EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Enhertu

International non-proprietary name: trastuzumab deruxtecan

Procedure No. EMEA/H/C/005124/II/0014

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
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
AUCss	area under the serum concentration-time curve at steady state
BC	breast cancer
BICR	blinded independent central review
Cavg	average concentration
CBR	clinical benefit rate
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
Cmax,ss	maximum serum concentration at steady state
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 drug, a topoisomerase I inhibitor derivative of exatecan
EAIR	exposure-adjusted incidence rate
ECOG PS	Eastern Cooperative Oncology Group performance status
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	EuroQoL-5 dimensions-5 levels of severity

ER	exposure-response
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GC	gastric cancer
GI	gastrointestinal
HEOR	Health Economics and Outcome Research
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
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
NCA	noncompartmental analysis
NE	not estimable
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival

PK	pharmacokinetic(s)
PMDA	Japan Pharmaceutical and Medical Devices Agency
PopPK	population pharmacokinetics
pp	percentage points
PPS	Per-Protocol Analysis Set
PR	partial response
PRO	patient reported outcome
PT	preferred term
Q3W	every 3 weeks
QLQ	quality-of-life questionnaire
QoL	quality of life
RDI	relative dose intensity
RECIST v1.1	Response Evaluation Criteria in Solid Tumours Version 1.1
RoW	rest of the world
SAE	serious adverse event
SAP	statistical analysis plan
SCS	summary of clinical safety
SoC	standard of care
T-DM1	trastuzumab emtansine, KADCYLA®
T-DXd	trastuzumab deruxtecan, Enhertu®
TEAE	treatment-emergent adverse event
THP	taxane/Herceptin/Perjeta
TTR	time to response
US	United States
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 30 November 2021 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 for Enhertu to include treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens; 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 1.2 of the RMP has also been submitted.

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 Decisions CW/0001/2015, EMA/384015/2017 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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 25 January 2018 (EMEA/H/SA/3714/1/2017/HTA/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	30 November 2021
Start of procedure:	25 December 2021
CHMP Rapporteur Assessment Report	22 February 2022
PRAC Rapporteur Assessment Report	25 February 2022
CHMP Co-Rapporteur Critique	2 March 2022
PRAC Outcome	10 March 2022
CHMP members comments	14 March 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 March 2022
Request for supplementary information (RSI)	24 March 2022
CHMP Rapporteur Assessment Report	24 May 2022
PRAC Rapporteur Assessment Report	27 May 2022
PRAC members comments	01 June 2022
Updated PRAC Rapporteur Assessment Report	02 June 2022
PRAC Outcome	10 June 2022
CHMP members comments	13 June 2022
Updated CHMP Rapporteur Assessment Report	16 June 2022
Opinion	23 June 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The claimed indication for Enhertu is 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.

Epidemiology and risk factors, screening tools/prevention

Breast cancer is the most commonly diagnosed cancer in women worldwide (11.7% of all cancer sites) and the leading cause of cancer death in women (6.9% of all cancer sites in 2020) (1). In 2020, there was an estimated 2.26 million new cases of female BC globally, with an estimated 684,996 deaths due to BC (1). Along with cancer staging, the determination of biologic markers status (estrogen receptor, progesterone receptor, and HER2) at the time of diagnosis is common medical practice, assisting in the evaluation of the risk of recurrence and predicting response to therapy (2,3).

Approximately 20% of patients with BC have HER2-positive tumours (ie, tumours scored as 3+ by immunohistochemistry [IHC] or that demonstrate gene amplification by in situ hybridization [ISH]) (4,5). Although treatment with anti HER2-targeted therapies has improved the disease outcomes, these are not curative in the locally advanced/metastatic setting and the disease invariably progresses.

Management

The current standard of care (SoC) for newly diagnosed metastatic HER2-positive BC in Europe (3), based on the results of the CLEOPATRA (6,7) study, is a combination of a taxane with trastuzumab, and the anti-HER2 pertuzumab (8,9) (THP regimen). In CLEOPATRA, newly diagnosed patients with HER2-positive metastatic BC were randomized to receive trastuzumab plus docetaxel with or without the addition of pertuzumab as first-line therapy, which improved the median PFS from 12.4 months to 18.5 months and the median OS from 40.8 months (95%CI: 35.8, 48.3) to 56.5 months (95%CI: 49.3, not reached) (Table 1.1).

After disease progression on the THP regimen, the current SoC in the second-line metastatic setting, based on the results of the EMILIA (10) study, is the antibody-drug conjugate (ADC) trastuzumab emtansine (T-DM1, (11,12)) as a single-agent. In EMILIA, T-DM1 was compared with combined therapy with lapatinib plus capecitabine in patients whose cancer had progressed after treatment with the trastuzumab plus taxane combination. Treatment with T-DM1 improved the disease outcomes compared with treatment with lapatinib plus capecitabine, with an ORR by independent central review (ICR) of 43.6% (95%CI: 38.6, 48.6) in the T-DM1 arm versus (vs.) 30.8% (95%CI: 26.3, 35.7) in the lapatinib plus capecitabine arm; a median PFS of 9.6 months vs. 6.4 months (HR 0.65 [95%CI: 0.55, 0.77), respectively; and a median OS of 30.9 months vs. 25.1 months (HR 0.68 [95%CI: 0.55, 0.85]), respectively (Table 1.1).

It should be noted that the EMILIA study was conducted before the pertuzumab-based combination was SoC in first-line therapy. Although the mechanism remains unclear, response rates to T-DM1 appear to be lower (13,14) and disease outcomes appear to be shorter (15,16) than those reported in the EMILIA study, when T-DM1 is given after pertuzumab-containing regimens. Hence, in the KATE2 study (15) comparing T-DM1 plus atezolizumab vs. T-DM1 plus placebo in previously treated patients with advanced HER2-positive BC, the median PFS was 6.8 months (95%CI: 4.0, 11.1) for patients in the T-DM1 plus placebo arm. These findings were consistent with those from retrospective, real-world evidence observational studies of the efficacy of T-DM1 showing a median PFS of 6 to 7 months for pre-treated patients with HER2-positive BC (16,17,18).

Other treatment options in the second-line setting include the kinase inhibitor tucatinib (19) in combination with trastuzumab and capecitabine, which was approved on the basis of the results from the HER2CLIMB study (20) in patients, who have received at least 2 prior anti-HER2 regimens. In the EU tucatinib is approved for third-line treatment and in the US for second-line treatment. In HER2CLIMB, patients previously treated with trastuzumab, pertuzumab, and T-DM1, were randomized to receive trastuzumab plus capecitabine with or without tucatinib. The addition of tucatinib to the

trastuzumab plus capecitabine combination improved median PFS from 5.6 months (95%CI: 4.2, 7.1) to 7.8 months (95%CI: 7.5, 9.6) (HR: 0.54 [95 CI: 0.42, 0.71]) and median OS from 17.4 months (95%CI: 13.6, 19.9) to 21.9 months (95%CI: 18.3, 31.0) (HR: 0.66 [95%CI: 0.50, 0.88], Table 1.1).

Table 1.1: Treatment Options in First Line and Second Line in the Metastatic Setting

Product Name	Relevant Indication	Dosing/Administration	Efficacy Information
Pertuzumab (PERJETA®[8,9]) Trastuzumab (HERCEPTIN®[21,22]) Docetaxel (TAXOTERE®[23,24])	**1L** Pertuzumab: For use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic BC who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. **1L** Trastuzumab: In combination with paclitaxel, for the first-line treatment of HER2-overexpressing metastatic BC. **1L** Docetaxel: Treatment of patients with locally advanced or metastatic BC after failure of prior chemotherapy.	Pertuzumab: Initial 840-mg dose as a 60-minute IV infusion, followed Q3W by a 420-mg dose as an IV infusion over 30 to 60 minutes. Trastuzumab (when administered with pertuzumab): Initial dose of 8 mg/kg as a 90-minute IV infusion followed Q3W by a dose of 6 mg/kg as an IV infusion over 30 to 90 minutes. Docetaxel: 60 mg/m^2 to 100 mg/m^2 administered IV over 1 hour, Q3W.	**CLEOPATRA**[6,7] Pertuzumab + trastuzumab + docetaxel (n = 402) • Median PFS by IRF: 18.5 months (95% CI not reported) (HR: 0.62 [95% CI: 0.51, 0.75]; *P*-value <0.001) • Median OS (final analysis): 56.5 months (95% CI: 49.3, NR) (HR: 0.68 [95% CI: 0.56, 0.84]; *P*-value <0.001) • ORR by IRF (population with baseline measurable disease): 80.2% (95% CI not reported) • Median DoR: 20.2 months (95% CI: 16.0, 24.0) Placebo + trastuzumab + docetaxel (n = 406) • Median PFS by IRF: 12.4 months (95% CI not reported) • Median OS (final analysis): 40.8 months (95% CI: 35.8, 48.3) • ORR by IRF (population with measurable baseline disease): 69.3% (95% CI not reported) • Median DoR: 12.5 months (95% CI: 10.0, 15.0)
Trastuzumab emtansine (KADCYLA®[11,12])	**2L** T-DM1: As a single agent, for the treatment of patients with HER2-positive, metastatic BC who previously received trastuzumab and a taxane (separately or in combination). Patients should have either received prior therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy.	T-DM1: 3.6 mg/kg as an IV infusion Q3W (21-day cycle). Administer first infusion over 90 minutes; administer subsequent infusions over 30 minutes if prior infusions were well tolerated.	**EMILIA**[10] T-DM1 (n = 495): • Median PFS by IRC: 9.6 months (HR: 0.65 [95% CI: 0.55, 0.77]; *P*-value <0.001) • Median OS: 30.9 months (HR: 0.68 [95% CI: 0.55, 0.85]; *P*-value <0.001) • ORR by IRC (population with measurable baseline disease): 43.6% (95% CI: 38.6, 48.6)

