2.2.1, 14.2.1.2.3.1, 14.2.1.2.4.1, and 14.2.1.2.8

The results of a post-hoc sensitivity analysis including both BICR-assessed and investigator-assessed progressive disease (and/or clinical progression) as events (with the earliest of the two being the event) is shown below.

Table 45 Sensitivity analysis of Progression-Free Survival per both BICR and Investigator Assessment FAS

T-DXd (N=373)			TPC (N=184)			
n	Number of Events (%)	Median (95% CI)[a] (months)	n	Number of Events (%)	Median (95% CI)[a] (months)	T-DXd vs. TPC Hazard Ratio (95% CI)[b]
373	297 (79.6)	8.1 (6.9, 8.4)	184	158 (85.9)	3.0 (2.8, 4.2)	0.3951 (0.3211, 0.4861)

BICR = blinded independent central review; CDK = cyclin-dependent kinase; CI = confidence interval; FAS = full analysis set; HER2 = human epidermal growth factor receptor 2; HR+/− = hormone receptor positive/negative; IHC = immunohistochemistry; ISH = in situ hybridisation; IXRS = Interactive Web/Voice Response System; PFS = progression-free survival; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice.
[a] Median PFS is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method.
[b] Hazard ratio and 95% CI from stratified Cox proportional hazards model with stratification factors: HER2 IHC status (1+ vs. 2+/ISH-), HR/CDK status (HR+ with prior CDK4/6 vs. HR+ without CDK4/6 vs. HR−), and number of prior lines of chemotherapy (1 vs. 2) as defined by the IXRS.
PFS is defined as the time from the date of randomisation to the date of the first radiographic disease progression, clinical progression, or death due to any cause, whichever comes first. The earliest event from BICR-assessed and investigator-assessed progressive disease will be used to compute PFS.
Source: Appendix 1 Table 7.

Biomarker analysis

The eligibility criteria for Study U303 required pathologically documented BC that was centrally assessed as having low HER2 protein expression using an Investigational Use Only (IUO) version of the PATHWAY/VENTANA HER2 (4B5) with a revised HER2-low scoring algorithm. The reagent formulation remained the same as the commercially available PATHWAY/VENTANA HER2 (4B5). Of note, the only difference between the IUO version of the assay used in this study and the approved assay will be the investigational scoring algorithm for the lower cut point bound on the HER2 IHC 1+ category. HER2 ISH testing will follow the scoring criteria specified in the package insert of Ventana INFORM Dual ISH kit.

To define low HER2 expression, it is necessary to clarify the boundary between IHC 0 and IHC 1+. The ASCO-CAP suggests a definition for IHC 1+ as incomplete membrane staining that is faint/barely perceptible and within >10% of the invasive tumour cells. The IHC 0 is defined as no staining observed or membrane staining that is incomplete and is faint/barely perceptible and within ≤10% of the invasive tumour cells. Because there is no difference in treatment algorithm for subjects with IHC 0 and IHC 1+ readings, several commercial HER2 tests use alternative cutoffs. To standardize this boundary, the Sponsor used the adapted ASCO-CAP cutoffs to provide the lower boundary for low HER2 expression. The scoring algorithm was revised to define the upper and lower boundary of low HER2 expression by using standard ASCO/CAP IHC definitions. The upper boundary for HER2-low (IHC 2+) remained the same as the lower boundary for HER2-positive BC. The lower boundary of HER2-low expression was defined as IHC 1+.

Analytical validation of the HER2-low cutoff was performed by Ventana Medical Systems, Inc. Analytical sensitivity, specificity, repeatability, reproducibility, immunoreactivity, cut-slide stability, intermediate precision, reader precision, and reagent stability were evaluated. All analytical performance studies conducted for HER2-low on the PATHWAY/VENTANA HER2 (4B5) assay met their prespecified acceptance criteria. The clinical validity of the assay was studied in Study U303 by its use for patient eligibility determination.

Reflex HER2 ISH testing of IHC 2+ cases was performed by using the INFORM HER2 Dual ISH Assay. The ISH assay reagent formulation remained unchanged and the assay was used according to the manufacturer's instructions.

Both local and central results were available for 1201 tumour samples submitted for central testing for determination of HER2 expression. The overall percent agreement between local and central HER2-low assessment was 0.75 (95% CI 0.73, 0.78).

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies 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 46 Summary of Efficacy for trial U303 (DestinyBreast04)

Title: 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	
Study identifier	DS8201-A-U303
Design	Randomised, 2-arm, Phase 3, open-label, multicenter study

	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		Trastuzumab deruxtecan iv 5.4 mg/kg every 3 weeks (Q3W), number randomized: 373
	TPC		Treatment per Physician's choice (single agent chemotherapy) options: capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel, number randomized: 184
Endpoints and definitions	Primary endpoint	PFS by BIRC	Progression-free survival by blinded independent review
	Secondary endpoint	OS	Overall survival
	Other secondary endpoints	PFS by INV, ORR, DoR	Progression-free survival by investigator, confirmed overall response rate, duration of response free text
Database lock	DCO 11 January 2022		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat: Primary analysis (for the HR+ population and the FAS*)		
Descriptive statistics and estimate variability	Treatment group	T-DXd (N=373)	TPC (N=184)
	Patients with events	243 (65.1%)	127 (69%)
	PFS by BIRC (months)	9.9	5.1
	95%CI	9.0; 11.3	4.2; 6.8
	OS (months)	23.4	16.8
	95%CI	20.0; 24.8	14.5; 20.0
	Confirmed ORR 95%CI	52.3% 47.1; 57.4	16.3% 11.3; 22.5
	DoR	10.7	6.8
	95%CI	8.5; 13.2	6.0; 9.9

Effect estimate per comparison	Primary endpoint	Comparison groups	T-DXd vs TPC
		Hazard ratio	0.5014
		95%CI	0.4013; 0.6265
		P-value	<0.0001
	Secondary endpoint: OS	Comparison groups	T-DXd vs TPC
		Hazard ratio	0.64
		95%CI	0.49; 0.84
		P-value	0.0010
Notes	*Results are only shown for the FAS, since this is the target population for the sought indication		

Supportive study

Study J101 was a Phase 1 first-in-human, multicenter, 2-part (dose escalation followed by dose expansion), open-label, nonrandomized, multiple-dose study of T-DXd in subjects with advanced solid tumors. The study was conducted in the US and Japan in several types of solid tumors at various doses of T-DXd ranging from 0.8 mg/kg to 8.0 mg/kg.

Results from patients with HER2-low breast cancer (n=54) from the phase I study J101 serve as supportive evidence. Of note, only 21 patients received the proposed dose of 5.4 mg/kg Q3W.

Table 47 Demographics and Baseline Characteristics of the HER2-low Breast Cancer Population Enrolled (Intent-to-Treat Analysis Set; Study J101)

Parameter	HER2-low BC 5.4 mg/kg (N = 21)	HER2-low BC 6.4 mg/kg (N = 33)	Overall HER2-low BC (N = 54)
Age at Informed Consent			
Median (Min-Max)	57.0 (37-74)	55.0 (33-75)	56.5 (33-75)
Age Group (Years), n (%)			
<65 Years	15 (71.4)	25 (75.8)	40 (74.1)
≥65 Years	6 (28.6)	8 (24.2)	14 (25.9)
<75 Years	21 (100.0)	32 (97.0)	53 (98.1)
≥75 Years	0 (0.0)	1 (3.0)	1 (1.9)
Sex, n (%)			
Female	21 (100.0)	33 (100.0)	54 (100.0)
Race, n (%)			
White	12 (57.1)	7 (21.2)	19 (35.2)
Black or African American	1 (4.8)	1 (3.0)	2 (3.7)
Asian	7 (33.3)	23 (69.7)	30 (55.6)
Other	1 (4.8)	2 (6.1)	3 (5.6)
Country, n (%)			
Japan	5 (23.8)	22 (66.7)	27 (50.0)
United States	16 (76.2)	11 (33.3)	27 (50.0)
ECOG PS, n (%)			
0	16 (76.2)	20 (60.6)	36 (66.7)
1	5 (23.8)	13 (39.4)	18 (33.3)
Hormone receptor status, n (%)			
Positive	19 (90.5)	28 (84.8)	47 (87.0)
Negative	2 (9.5)	5 (15.2)	7 (13.0)
HER2 IHC status (study site testing), n (%)			
1+	14 (66.7)	14 (42.4)	28 (51.9)
2+/ISH Negative	7 (33.3)	19 (57.6)	26 (48.1)
Number of prior anti-cancer regimens for locally advanced/metastatic,[a] n (%)			

Parameter	HER2-low BC 5.4 mg/kg (N = 21)	HER2-low BC 6.4 mg/kg (N = 33)	Overall HER2-low BC (N = 54)
Median (Min, Max)	7.0 (2-14)	7.0 (3-16)	7.0 (2-16)
Number of prior anti-cancer regimens for locally advanced/metastatic,[a] not including hormone therapy, n (%)			
Median (Min, Max)	3.0 (1-10)	4.0 (0-10)	4.0 (0-10)
Prior CDK4/6 inhibitor, n (%)			
Yes	10 (47.6)	6 (18.2)	16 (29.6)
No	11 (52.4)	27 (81.8)	38 (70.4)

BC = breast cancer; CDK4/6 = cyclin-dependent kinase 4/6; ECOG PS = Eastern Cooperative Oncology Group performance status; HER2 = human epidermal growth factor receptor 2: IHC = immunohistochemistry; ISH = in situ hybridization; Max = maximum; Min = minimum

[a] Therapies intended for "locally advanced/metastatic" or intended for "neo-adjuvant", "adjuvant", or "maintenance" if progressive disease within 6 months since the end of the therapy.

Data cut-off: 01 Aug 2019 Source: Module 5.3.5.3 SCE J101 HER2-low BC Tables 14.1.3.4.2.2 and 14.1.3.4.2.3

Table 48 Objective Response Rate in HER2-low Breast Cancer Population of Study J101 (Intent-to-Treat Analysis Set; Study J101)

Parameter	HER2-low BC 5.4 mg/kg (N = 21)	HER2-low BC 6.4 mg/kg (N = 33)	Overall HER2-low BC (N = 54)
Best overall response per ICR with confirmation of response, n (%)			
Complete Response	1 (4.8)	0 (0.0)	1 (1.9)
Partial response	6 (28.6)	13 (39.4)	19 (35.2)
Stable disease	11 (52.4)	16 (48.5)	27 (50.0)
Progressive disease	3 (14.3)	3 (9.1)	6 (11.1)
Not evaluable	0 (0.0)	1 (3.0)	1 (1.9)
Confirmed ORR[a] by ICR			
n (%)	7 (33.3)	13 (39.4)	20 (37.0)
95% CI[b]	14.6, 57.0	22.9, 57.9	24.3, 51.3
Confirmed ORR[a] by investigator assessment			
n (%)	8 (38.1)	17 (51.5)	25 (46.3)
95% CI[b]	18.1, 61.6	33.5, 69.2	32.6, 60.4
Subgroups			
Confirmed ORR[a] by ICR by HER2 status			
IHC 1+			
n	14	14	28
Confirmed ORR, n (%)	6 (42.9)	4 (28.6)	10 (35.7)
95% CI[b]	17.7, 71.1	8.4, 58.1	18.6, 55.9
IHC 2+/ISH-negative			
n	7	19	26
Confirmed ORR, n (%)	1 (14.3)	9 (47.4)	10 (38.5)
95% CI[b]	0.4, 57.9	24.4, 71.1	20.2, 59.4
Confirmed ORR[a] by ICR by hormone receptor status			
Hormone receptor-positive			
n	19	28	47

Parameter	HER2-low BC 5.4 mg/kg (N = 21)	HER2-low BC 6.4 mg/kg (N = 33)	Overall HER2-low BC (N = 54)
Confirmed ORR, n (%)	7 (36.8)	12 (42.9)	19 (40.4)
95% CI[b]	16.3, 61.6	24.5, 62.8	26.4, 55.7
Hormone receptor-negative			
n	2	5	7
Confirmed ORR, n (%)	0 (0.0)	1 (20.0)	1 (14.3)
95% CI[b]	0.0, 84.2	0.5, 71.6	0.4, 57.9

BC = breast cancer; CI = confidence interval; CR = complete response; HER2 = human epidermal growth factor receptor 2; ICR = independent central review; IHC = immunohistochemistry; ISH = in situ hybridization; ORR = objective response rate; PR = partial response

[a] CR+PR

[b] 95% exact binomial confidence interval

Data cut-off: 01 Aug 2019 Source: Module 5.3.5.3 SCE J101 HER2-low BC Tables 14.2.2.2, 14.2.2.2.1, 14.2.2.2.9, 14.2.2.3, 14.2.2.3.1, and 14.2.2.3.9

The median **DoR** (01 Aug 2019 DCO) for confirmed responses based on ICR was 10.4 months (95%CI: 8.5, NE) for the overall HER2-low population: 9.6 months (95%CI: 5.7, NE) for the 5.4 mg/kg group and 10.4 months (95%CI: 3.4, NE) for the 6.4 mg/kg group, respectively.

As of 01 Aug 2019 DCO, the median duration of survival follow-up was 12.4 months (range: 1.6 to 34.8) for the overall HER2-low BC population: 11.9 months (range: 2.5 to 33.6) in the 5.4 mg/kg group and 12.9 months (range: 1.6 to 34.8) in the 6.4 mg/kg group. Median **OS** was 29.4 months (95%CI: 12.9, NE) for the overall HER2-low population: NE (95% CI: 11.1, NE) in the 5.4 mg/kg group and 19.7 months (95% CI: 12.5, NE) in the 6.4 mg/kg group, respectively.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The data from Study U303, PopPK analysis and ER analyses support the chosen dose of 5.4 mg/kg.

The efficacy assessment of the applied extension of indication is based on the pivotal study Destiny Breast04 (Study U303), which is a phase 3, randomised, open-label two-arm study comparing trastuzumab deruxtecan (T-DXd) head-to-head with single-agent chemotherapy per Physician's choice (TPC) for the treatment of HER2-low unresectable or metastatic breast cancer. TPC included the currently recommended SOC in the proposed settings, which is single-agent chemotherapy using either capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel. As pointed out by the Scientific Advice given in 2018, the use of gemcitabine monotherapy is not endorsed in the proposed setting; however, it is considered acceptable and among the standard options used in the EU for the treatment of metastatic breast cancer. The SA also pointed out that prior anthracycline therapy ought to have been given prior to inclusion to the pivotal study, and while this is not specifically mentioned in the in- or exclusion criteria, it was a requirement that included patients must have had received chemotherapy in the metastatic setting or have developed disease recurrence during or within 6 months of completing adjuvant chemotherapy, which would probably have included an anthracycline-based chemotherapy. Single-agent chemotherapy according to physician's choice was to be determined prior to randomisation which is endorsed. The MAH did not consider anthracyclines as comparator as these are commonly given in the neoadjuvant/adjuvant setting, rendering patients ineligible for further anthracycline therapy in the metastatic setting. Furthermore, the risk for cardiotoxicity with cumulating

dose limits long term treatment. This appears reasonable; however, as about two-thirds of patients received prior anthracycline treatment, anthracyclines might have been a suitable comparator for part of the patients. A post-hoc sensitivity analysis showed that the beneficial effect of T-DXd was observed independent of prior anthracycline use, which is reassuring. Information on prior anthracycline use has been added to section 5.1 of the SmPC.

This extension of indication is for treatment of patients with HER2-low unresectable or metastatic breast cancer, who have received one prior systemic therapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy, i.e. both the 1L and the 2L setting. The percentage of patients who had prior anthracycline use in the (neo)adjuvant setting was 46.3% and 19.4% in the locally advanced and/or metastatic setting. In the metastatic setting, patients had a median of 3 prior lines of systemic therapy (range: 1 to 9) with 57.6% having 1 and 40.9% having 2 prior chemotherapy regimens; 3.9% were early progressors (progression in the neo/adjuvant setting). In HR+ patients, the median number of prior lines of endocrine therapy was 2 (range: 0 to 9) and 70% had prior CDK4/6 inhibitor treatment. The newly proposed indication does not totally reflect the included study population in the pivotal trial in terms of endocrine therapy. For example, a third of the patients included have had 2 prior lines of endocrine therapy in the metastatic setting. In addition, 22.4% of subjects received subsequent endocrine therapy either as single agent or in combination after completion of T-DXd treatment (data not shown). It is also acknowledged that the treating physician may have reasons to treat with chemotherapy, e.g., when there is rapid progression and imminent organ failure (typically due to liver metastases), because a rapid response is needed and the response from endocrine therapy occurs more slowly (Gennari et al. ESMO. 2021). Moreover, there is no reason to doubt effectiveness of T-DXd in patients who did not receive any prior lines of endocrine therapy, so it is considered acceptable to extrapolate the efficacy to patients, who are not previously treated with endocrine therapy.

Low HER2 expression was defined as IHC2+/ISH- or IHC1+ (ISH- or not tested) according to ASCO/CAP guidelines per central assessment using the most recent tumour tissue sample available, which is endorsed. Although there was a slight difference in the wording of the HER2 1+ definition between the ASCO/CAP guidelines, the protocol for the pivotal study, and the pathologist training material used to train DB-04 central pathologist, it is considered that the definitions are similar. This is agreed since the slight difference is only in the wording, not in the interpretation of the staining. In both definitions, the % of cells presenting such staining intensity needs to be >10%.