Product Name	Relevant Indication	Dosing/Administration	Efficacy Information
			• Median DoR by IRC: 12.6 months (95% CI: 8.4, 20.8) Lapatinib + capecitabine (n = 496): • Median PFS by IRC: 6.4 months • Median OS: 25.1 months • ORR by IRC: 30.8% (95% CI: 26.3, 35.7) • Median DoR by IRC: 6.5 months (95% CI: 5.5, 7.2)
Tucatinib (TUKYSA®[19]) Trastuzumab (HERCEPTIN®[21,22]) Capecitabine (XELODA®[25,26])	**2L+** Tucatinib: In combination with trastuzumab and capecitabine, for treatment of adult patients with advanced unresectable or metastatic HER2-positive BC, including patients with brain metastases, who have received 1 or more prior anti-HER2-based regimens in the metastatic setting. **2L+** Trastuzumab: As a single agent for treatment of HER2-overexpressing BC in patients who have received 1 or more chemotherapy regimens for metastatic disease. **2L+** Capecitabine: In combination with docetaxel, for the treatment of patients with metastatic BC after failure of prior anthracycline-containing chemotherapy. As monotherapy, for the treatment of patients with metastatic BC resistant to both paclitaxel and an anthracycline-containing	Tucatinib: 300 mg taken orally twice daily in combination with trastuzumab and capecitabine. Trastuzumab: Initial dose of 4 mg/kg as a 90-minute IV infusion followed by subsequent once weekly doses of 2 mg/kg as 30-minute IV infusions. Capecitabine: 1250 mg/m^2 orally twice daily for 2 weeks followed by a 1-week rest period, Q3W.	**HER2CLIMB**[19,20] Tucatinib + trastuzumab + capecitabine (n = 404): • Median PFS by BICR: 7.8 months (95% CI: 7.5, 9.6) (HR: 0.54 [95% CI: 0.42, 0.71]; *P*-value <0.001) o Median PFS in patients with a history or presence of brain metastases: 7.6 months (95% CI: 6.2, 9.5) • Median OS: 21.9 months (95% CI: 18.3, 31.0) (HR: 0.66 [95% CI: 0.50, 0.88]; *P*-value = 0.005) • Confirmed ORR (population with measurable baseline disease): 40.6% (95% CI: 35.3, 46.0) • Median DoR: 8.3 months (95% CI: 6.2, 9.7) Placebo + trastuzumab + capecitabine (n = 197): • Median PFS by BICR: 5.6 months (95% CI: 4.2, 7.1) o Median PFS in patients with a history or presence of brain metastases: 5.4 months (95% CI: 4.1, 5.7) • Median OS: 17.4 months (95% CI: 13.6, 19.9) • Confirmed ORR (population with baseline measurable disease): 22.8% (95% CI: 16.7, 29.8) • Median DoR: 6.3 (95% CI: 5.8, 8.9)
	chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated.		

1L = first line; 2L = second line; 2L+ = second and subsequent line; BC = breast cancer; BICR = blinded independent central review; failure; CI = confidence interval; DoR = duration of response; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; IRC = independent review committee; IRF = independent review facility; IV = intravenous; NR = not reached; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; Q3W = every 3 weeks; T-DM1 = trastuzumab emtansine

The limited duration of efficacy of the current SoC, T-DM1, in the second-line metastatic setting represents an unmet medical need, which might be addressed by newer agents that provide longer PFS. In that context, the mechanism of action of T-DXd is biologically relevant regardless of the sequence of prior anti-HER2 therapies and, therefore, meaningful clinical activity from T-DXd is expected in patients with heterogenous anti-HER2 treatment history.

2.1.2. About the product

T-DXd is a humanized HER2-targeted antibody and topoisomerase I inhibitor conjugate. The anti-HER2 component (monoclonal antibody [mAb]) has the same amino acid sequence as trastuzumab and is specifically targeted to HER2-expressing cells. The released drug DXd is a topoisomerase I inhibitor derivative of exatecan that is approximately 10 times more potent than the inhibitor SN-38, the active metabolite of irinotecan (27). DXd is cell-membrane permeable, giving the ability to penetrate and act in surrounding cells (28). The mAb is covalently conjugated to a drug-linker, deruxtecan, that is composed of a cleavable maleimide tetrapeptide linker and the released drug DXd (27,29,30). The tetrapeptide linker is designed to be stable in plasma to reduce systemic exposure to DXd (27,31).

T-DXd binds specifically to and is internalized by HER2-expressing cells, after which the linker is cleaved by lysosomal enzymes such as cathepsins B and L, which are overexpressed in cancer cells. The drug DXd is then released and exerts cytotoxic activity by inhibiting the activity of

topoisomerase I, leading to inhibition of cell proliferation and apoptosis of the target tumour cells. The released drug DXd has, by design, a short systemic half-life, and its active chemical moiety in the lactone form is present and active in the acidic tumoural environment, whereas the chemical moiety in the hydroxyl-acid form present in the neutral systemic environment is mostly inactive. As a result of drug-linker design and site-specific conjugation, the drug-to-antibody ratio (DAR) for T-DXd is approximately 8 compared with a DAR of 3 to 4 for other ADCs such as T-DM1 (27).

Enhertu was initially authorised on 18 January 2021 as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens. The recommended dose is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

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

In January 2018, scientific advice was given by the CHMP for trastuzumab deruxtecan (EMEA/H/SA/3714/1/2017/HTA/II). Part of the scientific advice discussed Study DS8201-A-U302 (DESTINY-Breast03; hereinafter referred to as Study U302), a randomized, active controlled Phase 3 study in which the target population are patients with unresectable or metastatic HER2-positive BC who had received a prior anti-HER2-based regimen received T-DXd at the target dose of 5.4 mg/kg or T-DM1, the SoC in the second-line metastatic setting. This is the pivotal study in the current application.

The patient population, primary endpoint, and the use of QoL questionnaires were discussed:

Patient population - The CHMP noted that the proposed trial mimics the study conducted with trastuzumab emtansine (i.e. TDM4370g/BO21977) in which patients with HER2-positive unresectable locally advanced breast cancer or metastatic breast cancer who had received prior taxane and trastuzumab-based therapy, including patients who received prior therapy with trastuzumab and a taxane in the adjuvant setting and who relapsed during or within six months of completing adjuvant therapy, were included. The proposed "replication" approach appears reasonable from a regulatory point of view but it may include a patient population not fully in line with that seen in clinical practice at the time of the running of the trial. It was, therefore, advised to include patients pretreated with pertuzumab + trastuzumab in the trial.

Stratification by ER status was recommended since patients may receive different therapeutic options upon subsequent progression that could influence their outcome e.g. in terms of OS.

Primary endpoint - The proposal to use PFS by BICRas primary endpoint was deemed acceptable in this setting. However, even if OS is not formally required as an additional primary endpoint, at the time of assessment, it would be required that available data are reassuring with respect to any potential detrimental effect on OS. The Applicant was encouraged to make an estimation of how many OS events are expected to have occurred at the time of the planned PFS final analysis and how mature OS data would be at that stage. Powering the study for OS, even if PFS is the primary endpoint, was highly recommended. Following patients beyond progression was also strongly encouraged.

When using PFS as a primary endpoint, the treatment effect on PFS would need to be large to allow confidence in the clinical benefit of DS-8201a. The proposed secondary endpoints were considered acceptable. Any reported contradictory findings in terms of secondary endpoint would raise concerns regarding potential approval based on PFS.

QoL data - The use of PROs is always recommended in order to capture patients' quality of life, even if the open label nature of the proposed trials could potentially limit the value of the reported evidence.

As to the inclusion of such data in the SmPC, this would depend on the final results and their reliability. In this context, it would be important that e.g. the completion rate of the questionnaires is sufficiently high. In addition, pre-specifying a statistical analysis plan and type I error control was recommended.

In general, the scientific advice was followed by the MAH and is discussed in further detail in the clinical efficacy discussion.

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

This application concerns a change in the indication from third line to second line treatment of Her-2 positive breast cancer. An updated environmental risk assessment was submitted to include and discuss the impact of the change from third to second line indication. As the ERA from the initial Market Authorisation was not considering the third line classification of the indication of Enhertu, i.e. worst-case scenarios for environmental exposure was used based on HER2-positive breast cancers irrespective of line of treatment, the conclusion from the initial ERA still holds (see EPAR for Enhertu).

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

included in the Population PK analysis

Table 3-1 Summary of studies included in the analysis

Study Identifier	Study Design	Study Drug Administration	Number of Subjects	Subject Diagnosis	PK Sampling Design for T-DXd and DXd
DS8201-A-J101 (Study J101) DCO: Aug 01, 2019	Phase 1, two-part, multicenter, non-randomized, open-label, multiple-dose, FIH human study	FL-DP1 or FL-DP2 T-DXd IV infusion Q3W Dose Escalation (Part 1) 0.8, 1.6, 3.2, 5.4, 6.4, or 8.0 mg/kg Dose Expansion (Part 2) 5.4 or 6.4 mg/kg	Planned Dose escalation (Part 1): At least 18 Dose expansion (Part 2): Approximately 260 Treated Part 1: 27 Part 2: 262 (BC: 182 Gastric or GEJ cancer: 47 Colorectal cancer: 20 Other cancers: 37)	Part 1: Advanced BC or GC Part 2a: T-DM1-treated HER2-positive BC Part 2b: Trastuzumab-treated HER2-positive GC Part 2c: Low HER2-expressing BC Part 2d: Other HER2-expressing solid malignant tumors Part 2e: HER2-expressing BC	PK sampling prior to and after the infusion for Cycles 1, 2, 3, 4, 6, and 8; at 2, 4, and 7 hours after start of infusion on Cycle 1; on Days 2, 4, 8, and 15 of Cycle 1; and on Days 8 and 15 of Cycle 3 For the dose-escalation phase, an additional PK sample at 4 hours from the start of infusion was collected on Cycle 3*
DS8201-A-U201 (Study U201) DCO: Jun 08, 2019	Phase 2, two-part, global, multicenter, randomized, open-label, multiple-dose study	FL-DP2 or Lyo-DP T-DXd IV infusion Q3W Part 1 5.4, 6.4, or 7.4 mg/kg Part 2 5.4 mg/kg	Planned Part 1: Approximately 120 Part 2: At least 100 Treated Part 1: 119 Part 2: 134	T-DM1-treated HER2-positive, unresectable and/or metastatic BC	PK sampling prior to and after the infusion on Cycles 1, 2, 3, 4, 6, and 8; at 2, 4, and 7 hours after start of infusion on Cycle 1; on Days 8 and 15 of Cycle 1; and at 4 and 7 hours after the start of infusion on Cycle 3. For PK stage of Part 1, additional PK sampling at Days 2 and 4 of Cycle 1
DS8201-A-J102 (Study J102) DCO: Dec 05, 2018	Phase 1, multicenter, non-randomized, open-label, multiple-dose study	Lyo-DP T-DXd 6.4 mg/kg IV infusion Q3W	Planned 50 Treated 51	HER2-expressing metastatic and/or unresectable BC	PK sampling as for PK stage of Part 1 for Study U201 PK; additional sampling points at 2 hours after the start of infusion and Days 2, 4, 8, and 15 of Cycle 3*