All patients had to have a history of low HER2 expression; however, the concordance rate between central and local testing was only 75%. According to the Applicant, differences in testing methodologies and/or local scoring criteria, lack of local pathologist training for determination of HER2-low scores, and intrasubject tumour heterogeneity are some of the factors that would likely have contributed to the observed differences between local and central assessment of HER2 expression. Although this is acknowledged, the data indicate that there could be a risk that patients may be selected erroneously for treatment with T-DXd based on unvalidated local tests. As no information was available for patients with discordant results on timing of local test compared to central test and prior therapies, the reasons for the discordant results remain unknown. As most patients had an archival tissue sample for HER2 determination, there is no need to request for fresh tissue samples in the SmPC. In the pivotal study, there were two reasons for tumour tissue collection (HER2 and exploratory biomarker analysis) with different timings of collection. Tumour samples for HER2 testing per inclusion criterion 5 allowed archival tissue prior to last treatment whereas samples for biomarker analysis per inclusion criterion 6 were mandatory after most recent treatment.

Patients were recruited from 19 countries and the median follow-up was 16.1 months in the T-DXd arm vs 13.5 months in the TPC arm at the DCO of 11 January 2022. A total of 713 patients were

screened and 557 were randomised 2:1 to the two treatment arms and this is an acceptable sample size. Most patients randomised to the TPC arm received eribulin (51%) followed by capecitabine (20%). Each of the other products made up 8-10% of the TPC arm.

Randomisation was stratified by HER2 IHC status (1+ or 2+), number of prior chemotherapies (1 or 2), and hormone receptor/CDK status (HR+ with CDK4/6 (min 240), HR+ without CDK4/6 (max 240), HR- (about 60)). The stratification factors are endorsed as these might influence efficacy.

Main exclusion criteria were prior treatment with an antibody drug conjugate (ADC) consisting of a topoisomerase I inhibitor, uncontrolled or significant cardiovascular disease, history of (non-infectious) interstitial lung disease (ILD)/pneumonitis that required steroids, current or suspected ILD/pneumonitis, clinically severe pulmonary compromised resulting from intercurrent pulmonary illnesses, and spinal cord compression or clinically active central nervous system (CNS) metastases. These are in line with previous Enhertu studies and adequately described in section 5.1 of the SmPC.

The pivotal study was fully recruited in approximately 4 years and a relevant fraction of the patients has been recruited from an EU like population (~60%). The presented data are from the primary analysis of the primary efficacy endpoint of blinded independent central review (BICR)-assessed progression-free survival (PFS).

The scientific advice given from CHMP in 2018 recommended to consider OS as a primary endpoint and to power the study to obtain robust OS data. The MAH designed the study to achieve at least 80% to test OS, which is endorsed. Of note, 60 subjects with hormone receptor-negative BC were enrolled for exploratory purposes, which is in line with the CHMP recommendations given during the scientific advice. The inclusion of HR-negative patients is endorsed; however, a larger sample size would have been preferred for a more accurate estimation of the effect size in this subgroup.

The primary efficacy endpoint of PFS was assessed by BIRC using RECIST v1.1 in the hormone receptor-positive cohort (HR+) and the key secondary endpoint was PFS by BIRC in all randomised patients (FAS) and OS in both populations. Other secondary endpoints were PFS as assessed by the investigator, confirmed objective response rate (ORR), and duration of response (DOR) and PFS on next-line treatment by the investigator (PFS2). The primary and secondary endpoints are acceptable and established in the current setting. The primary efficacy endpoint and the key secondary efficacy endpoints were tested hierarchically to maintain the overall 2-sided Type I error rate of 0.05 or less and the statistical methods used are acceptable.

After the initial release (v1.0, 23 Aug 2018), the study protocol was amended 4 times. Most changes related to clarifications and updates to the inclusion criteria. The main change was with amendment 4 (v5.0, 12 Oct 2020) adding two interim analyses for OS (originally OS analysis at time of final PFS analysis) to ensure adequate follow-up and statistical power. The Applicant clarified that no information from Study U303 was used or available at the time of protocol amendment 4. Furthermore, the rationale for the amendment was to provide adequate follow-up and statistical power to detect a statistically significant difference in OS with a clinically meaningful improvement of 6 months over the expected SoC survival of 15 months and the revision of the OS assumptions was based on updated OS analysis from Study DS8201-A-J101. Moreover, the timing of the first IA for OS was dependent on the final analysis for PFS, which was unchanged during the study conduct. The timing of the planned second IA of OS was based on the assumed hazard ratio=0.72 and the median OS for the TPC arm of 15 months. The second IA for OS was planned with 70% IF relative to the target number of PFS events at the final analysis. This is acceptable.

Because the Applicant is seeking an indication regardless of HR status, the FAS is the main focus of the assessment. Baseline characteristics in the FAS (T-DXd vs TPC) showed that the median age was ~57

and 56 years with ~78% and 74% of the patients being less than 65 years old and ~22% and 26% of the patients were ≥65 years, which is considered reflective of the targeted patient population. Two male patients were included, both in the T-DXd treatment arm, which is acceptable since breast cancer is rare in men. Moreover, the results from the pivotal trial are considered extrapolatable to men with HER2-low breast cancer based on the common biological and pharmacological rationale in line with previous EMA decisions. There is limited data in patients older than 75 years as already reflected in section 4.2 of the SmPC.

Most patients were from Europe or Israel (44.5% vs 46.2%) or Asia (39.4% and 35.9%, respectively), so the majority of the patients were White or Asian. Hence, the fraction of European patients is acceptable for interpretation of the study results in an EU context.

More than half of the included patients had received 1 prior line of chemotherapy, while 43.2% and 44% of the patients had 2 prior lines of chemotherapy. Regarding endocrine therapy, many patients had already received two (~30%) or ≥3 (~24%) prior lines of endocrine therapy. The number of patients who had received 2 prior lines of chemotherapy and/or ≥3 lines of endocrine therapy may be slightly more than what could be expected; however, the study population is considered reflective of the overall targeted patient population. Approximately two-thirds (~62%) of the patients had hormone receptor (HR)-positive tumours and had received a CDK4/6 inhibitor, which is the current SoC, while 26% had HR+ tumors but did not receive a CDK4/6 inhibitor in addition to their endocrine therapy. The latter is considered higher than what would be expected in a European population based on current treatment guidelines. Approximately 11% of the FAS had HR-negative disease, since the number of included patients with HR- tumors was capped, a higher number would have been preferred for a more robust estimation of the effect size. Information on baseline characteristics is, in general, adequately reflected in the SmPC.

The majority of the patients had a history of visceral metastases (89.0% and 85.3%), with presence of liver (71.3% vs 66.8) or lung metastases (32.2% vs 34.2%) at baseline. BRCA status was missing in more than 60% of the patients, so the efficacy of T-DXd in the low number of patients with a BRCA1/2 mutation at baseline cannot be firmly concluded. Relatively few patients had CNS metastases at baseline (5.7%), which is considered reflective of the study population, who had mostly HR+ disease.

Baseline characteristics in the HR- cohort were in general comparable to the overall study population, although the proportion of patients receiving 1 prior line was lower and more patients had ECOG 1 in the HR- population. Also, baseline characteristics were largely comparable between treatment arms, although numbers were small in each arm. It is noted that there were four patients in each treatment arm who had an HR+ status for the electronic data capture (EDC) but not for interactive web/voice response system (IXRS; these were all HR-).

Efficacy data and additional analyses

The primary endpoint was met and the primary analysis of **PFS by BIRC in the HR+ population** showed a statistically significant and clinically relevant improvement from 5.4 months (95%CI: 4.4; 7.1) with TPC to 10.1 months (95%CI: 9.5; 11.5) with T-DXd, HR 0.51 (95%CI: 0.40; 0.64). The data is mature with 63.7% events in the active T-DXd arm and 67.5% events in the control arm. The KM curves for PFS by BIRC separate early and remain separated. The performance of the control arm is considered within the expected range for the 2L+ setting as the study population in Destiny Breast04 was heavily pre-treated. In context, the median PFS was 6 months in the 2L setting after one line of chemotherapy (MONARCH1) and only a median PFS of 3.7 months was shown for a pooled analysis from two phase 3 studies (Eribulin vs TPC or capecitabine in a 2L+ setting of HER2-negative MBC).

Sensitivity analyses conducted on the PFS and those assessing the impact of stratification and censoring rules were consistent with the primary analysis (HR ranging from 0.44 to 0.53), showing PFS benefit for T-DXd over TPC. A post-hoc sensitivity analysis of PFS by BICR in the hormone receptor-positive cohort to assess the impact of censoring due to withdrawal of consent showed no impact on the outcome of the PFS analysis.

Median PFS based on investigator was 9.6 months (95% CI: 8.4, 10.0) in the T-DXd arm compared with 4.2 months (95% CI: 3.4, 4.9) in the TPC arm (HR: 0.37; 95% CI: 0.30, 0.47). The overall concordance rates of PFS between investigator and BICR assessment were about 80% in both arms. A post-hoc sensitivity analysis including both BICR-assessed and investigator-assessed PD (whichever occurred first) confirmed robustness of results.

The secondary endpoint of **PFS by BIRC in the FAS** also showed a statistically significant and clinically relevant improvement from 5.1 months (95%CI: 4.2; 6.8) with TPC to 9.9 months (95%CI: 9.0; 11.3) with T-DXd, HR 0.50 (95%CI: 0.40, 0.63). These results were similar to those from the HR+ population, which can be expected as the HR+ subgroup constitutes 90% of the FAS. The data from the FAS were also mature with 65.1% events in the active T-DXd arm and 69% events in the control arm and the KM curves also separated early and remained separated .

PFS in the HR- population was 6.6 months (95%CI: 4.1, 11.7) in the T-DXd arm vs 2.9 months (95%CI: 1.4, 4.0) in the TPC arm, HR 0.45 (95%CI: 0.23, 0.87). Hence, the PFS was shorter in both arms, which is considered to be due the generally poorer prognosis of the HR- population. Nevertheless, the difference in PFS between the two arms is considered clinically relevant and these results are considered supportive of the primary endpoint and the claimed hormone-receptor-agnostic indication.

The key secondary endpoint of **overall survival** in the HR+ population and the FAS was statistically and clinically significantly improved at the time of the first IA with only 38.1% events with T-DXd and 44.8% events in the control arm after 18.4 months of follow up. Hence, the median OS for the HR+ populations was 23.9 months (95%CI: 20.8, 24.8) in the T-DXd arm vs 17.5 months (95%CI: 15.2, 22.4) in the TPC arm, HR 0.64 (95%CI: 0.48, 0.86), while the median OS for the FAS was 23.4 months (95%CI: 20.0, 24.8) in the T-DXd arm vs 16.8 months (95%CI: 14.5, 20.0) in the TPC arm, which is consistent with the results in the HR+ population. A difference in OS of more than 6 months between the treatment arms is considered clinically meaningful. The MAH is recommended to submit the final OS analysis from Study U303, projected to occur in Q4 2024, post-authorisation when available (PAM-REC).

In the HR- subgroup, the median OS was 16.6 months (95%CI: 11.3, NE) in the T-DXd arm vs. 10.3 months (95%CI: 6.1, 15.2) in the TPC arm (HR: 0.63; 95%CI: 0.32, 1.23). Some uncertainty remains on the true effect size in the HR- subgroup due to the small sample size. Nevertheless, given the magnitude of the effect observed, the poor prognosis of the HR- patients and the mechanism of action of T-DXd, it is reasonable to assume that HR- patients will benefit from treatment and inclusion in the indication is sufficiently supported. Additional observational studies will be performed by the Applicant providing further data on effectiveness in the HR- subgroup.

ORR by IRC for the FAS is also clinically and statistically significantly improved from 16.3% in the control arm to 52.3% with T-DXd, and the results were in line with those from the HR+ population. The induced responses were durable: median **DoR** was 10.7 months in the T DXd arm vs 6.8 months in the TPC arm, and since data was mature with ~57% and ~67 events in each arm, respectively, no updated data has been requested. ORR and median DoR also support a beneficial effect of T-DXd in the HR- subgroup.

A post-hoc sensitivity analyses in the HR- subgroup based on EDC confirmed a beneficial effect in this subgroup.

The Applicant was advised to provide **PFS 2** data. Approximately a third of the patients treated with T-DXd in both populations had a second progression of disease on their next line therapy, while ~20% have died. There were slightly more patients who had a PFS2 event in the control arm compared to T-DXd in both populations (~40%), but a similar fraction of deaths across the treatment arms, so there is no sign of a detriment for the patients treated with T-DXd. The PFS2 was 15.4 months for the T-DXd treated in the FAS compared to 10.5 months in the control arm, which is reassuring. PFS2 analysis for the HR- subgroup showed a gain in 4 months, supporting a beneficial effect.

Subgroup analyses of PFS by BIRC in the FAS supported a benefit of T-DXd compared with TPC for important pre-specified subgroups including HR status, prior CDK4/6i treatment, number of prior chemotherapies, and IHC 1+ and IHC 2+/ISH- status.

In addition, the OS benefit was observed across the majority of prespecified subgroups with point estimates of HR<1, except for the subgroup who received 1 prior line of ET (HR: 1.02, 95%CI: 0.58, 1.80) and the subgroup with moderate renal impairment (HR: 1.91, 95%CI: 0.84, 4.36). Most patients on T-DXd in the moderate renal impairment subgroup died due to PD and only two patients had an AE as primary cause of death which is reassuring. Further, it is noted that the median PFS (23.6 months) in the TPC arm appears somewhat better than seen in other subgroups (mostly <20 months). Overall, there are no signs of a safety issue and results may be chance finding in this small subgroup (n=64). Information on somewhat worse safety profile in this subgroup, and especially occurrence of ILD, is already included in the SmPC.

Patient-reported outcomes: There seems to be no detriment on QoL in patients treated with T-DXd compared to TPC and numerical increases in QoL may support the beneficial effect of T-DXd; however, the open-label study design precludes firm conclusions. Hence, the PRO results are not presented in the SmPC.

2.4.3. Conclusions on the clinical efficacy

The results from the pivotal Study U303 showed a statistically significant and clinically relevant improvement of both progression-free survival and overall survival in the HR+ population and the ITT population (FAS) for treatment with T-DXd compared to treatment per Physician's choice (TPC) in patients with HER2-low, unresectable or metastatic breast cancer treated with a prior chemotherapy. Supportive data are available in the HR- population, though some uncertainty remains on the true effect size in the HR- subgroup due to the small sample size. Nevertheless, given the magnitude of efficacy observed, the poor prognosis of the HR- patients and the mechanism of action of T-DXd, it is reasonable to assume that HR- patients will benefit from treatment and inclusion in the indication is sufficiently supported. The Applicant was recommended to provide the final efficacy data from the pivotal U303 study post-approval.

2.5. Clinical safety

Introduction

Safety data were summarised from the pooled safety population, who had received at least one dose of Enhertu 5.4 mg/kg (n=944) across multiple tumour types in clinical studies. Moreover, safety data from the pivotal study (n=543) was provided (Safety Analyses Set).