Table 3-1 Summary of studies included in the analysis

Study Identifier	Study Design	Study Drug Administration	Number of Subjects	Subject Diagnosis	PK Sampling Design for T-DXd and DXd
DS8201-A-A103 (Study A103) DCO: Sep 14, 2018	Phase 1, multicenter, non-randomized, open-label study	Lyo-DP T-DXd 6.4 mg/kg IV infusion Q3W	Planned 12 Treated 12	HER2-positive advanced unresectable and/or refractory GC or BC	PK sampling as for PK stage of Part 1 for Study U201 PK; additional sampling points at 2 hours after the start of infusion and Days 2, 4, 8, and 15 of Cycle 3*
DS8201-A-A104 (Study A104) DCO: Sep 26, 2018	Phase 1, multicenter, non-randomized, open-label, single-sequence crossover DDI study	Lyo-DP T-DXd 5.4 mg/kg IV infusion Q3W Cohort 1 + ritonavir 200 mg BID on Day 17 of Cycle 2 until Day 21 of Cycle 3 Cohort 2 + itraconazole 200 mg BID on Day 17 of Cycle 2 followed by 200 mg QD until Day 21 of Cycle 3	Planned Cohort 1: 16 Cohort 2: 16 Treated Cohort 1: 17 Cohort 2: 23 (Breast cancer: 17 Gastric or GEJ cancer: 1 Colorectal cancer: 1 Other cancers: 21)	HER2-expressing advanced solid tumors	PK sampling prior to and after the infusion on Cycles 1, 2, 3, 4, 6, and 8; at 2, 4, and 7 hours after the start of infusion on Cycles 2 and 3; and at Days 2, 4, 8, 12, and 17 of Cycles 2 and 3*
DS8201-A-J202 (Study J202) DCO: Jun 03, 2020	Phase 2, randomized, parallel-arm study	Primary Cohort (Randomized) Lyo-DP T-DXd 6.4 mg/kg IV infusion Q3W group vs. physician's choice group (2:1) Exploratory Cohorts 1 and 2 Lyo-DP T-DXd 6.4 mg/kg IV infusion Q3W	Planned Primary Cohort: T-DXd: 120 Physician's choice: 60 Exploratory Cohort 1: 20 Exploratory Cohort 2: 20 Treated Primary Cohort: T-DXd: 125 Physician's choice: 62 Exploratory Cohorts: 44	HER2-expressing advanced GC who have progressed following two previous regimens including a fluoropyrimidine and a platinum-based agent Primary: HER2 positive (IHC3+ or IHC2+/ISH+) and progression on a trastuzumab-containing regimen Exploratory Cohort 1: HER2 IHC2+/ISH- and treatment naïve with anti-HER2 therapy Exploratory Cohort 2:	PK sampling prior to and after the infusion on Cycles 1, 2, 3, 4, 6, and 8; and at 4 and 7 hours after the start of infusion on Cycles 1 and 3*

Table 3-1 Summary of studies included in the analysis

Study Identifier	Study Design	Study Drug Administration	Number of Subjects	Subject Diagnosis	PK Sampling Design for T-DXd and DXd
				HER2 IHC1+ and treatment naïve with anti-HER2 therapy	
DS8201-A-U204 (Study U204) DCO: May 03, 2021	Phase 2, single arm, open-label study	Lyo-DP T-DXd 5.4 and 6.4 mg/kg I	Planned 130	HER2-overexpressing or HER2-mutated unresectable and/or metastatic non-squamous NSCLC	PK sampling prior to and after the infusion on Cycles 1, 2, 3, 4 and 6; at 5 hours after the start of infusion on Cycle 1; and at Days 8 and 15 of Cycle 1*
DS8201-A-U205 (Study U205) DCO: Apr 04, 2021	Phase 2, single arm, open-label study	Lyo-DP T-DXd 6.4 mg/kg IV infusion Q3W	Planned 80 Treated 79	HER2-expressing unresectable or metastatic GC who have progressed on or after a trastuzumab-containing regimen	PK sampling prior to and after the infusion on Cycles 1, 2, 3, 4, 6, and 8; at 5 hours after the start of infusion on Cycle 1; and at Days 8 and 15 of Cycle 1
DS8201-A-U302 (Study U302) DCO: May 21, 2021	Phase 3, randomized study	Lyo-DP DS-8201a 5.4 mg/kg IV infusion Q3W or T-DM1 per label	Planned 250 each arm Treated 257 in T-DXd arm 261 in T-DM1 arm	HER2-positive, unresectable and/or metastatic breast cancer previously treated with trastuzumab and taxane	PK sampling prior to and after the infusion on Cycles 1, 2, 3, 4, 6, and 8; and at 5 hours after the start of infusion on Cycle1

Abbreviations: BC = breast cancer; BID = twice daily; DCO = data cut-off; DDI = drug-drug interaction; FIH = first-in-human; FL-DP1 = frozen liquid drug product 1; FL-DP2 = frozen liquid drug product 2; GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ISH = in situ hybridization; IV = intravenous; Lyo-DP = lyophilized powder drug product; NSCLC = non-small cell lung cancer; PK = pharmacokinetics; Q3W = once every 3 weeks; QD = once daily; T-DM1 = trastuzumab emtansine; vs. = versus.

Note: *PK samples were also conditionally collected on Day 22 if the sampling on Day 1 of the next cycle was delayed by ≥3 days or the subject could not continue to the next cycle.

The current application is seeking marketing approval for the use of T-DXd 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. The currently approved and recommended T-DXd dosing regimens for breast cancer is 5.4 mg/kg as an intravenous (IV) infusion once every 3 weeks (Q3W).

The clinical pharmacology profile of T-DXd has been characterized previously in the initial T-DXd marketing application in BC. The clinical pharmacology package for the initial BC application included five studies (Studies J101, J102, A103, A104, and U201). The package included in the current application also includes data from the four additional studies listed below.

- Two Phase 2 studies in subjects with HER2-positive advanced GC or gastroesophageal junction (GEJ) adenocarcinoma (Studies J202 and U205)
- A Phase 2 study in subjects with metastatic HER2-mutant or HER2-overexpressing NSCLC (Study U204)
- A Phase 3 study in subjects with HER2-positive BC (Study U302).

Data from these nine studies were used in the PopPK and exposure-response (E-R) analyses.

Study U302 was a Phase 3, multicenter, randomized, open-label, two-arm, active-controlled study conducted in subjects with unresectable and/or metastatic HER2-positive BC previously treated with trastuzumab and a taxane in North America, Brazil, Asia, Europe, and Australia with a planned number of approximately 500 subjects. Subjects were randomized in a 1:1 ratio to T-DXd 5.4 mg/kg (261 subjects) or trastuzumab emtansine (T-DM1) (263 subjects). Serum concentrations of T-DXd, total anti-HER2 antibody, and DXd were evaluated and used for the PopPK and E-R analyses. Due to sparse PK sampling in the study, NCA was not conducted for Study U302.

2.3.2. Pharmacokinetics

Analytical methods

For characterization of T-DXd pharmacokinetics, three analytes were measured: T-DXd (the intact antibody-drug conjugate [ADC]), total anti-HER2 antibody, and DXd (the drug component of the ADC). Quantification of the three analytes in serum and determination of anti-T-DXd antibodies in serum were conducted using the same validated bioanalytical methods that were used in the initial BC application, with the exception of samples from subjects enrolled in study U302.

New assay measuring concentrations of intact T-DXd or total-HER2 antibody in human serum, using electrochemiluminescent methods, were developed and validated. The assays were cross-validated against the assay developed and both methods were determined to be comparable. T-DXd and total anti-HER2 antibody were analysed over the nominal concentration range of 0.400 to 25.6 µg/mL (with a 0.200 µg/mL anchor point standard). A LC-MS/MS assay measuring DXd was developed and validated and cross-validated against the DXd assay. The methods were comparable. DXd was analysed over the nominal concentration range of 10.0 to 2000 pg/mL.

An assay to detect and confirm ADA antibodies in human serum using an ECL method in a multi-tiered approach was developed and validated. The screening assay cut point for breast cancer individuals was determined statistically at the 95% upper prediction interval from 7 independent analyses of 25 drug-naïve breast cancer serum sample lots.

A cell-based assay to detect NAb against T-DXd in human serum was developed and validated. Study samples confirmed as ADA positive were further analysed by the NAb assay. The assay cut point for breast cancer human serum was determined statistically at the 99% upper bound prediction interval from six independent analyses of 30 individual drug-naïve breast cancer serum sample lots.

Population PK analyses

NONMEM (version 7.4.3) was used for PopPK analysis with FOCEI for model development. PsN was used for model diagnostics and covariate testing. R (version 4.0.4 or higher) was used for data exploration and simulations based on the final models for T-DXd and DXd.

Integrated data across Studies J101, J102, A103, A104, U201, J202, U204, U205, and U302 were used as the analysis data set and included 1313 subjects for evaluating T-DXd at doses ranging from 0.8 mg/kg to 8.0 mg/kg. Of these 1313 subjects, 766 had BC, 293 had GC, 199 had NSCLC, and 55 had other cancer types. There were 19584 and 19683 PK samples for serum T-DXd concentrations and serum DXd concentrations, respectively, included in the dataset. Outlier concentrations in Study U302 were identified using |CWRES|>5. A total of 2962 T-DXd and 2968 DXd PK-evaluable samples were available from 254 subjects in Study U302. The PK profile of total anti-HER2 antibody was not included in the analysis because of similarity to the PK profile of T-DXd.

Table 4-1 Summary of PK data in analysis

Category	Previous data		U302		Overall	
	T-DXd	DXd	T-DXd	DXd	T-DXd	DXd
Subjects						
Total Subjects	1070	1070	257	257	1327	1327
Subjects with evaluable observations	1059	1059	254	254	1313	1313
PK Observations						
Evaluable non-BQL observations included	16622 (92.4%)	16715 (93.0%)	2962 (90.5%)	2968 (90.9%)	19584 (92.1%)	19683 (92.7%)
Co-medication inhibitor excluded	68 (0.4%)	68 (0.4%)	37 (1.1%)	36 (1.1%)	105 (0.5%)	104 (0.5%)
Other excluded	196 (1.1%)	198 (1.1%)	5 (0.2%)	3 (0.1%)	201 (0.9%)	201 (0.9%)
Outlier excluded	72 (0.4%)	21 (0.1%)	-	-	72 (0.3%)	21 (0.1%)
Post-dose BQL excluded	82 (0.5%)	28 (0.2%)	19 (0.6%)	6 (0.2%)	101 (0.5%)	34 (0.2%)
Pre-dose BQL excluded	945 (5.3%)	946 (5.3%)	249 (7.6%)	252 (7.7%)	1194 (5.6%)	1198 (5.6%)
Missing data	-	-	1 (0.0%)	1 (0.0%)	1 (0.0%)	1 (0.0%)
Total Observations	17985	17976	3273	3266	21258	21242

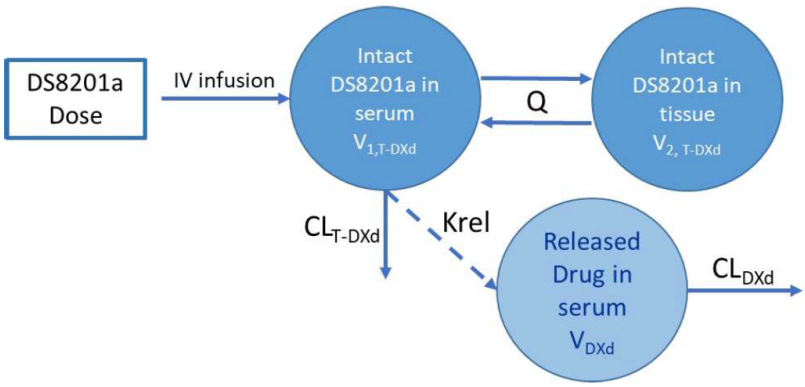
Abbreviations: BQL = below the lower limit of quantitation; PK = pharmacokinetic.
Source: DS8201_302-subject_count.csv, DS8201_302-observation_count.csv, 2021-08-20-ds8201_302_eda.r

In the previous PopPK analysis, T-DXd PK was described by a two-compartment model with linear clearance. The production of DXd was modeled by a two-component time-varying release rate from T-DXd. The previous PopPK model for T-DXd and DXd included data from all studies except for Study U302. The previous model was used as the basic structure where a sequential modeling approach was used to re-estimate model parameters with the updated analysis dataset. The final model included pre-specified covariates from the previous model were initially fit to the updated PK dataset. This step was conducted sequentially with the T-DXd parameters and corresponding covariate effects re-estimated using T-DXd PK data only. Then, using the T-DXd and DXd PK data, the DXd parameters and corresponding covariate effects were re-estimated, with fixed parameter estimates for PK and covariates for T-DXd, including fixed and random-effects terms. Any covariates that were not statistically significant were removed.

Re-running the previous final T-DXd model with the current dataset showed that parameters describing the effects of sex on V1,T-DXd, and Asian from Japan on V2,T-DXd changed by >20% relative to the previous estimates. Removal of these parameters increased the OFV significantly. The sex effect on V1,T-DXd and Asian from Japan effect on V2,T-DXd were therefore retained in the T-DXd model. Sex and CrCL on CLT-DXd, and country on V1,TDXd showed significant trends ($p<0.01$). However, several covariates were correlated, thus cancer type and body weight on CLT-DXd were retained while sex and CrCL were not tested as covariates. None of the candidate covariates were added to the base model, and the T-DXd base model was accepted as the final model (run413). The final T-DXd model suggests that CLT-DXd increases with increasing body weight, baseline tumour size, and for GC, NSCLC or other cancers; CLT-DXd decreases with increasing albumin and being Asian from Japan; V1,T-DXd increases with increasing body weight, in males and for GC; and V2,T-DXd decreases in Asian subjects from Japan. The previously developed DXd PopPK model with T-DXd parameters fixed (estimates from run413) was fit to the current dataset with inclusion of Study U302. The covariate effects of AST and cancer type on CLDXd, and age, formulation, NSCLC or other cancers on VDXd changed by more than 20%. Further exploratory analysis identified that other cancer types on CLDXd and VDXd effects were no longer supported by the data and were removed. The DXd base model (run649) was a one-compartment model with a 2-component, time-varying release rate from T-DXd. The components of the decrease in Krel over time were a constant reduction in Krel after Cycle 1 (FPC1) and a gradual decline in Krel per cycle (FPC2). The model included proportional RUV and exponential BSV on CLDXd, VDXd, Krel, and FPC1. With the addition of Study U302, new covariate correlations were identified and no new covariates were included. The DXd base model was accepted as the final model (run649). The final DXd model suggests that CLDXd increases with increasing body weight; CLDXd decreases with

increasing total bilirubin and AST, co-administration of itraconazole or ritonavir, and having GC or NSCLC; VDXd increases with increasing BSA, age, and FL-DP2 formulation; VDXd decreases with FL-DP1 formulation, having NSCLC and in non-Asians. The structural model for T-DXd and DXd PK is shown in Figure 3.1.

Figure 3-1 Structural model schematic



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

Between-subject variance terms were included on CLT-DXd, distributional clearance of T-DXd, V1,T-DXd, and V2,T-DXd. In addition, the model included a correlated variance structure on CLT-DXd and V1,T-DXd. Residual unexplained variability was described using a combined additive plus proportional model on T-DXd and proportional only on DXd. The final parameter estimates for T-DXd and DXd are shown in tables 4.6 and 4.8.

Table 4-6 Parameters of the T-DXd base model (run413)

Parameter	T-DXd Base Model (run413)					Typical Value From Previous Analysis without Study U302 (RSE %)
	Estimate		Between-subject Variability			
	Typical Value	RSE (%)	Magnitude (%CV)	RSE (%)	Shrinkage (%)	
Clearance ($CL_{T\text{-}DXd}$, L/day)	0.415	1.10	24.3	2.30	8.84	0.418 (1.32)
Central volume of distribution ($V_{1,T\text{-}DXd}$, L)	2.71	0.553	15.2	2.18	7.74	2.75 (0.645)
Distributional clearance ($Q_{T\text{-}DXd}$, L/day)	0.201	1.31	28.9	4.36	36.3	0.208 (1.31)
Peripheral volume of distribution ($V_{2,T\text{-}DXd}$, L)	5.84	2.32	81.0	3.23	22.9	4.94 (4.04)
Albumin (g/L) on $CL_{T\text{-}DXd}$	-0.497	10.6	-	-	-	-0.551 (9.74)
Race-Country (Japan) on $CL_{T\text{-}DXd}$	-0.0987	13.8	-	-	-	-0.0941 (15.4)
Tumor size (mm) on $CL_{T\text{-}DXd}$	0.0564	16.8	-	-	-	0.0654 (15.9)
Body weight (kg) on $CL_{T\text{-}DXd}$	0.407	8.61	-	-	-	0.451 (8.67)
Gastric cancer on $CL_{T\text{-}DXd}$	0.168	13.7	-	-	-	0.165 (14.5)
NSCLC and other cancer (not breast or gastric) on $CL_{T\text{-}DXd}$	0.0996	18.1	-	-	-	0.113 (18.3)
Male effect on $V_{1,T\text{-}DXd}$	0.124	11.4	-	-	-	0.108 (12.7)
Body weight (kg) on $V_{1,T\text{-}DXd}$	0.441	5.13	-	-	-	0.467 (5.29)
Gastric cancer on $V_{1,T\text{-}DXd}$	0.0924	16.2	-	-	-	0.0823 (17.4)
Race-Country (Japan) on $V_{2,T\text{-}DXd}$	-0.194	19.7	-	-	-	-0.134 (30.9)
Residual unexplained variability						
Proportional residual error SD	0.163	0.231	-	-	-	0.153 (0.346)
Additive residual error SD (ng/mL)	1088	1.83	-	-	-	1222 (2.14)
Covariance of $CL_{T\text{-}DXd}$ and $V_{1,T\text{-}DXd}$	0.0188	3.58	-	-	-	0.0191 (3.82)

Abbreviations: CV = coefficient of variation; RSE = relative standard error; SD = standard deviation; SE = standard error; sqrt = square root.

Notes: RSE of parameter estimate are calculated as 100×(SE/typical value); RSE of between-subject variability magnitude are calculated as 100×(SE/variance estimate)/2. CV% for the between-subject variability estimates are based on the estimated variances. Shrinkage (%) is calculated as 100×(1-SD(ETA)/sqrt(variance). Overall residual unexplained variability shrinkage was estimated to be 8.84%. The correlation coefficient between $CL_{T\text{-}DXd}$ and $V1_{T\text{-}DXd}$ was estimated as 0.520.

Source: run413.lst, intact-rerun-base-413-nmtable.csv, 2021-08-31-ds8201a-302-intact.r

Table 4-8 Parameters of the DXd base model (run649)

Parameters	DXd Base Model (run649)					Typical Value From Previous Analysis without Study U302 (RSE %)
	Estimate		Between-subject Variability			
	Typical Value	RSE (%)	Magnitude (%CV)	RSE (%)	Shrinkage (%)	
DXd clearance (CL_{DXd}, L/hour)	19.4	2.88	25.5	5.15	39.7	18.3 (3.56)
DXd volume of distribution (V_{DXd}, L)	Fixed 17*BSA	-	45.3	2.98	22.0	Fixed 17*BSA
Release rate (K_{rel}, 1/hour)	0.0176	2.71	36.5	3.49	19.0	0.0149 (3.20)
Fraction of K_{rel} at Cycle >1 (FPC1)	0.746	1.23	27.0	3.12	18.9	0.762 (1.37)
Exponent of Cycle effect on K_{rel} (FPC2)	-0.162	3.23	-	-	-	-0.140 (4.51)
Ritonavir on CL_{DXd}	-0.124	14.0	-	-	-	-0.118 (14.9)
Itraconazole on CL_{DXd}	-0.111	19.8	-	-	-	-0.104 (21.9)
AST (U/L) on CL_{DXd}	-0.171	12.9	-	-	-	-0.230 (10.1)
Total bilirubin (µmol/L) on CL_{DXd}	-0.138	16.2	-	-	-	-0.136 (18.4)
Body weight (kg) on CL_{DXd}	0.404	13.7	-	-	-	0.438 (13.6)
Gastric cancer on CL_{DXd}	-0.0961	27.1	-	-	-	-0.153 (17.4)
NSCLC on CL_{DXd}	-0.107	37.4	-	-	-	-0.210 (17.4)
Age (y) on V_{DXd}	0.655	10.4	-	-	-	0.487 (14.8)
FL-DP2 formulation on V_{DXd}	0.465	14.6	-	-	-	0.314 (18.6)
FL-DP1 formulation on V_{DXd}	-0.100	37.4	-	-	-	-0.169 (20.3)
NSCLC on V_{DXd}	-0.304	13.6	-	-	-	-0.392 (8.60)
Race-Country (Non-Asian) on V_{DXd}	-0.202	13.0	-	-	-	-0.207 (13.2)
Residual unexplained variability						
Proportional residual error SD	0.307	0.380	-	-	-	0.308 (0.430)