Table 49: Summary of Groups Included in Safety Data Presentations

Evaluation	Drug / Dose	Number of Subjects Treated
Data for Primary Analysis Subjects with HER2-low BC from Study U303	T-DXd 5.4 mg/kg TPC	T-DXd: 371 TPC: 172
All BC T-DXd 5.4 mg/kg Pool Multi-study pool of subjects with HER2-positive or HER2-low BC who received T-DXd 5.4 mg/kg (N = 883)	T-DXd 5.4 mg/kg	883 Study U303: 371 Study U302: 257 Study U201: 184 Study J101: 71
All Tumor Types T-DXd ≥5.4 mg/kg Pool Multi-study pool of subjects with any tumor type who received T-DXd ≥5.4 mg/kg (N = 1590)	T-DXd 5.4 mg/kg	944 Study U303: 371 Study U302: 257 Study U201: 184 Study J101: 91 Study U204: 41
	T-DXd 6.4 mg/kg	619 Study J101: 183 Study J202: 169 Study U201: 48 Study U204: 140 Study U205: 79
	T-DXd 7.4 mg/kg	Study U201: 21
	T-DXd 8.0 mg/kg	Study J101: 6

BC = breast cancer; HER2 = human epidermal growth factor receptor 2; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice

Source:, Module 5.3.5.3 SCS SAP v1.0

Patient exposure

Table 50: Summary of Exposure in Study U303 (Safety Analysis Set)

Parameter	T-DXd (N = 371)	Overall TPC (N = 172)	Eribulin (N = 89)	Capecitabine (N = 36)	Nab-paclitaxel (N = 17)	Gemcitabine (N = 16)	Paclitaxel (N = 14)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Treatment duration (months) [a]								
Mean	9.17	4.44	4.32	5.82	3.91	2.61	4.33	11.68
Std Dev	6.428	3.722	3.360	5.064	3.747	1.809	2.406	7.641
Median	8.21	3.47	3.65	4.11	2.76	1.63	4.29	9.89
Minimum, Maximum	0.2, 33.3	0.3, 17.6	0.3, 17.5	0.3, 17.6	0.7, 16.8	1.1, 6.9	0.4, 9.0	0.2, 37.1
Duration of treatment as of data cut-off,[a] n (%)								
≤3 months	71 (19.1)	79 (45.9)	36 (40.4)	15 (41.7)	10 (58.8)	13 (81.3)	5 (35.7)	120 (13.6)
>3 to ≤6 months	71 (19.1)	57 (33.1)	38 (42.7)	7 (19.4)	4 (23.5)	2 (12.5)	6 (42.9)	142 (16.1)
>6 to ≤9 months	73 (19.7)	20 (11.6)	9 (10.1)	5 (13.9)	2 (11.8)	1 (6.3)	3 (21.4)	139 (15.7)
>9 to ≤12 months	47 (12.7)	6 (3.5)	3 (3.4)	3 (8.3)	0	0	0	100 (11.3)
>12 to ≤18 months	66 (17.8)	10 (5.8)	3 (3.4)	6 (16.7)	1 (5.9)	0	0	163 (18.5)
>18 to ≤24 months	33 (8.9)	0	0	0	0	0	0	163 (18.5)
>24 months	10 (2.7)	0	0	0	0	0	0	56 (6.3)
Total patient-years of exposure [b]	283.5	63.6	32.1	17.5	5.5	3.5	5.1	859.6
Cumulative dose level [c]								
Mean (Std Dev)	65.57 (45.261)	--	14.39 (10.561)	218082.70 (191731.884)	1178.87 (991.607)	7256.68 (5455.184)	1096.40 (658.832)	82.74 (53.548)
Median	54.78	--	12.85	166586.37	794.12	5696.43	942.15	72.39

Parameter	T-DXd (N = 371)	Overall TPC (N = 172)	Eribulin (N = 89)	Capecitabine (N = 36)	Nab-paclitaxel (N = 17)	Gemcitabine (N = 16)	Paclitaxel (N = 14)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Minimum, Maximum	5.3, 219.8	--	1.2, 54.2	6930.4, 772970.1	260, 4334.9	1986.8, 25000	163.2, 2369.4	5.3, 239.0
Number of cycles								
Mean (Std Dev)	12.6 (8.75)	6.2 (5.00)	6.2 (4.61)	7.9 (6.64)	5.3 (5.10)	3.9 (2.55)	5.9 (3.25)	16.0 (10.38)
Median	11.0	5.0	6.0	6.0	4.0	3.0	6.0	14.0
Minimum, Maximum	1, 47	1, 25	1, 25	1, 23	1, 23	2, 10	1, 13	1, 47
Dose intensity [d]								
Mean (Std Dev)	5.13 (1.165)	--	2.33 (0.421)	26953.47 (5656.888)	232.98 (34.103)	2016.24 (544.569)	182.58 (46.284)	5.03 (0.883)
Median	5.24	--	2.34	26922.86	241.20	2140.46	180.80	5.21
Minimum, Maximum	2.6, 22.7	--	1.3, 3.3	14553.8, 35965.5	152.6, 282.2	1192.1, 2678.6	85.8, 263.6	2.5, 22.7
Relative dose intensity [e] (%)								
Mean (Std Dev)	99.78 (1.796)	102.65 (20.083)	99.22 (4.555)	114.10 [f] (41.730)	100.35 (1.096)	100.16 (2.392)	100.65 (2.443)	97.56 (7.196)
Median	99.97	100.00	99.92	99.71	100.05	100.18	100.23	99.81
Minimum, Maximum	91.5, 107.9	59.0, 198.5	78.5, 113.0	59.0, 198.5	98.5, 103.4	94.6, 104.4	97.6, 108.1	46.1, 107.9
Relative dose intensity categories, n (%)								
≥90%	371 (100.0)	157 (91.3)	84 (94.4)	26 (72.2)	17 (100.0)	16 (100.0)	14 (100.0)	813 (92.1)
<90% to ≥80%	0	9 (5.2)	4 (4.5)	5 (13.9)	0	0	0	34 (3.9)
<80% to ≥60%	0	5 (2.9)	1 (1.1)	4 (11.1)	0	0	0	29 (3.3)
<60%	0	1 (0.6)	0	1 (2.8)	0	0	0	7 (0.8)

BC = breast cancer; CSR = clinical study report; N = total number of treated subjects; RDI = relative dose intensity; SAP = Statistical Analysis Plan; Std Dev = standard deviation; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
Units: T-DXd = mg/kg; capecitabine, gemcitabine, paclitaxel, nab-paclitaxel = mg/m^2; eribulin = mg*/m^2, where * refers to eribulin mesylate. 1.23 mg eribulin base = 1.4 mg eribulin mesylate
For the exposure summary for TPC in Study U303, the study conventions specified in the CSR SAP were followed.
1 month = 365.25/12 = 30.44 days
[a] Treatment duration (months) = (date of last dose – date of first dose) + a cycle length [days]/30.44
[b] Total patient-years of exposure = sum of treatment duration (months) of all subjects/12
[c] Cumulative dose level (units) = sum of the actual dose levels received (units given above). Due to different dosing schedules and units among the individual TPC treatments, cumulative dose level is not presented for the overall TPC arm.
[d] Dose intensity (units/cycle length in weeks) = cumulative dose level (units given above) / (duration of treatment [days]/cycle length [days]).
[e] Relative dose intensity (%) derivation/definition for each study followed the study convention specified in the specific CSR SAP.
[f] For capecitabine, the planned dose was derived based on the total daily dose on the first day of dosing/body surface area, and RDI was calculated as the planned dose on the first dosing day × the duration of exposure (days). For 11 subjects, the dose received on the first day of dosing was lower than any subsequent dose for that subject; therefore, the RDI for these subjects exceeded 100%, and resulted in the mean RDI >100% for the subjects treated with capecitabine.
Source: Module 5.3.5.3 SCS Table 1.1.3; Module 5.3.5.1 DS8201-A-U303 CSR Table 14.1.5.1.1.

Adverse events

Table 51: Summary of Subject Disposition (Safety Analysis Set)

Parameter	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 172)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Subjects who were ongoing study drug as of the DCO	58 (15.6)	3 (1.7)	223 (25.3)
Subjects who discontinued study drug for any reason	313 (84.4)	169 (98.3)	660 (74.7)
Progressive disease [a]	220 (59.3)	130 (75.6)	395 (44.7)
Adverse event	60 (16.2)	14 (8.1)	146 (16.5)
Withdrawal by subject	12 (3.2)	11 (6.4)	41 (4.6)
Clinical progression [b]	10 (2.7)	8 (4.7)	33 (3.7)
Death	5 (1.3)	2 (1.2)	16 (1.8)
Physician decision	4 (1.1)	3 (1.7)	14 (1.6)
Lost to follow-up	0	1 (0.6)	0
Other	2 (0.5) [c]	0	15 (1.7)

BC = breast cancer; DCO = data cut-off; N = total number of treated subjects; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
[a] Based on RECIST v1.1
[b] Per investigator assessment
[c] Subject No. [redacted] (dose delay of longer than 28 days); Subject No. [redacted] (physician decision entered as Other in electronic data capture) (Module 5.3.5.1 DS8201-A-U303 CSR Listing 16.2.1.1). Source: Module 5.3.5.3 SCS Table 1.1.1

Table 52: Overview of Treatment-emergent Adverse Events (Safety Analysis Set)

Parameter	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 172)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Subjects with any TEAE	369 (99.5)	169 (98.3)	878 (99.4)
TEAEs with worst CTCAE ≥Grade 3 [a]	195 (52.6)	116 (67.4)	479 (54.2)
Serious TEAEs	103 (27.8)	43 (25.0)	222 (25.1)
TEAEs associated with study drug discontinuation	60 (16.2)	14 (8.1)	143 (16.2)

Parameter	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 172)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
TEAEs associated with dose reduction	84 (22.6)	66 (38.4)	195 (22.1)
TEAEs associated with study drug interruption	143 (38.5)	72 (41.9)	369 (41.8)
TEAEs associated with an outcome of death [b]	14 (3.8)	5 (2.9)	32 (3.6)
Subjects with any drug-related TEAE [c]	357 (96.2)	162 (94.2)	862 (97.6)
Drug-related TEAEs with worst CTCAE ≥Grade 3 [a]	154 (41.5)	99 (57.6)	397 (45.0)
Drug-related serious TEAEs	48 (12.9)	19 (11.0)	112 (12.7)
Drug-related TEAEs associated with study drug discontinuation	56 (15.1)	12 (7.0)	133 (15.1)
Drug-related TEAEs associated with dose reduction	77 (20.8)	64 (37.2)	181 (20.5)
Drug-related TEAEs associated with study drug interruption	106 (28.6)	62 (36.0)	286 (32.4)
Drug-related TEAEs associated with an outcome of death [b]	7 (1.9)	0	11 (1.2)

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, Version 5.0; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
[a] A subject was counted once at the maximum severity.
[b] For specific TEAEs associated with an outcome of death, refer to Table 2.10.
[c] If relationship was missing, the TEAE was considered to be related to the drug. Source: Module 5.3.5.3 SCS Table 1.2.1.1.1

Table 53: Treatment-emergent Adverse Events Reported in ≥10% of Subjects in Either Treatment Arm in Study U303, by Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA Preferred Term/ Grouped Term [a]	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 172)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Subjects with any TEAE	369 (99.5)	169 (98.3)	878 (99.4)
Nausea	282 (76.0)	52 (30.2)	682 (77.2)
Fatigue [a]	199 (53.6)	83 (48.3)	496 (56.2)
Vomiting	150 (40.4)	23 (13.4)	406 (46.0)
Alopecia	147 (39.6)	57 (33.1)	360 (40.8)
Anemia [a]	143 (38.5)	47 (27.3)	317 (35.9)
Constipation	126 (34.0)	38 (22.1)	308 (34.9)
Neutropenia [a]	126 (34.0)	90 (52.3)	318 (36.0)
Transaminases increased [a]	120 (32.3)	54 (31.4)	254 (28.8)
Decreased appetite	118 (31.8)	33 (19.2)	285 (32.3)
Diarrhoea	100 (27.0)	38 (22.1)	260 (29.4)
Musculoskeletal pain [a]	99 (26.7)	45 (26.2)	238 (27.0)
Thrombocytopenia [a]	95 (25.6)	16 (9.3)	220 (24.9)
Leukopenia [a]	89 (24.0)	56 (32.6)	223 (25.3)

MedDRA Preferred Term/ Grouped Term [a]	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 172)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Abdominal pain [a]	65 (17.5)	23 (13.4)	173 (19.6)
Weight decreased	60 (16.2)	14 (8.1)	129 (14.6)
Headache [a]	55 (14.8)	11 (6.4)	164 (18.6)
Upper respiratory tract infection [a]	51 (13.7)	9 (5.2)	176 (19.9)
Stomatitis [a]	49 (13.2)	19 (11.0)	142 (16.1)
Pyrexia	46 (12.4)	22 (12.8)	107 (12.1)
Interstitial lung disease [b]	45 (12.1)	1 (0.6)	112 (12.7)
Arthralgia	43 (11.6)	20 (11.6)	107 (12.1)
Blood potassium decreased [a]	41 (11.1)	13 (7.6)	108 (12.2)
Epistaxis	39 (10.5)	2 (1.2)	105 (11.9)
Dyspnoea	38 (10.2)	16 (9.3)	99 (11.2)
Peripheral sensory neuropathy	18 (4.9)	19 (11.0)	55 (6.2)
Palmar-plantar erythrodysaesthesia syndrome	5 (1.3)	24 (14.0)	14 (1.6)

BC = breast cancer; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities, Version 24.0; N = total number of treated subjects; PT = preferred term; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

If a subject had multiple occurrences of the same PT/grouped term, the subject was counted once for that PT/grouped term. If a subject had multiple PTs/grouped terms, the subject was counted in each of the different PTs/grouped terms.

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

TEAEs are sorted by descending frequency in the T-DXd arm.

[a] The PTs included in each grouped term are listed in Table 2.1.

[b] Interstitial lung disease includes events that were adjudicated as ILD and related to use of T-DXd or TPC.

Source: Module 5.3.5.3 SCS Tables 1.2.1.3.1, 1.2.2.1, 1.2.4.1

Treatment-related AEs

Table 54: Drug-related Treatment-emergent Adverse Events Reported in ≥10% of Subjects in Either Treatment Arm in Study U303, by Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA Preferred Term/ Grouped Term [a]	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 172)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Subjects with any drug-related TEAE	357 (96.2)	162 (94.2)	862 (97.6)
Nausea	271 (73.0)	41 (23.8)	657 (74.4)
Fatigue [a]	177 (47.7)	73 (42.4)	447 (50.6)
Alopecia	140 (37.7)	56 (32.6)	347 (39.3)
Vomiting	126 (34.0)	17 (9.9)	349 (39.5)
Anemia [a]	123 (33.2)	39 (22.7)	279 (31.6)
Neutropenia [a]	123 (33.2)	88 (51.2)	311 (35.2)
Decreased appetite	106 (28.6)	28 (16.3)	258 (29.2)
Thrombocytopenia [a]	88 (23.7)	16 (9.3)	209 (23.7)
Transaminases increased [a]	87 (23.5)	39 (22.7)	200 (22.7)

MedDRA Preferred Term/ Grouped Term [a]	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 172)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Leukopenia [a]	86 (23.2)	54 (31.4)	217 (24.6)
Diarrhoea	83 (22.4)	31 (18.0)	209 (23.7)
Constipation	79 (21.3)	22 (12.8)	191 (21.6)
Weight decreased	46 (12.4)	8 (4.7)	95 (10.8)
Abdominal pain [a]	45 (12.1)	4 (2.3)	108 (12.2)
Interstitial lung disease [b]	45 (12.1)	1 (0.6)	112 (12.7)
Stomatitis [a]	42 (11.3)	18 (10.5)	126 (14.3)
Musculoskeletal pain [a]	34 (9.2)	20 (11.6)	92 (10.4)
Palmar-plantar erythrodysaesthesia syndrome	4 (1.1)	24 (14.0)	11 (1.2)

BC = breast cancer; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities, Version 24.0; N = total number of treated subjects; PT = preferred term; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

If a subject had multiple occurrences of the same PT/grouped term, the subject was counted once for that PT/grouped term. If a subject had multiple PTs/grouped terms, the subject was counted in each of the different PTs/grouped terms.

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

TEAEs are sorted by descending frequency in the T-DXd arm.

[a] The PTs included in each grouped term are listed in 2.1.

[b] Interstitial lung disease includes events that were adjudicated as ILD and related to use of T-DXd or TPC.

Source: Module 5.3.5.3 SCS Tables 1.2.1.4, 1.2.2.2, 1.2.4.1

Table 55: Treatment-emergent Adverse Events of CTCAE Grade 3 or Higher Reported in ≥5% of Subjects in Either Treatment Arm in Study U303, by Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA Preferred Term/ Grouped Term [a]	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 272)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Subjects with any TEAE ≥Grade 3 [b]	195 (52.6)	116 (67.4)	479 (54.2)
Neutropenia [a]	52 (14.0)	71 (41.3)	152 (17.2)
Anemia [a]	38 (10.2)	9 (5.2)	81 (9.2)
Fatigue [a]	32 (8.6)	8 (4.7)	68 (7.7)
Leukopenia [a]	25 (6.7)	33 (19.2)	59 (6.7)
Thrombocytopenia [a]	22 (5.9)	1 (0.6)	53 (6.0)
Transaminases increased [a]	21 (5.7)	17 (9.9)	37 (4.2)
Lymphopenia [a]	20 (5.4)	6 (3.5)	44 (5.0)

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, Version 5.0; MedDRA = Medical Dictionary for Regulatory Activities, Version 24.0; N = total number of treated subjects; PT = preferred term; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

If a subject had multiple occurrences of the same PT/grouped term, the subject was counted once for that PT/grouped term. If a subject had multiple PTs/grouped terms, the subject was counted in each of the different PTs/grouped terms.

TEAEs are sorted by descending frequency in the T-DXd arm.

[a] The PTs included in each grouped term are listed in Table 2.1.

[b] For each PT/grouped term, a subject was counted once at the maximum severity.

Source: Module 5.3.5.3 SCS Tables 1.2.1.5, 1.2.2.1

Table 56

Table 10.7: Drug-related Treatment-emergent Adverse Events of CTCAE ≥Grade 3 Reported in ≥2% of Subjects in Either Treatment Arm, by Preferred Term or Grouped Term (Safety Analysis Set)

MedDRA Preferred Term or Grouped Term [a]	Number (%) of Subjects	
	T-DXd (N = 371)	TPC (N = 172)
Any drug-related TEAE ≥Grade 3	154 (41.5)	99 (57.6)
Neutropenia [a]	51 (13.7)	70 (40.7)
Anemia [a]	30 (8.1)	8 (4.7)
Fatigue [a]	28 (7.5)	8 (4.7)
Leukopenia [a]	24 (6.5)	33 (19.2)
Thrombocytopenia [a]	19 (5.1)	1 (0.6)
Nausea	17 (4.6)	0
Lymphopenia [a]	16 (4.3)	6 (3.5)
Transaminases increased [a]	12 (3.2)	14 (8.1)
Decreased appetite	9 (2.4)	2 (1.2)
Interstitial lung disease [b]	8 (2.2)	0
Febrile neutropenia	1 (0.3)	5 (2.9)
Palmar-plantar erythrodysaesthesia syndrome	0	7 (4.1)
Neuropathy peripheral	0	4 (2.3)

CTCAE = Common Terminology Criteria for Adverse Events v5.0; MedDRA = Medical Dictionary for Regulatory Activities v24.0; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

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

[a] The preferred terms included in each of the grouped terms in this table are listed in Table 6.5.