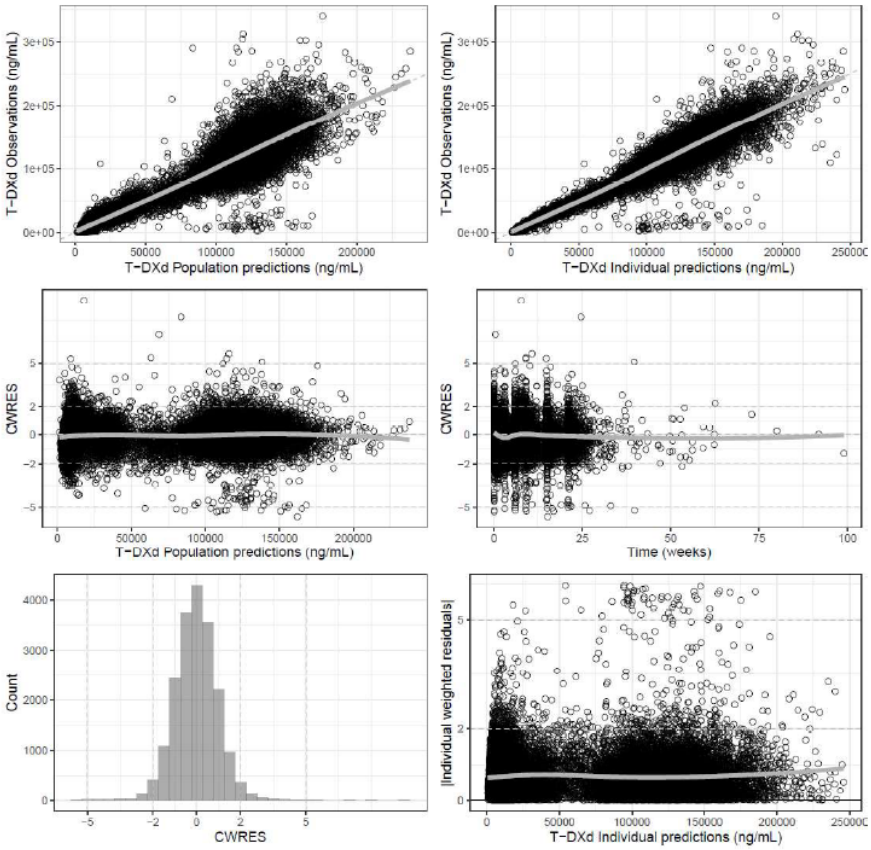
Abbreviations: AST = aspartate aminotransferase; BSA = body surface area; CL_{DXd} = DXd clearance; CV = coefficient of variation; FL-DP1 = frozen liquid drug product 1; FL-DP2 = frozen liquid drug product 2; NSCLC = non-small cell lung cancer; RSE = relative standard error; SD = standard deviation; SE=standard error; sqrt = square root; V_{DXd} = DXd central volume of distribution.

Notes: RSE of parameter estimate are calculated as 100×(SE/typical value); RSE of between-subject variability magnitude are calculated as 100×(SE/variance estimate)/2. CV% for the between-subject variability estimates are based on the estimated variances. Shrinkage (%) is calculated as 100×(1-SD(ETA)/sqrt(variance). Overall residual unexplained variability shrinkage was estimated to be 7.26%.

Source: payload-final-649-nmtable.csv, 2021-08-ds8201a-302-payload.r.

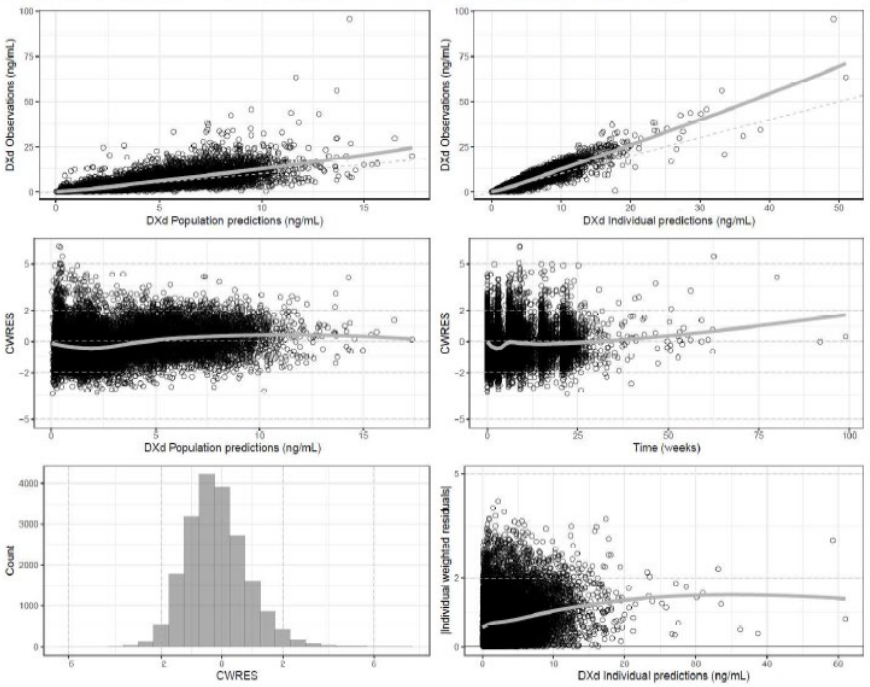
The models were evaluated by GoF plots and pcVPCs. See Figures 4-8, 4-10 and 4-13.

Figure 4-8 Goodness-of-fit diagnostics of the T-DXd base model (run413)



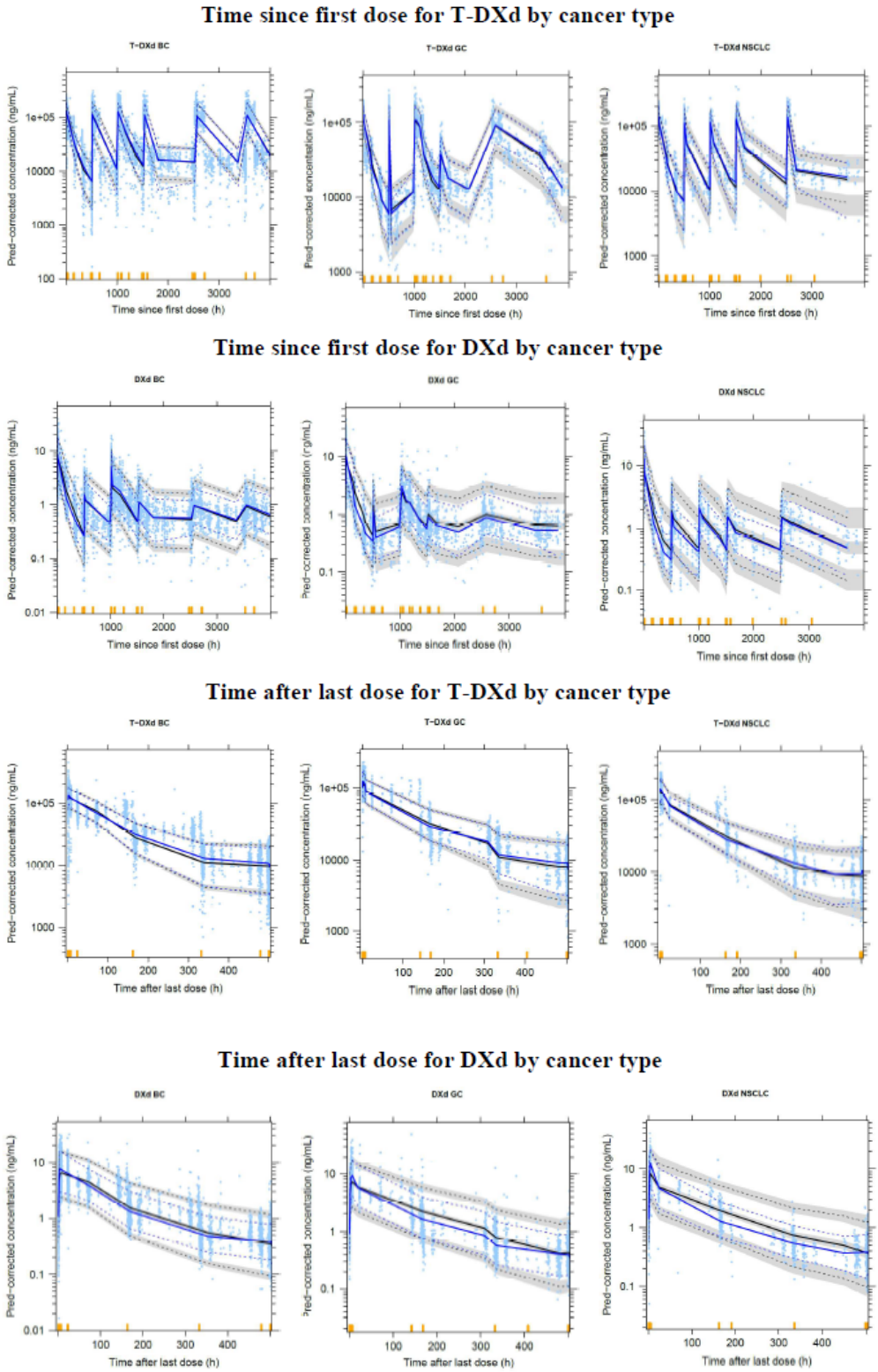
Abbreviations: CWRES = conditional weighted residual.
Note: The dots represent observations, the black dashed lines represent identity lines, and gray curves represent loess smoothers.
Source: gof-INonly-base413-all.pdf, 2021-21-05-ds8201-302-gof.r

Figure 4-10: Goodness-of-fit diagnostics of the DXd base model (run649)



CWRES = conditional weighted residuals.
Note: The dots represent observations, the black dashed lines represent identity lines, and gray curves represent loess smoothers.
Source: gof-PAY-FINAL-combined-649-all.pdf, 2021-08-25-ds8201-302-gof.r.

Figure 4-13 Prediction-corrected VPC for the T-DXd and DXd PopPK model (run649), by cancer type



Abbreviations: BC = breast cancer; GC = gastric/gastroesophageal junction cancer; 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-Poptyp-649.pdf, VPC-TAD-both-Poptyp-649.pdf, 2021-08-25-ds8201-302-gof.R

Exposure-response analyses

Exposure-efficacy relationships for PFS, OS and ORR were investigated in Study U302 BC subjects. A total of 249 HER2 positive BC subjects were included in the exposure-efficacy evaluation. Exposure-safety relationships were evaluated in the nine T-DXd studies including Study U302 which were included in the Pop PK analysis, with focus on BC subjects. The safety endpoints were: discontinuation associated with AE, dose reduction associated with AE, Grade ≥3 AE, SERAEs, Grade ≥3 anaemia, Any Grade and Grade ≥3 neutropenia, Any Grade and Grade ≥3 thrombocytopenia, Any Grade and Grade ≥3 ILD, Grade ≥2 LVEF (ECHO).

First exploratory plots were used to assess the ER relationship. For binary variables, the data were split by exposure quartiles and the response probability was plotted vs. median exposure for each quartile. For time-to-event variables, Kaplan-Meier curves were plotted by exposure quartile. If an ER relationship was observed using logistic regression ($p<0.05$ on slope) or using Cox regression ($p<0.05$), further modelling was considered. Most endpoints were treated as binary variables and analysed with logistic regression, with exception of PFS and OS, which were treated as time-to-event variables. ILD AEs were treated as both a binary and time-to-event variable. Covariates analysis was performed using a forward search at $p<0.05$ and a backward search at $p<0.01$ using a likelihood ratio test. All covariates were tested on both the intercept and the slope of the ER relationship. The selected ER models were evaluated graphically by overlaying model predictions with observed response data (Kaplan-Meier) and by numerical predictive checks. 90% CIs were computed using 1000 sampled ER models.