[b] Interstitial lung disease includes events that were adjudicated as ILD and related to use of T-DXd or TPC.

Data cut-off: 11 Jan 2022

Source: Tables 14.3.1.6.3, 14.3.1.7.7, 14.3.1.8.1

Adverse events of special interest

Table 57: Selected Preferred Terms in Adverse Events of Special Interest in Study U303

Category	Selected Preferred Terms for Review
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

Category	Selected Preferred Terms for Review
	Ejection fraction decreased Left ventricular dysfunction Left ventricular failure Right ventricular failure Ventricular failure

ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities, Version 24.0; PT = preferred term; SMQ = Standardised MedDRA Query

ILD/pneumonitis

Table 58: ILD Events by Adjudicated Outcome and Adjudicated Grade in Study U303 (Safety Analysis Set)

Adjudicated Outcome / CTCAE Grade Reported by Adjudication Committee [a]	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 172)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Subjects with any event of potential ILD (ie, event sent for adjudication)	56 (15.1)	2 (1.2)	147 (16.6)
Subjects with any event adjudicated as ILD	46 (12.4)	1 (0.6)	117 (13.3)
Grade 1	13 (3.5)	1 (0.6)	28 (3.2)
Grade 2	25 (6.7)	0	67 (7.6)
Grade 3	5 (1.3)	0	9 (1.0)
Grade 4	0	0	1 (0.1)
Grade 5	3 (0.8)	0	12 (1.4)
≥Grade 3	8 (2.2)	0	22 (2.5)
Subjects with any event adjudicated as drug-related ILD	45 (12.1)	1 (0.6)	112 (12.7)
Grade 1	13 (3.5)	1 (0.6)	28 (3.2)
Grade 2	24 (6.5)	0	65 (7.4)
Grade 3	5 (1.3)	0	9 (1.0)
Grade 4	0	0	0
Grade 5	3 (0.8)	0	10 (1.1)
≥Grade 3	8 (2.2)	0	19 (2.2)

AC = Adjudication Committee; BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, Version 5.0; ILD = interstitial lung disease; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

Table includes all events that were submitted to the ILD AC.

If a subject had multiple ILD events, the CTCAE grade is shown for the event with the worst grade.

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

[a] The ILD AC assigned grades to those events that were determined to be ILD.

Source: Module 5.3.5.3 SCS Table 1.2.5.1

Table 59: Overview of Adjudicated Drug-related ILD Events (Safety Analysis Set)

Adjudicated Outcome / CTCAE Grade Reported by Adjudication Committee	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 172)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Subjects with any event adjudicated as drug-related ILD	45 (12.1)	1 (0.6)	112 (12.7)
ILD CTCAE ≥Grade 3 [a]	8 (2.2)	0	19 (2.2)

Adjudicated Outcome / CTCAE Grade Reported by Adjudication Committee	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 172)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Serious ILD	16 (4.3)	1 (0.6)	36 (4.1)
ILD associated with study drug discontinuation [b]	31 (8.4)	0	78 (8.8)
ILD associated with dose reduction [b]	2 (0.5)	0	8 (0.9)
ILD associated with study drug interruption [b]	11 (3.0)	0	26 (2.9)
ILD associated with an outcome of death [c]	3 (0.8)	0	10 (1.1)

AC = Adjudication Committee; BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, Version 5.0; ILD = interstitial lung disease; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
[a] The ILD AC assigned grades to those events that were determined to be ILD. A subject was counted once at the maximum severity.
[b] Based on investigator assessment
[c] Adjudicated drug-related ILD associated with death was derived based on adjudicated CTCAE Grade 5 events.
Source: Module 5.3.5.3 SCS Tables 1.2.4.1, 1.2.4.2, 1.2.4.3, 1.2.4.4, 1.2.4.5, 1.2.4.6

Table 60: Outcome of Events Adjudicated as Drug-related ILD (Safety Analysis Set)

Outcome of Event	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 172)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Subjects with any event adjudicated as drug-related ILD	45 (12.1)	1 (0.6)	112 (12.7)
Recovered/resolved	25 (55.6)	0	59 (52.7)
Not recovered/not resolved	10 (22.2)	1 (100.0)	29 (25.9)
Ongoing	0	0	1 (0.9)
Recovering/resolving	4 (8.9)	0	7 (6.3)
Recovered/resolved with sequelae	2 (4.4)	0	5 (4.5)
Death [a]	2 (4.4)	0	8 (7.1)
Missing/unknown	2 (4.4)	0	3 (2.7)

BC = breast cancer; ILD = interstitial lung disease; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice
For the 3 subjects who had more than 1 event of adjudicated drug-related ILD, the worst-grade event is included.
Percentage for adjudicated drug-related ILD (first row of results) was calculated using the number of subjects in the Safety Analysis Set as the denominator.
Percentage for each outcome was calculated using the number of subjects with adjudicated drug-related ILD as the denominator.
[a] Based on investigator assessment. One of the 3 events adjudicated as Grade 5 ILD is not included in ILD associated with an outcome of death as assessed by the investigator. One subject who experienced an investigator-assessed Grade 3 ILD event died due to disease progression (>47 days after last study drug administration); the ILD Adjudication Committee adjudicated the event as Grade 5.
Source: Module 5.3.5.3 SCS Table 1.2.5.4, Module 5.3.5.1 DS8201-A-U303 CSR Table 10.25

LVEF decrease/Left ventricular dysfunction

Table 61: Summary of LVEF Values, Based on ECHO/MUGA Scan Data (Safety Analysis Set)

Parameter	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 172)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Subjects with worst LVEF CTCAE grade post-baseline, n (%)			
Non-missing n [a]	335	142	827
Grade 2	50 (14.9)	11 (7.7)	131 (15.8)

Parameter	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 172)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Subjects with LVEF measurement after worst grade	36	5	100
Recovered from worst grade to ≥90% of baseline, [b] n (%) [c]	26 (72.2)	3 (60.0)	78 (78.0)
Grade 3	5 (1.5)	0	7 (0.8)
Subjects with LVEF measurement after worst grade	4	0	6
Recovered from worst grade to ≥90% of baseline, [b] n (%) [c]	3 (75.0)	0	5 (83.3)
LVEF measurements at baseline			
n	370	171	882
Mean (Std Dev)	64.1 (6.10)	63.8 (6.12)	64.2 (6.31)
Median	64.0	64.0	64.0
Minimum, Maximum	50, 83	50, 87	50, 86
40% to 49%	0	0	0
20% to 39%	0	0	0
<20%	0	0	0
Lowest LVEF measurement post-baseline			
n	335	142	827
Mean (Std Dev)	60.4 (6.29)	62.6 (6.23)	60.3 (5.87)
Median	61.0	63.0	60.0
Minimum, Maximum	37, 79	42, 79	37, 79
40% to 49%	13 (3.5)	2 (1.2)	23 (2.6)
20% to 39%	2 (0.5)	0	2 (0.2)
<20%	0	0	0
Change from baseline to lowest post-baseline measurement			
n	335	142	827
Mean (Std Dev)	-3.9 (5.70)	-1.6 (5.32)	-3.9 (5.35)
Median	-3.0	-1.0	-3.0
Minimum, Maximum	-36, 13	-17, 14	-36, 13
10% to 19% decrease in absolute value	44 (11.9)	10 (5.8)	120 (13.6)
≥20% decrease in absolute value	4 (1.1)	0	6 (0.7)
Highest LVEF measurement post-baseline			
n	335	142	827
Mean (Std Dev)	65.8 (6.93)	64.6 (5.97)	67.0 (6.60)
Median	66.0	65.0	67.0
Minimum, Maximum	43, 90	46, 80	43, 90
Change from baseline to highest post-baseline measurement			
n	335	142	827

Parameter	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 172)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Mean (Std Dev)	1.5 (5.65)	0.4 (5.15)	2.7 (5.78)
Median	1.0	0	2.0
Minimum, Maximum	-20, 21	-17, 14	-20, 22
10% to 19% increase in absolute value	23 (6.2)	7 (4.1)	97 (11.0)
≥20% increase in absolute value	1 (0.3)	0	3 (0.3)

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, Version 5.0; ECHO = echocardiogram; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition; N = total number of subjects treated; Std Dev = standard deviation; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice

Per CTCAE, LVEF decrease 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%.

[a] Non-missing n was the number of subjects with both baseline and post-baseline data. Percentages were calculated using the non-missing n as the denominator.

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

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

Source: Module 5.3.5.3 SCS Table 1.2.6.8

Serious adverse event/deaths/other significant events

Table 62: Serious Treatment-emergent Adverse Events Reported in ≥1% of Subjects in Either Treatment Arm in Study U303, by Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA Preferred Term/Grouped Term [a]	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 172)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Any subject with a serious TEAE	103 (27.8)	43 (25.0)	222 (25.1)
Interstitial lung disease [b,c]	16 (4.3)	1 (0.6)	36 (4.1)
Pneumonia [c]	7 (1.9)	1 (0.6)	17 (1.9)
Dyspnoea	5 (1.3)	2 (1.2)	7 (0.8)
Musculoskeletal pain [a]	5 (1.3)	0	8 (0.9)
Sepsis	5 (1.3)	0	7 (0.8)
Febrile neutropenia	4 (1.1)	4 (2.3)	8 (0.9)
Anemia [a]	4 (1.1)	1 (0.6)	10 (1.1)
Hypercalcaemia	4 (1.1)	0	4 (0.5)
Nausea	4 (1.1)	0	9 (1.0)
Pyrexia	4 (1.1)	0	8 (0.9)
Vomiting	4 (1.1)	0	13 (1.5)
Fatigue [a]	3 (0.8)	2 (1.2)	4 (0.5)
Pleural effusion	3 (0.8)	2 (1.2)	6 (0.7)
Neutropenia [a]	2 (0.5)	4 (2.3)	3 (0.3)
Disease progression	2 (0.5)	2 (1.2)	7 (0.8)
Hepatic failure	1 (0.3)	2 (1.2)	1 (0.1)
Hyponatraemia	1 (0.3)	2 (1.2)	1 (0.1)
Colitis	0	2 (1.2)	1 (0.1)
Femur fracture	0	2 (1.2)	1 (0.1)

MedDRA Preferred Term/Grouped Term [a]	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 172)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Medication error	0	3 (1.7)	0
Overdose	0	5 (2.9) [d]	0

BC = breast cancer; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities, Version 24.0; N = total number of treated subjects; PT = preferred term; TEAE = treatment-emergent adverse event; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

If a subject had multiple occurrences of the same serious PT/grouped term, the subject was counted once for that serious PT/grouped term. If a subject had multiple serious PTs/grouped terms, the subject was counted once for each of the different PTs/grouped terms.

TEAEs are sorted by descending frequency in the T-DXd arm.

[a] The PTs included in each grouped term are listed in Table 2.1.

[b] Interstitial lung disease includes events that were adjudicated as ILD and related to use of T-DXd or TPC.

[c] Includes 2 subjects in the T-DXd arm with a PT of pneumonia that was adjudicated as drug-related ILD. These subjects are counted under both adjudicated drug-related ILD and pneumonia.

[d] For more information on subjects with a TEAE of overdose, refer to Section 5.5

Source: Module 5.3.5.3 SCS Tables 1.2.1.8, 1.2.2.3, 1.2.4.2

Deaths

Table 63: Primary Cause of Any Deaths and On-treatment Deaths (Safety Analysis Set)

Primary Cause of Death	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 172)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Any death	148 (39.9)	88 (51.2)	280 (31.7)
Disease progression	122 (32.9)	79 (45.9)	217 (24.6)
Adverse event	10 (2.7) [a]	0	20 (2.3)
Other	3 (0.8) [b]	3 (1.7) [c]	13 (1.5)
Unknown	13 (3.5)	6 (3.5)	30 (3.4)
On-treatment death [d]	14 (3.8)	8 (4.7)	30 (3.4)
Disease progression	4 (1.1)	7 (4.1)	12 (1.4)
Adverse event	8 (2.2) [a]	0	14 (1.6)
Other	1 (0.3)	1 (0.6)	2 (0.2)
Unknown	1 (0.3)	0	2 (0.2)

BC = breast cancer; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

[a] Adverse events with outcome of death in the T-DXd arm were pneumonitis for Subject Nos. [redacted] (on-treatment death for the latter subject), respiratory failure for Subject N[redacted]xxx (on-treatment death), general physical health deterioration for Subject N[redacted] xxxxxx, colitis ischaemic for Sub[redacted]xxxxxxx (on-treatment death), dyspnoea for Sub[redacted]xxxxxxx (on-treatment death), sepsis for [redacted]xxxxxxxxxx (both were on-treatment deaths), disseminated intravascular coagulation fo[redacted]No. ~~xxxxxxxx~~(on-treatment death), and febrile neutro[redacted]Subject No. ~~xxxxxxxx~~ (on-treatment death).

[b] The investigator recorded a primary cause of death as "Other: disease worsening under study" for Subject No. [redacted], "Other: clinical progression" for Subject No. [redacted], and "Other: cachexia due to cancer" for Subject No. [redacted] (on-treatment death).

[c] The investigator recorded a primary cause of death as "Other: respiratory arrest" for Subject No. [redacted], "Other: respiratory failure due to pneumonitis, pulmonary embolus" for Subject No. [redacted], and "Other: disease progression (liver dysfunction)" for Subject No. [redacted] ~~xxxxxxxx~~ (on-treatment death).

[d] On-treatment death was defined as any death that occurred from the date of the first dose to 28 days after the last dose of study drug for Study J101 and to 47 days after the last dose of study drug for other studies in the All BC T-DXd 5.4 mg/kg Pool.

Source: Module 5.3.5.3 SCS Table 1.2.7, Listings 1.1, 1.2

Table 64: Treatment-emergent Adverse Events Associated with an Outcome of Death, by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 172)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Any subject with a TEAE associated with an outcome of death	14 (3.8)	5 (2.9)	32 (3.6)
Disease progression	2 (0.5)	2 (1.2)	7 (0.8)
Pneumonitis	2 (0.5)	0	4 (0.5)
Sepsis	2 (0.5)	0	2 (0.2)
Colitis ischaemic	1 (0.3)	0	1 (0.1)
Death	1 (0.3)	0	1 (0.1)
Disseminated intravascular coagulation	1 (0.3)	0	1 (0.1)
Dyspnoea	1 (0.3)	1 (0.6)	1 (0.1)
Febrile neutropenia	1 (0.3)	0	1 (0.1)
General physical health deterioration	1 (0.3)	0	2 (0.2)
Pleural effusion	1 (0.3)	0	1 (0.1)
Respiratory failure	1 (0.3)	0	4 (0.5)
Acute hepatic failure	0	0	1 (0.1)
Acute kidney injury	0	0	1 (0.1)
Acute respiratory failure	0	0	1 (0.1)
COVID-19	0	0	1 (0.1)
Hepatic failure	0	2 (1.2)	0
Lymphangitis	0	0	1 (0.1)
Pneumonia	0	0	1 (0.1)
Shock haemorrhagic	0	0	1 (0.1)
Sudden death	0	0	1 (0.1)

BC = breast cancer; MedDRA = Medical Dictionary for Regulatory Activities, Version 24.0; N = total number of treated subjects; PT = preferred term; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
A death could be associated with multiple preferred terms.
If a subject had multiple occurrences of the same PT, the subject was counted once for the specific PT. If a subject had multiple PTs, the subject was counted in each of the different PTs.
TEAEs are sorted by descending frequency in the T-DXd arm.
Source: Module 5.3.5.3 SCS Table 1.2.1.16

Laboratory findings

Table 65: Laboratory Abnormality Adverse Drug Reactions in Study U303 (Safety Analysis Set)

Laboratory Abnormality	Number (%) of Subjects			
	T-DXd (N = 371)		TPC (N = 172)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Hematology				
White blood cell count decreased	255 (69.7)	33 (9.0)	132 (78.1)	42 (24.9)
Hemoglobin decreased	234 (63.9)	28 (7.7)	90 (53.3)	10 (5.9)
Neutrophil count decreased	233 (64.0)	52 (14.3)	123 (72.8)	64 (37.9)
Lymphocyte count decreased	202 (55.5)	65 (17.9)	67 (39.6)	19 (11.2)
Platelet count decreased	162 (44.3)	21 (5.7)	36 (21.3)	1 (0.6)
Chemistry				
Aspartate aminotransferase increased	140 (38.4)	8 (2.2)	64 (37.9)	7 (4.1)
Alanine aminotransferase increased	132 (36.2)	3 (0.8)	65 (38.5)	7 (4.1)
Blood alkaline phosphatase increased	123 (33.7)	1 (0.3)	41 (24.3)	0
Blood potassium decreased	92 (25.2)	12 (3.3)	28 (16.7)	2 (1.2)
Blood bilirubin increased	59 (16.2)	10 (2.7)	25 (14.8)	1 (0.6)
Blood creatinine increased	53 (14.5)	4 (1.1)	16 (9.5)	1 (0.6)

CTCAE = Common Terminology Criteria for Adverse Events, Version 5.0; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice
Percentages were calculated using the number of subjects with both baseline and post-treatment measurements as the denominator, based on CTCAE grade-derived laboratory abnormalities.
Baseline was defined as the last non-missing value recorded before the first dose of study drug.
Parameters are presented in descending order of incidence in the All Grades column of the T-DXd arm.
Source: Module 5.3.5.3 ADR Table 10.20

Table 66: Hepatic Function Abnormalities (Safety Analysis Set)

Hepatic Parameter	Number (%) of Subjects		
	Study U303		All BC T-DXd 5.4 mg/kg Pool (N = 883)
	T-DXd (N = 371)	TPC (N = 172)	
Alanine aminotransferase (ALT)			
Non-missing n [a]	365	169	875
Baseline ≥ULN	122 (33.4)	59 (34.9)	205 (23.4)
Maximum post-baseline value			
≥3 × ULN	43 (11.8)	29 (17.2)	75 (8.6)
≥5 × ULN	6 (1.6)	12 (7.1)	12 (1.4)
≥8 × ULN	2 (0.5)	4 (2.4)	3 (0.3)
≥10 × ULN	1 (0.3)	3 (1.8)	2 (0.2)
≥20 × ULN	0	1 (0.6)	0
Aspartate aminotransferase (AST)			

Hepatic Parameter	Number (%) of Subjects		
	Study U303		All BC T-DXd 5.4 mg/kg Pool (N = 883)
	T-DXd (N = 371)	TPC (N = 172)	
Non-missing n [a]	365	169	875
Baseline ≥ULN	199 (54.5)	81 (47.9)	366 (41.8)
Maximum post-baseline value			
≥3 × ULN	72 (19.7)	40 (23.7)	107 (12.2)
≥5 × ULN	20 (5.5)	17 (10.1)	31 (3.5)
≥8 × ULN	8 (2.2)	6 (3.6)	11 (1.3)
≥10 × ULN	5 (1.4)	4 (2.4)	7 (0.8)
≥20 × ULN	2 (0.5)	0	3 (0.3)
ALT or AST			
Non-missing n [a]	365	169	875
Baseline ≥ULN	208 (57.0)	89 (52.7)	386 (44.1)
Maximum post-baseline value			
≥3 × ULN	85 (23.3)	51 (30.2)	138 (15.8)
≥5 × ULN	24 (6.6)	21 (12.4)	39 (4.5)
≥8 × ULN	8 (2.2)	7 (4.1)	11 (1.3)
≥10 × ULN	5 (1.4)	6 (3.6)	7 (0.8)
≥20 × ULN	2 (0.5)	1 (0.6)	3 (0.3)
Total bilirubin (TBL)			
Non-missing n [a]	365	169	877
Baseline ≥ULN	14 (3.8)	5 (3.0)	25 (2.9)
Maximum post-baseline value			
≥1.5 × ULN	31 (8.5)	7 (4.1)	62 (7.1)
≥2 × ULN	19 (5.2)	6 (3.6)	30 (3.4)
≥3 × ULN	11 (3.0)	1 (0.6)	13 (1.5)
Alkaline phosphatase (ALP)			
Non-missing n [a]	365	169	877
Baseline ≥ULN	152 (41.6)	64 (37.9)	291 (33.2)
Maximum post-baseline value			
≥1.5 × ULN	170 (46.6)	62 (36.7)	362 (41.3)
≥2 × ULN	120 (32.9)	42 (24.9)	219 (25.0)
Concurrent TBL elevation with ALT or AST elevation [b]			
Non-missing n [a]	365	169	875

Hepatic Parameter	Number (%) of Subjects		
	Study U303		All BC T-DXd 5.4 mg/kg Pool (N = 883)
	T-DXd (N = 371)	TPC (N = 172)	
ALT or AST ≥3 × ULN and TBL ≥2 × ULN	13 (3.6)	5 (3.0)	17 (1.9)
Concurrent TBL elevation with ALT or AST elevation and ALP <2 × ULN [b]			
Non-missing n [a]	365	169	875
ALT or AST ≥3 × ULN and TBL ≥2 × ULN and ALP <2 × ULN	5 (1.4)	2 (1.2)	9 (1.0)

BC = breast cancer; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice; ULN = upper limit of normal
Percentages were calculated using the non-missing n as the denominator.
Each subject was counted for only the worst case observed post-baseline.
[a] Non-missing n is the number of subjects with both baseline and post-baseline data.
[b] Concurrent was defined as abnormalities that occurred within a 28-day window.
Source: Module 5.3.5.3 SCS Table 1.3.1.3

Safety in special populations

Intrinsic factors

Table 67: Overall Summary of Treatment-emergent Adverse Events, by Age Group (Safety Analysis Set)

Parameter	Age Group <65 years			Age Group ≥65 years		
	T-DXd (N = 289)	TPC (N = 126)	All BC T-DXd 5.4 mg/kg Pool (N = 686)	T-DXd (N = 82)	TPC (N = 46)	All BC T-DXd 5.4 mg/kg Pool (N = 197)
Duration of treatment (months)						
Median	8.25	3.12	10.00	6.98	4.14	9.43
Minimum, Maximum	0.2, 28.1	0.3, 17.6	0.2, 37.1	0.6, 33.3	0.4, 15.8	0.6, 33.3
Subjects with any TEAE	287 (99.3)	123 (97.6)	681 (99.3)	82 (100.0)	46 (100.0)	197 (100.0)
TEAEs with worst CTCAE ≥Grade 3 [a]	143 (49.5)	83 (65.9)	352 (51.3)	52 (63.4)	33 (71.7)	127 (64.5)
Serious TEAEs	74 (25.6)	31 (24.6)	155 (22.6)	29 (35.4)	12 (26.1)	67 (34.0)
TEAEs associated with study drug discontinuation	40 (13.8)	12 (9.5)	99 (14.4)	20 (24.4)	2 (4.3)	44 (22.3)
TEAEs associated with dose reduction	60 (20.8)	45 (35.7)	145 (21.1)	24 (29.3)	21 (45.7)	50 (25.4)
TEAEs associated with study drug interruption	106 (36.7)	48 (38.1)	274 (39.9)	37 (45.1)	24 (52.2)	95 (48.2)
TEAEs associated with an outcome of death [b]	12 (4.2)	3 (2.4)	23 (3.4)	2 (2.4)	2 (4.3)	9 (4.6)
Subjects with any drug-related TEAE [c]	278 (96.2)	118 (93.7)	669 (97.5)	79 (96.3)	44 (95.7)	193 (98.0)
Drug-related TEAEs with worst CTCAE ≥Grade 3 [a]	115 (39.8)	71 (56.3)	295 (43.0)	39 (47.6)	28 (60.9)	102 (51.8)
Drug-related serious TEAEs	35 (12.1)	14 (11.1)	80 (11.7)	13 (15.9)	5 (10.9)	32 (16.2)

Parameter	Age Group <65 years			Age Group ≥65 years		
	T-DXd (N = 289)	TPC (N = 126)	All BC T-DXd 5.4 mg/kg Pool (N = 686)	T-DXd (N = 82)	TPC (N = 46)	All BC T-DXd 5.4 mg/kg Pool (N = 197)
Drug-related TEAEs associated with study drug discontinuation	36 (12.5)	10 (7.9)	91 (13.3)	20 (24.4)	2 (4.3)	42 (21.3)
Drug-related TEAEs associated with dose reduction	57 (19.7)	45 (35.7)	140 (20.4)	20 (24.4)	19 (41.3)	41 (20.8)
Drug-related TEAEs associated with study drug interruption	79 (27.3)	42 (33.3)	211 (30.8)	27 (32.9)	20 (43.5)	75 (38.1)
Drug-related TEAEs associated with an outcome of death [b]	6 (2.1)	0	9 (1.3)	1 (1.2)	0	2 (1.0)

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, Version 5.0; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

Percentages were calculated using the number of subjects in the category as the denominator. Age in years was calculated using the date of birth and the date of informed consent. [a]A subject was counted once at the maximum severity. [b]For specific TEAEs associated with an outcome of death, refer to Table 2.10. [c]If relationship was missing, the TEAE was considered to be related to the drug. Source: Module 5.3.5.3 SCS Tables 1.4.2, 1.4.3

Table 68: Treatment-emergent Adverse Events with a 10-percentage-point Difference Between Age Categories in Either Treatment Arm in Study U303, by Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA Preferred Term/Grouped Term [a]	Number (%) of Subjects			
	T-DXd		TPC	
	Age <65 years (N = 289)	Age ≥65 years (N = 82)	Age <65 years (N = 126)	Age ≥65 years (N = 46)
Subjects with any TEAE	287 (99.3)	82 (100.0)	123 (97.6)	46 (100.0)
Nausea	221 (76.5)	61 (74.4)	33 (26.2)	19 (41.3)
Diarrhoea	76 (26.3)	24 (29.3)	24 (19.0)	14 (30.4)
Headache [a]	50 (17.3)	5 (6.1)	8 (6.3)	3 (6.5)
Palmar-plantar erythrodysaesthesia syndrome	5 (1.7)	0	13 (10.3)	11 (23.9)

MedDRA = Medical Dictionary for Regulatory Activities, Version 24.0; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

Percentages were calculated using the number of subjects in the category as the denominator.

TEAEs are presented in descending order of incidence within the T-DXd age <65 years column.

[a] The preferred terms included in each grouped term are listed in Table 2.1.

Source: Module 5.3.5.1 DS8201-A-U303 CSR Table 10.10

Table 69: Overall Summary of Treatment-emergent Adverse Events by Race (Safety Analysis Set)

Parameter	White			Asian			Other		
	T-DXd (N = 175)	TPC (N = 85)	All BC T-DXd 5.4 mg/kg Pool (N = 377)	T-DXd (N = 151)	TPC (N = 69)	All BC T-DXd 5.4 mg/kg Pool (N = 404)	T-DXd (N = 45)	TPC (N = 17)	All BC T-DXd 5.4 mg/kg Pool (N = 98)
Duration of treatment (months)									
Median	8.21	3.19	9.63	8.41	3.52	10.99	6.21	4.34	9.64
Minimum, Maximum	0.2, 28.1	0.3, 17.6	0.2, 31.7	0.7, 33.3	0.5, 17.5	0.7, 37.1	0.6, 22.0	1.4, 10.3	0.6, 28.5
Subjects with any TEAE	173 (98.9)	82 (96.5)	374 (99.2)	151 (100.0)	69 (100.0)	403 (99.8)	45 (100.0)	17 (100.0)	97 (99.0)
TEAEs with worst CTCAE ≥Grade 3 [a]	83 (47.4)	53 (62.4)	200 (53.1)	90 (59.6)	52 (75.4)	226 (55.9)	22 (48.9)	11 (64.7)	50 (51.0)
Serious TEAEs	50 (28.6)	21 (24.7)	107 (28.4)	41 (27.2)	16 (23.2)	90 (22.3)	12 (26.7)	6 (35.3)	23 (23.5)
TEAEs associated with study drug discontinuation	30 (17.1)	7 (8.2)	55 (14.6)	27 (17.9)	4 (5.8)	72 (17.8)	3 (6.7)	3 (17.6)	16 (16.3)
TEAEs associated with dose reduction	33 (18.9)	27 (31.8)	74 (19.6)	42 (27.8)	35 (50.7)	99 (24.5)	9 (20.0)	4 (23.5)	20 (20.4)
TEAEs associated with study drug interruption	62 (35.4)	35 (41.2)	145 (38.5)	63 (41.7)	30 (43.5)	180 (44.6)	18 (40.0)	7 (41.2)	41 (41.8)
TEAEs associated with an outcome of death [b]	10 (5.7)	4 (4.7)	24 (6.4)	2 (1.3)	1 (1.4)	6 (1.5)	2 (4.4)	0	2 (2.0)
Subjects with any drug-related TEAE [c]	164 (93.7)	77 (90.6)	363 (96.3)	150 (99.3)	67 (97.1)	400 (99.0)	43 (95.6)	17 (100.0)	95 (96.9)
Drug-related TEAEs with worst CTCAE ≥Grade 3 [a]	61 (34.9)	40 (47.1)	155 (41.1)	78 (51.7)	49 (71.0)	200 (49.5)	15 (33.3)	10 (58.8)	40 (40.8)
Drug-related serious TEAEs	22 (12.6)	7 (8.2)	48 (12.7)	22 (14.6)	10 (14.5)	50 (12.4)	4 (8.9)	2 (11.8)	13 (13.3)
Drug-related TEAEs associated with study drug discontinuation	27 (15.4)	6 (7.1)	49 (13.0)	26 (17.2)	4 (5.8)	68 (16.8)	3 (6.7)	2 (11.8)	16 (16.3)
Drug-related TEAEs associated with dose reduction	28 (16.0)	26 (30.6)	62 (16.4)	41 (27.2)	34 (49.3)	98 (24.3)	8 (17.8)	4 (23.5)	19 (19.4)
Drug-related TEAEs associated with study drug interruption	39 (22.3)	29 (34.1)	97 (25.7)	53 (35.1)	27 (39.1)	152 (37.6)	14 (31.1)	6 (35.3)	34 (34.7)
Drug-related TEAEs associated with an outcome of death [b]	7 (4.0)	0	10 (2.7)	0	0	1 (0.2)	0	0	0

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, Version 5.0; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

Percentages were calculated using the number of subjects in the category as the denominator.

[a] A subject was counted once at the maximum severity.

[b] For specific TEAEs associated with outcome of death, refer to Table 2.10.

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

Source: Module 5.3.5.3 SCS Tables 1.4.2, 1.4.3

Table 70: Overall Summary of Treatment-emergent Adverse Events by ECOG Performance Status (Safety Analysis Set)

Parameter	ECOG Performance Status 0			ECOG Performance Status 1		
	T-DXd (N = 199)	TPC (N = 95)	All BC T-DXd 5.4 mg/kg Pool (N = 502)	T-DXd (N = 172)	TPC (N = 77)	All BC T-DXd 5.4 mg/kg Pool (N = 380)
Duration of treatment (months)						
Median	8.67	3.48	11.35	6.90	3.35	8.36
Minimum, Maximum	0.4, 33.3	0.3, 17.6	0.4, 33.3	0.2, 24.8	0.4, 17.4	0.2, 37.1
Subjects with any TEAE	197 (99.0)	92 (96.8)	497 (99.0)	172 (100.0)	77 (100.0)	380 (100.0)
TEAEs with worst CTCAE ≥Grade 3 [a]	93 (46.7)	58 (61.1)	253 (50.4)	102 (59.3)	58 (75.3)	225 (59.2)
Serious TEAEs	37 (18.6)	21 (22.1)	96 (19.1)	66 (38.4)	22 (28.6)	125 (32.9)
TEAEs associated with study drug discontinuation	30 (15.1)	8 (8.4)	80 (15.9)	30 (17.4)	6 (7.8)	63 (16.6)
TEAEs associated with dose reduction	37 (18.6)	39 (41.1)	92 (18.3)	47 (27.3)	27 (35.1)	103 (27.1)
TEAEs associated with study drug interruption	74 (37.2)	39 (41.1)	205 (40.8)	69 (40.1)	33 (42.9)	164 (43.2)
TEAEs associated with an outcome of death [b]	3 (1.5)	1 (1.1)	10 (2.0)	11 (6.4)	4 (5.2)	21 (5.5)
Subjects with any drug-related TEAE [c]	194 (97.5)	86 (90.5)	494 (98.4)	163 (94.8)	76 (98.7)	367 (96.6)
Drug-related TEAEs with worst CTCAE ≥Grade 3 [a]	78 (39.2)	50 (52.6)	219 (43.6)	76 (44.2)	49 (63.6)	177 (46.6)
Drug-related serious TEAEs	20 (10.1)	10 (10.5)	56 (11.2)	28 (16.3)	9 (11.7)	56 (14.7)
Drug-related TEAEs associated with study drug discontinuation	28 (14.1)	8 (8.4)	76 (15.1)	28 (16.3)	4 (5.2)	57 (15.0)
Drug-related TEAEs associated with dose reduction	36 (18.1)	38 (40.0)	88 (17.5)	41 (23.8)	26 (33.8)	93 (24.5)
Drug-related TEAEs associated with study drug interruption	61 (30.7)	36 (37.9)	170 (33.9)	45 (26.2)	26 (33.8)	116 (30.5)
Drug-related TEAEs associated with an outcome of death [b]	3 (1.5)	0	6 (1.2)	4 (2.3)	0	5 (1.3)

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, Version 5.0; ECOG = Eastern Cooperative Oncology Group; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

Percentages were calculated using the number of subjects in the category as the denominator.

[a] A subject was counted once at the maximum severity.

[b] For specific TEAEs associated with an outcome of death, refer to Table 2.10.