Efficacy models

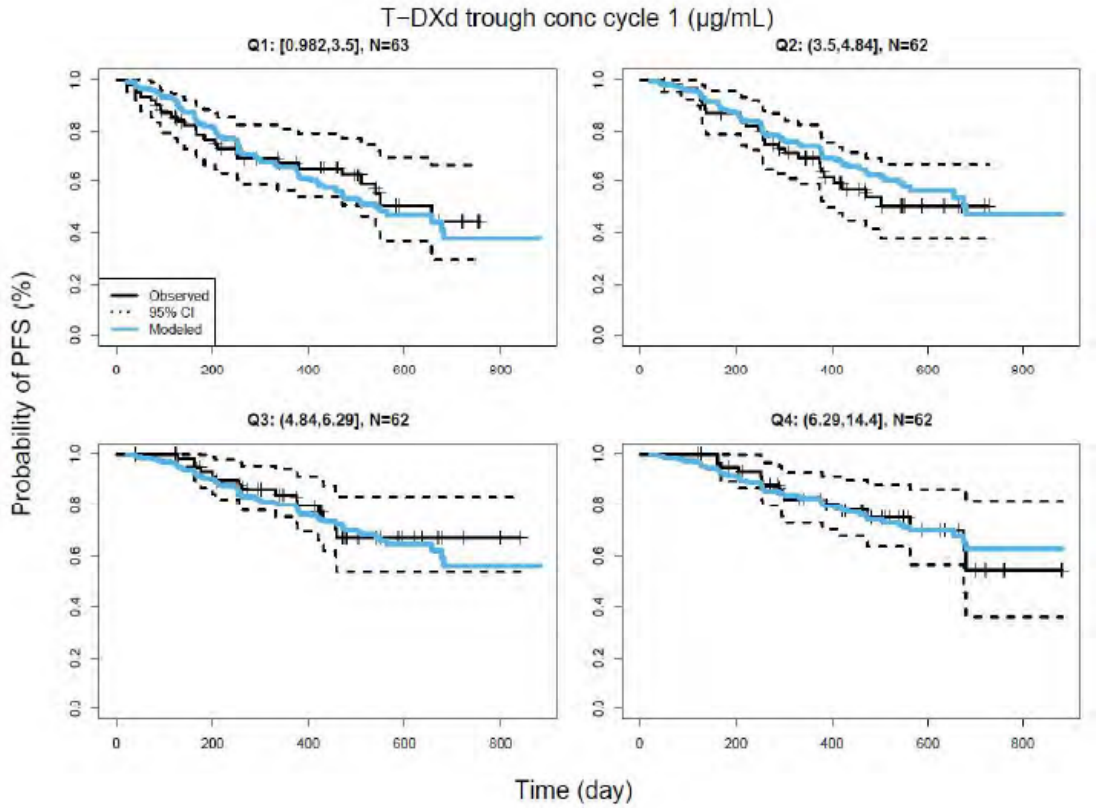
T-DXd Cmin1 was the selected metric for PFS and OS based on univariate Cox regression. T-DXd Cmin1 was the only or the most significant metric ($p<0.05$) with a negative slope, corresponding to decreasing PFS or OS hazard with increasing exposures. A significant difference ($p<0.05$) was found between ORR and all T-DXd exposure metrics, however, the p-value of the slope was most significant for AUC1. No exposure relationship was found between ORR and DXd exposure metrics.

Table 5-4: PFS final model parameters

Exposure-Response Model		Parameter	Estimate	Standard Error	RSE (%)
Exposure Metric	Endpoint				
T-DXd trough conc Cycle 1 (µg/mL)	PFS	Slope	-0.119	0.0526	44
		Baseline tumor size	0.0126	0.00232	18
		CNS metastases	0.788	0.236	30

Abbreviations: CNS = central nervous system; conc = concentration; PFS = progression free survival; RSE = relative standard error.
Source: ee.analysis.r

Figure 5-3: Kaplan-Meier curves with multivariate Cox regression fit for PFS at exposure quartiles



Abbreviations: CI = confidence interval; N = number of subjects; PFS = progression-free survival; Q = exposure quartile.

Note: Each 2 × 2 grouping of plots represents the Cox-regression fit. The exposure metric and exposure quartile are indicated in the title of each plot. The solid black line represents the estimated Kaplan-Meier curves. The dashed lines are 95% CIs. The solid blue line represents the estimated Kaplan-Meier curve determined with multivariate Cox regression.

Source: ee.analysis.r

Table 5-5: Numerical predictive check of the PFS final model in breast cancer subjects

Exposure Quantile	Observed PFS rate (%)			Model-predicted PFS rate (Estimate [90% PI])		
	Day 90	Day 180	Day 360	Day 90	Day 180	Day 360
Quartile 1	90.5	78.7	67.6	94.8 [90.6, 97.5]	82.6 [75.3, 88.4]	66.2 [57.6, 74.0]
Quartile 2	96.7	86.9	69.7	96.9 [94.9, 98.5]	88.4 [83.7, 91.7]	74.4 [68.4, 79.9]
Quartile 3	100	93.2	84.2	97.8 [96.3, 98.9]	91.3 [88.2, 93.9]	80.3 [75.3, 84.5]
Quartile 4	100	94.9	82.3	98.0 [96.5, 99]	92.3 [88.4, 95.0]	83.1 [76.2, 88.1]

Abbreviations: PFS = progression-free survival; PI = prediction interval.

Source: ee.analysis.r

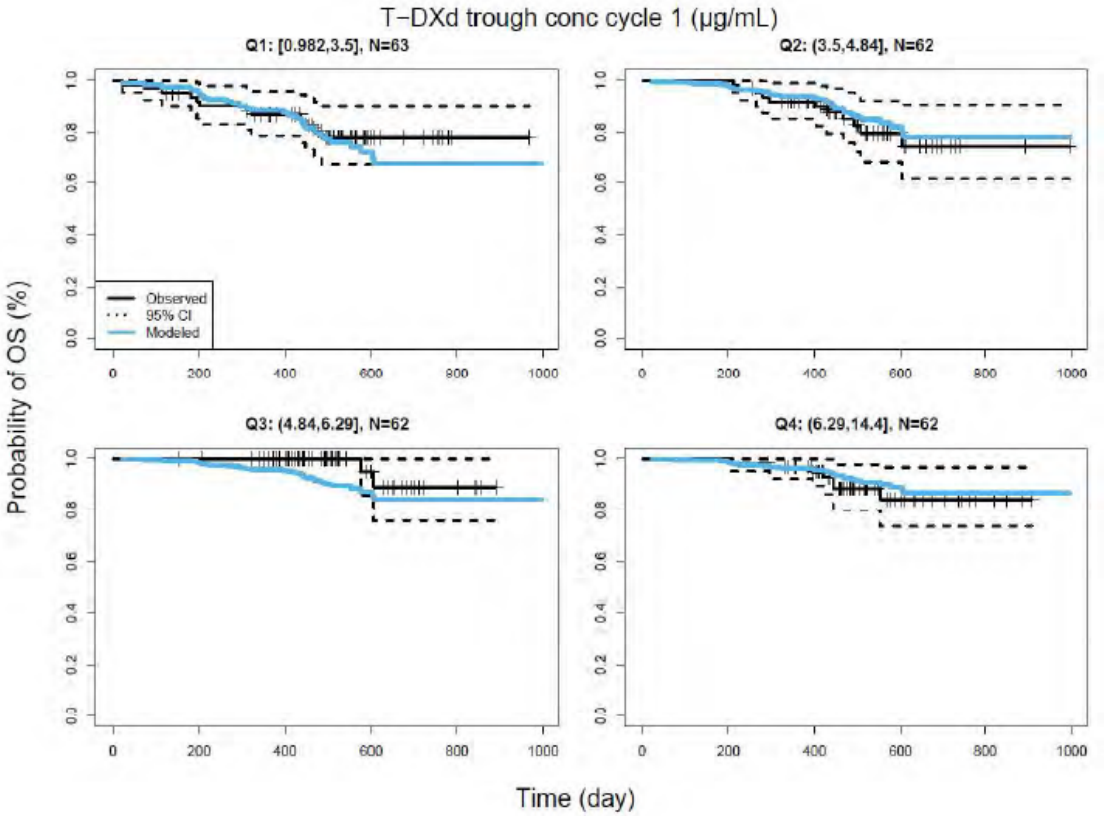
Table 5-8: OS final model parameters

Exposure-Response Model		Parameter	Estimate	Standard Error	RSE (%)
Exposure Metric	Endpoint				
T-DXd trough conc Cycle 1 (µg/mL)	OS	Slope	-0.094	0.0889	95
		ECOG ≥ 1	1.29	0.388	30
		Baseline tumor size	0.0157	0.00343	22

Abbreviations: ECOG = Eastern Cooperative Oncology Group; OS = Overall survival; RSE = relative standard error.

Source: ee.analysis.r

Figure 5-7: Kaplan-Meier curves with multivariate Cox regression fit for overall survival at exposure quartiles



Abbreviations: CI = confidence interval; conc = concentration; N = number of subjects; OS = overall survival; Q = exposure quartile.

Note: Each 2 × 2 grouping of plots represents the Cox-regression fit. The exposure metric and exposure quartile are indicated in the title of each plot. The solid black line represents the estimated Kaplan-Meier curves. The dashed lines are 95% CIs. The solid blue line represents the estimated Kaplan-Meier curve determined with multivariate Cox regression.

Source: ee.analysis.r

Table 5-9: Numerical predictive check of the OS final model in breast cancer subjects

Exposure Quantile	Observed OS rate (%)			Model-predicted OS rate (Estimate [90% PI])		
	Day 90	Day 180	Day 360	Day 90	Day 180	Day 360
Quartile 1	96.8	95.2	86.9	98.5 [96.0, 100]	97.7 [94.3, 99.5]	88.7 [82.4, 93.5]
Quartile 2	100	100	91.9	99.4 [98.7, 100]	99.0 [98.0, 99.7]	94.0 [90.9, 96.4]
Quartile 3	100	100	100	99.6 [99.1, 100]	99.4 [98.7, 99.8]	96.1 [93.9, 97.7]
Quartile 4	100	100	96.7	99.7 [99.1, 100]	99.5 [98.7, 99.9]	96.5 [93.5, 98.4]

Abbreviations: OS = overall survival; PI = prediction interval.

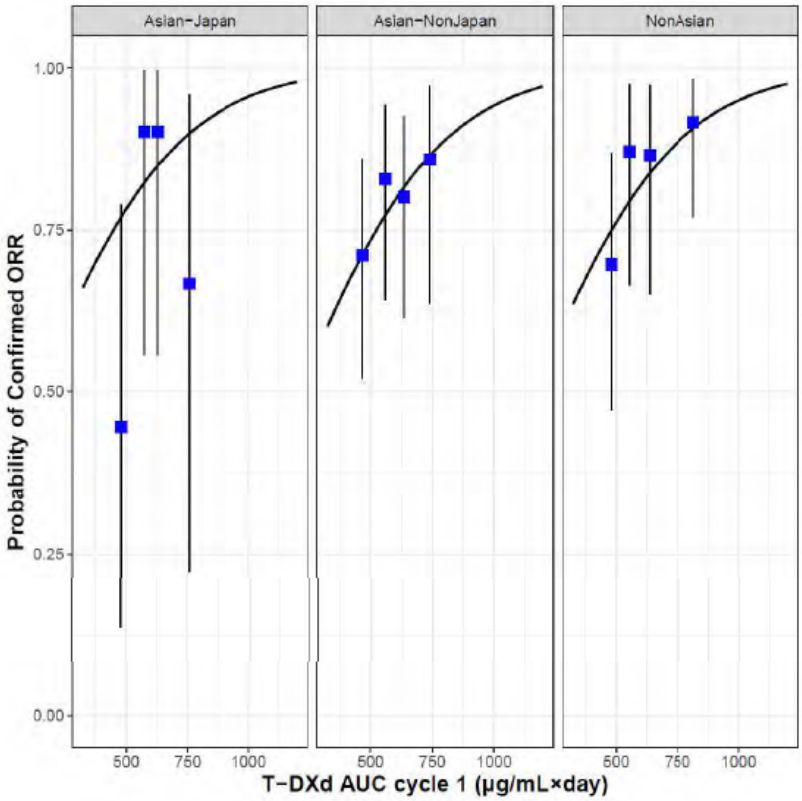
Source: ee.analysis.r

Table 5-13: Summary of ORR final model parameters

Exposure-Response Model		Parameter	Estimate	Standard Error	RSE (%)
Exposure Metric	Efficacy Endpoint				
T-DXd AUC Cycle 1 (µg/mL×day)	ORR	Intercept	-0.354	0.889	-
		Slope	0.00352	0.00145	41
		ECOG ≥1	-0.665	0.332	50

Abbreviations: AUC = area-under-the-curve; ECOG = Eastern Cooperative Oncology Group performance status; 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

Figure 5-11: Multivariate fit of ORR final model stratified by race-country



Abbreviations: AUC = area under the concentration-time curve; ORR = confirmed objective response rate by independent central review.
Note: Subjects per group are stratified into exposure quartiles. Points are ORR rate per exposure quartile plotted at the median exposure of the quartile. Vertical bars are 90% CIs of the AE rate. The curve is the modeled exposure-response relationship using the multivariate model, averaging across covariate-specific curves for each subject in the group.
Source: ee.analysis.r

Table 5-14: Numerical predictive check of ORR final model

Population	Exposure	Rate of ORR (%)	
		Observed	Model-predicted (Estimate [90% PI])
Subjects with breast cancer	Quartile 1	66.7	71.4 [61.9, 81.0]
	Quartile 2	85.5	79.0 [69.4, 85.5]
	Quartile 3	83.9	83.9 [75.8, 90.3]
	Quartile 4	87.1	90.3 [83.9, 95.2]

Abbreviations: ORR = confirmed objective response rate by independent central review; PI = prediction interval.
Source: ee.analysis.r

Safety models

A summary of exposure-safety models is shown in Table 5-76. Overall, the NPCs suggest the models concurs with the observed data.

Table 5-76: Summary of exposure-safety analyses

Safety Endpoint	Exposure Metric	Covariates
Discontinuation associated with AE	T-DXd steady state AUC	baseline total bilirubin, tumor type, age, oxygen saturation, race-country
Dose reduction associated with AE	DXd Cavg to event time	HER2, tumor type, liver metastases, gastrectomy, baseline weight, baseline total bilirubin
Any AE, Grade ≥3	DXd Cavg to event time	baseline albumin, baseline weight, tumor type
Any serious AE	DXd Cavg to event time	baseline albumin, race-country, ECOG PS, baseline CrCL
Anemia, Grade ≥3	DXd Cavg to event time	prior non-hormonal cancer therapies, ECOG PS, baseline hemoglobin, baseline total bilirubin, race-country, tumor type, baseline CrCL
Neutropenia, any Grade	DXd Cavg to event time	prior non-hormonal cancer therapies, baseline neutrophils, lung metastases, weight, race-country, baseline total bilirubin
Neutropenia, Grade ≥3	DXd Cavg to event time	baseline neutrophils, HER2, checkpoint therapy, race-country, baseline albumin
Thrombocytopenia, any Grade	DXd Cavg to event time	baseline platelets, lung metastases, race-country, baseline albumin
Thrombocytopenia, Grade ≥3	DXd Cavg to event time	baseline platelets, race-country, AST
LVEF decrease (ECHO), Grade ≥2	T-DXd steady state Cmax	tumor location, race-country, sex
Interstitial Lung Disease, Any Grade	T-DXd steady state AUC	baseline CrCL, race-country, oxygen saturation
Interstitial Lung Disease, Grade ≥3	T-DXd steady state Cmax	ECOG PS, oxygen saturation

Abbreviations: AE = adverse event; AST = aspartate aminotransferase; AUC = area under the concentration-time curve; Cavg = average concentration; Cmax = maximum concentration; CrCL = creatinine clearance; ECHO = echocardiogram-based; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction.

Source: es.analysis.r

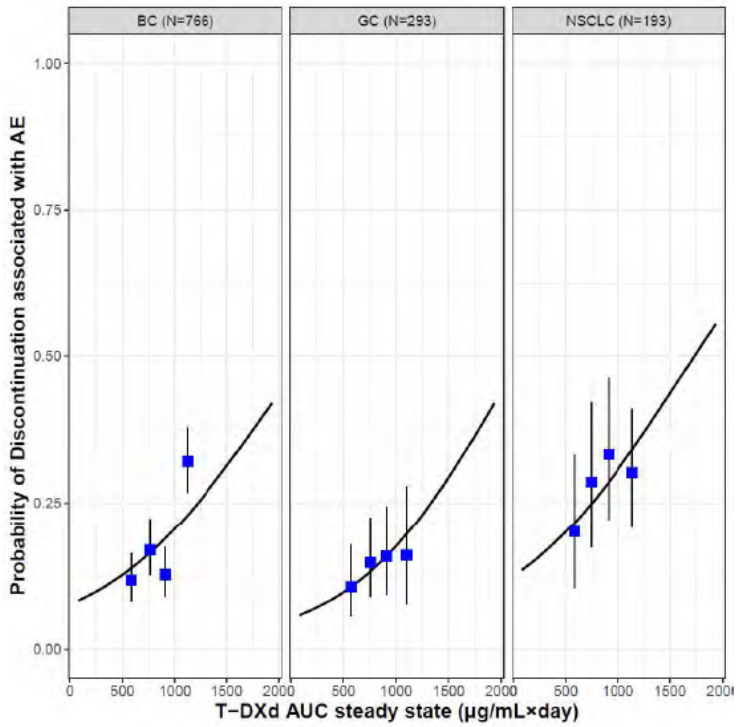
Final models with diagnostics for a few safety-endpoints that fitted the observed data for breast cancer less well (observed not within the model estimated 90%PI) are displayed in the following:

Table 5-22: Discontinuations associated with AE final model parameters

Exposure-Response Model		Parameter	Estimate	Standard Error	RSE (%)
Exposure	Endpoint				
T-DXd AUC steady state (µg/mL×day)	Discontinuation associated with AE	Intercept	-2.48	0.294	--
		Slope	0.00159	0.000315	20
		Total bilirubin (µmol/L)	-0.0338	0.0187	55
		Gastric cancer type	-0.528	0.207	39
		NSCLC (HER2 mutant)	0.49	0.246	50
		NSCLC (HER2 overexpressing)	0.0312	0.278	891
		Other tumor type	-1.02	0.453	44
		Age (years)	0.0236	0.00681	29
		Oxygen saturation (%)	-0.112	0.0426	38
		Non-Asian on slope	-0.00052	0.000179	34
		Asian not from Japan on slope	-0.00097	0.000283	29

Abbreviations: AE = adverse event; AUC = area under the concentration-time curve; BC = breast cancer; 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 NSCLC HER2 overexpressing indicates that this tumor type is not significantly different from BC for discontinuations associated with AEs. Overall, tumor type was still significant as a categorical variable.
Source: es.analysis.r

Figure 5-16: Multivariate fit of discontinuations associated with AE final model stratified by tumor type



Abbreviations: AE = adverse event; AUC = area under the concentration-time curve; BC = breast cancer; CI = confidence interval; GC = Gastric cancer; N = number of subjects; NSCLC = non-small lung cancer.
Note: Subjects per group are stratified into exposure quartiles. Points are discontinuation rate per exposure quartile plotted at the median exposure of the quartile. Vertical bars are 90% CIs of the discontinuation rate. The curve is the modeled exposure-response relationship using the multivariate model, averaging across covariate-specific curves for each subject in the group.
Source: es.analysis.r

Table 5-23: Numerical predictive check of discontinuations associated with AE final model

Population	Exposure	Rate of Discontinuations Associated with AE (%)	
		Observed	Model-predicted (Estimate [90% PI])
All subjects	Quartile 1	11.9	12.7 [9.7, 15.8]
	Quartile 2	17.7	16 [12.9, 19.5]
	Quartile 3	15.5	19.4 [16.1, 23.3]
	Quartile 4	29.6	26.3 [22.4, 30.2]
Subjects with breast cancer	Quartile 1	11.7	12.9 [9, 16.9]
	Quartile 2	16.9	15.9 [11.6, 20.8]
	Quartile 3	12.6	19.2 [14.7, 24.4]
	Quartile 4	32.2	26 [20.6, 31.3]
Subjects with gastric cancer	Quartile 1	10.5	10.6 [5.4, 17]
	Quartile 2	15.9	12.9 [7.1, 19.5]
	Quartile 3	14.7	15.7 [9, 23.2]
	Quartile 4	15.9	18.2 [9.1, 28.6]
Subjects with NSCLC	Quartile 1	20	19.2 [9.5, 30.6]
	Quartile 2	28.6	26 [15.4, 37.9]
	Quartile 3	33.3	28.6 [18.8, 39.7]
	Quartile 4	30.2	35.1 [25.5, 45.3]