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

Source: Module 5.3.5.3 SCS Tables 1.4.2, 1.4.3

Table 71: Overall Summary of Treatment-emergent Adverse Events by Baseline Renal Function (Safety Analysis Set)

Parameter	Normal Renal Function			Mild Renal Impairment			Moderate Renal Impairment		
	T-DXd (N = 201)	TPC (N = 80)	All BC T-DXd 5.4 mg/kg Pool (N = 456)	T-DXd (N = 123)	TPC (N = 65)	All BC T-DXd 5.4 mg/kg Pool (N = 319)	T-DXd (N = 41)	TPC (N = 23)	All BC T-DXd 5.4 mg/kg Pool (N = 101)
Duration of treatment (months)									
Median	8.21	3.42	10.58	7.59	2.99	9.89	7.62	4.63	8.21
Minimum, Maximum	0.4, 33.3	0.3, 17.5	0.4, 33.3	0.2, 25.5	0.3, 17.6	0.2, 37.1	0.7, 22.1	0.4, 17.4	0.7, 28.3
Subjects with any TEAE	200 (99.5)	79 (98.8)	453 (99.3)	122 (99.2)	63 (96.9)	318 (99.7)	41 (100.0)	23 (100.0)	100 (99.0)
TEAEs with worst CTCAE ≥Grade 3 [a]	101 (50.2)	53 (66.3)	240 (52.6)	63 (51.2)	45 (69.2)	176 (55.2)	26 (63.4)	16 (69.6)	57 (56.4)
Serious TEAEs	51 (25.4)	19 (23.8)	111 (24.3)	36 (29.3)	18 (27.7)	76 (23.8)	15 (36.6)	6 (26.1)	34 (33.7)
TEAEs associated with study drug discontinuation	26 (12.9)	7 (8.8)	64 (14.0)	20 (16.3)	5 (7.7)	46 (14.4)	12 (29.3)	1 (4.3)	30 (29.7)
TEAEs associated with dose reduction	41 (20.4)	29 (36.3)	97 (21.3)	31 (25.2)	23 (35.4)	71 (22.3)	9 (22.0)	13 (56.5)	24 (23.8)
TEAEs associated with study drug interruption	71 (35.3)	33 (41.3)	181 (39.7)	50 (40.7)	25 (38.5)	139 (43.6)	19 (46.3)	14 (60.9)	45 (44.6)
TEAEs associated with an outcome of death [b]	5 (2.5)	2 (2.5)	14 (3.1)	5 (4.1)	3 (4.6)	12 (3.8)	4 (9.8)	0	6 (5.9)
Subjects with any drug-related TEAE [c]	194 (96.5)	76 (95.0)	445 (97.6)	118 (95.9)	60 (92.3)	313 (98.1)	39 (95.1)	22 (95.7)	97 (96.0)
Drug-related TEAEs with worst CTCAE ≥Grade 3 [a]	78 (38.8)	43 (53.8)	196 (43.0)	52 (42.3)	40 (61.5)	148 (46.4)	20 (48.8)	14 (60.9)	48 (47.5)
Drug-related serious TEAEs	25 (12.4)	9 (11.3)	63 (13.8)	16 (13.0)	7 (10.8)	31 (9.7)	7 (17.1)	3 (13.0)	18 (17.8)
Drug-related TEAEs associated with study drug discontinuation	24 (11.9)	6 (7.5)	59 (12.9)	18 (14.6)	4 (6.2)	43 (13.5)	12 (29.3)	1 (4.3)	28 (27.7)
Drug-related TEAEs associated with dose reduction	39 (19.4)	29 (36.3)	93 (20.4)	27 (22.0)	23 (35.4)	64 (20.1)	8 (19.5)	11 (47.8)	21 (20.8)
Drug-related TEAEs associated with study drug interruption	52 (25.9)	29 (36.3)	142 (31.1)	39 (31.7)	23 (35.4)	106 (33.2)	12 (29.3)	10 (43.5)	34 (33.7)
Drug-related TEAEs associated with an outcome of death [b]	3 (1.5)	0	6 (1.3)	2 (1.6)	0	2 (0.6)	2 (4.9)	0	3 (3.0)

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, Version 5.0; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

Percentages were calculated using the number of subjects in the category as the denominator.

[a] A subject was counted once at the maximum severity.

[b] For specific TEAEs associated with an outcome of death, refer to Table 2.10.

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

Source: Module 5.3.5.3 SCS Tables 1.4.2, 1.4.3

Table 72: Overall Summary of Treatment-emergent Adverse Events by Baseline Hepatic Function (Safety Analysis Set)

Parameter	Normal Hepatic Function			Mild Hepatic Impairment		
	T-DXd (N = 170)	TPC (N = 88)	All BC T-DXd 5.4 mg/kg Pool (N = 520)	T-DXd (N = 194)	TPC (N = 82)	All BC T-DXd 5.4 mg/kg Pool (N = 353)
Duration of treatment (months)						
Median	9.61	4.11	12.27	6.85	2.94	8.21
Minimum, Maximum	0.4, 33.3	0.3, 17.5	0.4, 37.1	0.2, 25.5	0.3, 17.6	0.2, 29.0
Subjects with any TEAE	168 (98.8)	88 (100.0)	515 (99.0)	194 (100.0)	79 (96.3)	353 (100.0)
TEAEs with worst CTCAE ≥Grade 3 [a]	86 (50.6)	58 (65.9)	274 (52.7)	104 (53.6)	57 (69.5)	197 (55.8)
Serious TEAEs	51 (30.0)	17 (19.3)	128 (24.6)	49 (25.3)	26 (31.7)	90 (25.5)
TEAEs associated with study drug discontinuation	23 (13.5)	9 (10.2)	82 (15.8)	36 (18.6)	5 (6.1)	59 (16.7)
TEAEs associated with dose reduction	40 (23.5)	33 (37.5)	117 (22.5)	43 (22.2)	32 (39.0)	75 (21.2)
TEAEs associated with study drug interruption	69 (40.6)	42 (47.7)	224 (43.1)	70 (36.1)	30 (36.6)	140 (39.7)
TEAEs associated with an outcome of death [b]	4 (2.4)	0	15 (2.9)	9 (4.6)	5 (6.1)	16 (4.5)
Subjects with any drug-related TEAE [c]	164 (96.5)	86 (97.7)	508 (97.7)	187 (96.4)	74 (90.2)	345 (97.7)
Drug-related TEAEs with worst CTCAE ≥Grade 3 [a]	67 (39.4)	54 (61.4)	227 (43.7)	84 (43.3)	44 (53.7)	164 (46.5)
Drug-related serious TEAEs	24 (14.1)	9 (10.2)	66 (12.7)	24 (12.4)	10 (12.2)	46 (13.0)
Drug-related TEAEs associated with study drug discontinuation	22 (12.9)	8 (9.1)	76 (14.6)	34 (17.5)	4 (4.9)	56 (15.9)
Drug-related TEAEs associated with dose reduction	37 (21.8)	31 (35.2)	108 (20.8)	39 (20.1)	32 (39.0)	70 (19.8)
Drug-related TEAEs associated with study drug interruption	51 (30.0)	38 (43.2)	170 (32.7)	53 (27.3)	24 (29.3)	113 (32.0)
Drug-related TEAEs associated with an outcome of death [b]	3 (1.8)	0	7 (1.3)	4 (2.1)	0	4 (1.1)

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, Version 5.0; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

Percentages were calculated using the number of subjects in the category as the denominator.

[a] A subject was counted once at the maximum severity.

[b] For specific TEAEs associated with an outcome of death, refer to Table 2.10.

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

Source: Module 5.3.5.3 SCS Tables 1.4.2, 1.4.3

Extrinsic factors

Table 73: Overall Summary of Treatment-emergent Adverse Events in Study U303 by Country (Safety Analysis Set)

Parameter	Japan			Non-Japan		
	T-DXd (N = 56)	TPC (N = 29)	All BC T-DXd 5.4 mg/kg Pool (N = 148)	T-DXd (N = 315)	TPC (N = 143)	All BC T-DXd 5.4 mg/kg Pool (N = 735)
Duration of treatment (months)						
Median	6.08	2.76	9.66	8.25	3.52	9.99
Minimum, Maximum	0.7, 33.3	0.5, 17.5	0.7, 37.1	0.2, 28.1	0.3, 17.6	0.2, 31.7
Subjects with any TEAE	56 (100.0)	29 (100.0)	148 (100.0)	313 (99.4)	140 (97.9)	730 (99.3)
TEAEs with worst CTCAE ≥Grade 3 [a]	33 (58.9)	22 (75.9)	83 (56.1)	162 (51.4)	94 (65.7)	396 (53.9)
Serious TEAEs	10 (17.9)	5 (17.2)	26 (17.6)	93 (29.5)	38 (26.6)	196 (26.7)
TEAEs associated with study drug discontinuation	16 (28.6)	2 (6.9)	41 (27.7)	44 (14.0)	12 (8.4)	102 (13.9)
TEAEs associated with dose reduction	13 (23.2)	13 (44.8)	30 (20.3)	71 (22.5)	53 (37.1)	165 (22.4)
TEAEs associated with study drug interruption	23 (41.1)	16 (55.2)	75 (50.7)	120 (38.1)	56 (39.2)	294 (40.0)
TEAEs associated with an outcome of death [b]	0	1 (3.4)	1 (0.7)	14 (4.4)	4 (2.8)	31 (4.2)
Subjects with any drug-related TEAE [c]	55 (98.2)	29 (100.0)	147 (99.3)	302 (95.9)	133 (93.0)	715 (97.3)
Drug-related TEAEs with worst CTCAE ≥Grade 3 [a]	30 (53.6)	21 (72.4)	77 (52.0)	124 (39.4)	78 (54.5)	320 (43.5)
Drug-related serious TEAEs	6 (10.7)	3 (10.3)	16 (10.8)	42 (13.3)	16 (11.2)	96 (13.1)
Drug-related TEAEs associated with study drug discontinuation	16 (28.6)	2 (6.9)	39 (26.4)	40 (12.7)	10 (7.0)	94 (12.8)
Drug-related TEAEs associated with dose reduction	12 (21.4)	13 (44.8)	29 (19.6)	65 (20.6)	51 (35.7)	152 (20.7)
Drug-related TEAEs associated with study drug interruption	21 (37.5)	15 (51.7)	65 (43.9)	85 (27.0)	47 (32.9)	221 (30.1)
Drug-related TEAEs associated with an outcome of death [b]	0	0	0	7 (2.2)	0	11 (1.5)

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, Version 5.0; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

[a] A subject was counted once at the maximum severity.

[b] For specific TEAEs associated with an outcome of death, refer to Table 2.10.

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

Source: Module 5.3.5.3 SCS Tables 1.4.2, 1.4.3

Table 74: Overall Summary of Treatment-emergent Adverse Events by Geographic Region (Safety Analysis Set)

Parameter	Asia [a]			North America [b]			Europe [c]			Rest of World [d]		
	T-DXd (N = 147)	TPC (N = 63)	All BC T-DXd 5.4 mg/kg Pool (N = 383)	T-DXd (N = 58)	TPC (N = 28)	All BC T-DXd 5.4 mg/kg Pool (N = 173)	T-DXd (N = 154)	TPC (N = 73)	All BC T-DXd 5.4 mg/kg Pool (N = 274)	T-DXd (N = 12)	TPC (N = 8)	All BC T-DXd 5.4 mg/kg Pool (N = 53)
Duration of treatment (months)												
Median	8.41	3.52	11.01	6.96	2.81	8.57	7.79	3.35	9.46	8.44	3.75	14.45
Minimum, Maximum	0.7, 33.3	0.5, 17.5	0.7, 37.1	0.7, 24.3	0.4, 9.8	0.7, 31.7	0.2, 28.1	0.3, 17.6	0.2, 28.5	0.7,20.9	1.8,17.4	0.7, 28.5
Subjects with any TEAE	147 (100.0)	63 (100.0)	382 (99.7)	58 (100.0)	27 (96.4)	172 (99.4)	152(98.7)	71(97.3)	271 (98.9)	12 (100.0)	8 (100.0)	53 (100.0)
TEAEs with worst CTCAE ≥Grade 3 [e]	87 (59.2)	48 (76.2)	217 (56.7)	29 (50.0)	20 (71.4)	94 (54.3)	73 (47.4)	43(58.9)	141 (51.5)	6 (50.0)	5 (62.5)	27 (50.9)
Serious TEAEs	38 (25.9)	15 (23.8)	83 (21.7)	24 (41.4)	6 (21.4)	49 (28.3)	36 (23.4)	20(27.4)	74 (27.0)	5 (41.7)	2 (25.0)	16 (30.2)
TEAEs associated with study drug discontinuation	26 (17.7)	4 (6.3)	71 (18.5)	8 (13.8)	2 (7.1)	22 (12.7)	23 (14.9)	8 (11.0)	40 (14.6)	3 (25.0)	0	10 (18.9)
TEAEs associated with dose reduction	42 (28.6)	30 (47.6)	96 (25.1)	7 (12.1)	12 (42.9)	33 (19.1)	32 (20.8)	21 (28.8)	56 (20.4)	3 (25.0)	3 (37.5)	10 (18.9)
TEAEs associated with study drug interruption	60 (40.8)	28 (44.4)	172 (44.9)	23 (39.7)	13 (46.4)	65 (37.6)	53 (34.4)	27 (37.0)	109 (39.8)	7 (58.3)	4 (50.0)	23 (43.4)
TEAEs associated with an outcome of death [f]	2 (1.4)	1 (1.6)	5 (1.3)	3 (5.2)	0	9 (5.2)	8 (5.2)	4 (5.5)	15 (5.5)	1 (8.3)	0	3 (5.7)
Subjects with any drug-related TEAE [g]	146 (99.3)	63 (100.0)	379 (99.0)	57 (98.3)	25 (89.3)	170 (98.3)	144 (93.5)	66 (90.4)	263 (96.0)	10 (83.3)	8 (100.0)	50 (94.3)
Drug-related TEAEs with worst CTCAE ≥Grade 3 [e]	77 (52.4)	46 (73.0)	193 (50.4)	18 (31.0)	14 (50.0)	73 (42.2)	55 (35.7)	34 (46.6)	112 (40.9)	4 (33.3)	5 (62.5)	19 (35.8)
Drug-related serious TEAEs	21 (14.3)	10 (15.9)	47 (12.3)	9 (15.5)	0	22 (12.7)	17 (11.0)	7 (9.6)	39 (14.2)	1 (8.3)	2 (25.0)	4 (7.5)
Drug-related TEAEs associated with study drug discontinuation	25 (17.0)	4 (6.3)	67 (17.5)	6 (10.3)	1 (3.6)	18 (10.4)	22 (14.3)	7 (9.6)	38 (13.9)	3 (25.0)	0	10 (18.9)
Drug-related TEAEs associated with dose reduction	41 (27.9)	30 (47.6)	95 (24.8)	6 (10.3)	11 (39.3)	27 (15.6)	27 (17.5)	20 (27.4)	49 (17.9)	3 (25.0)	3 (37.5)	10 (18.9)
Drug-related TEAEs associated with study drug interruption	51 (34.7)	25 (39.7)	147 (38.4)	13 (22.4)	10 (35.7)	44 (25.4)	38 (24.7)	23 (31.5)	80 (29.2)	4 (33.3)	4 (50.0)	15 (28.3)
Drug-related TEAEs associated with an outcome of death [f]	0	0	0	2 (3.4)	0	4 (2.3)	4 (2.6)	0	6 (2.2)	1 (8.3)	0	1 (1.9)

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, Version 5.0; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

[a] Asia included the following countries: Japan, China, Republic of Korea, Taiwan, and Hong Kong

[b] North America included the following countries: United States (n = 55 T-DXd and 27 TPC) and Canada (n = 3 T-DXd and 1 TPC)

[c] For Study U303, Europe included the following countries: Austria, Belgium, France, Greece, Hungary, Italy, Portugal, Russia, Spain, Sweden, Switzerland, and United Kingdom; for the All BC T-DXd 5.4 mg/kg Pool, Europe also included Netherlands.

[d] For Study U303, Rest of World included only Israel; for the All BC T-DXd 5.4 mg/kg Pool, Rest of World included Australia, Brazil, and Israel

[e] A subject was counted once at the maximum severity.

[f] For specific TEAEs associated with an outcome of death, refer to Table 2.10.

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

Source: Module 5.3.5.3 SCS Tables 1.4.2, 1.4.3

Safety related to drug-drug interactions and other interactions

No clinically meaningful changes in T-DXd or DXd steady state area under the plasma/serum concentration time curve from time 0 to 17 days (AUC0-17) days were observed after coadministration of itraconazole or ritonavir (study A104).

Discontinuation due to adverse events

Table 75: Treatment-emergent Adverse Events Associated with Study Drug Discontinuation in at Least 2 Subjects in Either Treatment Arm of Study U303, by Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA Preferred Term/ Grouped Term [a]	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 172)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Any subject with TEAE associated with study drug discontinuation	60 (16.2)	14 (8.1)	143 (16.2)
Interstitial lung disease [b]	31 (8.4)	0	78 (8.8)
Left ventricular dysfunction [c]	3 (0.8)	0	4 (0.5)
Blood bilirubin increased [a]	2 (0.5)	0	2 (0.2)
Dyspnoea	2 (0.5)	0	3 (0.3)
Pleural effusion	2 (0.5)	0	3 (0.3)
Peripheral sensory neuropathy	0	4 (2.3)	0

AESI = adverse event of special interest; BC = breast cancer; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities, Version 24.0; N = total number of treated subjects; PT = preferred term; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

If a subject had multiple occurrences of the same PT/grouped term, the subject was counted once for that PT/grouped term. If a subject had multiple PTs/grouped terms, the subject was counted in each of the different PTs/grouped terms.

[a] The PTs included in each grouped term are listed in Table 2.1.

[b] ILD includes events that were adjudicated as ILD and related to use of T-DXd or TPC. Note that, per protocol, discontinuation was required for any subject with ≥Grade 2 ILD in the studies in the All BC T-DXd 5.4 mg/kg Pool except for Study J101 and Study U201, which used a different criterion for discontinuation due to ILD when the studies started: prior to Study J101 protocol v11.0 (effective 25 Jan 2018) and prior to Study U201 v3.0 (effective 22 Jan 2018).

[c] The PTs included in the AESI of left ventricular dysfunction are listed in Table 2.22.

Source: Module 5.3.5.3 SCS Tables 1.2.1.10, 1.2.2.4, 1.2.4.3, 1.2.6.3

Table 76: Treatment-emergent Adverse Events Associated with Dose Reduction Reported in ≥1% of Subjects in Either Treatment Arm in Study U303, by Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA Preferred Term/Grouped Term [a]	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 172)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Any subject with TEAE associated with dose reduction	84 (22.6)	66 (38.4)	195 (22.1)
Fatigue [a]	17 (4.6)	8 (4.7)	34 (3.9)
Nausea	17 (4.6)	4 (2.3)	43 (4.9)
Thrombocytopenia [a]	13 (3.5)	0	21 (2.4)
Neutropenia [a]	11 (3.0)	24 (14.0)	28 (3.2)
Anemia [a]	7 (1.9)	3 (1.7)	9 (1.0)
Decreased appetite	7 (1.9)	2 (1.2)	11 (1.2)
Diarrhoea	5 (1.3)	2 (1.2)	9 (1.0)
Leukopenia [a]	3 (0.8)	7 (4.1)	5 (0.6)
Transaminases increased [a]	3 (0.8)	6 (3.5)	7 (0.8)
Electrocardiogram QT prolonged	2 (0.5)	2 (1.2)	3 (0.3)
Febrile neutropenia	1 (0.3)	3 (1.7)	4 (0.5)

MedDRA Preferred Term/Grouped Term [a]	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 172)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Neuropathy peripheral	0	3 (1.7)	2 (0.2)
Neurotoxicity	0	2 (1.2)	0
Overdose	0	2 (1.2)	0
Palmar-plantar erythrodysaesthesia syndrome	0	9 (5.2)	0
Peripheral sensory neuropathy	0	4 (2.3)	1 (0.1)

BC = breast cancer; MedDRA = Medical Dictionary for Regulatory Activities, Version 24.0; N = total number of treated subjects; PT = preferred term; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
If a subject had multiple occurrences of the same PT/grouped term, the subject was counted once for that PT/grouped term. If a subject had multiple PTs/grouped terms, the subject was counted in each of the different PTs/grouped terms.
TEAEs are sorted by descending frequency in the T-DXd arm.
[a] The PTs included in each grouped term are listed in Table 2.1.
Source: Module 5.3.5.3 SCS Tables 1.2.1.14, 1.2.2.5

Table 77: Treatment-emergent Adverse Events Associated with Study Drug Interruption Reported in ≥1% of Subjects in Either Treatment Arm in Study U303, by Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA Preferred Term/ Grouped Term [a]	Number (%) of Subjects		
	T-DXd (N = 371)	TPC (N = 172)	All BC T-DXd 5.4 mg/kg Pool (N = 883)
Any subject with TEAE associated with study drug interruption	143 (38.5)	72 (41.9)	369 (41.8)
Neutropenia [a]	34 (9.2)	39 (22.7)	114 (12.9)
Fatigue [a]	19 (5.1)	4 (2.3)	41 (4.6)
Anemia [a]	17 (4.6)	4 (2.3)	35 (4.0)
Leukopenia [a]	13 (3.5)	10 (5.8)	34 (3.9)
COVID-19 [b]	11 (3.0)	2 (1.2)	18 (2.0)
Interstitial lung disease [c]	11 (3.0)	0	26 (2.9)
Transaminases increased [a]	11 (3.0)	6 (3.5)	16 (1.8)
Blood bilirubin increased [a]	8 (2.2)	0	15 (1.7)
Pneumonia	7 (1.9)	0	18 (2.0)
Thrombocytopenia [a]	7 (1.9)	2 (1.2)	25 (2.8)
Left ventricular dysfunction [d]	5 (1.3)	0	10 (1.1)
Nausea	5 (1.3)	4 (2.3)	18 (2.0)
Pyrexia	5 (1.3)	1 (0.6)	15 (1.7)
Upper respiratory tract infection [a]	5 (1.3)	0	21 (2.4)
Decreased appetite	2 (0.5)	3 (1.7)	6 (0.7)
Diarrhoea	2 (0.5)	4 (2.3)	6 (0.7)
Dyspnoea	2 (0.5)	2 (1.2)	12 (1.4)
Abdominal pain [a]	1 (0.3)	2 (1.2)	4 (0.5)
Palmar-plantar erythrodysaesthesia syndrome	0	6 (3.5)	0
Peripheral sensory neuropathy	0	4 (2.3)	0
Febrile neutropenia	0	2 (1.2)	2 (0.2)

AESI = adverse event of special interest; BC = breast cancer; COVID-19 = coronavirus disease 2019; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities, Version 24.0; N = total number of treated subjects; PT = preferred term; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
If a subject had multiple occurrences of the same PT/grouped term, the subject was counted once for that PT/grouped term. If a subject had multiple PTs/grouped terms, the subject was counted in each of the different PTs/grouped terms.
TEAEs are sorted by descending frequency in the T-DXd arm.
[a] The PTs included in each grouped term are listed in Table 2.1.
[b] The PTs included in the TEAE of COVID-19 are listed in Section 5.10.
[c] Interstitial lung disease includes events that were adjudicated as ILD and related to use of T-DXd or TPC.
[d] The PTs included in the AESI of left ventricular dysfunction are listed in Table 2.22.
Source: Module 5.3.5.3 SCS Tables 1.2.1.12, 1.2.2.6, 1.2.4.5, 1.2.6.5; Module 5.3.5.1 DS8201-A-U303 CSR Listing 16.2.7.8.1

Post marketing experience

Cumulatively, since the first approval of T-DXd in the US on 20 December 2019 through 01 March 2022, 480,209 vials of T-DXd were distributed to hospitals/clinics worldwide (Austria, Brazil, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Israel, Japan, Norway, Poland, Portugal, Puerto Rico, Slovenia, Sweden, Switzerland, United Kingdom, and US).

For the period from 20 December 2021 through 01 March 2022, a total of 840 new AEs meeting PBRER reporting criteria were reported; the majority (670) of those events were non-serious. Reported events were generally consistent with the established safety profile of T-DXd. There were no new safety findings during this period.

2.5.1. Discussion on clinical safety

Safety data has been provided for 883 patients that received trastuzumab deruxtecan (T-DXd) 5.4 mg/kg in the breast cancer pool (BC pool). The other safety population of interest are patients from the pivotal study Destiny Breast04 or U303 (n=371 who received T-DXd). The size of the safety data available on patients who have received T-DXd at the proposed dose of 5.4 mg/kg Q3W is considered acceptable. The median treatment duration of T-DXd for in study U303 and the BC pool were 8.21 months and 9.9 months, respectively. A total of 70% of the patients in the BC pool, which includes the T-DXd-treated patients from study U303, had an exposure of T-DXd for more than 6 months and 43% were exposed for more than 12 months, which is acceptable and considered a relevant exposure for the safety assessment.

Almost all patients experienced at least one **adverse event** (AE) in the pivotal study U303 and the most frequently observed adverse events in the T-DXd arm vs the TPC arm were nausea (76% vs 30.2%), fatigue (53.6% vs 48.3%), vomiting (40.4% vs 13.4%), anaemia (38.5% vs 27.3%), and neutropenia (34.0% vs 52.3%). Alopecia was almost similar in both arms with T-DXd compared to TPC (39.6% vs 33.1%). GI toxicity of T-DXd was more frequent for most AEs such as constipation (34.0% vs 22.1%), decreased appetite (31.8% vs 19.2%) and diarrhoea (27.0% vs 22.1%). Thrombocytopenia and epistaxis were reported at a much higher incidence for T-DXd compared to TPC (25.6% vs 9.3% and 10.5% vs 1.2%, respectively). These incidences are in line with those reported in the BC pool and the SmPC.

Treatment-related AEs with T-DXd vs TPC were also nausea (73% vs 23.8%), fatigue (47.7% vs 42.4%), vomiting (34% vs 9.9%), anaemia (33.2% vs 22.7%) and neutropenia (33.2% vs 51.2%) of almost the same incidences as for the AEs. Gastrointestinal toxicity was markedly increased with T-DXd vs TPC, and besides vomiting, AEs of decreased appetite (28.6% vs 16.3%), constipation (21.3% vs 12.8%) and decreased weight (12.4% vs 4.7%) were clinically significantly more commonly observed.

Interstitial lung disease (ILD) was very commonly observed with T-DXd versus TPC (12.1% vs 0.6%), and this high risk of ILD/pneumonitis with T-DXd is important information for the prescriber

and should be considered if the patients had prior clinical lung problems (see SmPC section 4.2 and 4.4). It should be noted that patients with a history of (non-infectious) ILD/pneumonitis that required steroids, current ILD/pneumonitis, or suspected ILD/pneumonitis that could not be ruled out by imaging at screening were excluded from the pivotal Study U303, and this is adequately reflected in section 5.1 of the SmPC.

Grade ≥3 AEs in the T-DXd arm vs the TPC arm were: neutropenia (14% and 41.3%), anaemia (10.2% and 5.2%) and fatigue (8.6% vs 4.7%). Hence, more high-grade neutropenia was observed with TPC while anaemia was more frequent with T-DXd. The incidences of the treatment-related grade ≥3 adverse events were much in line with this. No major bleedings were seen within 14 days of any grade thrombocytopaenia among the patients from the T-DXd arm of Study U303 and the 'All BC T-DXd 5.4 mg/kg Pool' (see SmPC section 4.8).

Adverse events of special interest include **ILD/pneumonitis** and Left ventricular dysfunction, which are important identified risks of treatment with trastuzumab deruxtecan (see RMP section). ILD was as expected commonly observed in both the pivotal study U303 (12.4%) and in the BC pool (13.3%), and these events were most often of grade 2 (6.7% vs 7.6%). The majority of these events were assessed to be treatment-related (12.1% vs 12.7%) and often led to discontinuations (8.4% vs 8.8%). Approximately half (55.6%) of the patients had recovered/resolved events of ILD, while 22.2% had not recovered/not resolved events. 2 patients (4.4%) died of ILD in study U303. This is not totally in line with what was reported for the BC pool, where deaths due to treatment-related ILD were even more frequent (7.1%), which is probably more in line with the true incidence. Lower frequencies of high-grade ILD compared to earlier studies are likely related to enhanced awareness and risk minimisation measures. However, it remains an important safety issue and the occurrence of drug-related fatal cases stresses the importance of continuous monitoring of this AESI.

Left ventricular dysfunction was observed as grade 2 decreased LVEF in 13.5% and 16.1%, or as grade 3 decrease of LVEF (0.4% and 0.2%), and the incidences were similar in the T-DXd arm and the BC pool, respectively. In the BC pool, 14.5% of the patients had a 10%-19% decrease in absolute value of LVEF, and only one patient had ≥20% increase in absolute value. It is noted that patients in the All BC T-DXd 5.4 mg/kg Pool the majority of discontinuations due to LV dysfunction were from Study U303 (3 out of 4). Also, the Grade 3 LVEF decreases in the All BC T-DXd 5.4 mg/kg Pool were mainly caused by patients from Study 303 (5 out of 7). In 12 of the 17 patients experiencing an event of LV dysfunction in the T-DXd arm of Study U303, there was a concurrent or underlying cardiovascular condition and/or other medical condition associated with increased cardiovascular risk. All 17 patients had previous exposure to at least one potentially cardiotoxic agents and 13 of the 17 patients (76%) had previous lines of treatment with anthracyclines. Two events were Grade 3 and no Grade 4 or 5 events were reported. Regarding prior treatment with anthracyclines, in the All BC T-DXd 5.4 mg/kg Pool 20 out of 34 patients (59%) with an event of LV dysfunction had prior anthracycline exposure. Prior treatment with anthracyclines could play a role in the development of LV dysfunction events, although the causality is likely multifactorial including comorbidity, prior and concurrent comedication, and T-DXd treatment. LVEF decrease is already an important identified risk for T-DXd and there were no new safety signals. No further additional measures are required at this point.

Serious adverse events (SAEs) were observed in 25.1% of the patients in the BC pool, which is similar to the incidences observed in the T-DXd arm (27.8%) and the TPC arm (25%). The most commonly observed SAEs in the BC pool and the T-DXd arm were interstitial lung disease (ILD) in 4.19% vs 4.3% of the patients, respectively, and pneumonia (1.9% in both arms). The pattern was different for the TPC arm, where the most common SAEs were overdose (2.9%, febrile neutropenia and neutropenia (2.3% each), which is in line with the known toxicities of single-agent chemotherapy.

In the BC pool, 31.7% of the patients had died, most commonly due to disease progression (24.6%) and rarely due to an AE (2.3%) or other/unknown reasons (1.5%/3.4%). In the T-DXd arm of Study U303, 39.9% had died, 32.9% of disease progression and 2.7% of an adverse event. In comparison, more patients had died in the TPC arm, 45.9% of disease progression and no patients died from an adverse event. AEs associated with an outcome of death were reported in 3.8% of patients in the T-DXd arm and 2.9% of patients in the TPC arm. Among these patients, the following AEs in the T-DXd arm were considered to be treatment-related by the investigator: pneumonitis in 2 patients, and colitis ischaemic, disseminated intravascular coagulation, dyspnea, febrile neutropenia, and sepsis in 1 patient each. None of the deaths in the TPC arm were considered to be treatment-related. It is noted that 7 out of the 11 treatment-related AEs associated with an outcome of death in the All BC T-DXd 5.4 mg/kg Pool were observed in Study U303. In addition, new treatment-related AEs leading to death were reported in Study U303, such as colitis ischaemic, disseminated intravascular coagulation, dyspnoea/pneumonia, febrile neutropenia, and sepsis. SmPC 4.4 and 4.8 has been updated to include the fatal cases of febrile neutropenia that were observed.

Hence, treatment with T-DXd carries more severe toxicity. The narratives for the patients who died from other causes in the pivotal study were provided. The overall incidence of deaths due to adverse events could be considered acceptable for this non-curative treatment setting and considering the underlying metastatic breast cancer.

The overall **discontinuation rate** due to AEs in the BC pool was 16.2%, which is double as many compared to the TPC arm (8.2%), but in line with the rate for the T-DXd arm (16.2%). Most often, patients discontinued treatment due to ILD/pneumonitis in both the BC pool (8.8%) and the T-DXd arm (8.4%), which is in line with the known safety profile of trastuzumab deruxtecan and the incidence of ILD in other studies using the dosing of 5.4 mg/kg Q3W. Other reasons were left ventricular dysfunction, bilirubin increased, dyspnoea, and pleural effusion. In the TPC arm, the most common AE leading to discontinuations was peripheral neuropathy (2.3%). Overall, the rate of discontinuations is considered acceptable for the proposed extension of indication and targeted patient population.

Laboratory findings were in line with the reported AEs and may also reflect that liver metastases are very common in the targeted patient population. Increasing toxicity of T-DXd was observed with increasing age regarding grade ≥3 AEs and serious adverse events (SAEs) both in the pivotal study and the BC pool. However, the increased toxicity with age is considered acceptable. The higher incidence of Grade 3-4 adverse reactions observed in patients aged 65 years or older was already reflected in section 4.8 of the SmPC.

It is noted that significantly more patients had an ADR of ≥grade 3 in the Asian population both for the T-DXd arms (51.7% vs 34.9%) and the BC pool. This may be explained by the known ethnic differences in drug toxicity, which is documented in the scientific literature where higher haematologic toxicity have been described for Asian vs. Non-Asian cancer patients. This was already reflected in section 4.8 of the SmPC.

Hence, the overall toxicity observed with T-DXd 5.4 mg/kg is, in general, considered manageable and in line with what has previously been observed in other clinical trials and the incidences reflected in the BC pool. No new toxicities were observed in the pivotal study. The occurrence of fatal ILD/pneumonitis remains a major safety issue as reflected in the SmPC and RMP. Additional risk minimisation measures are in place to manage this risk.

2.5.2. Conclusions on clinical safety

Based on safety data from ~880 patients with breast cancer who have had relevant exposure to the approved dose of trastuzumab deruxtecan (5.4 mg/kg Q3W) no clinically significant changes of the

known safety profile nor any new safety findings were detected. The safety profile of T-DXd was compared head-to-head with treatment per Physicians' choice of single-agent chemotherapy in the metastatic treatment setting, and the toxicities observed with TPC are considered clinically significantly different from those observed with T-DXd. Although tolerability of T-DXd appears lower compared to single-agent chemotherapy, it remains mostly manageable. ILD/pneumonitis is still the greatest risk in the treatment with trastuzumab deruxtecan 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.

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 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 4.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 4.0 with the following content:

Safety concerns

Table 78: 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 moderate or severe hepatic impairment • Long-term safety

Pharmacovigilance plan

Table 79: 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				

Study: Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Prescriber Survey preparations ongoing	EU survey of relevant healthcare professionals on understanding of key risk minimization measures pertaining to ILD/pneumonitis	ILD	Final Report	Q2 2024
Phase 2 or 3 studies preparations ongoing	Collection of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies	Use in patients with moderate or severe hepatic impairment	Final report (for 10 subjects)	Q4 2023

EU = European Union; ILD = interstitial lung disease

Risk minimisation measures

Table 80: 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: Prescriber survey
Left ventricular dysfunction	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Patient Information Leaflet Section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	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	

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

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:

The posology, administration and method of reconstitution for the extension of the indication is unchanged. The updates to the PL, including the safety sections, are not significant and utilise well recognised lay terms. Furthermore, the PL will be kept in an identical format size, colours and layout/design.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Treatment of adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

3.1.2. Available therapies and unmet medical need

Metastatic breast cancer remains an incurable disease. Although treatment has improved disease outcomes over the years, the disease will invariably progress. The aim of therapy is to prolong progression-free survival (PFS) and overall survival (OS).

Treatment outcomes with currently approved therapies in patients with metastatic HER2 negative breast cancer who progressed on at least 1 line of chemotherapy illustrate the high unmet medical need for new treatment options. No targeted therapy is specifically approved for patients with HER2-low breast cancer (BC). The most recently approved single agents for patients with metastatic hormone receptor-positive HER2-low/negative BC, are abemaciclib and eribulin. Abemaciclib has since been approved in earlier lines of therapy and is rarely used in the proposed setting where the cornerstone of treatment remains conventional chemotherapy (Gennari et al. ESMO. 2021). For

patients with TNBC who have received at least 2 previous regimens, with at least one of them in the metastatic setting, the antibody-drug conjugate (ADC) sacituzumab govitecan is also approved.

Despite available therapies, the high unmet medical need for new therapeutic options that would provide a clinically meaningful delay in time to progression and improved survival remains.

3.1.3. Main clinical studies

The single pivotal study Destiny breast04 (Study U303) is a phase 3 randomised open-label two-arm study comparing trastuzumab deruxtecan (T-DXd) head-to-head with the current SOC in patients with HER2-low, unresectable and/or metastatic breast cancer.

Patients were randomised 2:1 to receive T-DXd or single-agent chemotherapy by Physician's choice (TPC; capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel). 557 patients were recruited from 19 countries. Randomisation was stratified by HER2 IHC status (ICH 1+ vs ICH2+/ISH negative), number prior lines of chemotherapy (1 vs 2), and HR/CDK4/6 status (HR+ with CDK4/6 (min 240) vs HR+ without CDK4/6 (max 240) vs HR- (max 60)).

The primary endpoint of the pivotal trial was PFS by BIRC in the hormone receptor-positive cohort (HR+) and the key secondary endpoints were PFS by BIRC in all randomised patients (FAS) and OS of both populations.

3.2. Favourable effects

The presented data are from the primary analysis of the primary efficacy endpoint of blinded independent central review (BICR)-assessed progression-free survival (PFS) at DCO 11 January 2022. The median duration of follow-up was 16.1 months in the T-DXd arm vs 13.5 months in the TPC arm at the DCO. The primary endpoint was met and the primary analysis of PFS by BIRC in the HR+ population (n=494) showed a statistically significant improvement from 5.4 months (95%CI: 4.4; 7.1) with TPC to 10.1 months (95%CI: 9.5; 11.5) with T-DXd, HR 0.51 (95%CI: 0.40; 0.64). The data were mature with 63.7% events in the active T-DXd arm and 67.5% events in the control arm. The KM curves for PFS by BIRC separated early and remained separated.

The key secondary endpoint of PFS by BIRC in the FAS (n=557) was improved from 5.1 months (95%CI: 4.2; 6.8) with TPC to 9.9 months (95%CI: 9.0; 11.3) with T-DXd, HR 0.50 (95%CI: 0.40, 0.63). The data from the FAS were also mature with 65.1% events in the active T-DXd arm and 69% events in the control arm and the KM curves also separated early and stayed separated.

The key secondary endpoint of overall survival in the HR+ population and the FAS was statistically significantly improved at the time of the first IA with 38.1% events with T-DXd and 44.8% events in the control arm after 18.4 months of follow up and the efficacy stopping boundary of 0.00748 was crossed. The median OS for the HR+ population was 23.9 months (95%CI: 20.8, 24.8) in the T-DXd arm vs 17.5 months (95%CI: 15.2, 22.4) in the TPC arm, HR 0.64 (95%CI: 0.48, 0.86), while the median OS for the FAS was 23.4 months (95%CI: 20.0, 24.8) in the T DXd arm vs 16.8 months (95%CI: 14.5, 20.0) in the TPC arm.

Confirmed ORR by IRC was improved from 16.3% in the control arm to 52.3% with T-DXd in the FAS and the median DoR was 10.7 months in the T DXd arm vs 6.8 months in the TPC arm after ~57% and ~67 events in each arm, respectively.

In the HR- population (n=58), PFS was 6.6 months (95%CI: 4.1, 11.7) in the T DXd arm vs 2.9 months (95% CI: 1.4, 4.0) in the TPC arm, HR 0.45 (95% CI: 0.23, 0.87). Median OS was 16.6

months (95% CI: 11.3, NE) in the T-DXd arm vs 10.3 months (95% CI: 6.1, 15.2) in the TPC arm (HR: 0.63, 95% CI: 0.32, 1.23). Confirmed ORR by ICR was improved from 14.3% in the control arm to 47.6% in the T-DXd arm and median DoR was 8.6 months in the T-DXd arm vs 4.9 months in the TPC arm.

Subgroup analyses of PFS and OS by BIRC in the FAS supported a benefit of T-DXd compared with TPC for important pre-specified subgroups including HR status, prior CDK4/6i treatment, number of prior chemotherapies, and IHC 1+ and IHC 2+/ISH- status.

3.3. Uncertainties and limitations about favourable effects

There was a limited number of patients in the HR- cohort (n=40 T-DXd arm and n=18 TPC arm), leaving some uncertainty in the true effect size in this subpopulation. Sensitivity analysis based on electronic data capture data showed a beneficial effect. In addition, the Applicant plans additional observational studies which most likely will provide additional data in the HR- subgroup.

A difference in OS of more than 6 months between the treatment arms is considered clinically meaningful. Based on the available data, a later detriment in OS is considered unlikely. Results from the final OS analysis are projected to occur in Q4 2024 and will be provided post-authorisation when available (PAM-REC).

3.4. Unfavourable effects

In the pivotal Study U303, median treatment duration in Study U303 was 8.2 months for T-DXd and 3.5 months in the TPC arm.

Almost all the patients experienced at least one adverse event (AE) in the pivotal study U303 and the most frequently observed adverse events in the T-DXd arm vs the TPC arm were nausea (76% vs 30.2%), fatigue (53.6% vs 48.3%), vomiting (40.4% vs 13.4%), anaemia (38.5% vs 27.3%), and neutropenia (34.0% vs 52.3). Alopecia was almost similar in both arms (39.6% vs 33.1%). Gastrointestinal toxicity of T-DXd was more frequent for most AEs such as constipation (34.0% vs 22.1%), decreased appetite (31.8% vs 19.2%) and diarrhoea (27.0% vs 22.1%). Thrombocytopenia and epistaxis were reported at a much higher incidence for T-DXd compared to TPC (25.6% vs 9.3% and 10.5% vs 1.2%, respectively). These incidences are in line with those reported in the BC pool and the SmPC.

Treatment-related AEs with T-DXd vs TPC were also nausea (73% vs 23.8%), fatigue (47.7% vs 42.4%), vomiting (34% vs 9.9%), anaemia (33.2% vs 22.7%) and neutropenia (33.2% vs 51.2%) of almost the same incidences. Gastrointestinal toxicity was as mentioned markedly increased with T-DXd vs TPC, and besides vomiting, ADR of decreased appetite (28.6% vs 16.3%), constipation (21.3% vs 12.8%) and decreased weight (12.4% vs 4.7%) were clinically significantly more commonly observed.

Grade ≥3 AEs in the T-DXd arm vs the TPC arm were neutropenia (14% and 41.3%), anaemia (10.2% and 5.2%) and fatigue (8.6% vs 4.7%) which were consistent with. treatment related grade ≥3 adverse events reported.

Adverse events of special interest include ILD/pneumonitis and left ventricular dysfunction. ILD was commonly observed in both the pivotal study U303 (12.4%) and in the BC pool (13.3%), most often of grade 2 (6.7% vs 7.6%). Approximately half (55.6%) of the patients had recovered/resolved at DCO, while 22.2% had not recovered/not resolved events. 2 patients (4.4%) died of ILD. In the BC pool, deaths due to treatment-related ILD were even more frequent (7.1%). LVEF dysfunction was observed of grade 2 in 13.5% and 16.1%, or grade 3 decrease of LVEF (0.4% and 0.2%) and the incidences

were similar in the T-DXd arm and the BC pool, respectively. All events except one with T-DXd were resolved at DCO.

Serious adverse events (SAEs) were observed in 25.1% of the patients in the BC pool, which is similar to the SAEs observed in the T-DXd arm (27.8%) and the TPC arm (25%). The most common SAE observed were interstitial lung disease (ILD) and pneumonia. In the TPC arm, the most common SAEs were overdose, febrile neutropenia and neutropenia, which is in line with the known toxicities of single-agent chemotherapy.

In the BC pool, 31.7% of the patients had died, most commonly due to disease progression (24.6%) and rarely due to an AE (2.3%) or other/unknown reasons (1.5%/3.4%). In the T-DXd arm, 39.9% had died, 32.9% of disease progression and 2.7% of an adverse event. In comparison, more patients had died in the TPC arm, 45.9% of disease progression and no patients died from an adverse event. Regarding fatal AEs, 7 out of the 11 treatment-related AEs association with an outcome of death in the All BC T-DXd 5.4 mg/kg Pool were observed in Study U303. In addition, new treatment-related AEs leading to death were reported in Study U303, such as colitis ischaemic, disseminated intravascular coagulation, dyspnoea, febrile neutropenia, and sepsis.

The overall discontinuation rate due to AEs in the BC pool was 16.2%, which is double as many compared to the TPC arm (8.2%), but in line with the rate for the T-DXd arm (16.2%) and was most commonly due to ILD/pneumonitis.

Laboratory findings were in line with the reported AEs and may also reflect that liver metastases are very common in the targeted patient population. Increasing toxicity of T-DXd was observed with increasing age regarding grade ≥3 AEs and serious adverse events (SAEs) both in the pivotal study and the BC pool.

3.5. Uncertainties and limitations about unfavourable effects

Safety data in patients >75 years, patients with severe renal impairment, and patients with moderate/severe hepatic impairment remain limited. These uncertainties have been reflected in the SmPC (see SmPC section 4.2 and 4.4).

3.6. Effects Table

Table 81 Effects Table for Enhertu (T-DXd) for unresectable or metastatic HER2-low BC (data cut-off: 11 January 2022)

Effect	Short description	Unit	Treatment T-DXd N=373	Control TPC N=184	Uncertainties / Strength of evidence	Ref
Favourable Effects						
PFS by BIRC HR+	Progression-free survival	Months (95%CI)	10.1 9.5; 11.5	5.4 4.4; 7.1	HR 0.51 0.40; 0.64 Strengths: RCT, blinded review	
PFS by BIRC FAS	Progression-free survival	Months (95%CI)	9.9 9.0; 11.3	5.1 4.2; 6.8	HR 0.50 0.40; 0.63 Strengths: RCT, blinded review	

Effect	Short description	Unit	Treatment T-DXd N=373	Control TPC N=184	Uncertainties / Strength of evidence	Ref
OS HR+	Overall survival	Months (95%CI)	23.9 20.8; 24.8	17.5 15.2; 22.4	HR 0.64 0.48; 0.86 Strengths: RCT Uncertainties: Immaturity	
OS FAS	Overall survival	Months (95%CI)	23.4 20.0; 24.8	16.8 14.5; 20.0	HR 0.64 0.49; 0.84 Strengths: RCT Uncertainties: Immaturity	
Unfavourable Effects (N=543)						
Grade ≥3 AEs		%	52.6	67.4		
SAEs		%	27.8	25.0		
AEs leading to discontinuation		%	16.2	8.1		
AEs associated with death		%	3.8	2.9		
ILD/pneumonitis		%	12.1	0.6	8.4% discontinue treatment and 0.8% with outcome of death T-DXd arm	
LV dysfunction - AE LV dysfunction - Grade 2 LVEF decrease		 % %	 4.6 14.9	 0.0 7.7		

Abbreviations: HR+: Hormone-receptor positive cohort; FAS: Full Analysis Set; SAE: Serious Adverse event.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy of trastuzumab deruxtecan (T-DXd) compared to single-agent chemotherapy per Physicians' choice (TPC) in the proposed setting after a prior systemic chemotherapy in the metastatic setting is considered clinically meaningful, since the primary endpoint of PFS by BIRC for the hormone-receptor positive cohort was prolonged from 5.4 months to 10.1 months, HR 0.51. Similar results were observed for the FAS, as expected given that the HR+ cohort constituted about 90% of the FAS.

OS was also clinically significantly improved for both the HR+ and the FAS populations (HR 0.64) and although data are only partly mature, a detriment in OS at a later time point is considered unlikely. The MAH is recommended to provide final efficacy data from the pivotal U303 study post-authorisation.

PFS and OS results support a beneficial effect of T-DXd in the hormone-receptor negative cohort as well, although some uncertainty exists on the true effect size in the HR- cohort due to the small sample size. However, given the magnitude of the effect size (increase of 3.7 months in median PFS and 6 months in median OS) it is reasonable to exclude a detrimental effect compared to TPC. Further,

although the prognosis is worse in the HR- cohort, it is unlikely that T-DXd would act differently in the HR- cohort compared to the HR+ cohort given the mechanism of action. Furthermore, post hoc sensitivity analyses showed a beneficial effect. The Applicant plans additional observational studies which most likely will provide additional data in the HR- subgroup.

Overall, treatment options in HR- population are limited in this patient population. T-DXd could offer an alternative to existing therapies with a different safety profile.

The safety profile of T-DXd was not significantly changed with added safety data from the pivotal study U303 and the most frequently reported adverse events of trastuzumab deruxtecan are haematological and gastrointestinal nature. The major safety concern continues to be the risk of ILD/pneumonitis (12.1%), which frequently led to drug discontinuation and was fatal in 4 cases. The current guidance for the handling of ILD/pneumonitis is considered adequately reflected in the SmPC. Also, a higher rate of LV dysfunction events was observed in the T-DXd arm compared to the TPC arm. This was already reflected in 4.4 and 4.8 of the SmPC.

Overall, the toxicity of T-DXd is not negligible and the risk of fatal ILD/pneumonitis stresses the importance of continuous monitoring of this AESI. Most AEs are manageable and, overall, the safety is considered outweighed by the benefits associated with T-DXd in terms of PFS and OS improvement.

3.7.2. Balance of benefits and risks

The shown improvement of PFS and OS are considered clinically relevant and outweigh the risks of treatment with T-DXd in the target population, including both HR+ and HR- patients. Though some uncertainty remains on the true effect size in the HR- subgroup due to the small sample size, given the magnitude of efficacy observed, the poor prognosis of the HR- patients and the mechanism of action of T-DXd, it is reasonable to assume that HR- patients will benefit from treatment and inclusion in the indication is sufficiently supported. Treatment with T-DXd carries more severe toxicity, which is considered to be outweighed by a lower risk of disease progression and death compared to standard of care (TPC).

3.7.3. Additional considerations on the benefit-risk balance

Low HER2 expression was defined as IHC2+/ISH- or ICH1+ (ISH- or not tested) according to ASCO/CAP guidelines per central assessment using the most recent tumour tissue sample available, which is endorsed. Although there was a slight difference in the wording of the HER2 1+ definition between the ASCO/CAP guidelines, the protocol for the pivotal study, and the pathologist training material used to train DB-04 central pathologist, it is considered that the definitions are similar. This is agreed since the slight difference is only in the wording, not in the interpretation of the staining. In both definitions, the % of cells presenting such staining intensity needs to be >10%. This has been reflected in SmPC 5.1.

3.8. Conclusions

The overall B/R of Enhertu in the treatment of adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy is 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 and IIIB

Extension of indication to include treatment of adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy; for ENHERTU, based on final results from study DS8201-A-U303 (DESTINY-Breast04). This is a Phase III, multicentre, randomised, 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.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.0 of the RMP is approved.

The variation leads to amendments to the Summary of Product Characteristics 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 Annex(es) I and IIIB and to the Risk Management Plan are recommended.

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

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion “Enhertu-005124-II-22”