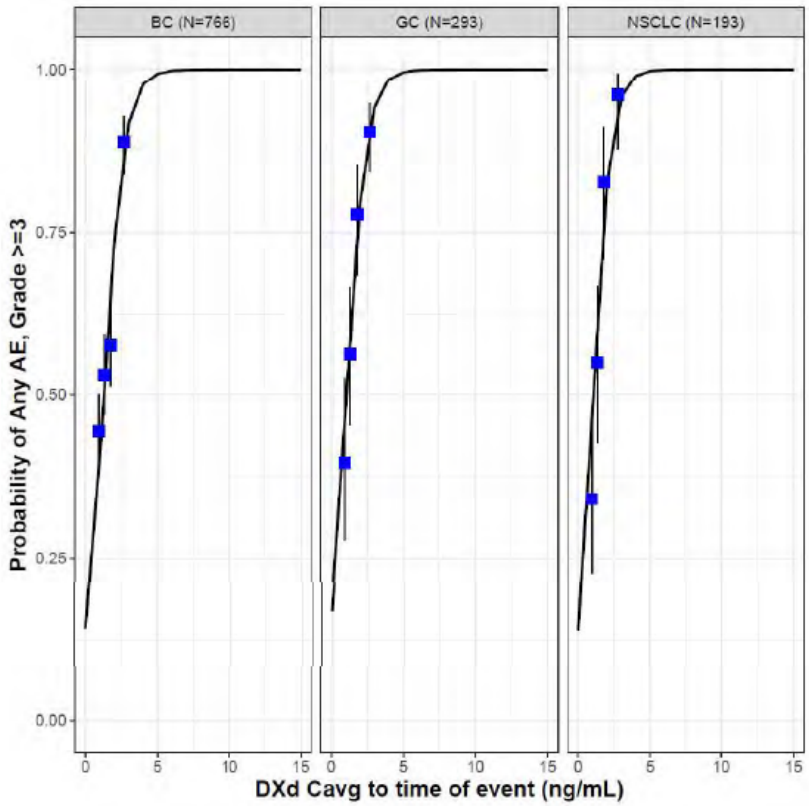
Abbreviations: AE = adverse event; PI = prediction interval.
Source: es.analysis.r

Table 5-33: Grade ≥3 AE final model parameters

Exposure-Response Model		Parameter	Estimate	Standard Error	RSE (%)
Exposure Metric	Endpoint				
DXd Cavg to time of event (ng/mL)	Grade ≥3 AE	Intercept	-1.82	0.189	--
		Slope	1.46	0.132	9
		Albumin (g/L)	-0.0549	0.0152	28
		Weight on slope	-0.011	0.00264	24
		Gastric cancer type on slope	0.089	0.105	118
		NSCLC (HER2 mutant) on slope	0.592	0.193	33
		NSCLC (HER2 overexpressing) on slope	0.16	0.155	97
		Other tumor type on slope	-0.291	0.166	57

Abbreviations: AE = adverse event; Cavg= average concentration; 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 gastric cancer indicates that this tumor type is not significantly different from BC for Grade 3 or greater AEs. Overall, tumor type was still significant as a categorical variable. The large RSE for NSCLC HER2 overexpressing reflects limited sample size of this population.
Source: es.analysis.r

Figure 5-27: Multivariate fit of Grade ≥3 AE final model stratified by tumor type



Abbreviations: AE = adverse event; BC = breast cancer; Cavg = average concentration; CI = confidence interval; GC = gastric cancer; N = number of subjects; NSCLC = non-small cell lung cancer.
Note: Subjects per group are stratified into exposure quartiles. Points are AE rate per exposure quartile plotted at the median exposure of the quartile. Vertical bars are 90% CIs of the AE rate. The curve is the modeled exposure-response relationship using the multivariate model, averaging across covariate-specific curves for each subject in the group.
Source: es.analysis.r

Table 5-34: Numerical predictive check of Grade ≥3 AE final model

Population	Exposure	Rate of Grade ≥3 AE (%)	
		Observed	Model-predicted (Estimate [90% PI])
All subjects	Quartile 1	40.8	39.6 [35.5, 44.0]
	Quartile 2	54.7	54.0 [49.4, 58.5]
	Quartile 3	65.7	68.8 [64.6, 73.0]
	Quartile 4	89.9	88.7 [85.6, 91.5]
Subjects with breast cancer	Quartile 1	44.4	37.2 [31.7, 42.9]
	Quartile 2	52.5	51.4 [44.9, 57.4]
	Quartile 3	58.2	66.3 [60.8, 71.8]
	Quartile 4	89.1	86.8 [82.2, 91.2]
Subjects with gastric cancer	Quartile 1	38.0	45.7 [34.0, 56.6]
	Quartile 2	59.7	60.6 [50.0, 70.5]
	Quartile 3	77.0	74.0 [65.2, 82.4]
	Quartile 4	90.2	91.2 [85.8, 95.7]
Subjects with NCSLC	Quartile 1	34.0	45.7 [33.8, 58.5]
	Quartile 2	55.8	60.0 [48.1, 71.4]
	Quartile 3	82.2	76.9 [65.2, 86.7]
	Quartile 4	95.9	92.9 [86.5, 97.9]

Abbreviations: AE = adverse event; NSCLC = non-small-cell lung cancer; PI = prediction interval.
Source: es.analysis.r

Table 5-49: Any Grade neutropenia final model parameters

Exposure-Response Model		Parameter	Estimate	Standard Error	RSE (%)
Exposure Metric	Safety Endpoint				
DXd Cavg to time of event (ng/mL)	Any Grade neutropenia	Intercept	-2.01	0.217	--
		Slope	1.69	0.14	8
		Number non-hormone prior therapies ≥ 5	0.591	0.201	34
		Neutrophils (10^9/L)	-0.442	0.0397	9
		Lung metastases	0.505	0.148	29
		Weight (kg)	-0.019	0.00579	30
		Non-Asian on slope	-0.197	0.108	55
		Asian not from Japan on slope	0.383	0.144	38
		Total bilirubin on slope	-0.0237	0.00769	32

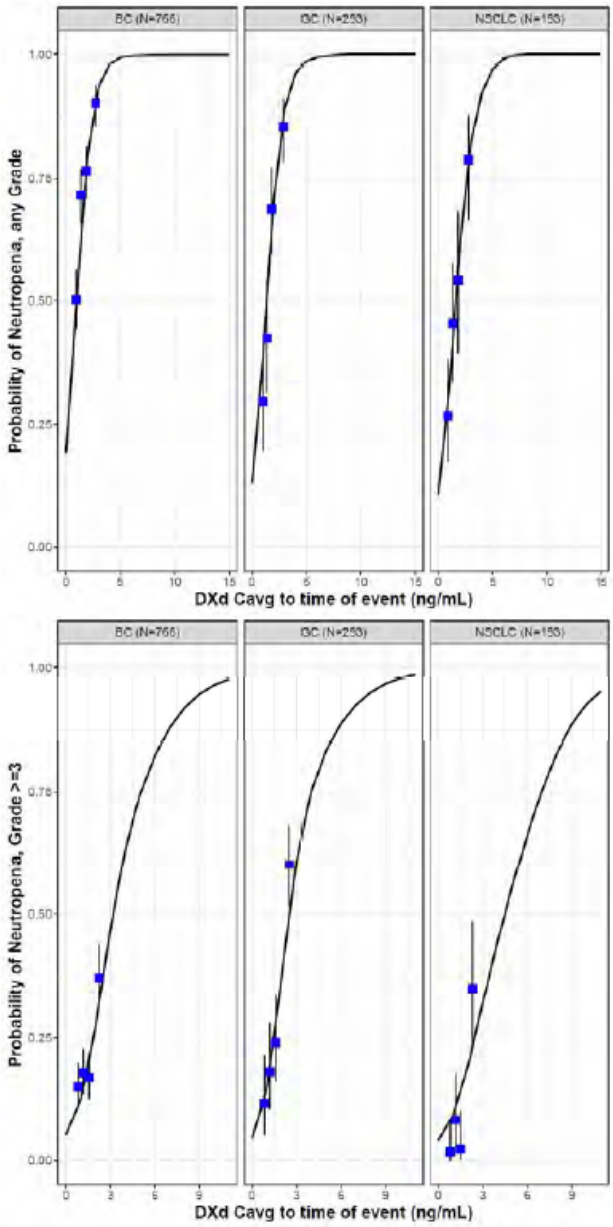
Abbreviations: Cavg = average concentration; RSE = relative standard error.
Note: RSE value not reported for the intercept term, because not relevant for logistic regression.
Source: es.analysis.r

Table 5-50: 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	0.195	--
		Slope	1.34	0.123	9
		Neutrophils (10^9/L)	-0.262	0.0441	17
		HER2 negative on slope	-0.152	0.114	75
		HER2 missing on slope	-0.543	0.461	85
		Prior checkpoint inhibitor on slope	0.487	0.167	34
		Non-Asian on slope	-0.724	0.101	14
		Asian not from Japan on slope	-0.241	0.117	49
		Albumin on slope	-0.0231	0.00887	38

Abbreviations: Cavg = average concentration; HER2 = human epidermal growth factor receptor 2; RSE = relative standard error.
Note: RSE value not reported for the intercept term, because not relevant for logistic regression. The RSE for HER2 negative on slope is relatively large. HER2 was a covariate that was significant in the base model using the z-test at (Table 5-48, $p<0.05$ for HER2 other on slope) and was therefore retained in the final model.
Source: es.analysis.r

Figure 5-42: Multivariate fit of Any Grade and Grade ≥3 neutropenia final models stratified by tumor type



Abbreviations: AE = adverse event; BC = breast cancer; Cavg = average concentration; CI = confidence interval; GC = gastric cancer; N = number of subjects; NSCLC = non-small cell lung cancer.

Note: Subjects per group are stratified into exposure quartiles. Points are AE rate per exposure quartile plotted at the median exposure of the quartile. Vertical bars are 90% CIs of the AE rate. The curve is the modeled exposure-response relationship using the multivariate model, averaging across covariate-specific curves for each subject in the group.

Source: es.analysis.r

Table 5-51: Numerical predictive check of Any Grade neutropenia final model

Population	DXd $Cavg_{TOE}$	Any Grade Neutropenia Rate (%)	
		Observed	Model-predicted (Estimate [90% PI])
All subjects	Quartile 1	42.6	42.7 [38, 46.7]
	Quartile 2	61.9	59.6 [54.9, 63.8]
	Quartile 3	71.9	73.3 [69.2, 77.2]
	Quartile 4	86.2	87.3 [84.1, 90.2]
Subjects with breast cancer	Quartile 1	50.5	47.9 [42, 53.4]
	Quartile 2	71.8	64.7 [59.3, 69.8]
	Quartile 3	76.7	79.3 [74, 83.9]
	Quartile 4	90.2	91.9 [88.2, 95.2]
Subjects with gastric cancer	Quartile 1	30.4	39 [28.3, 50]
	Quartile 2	44.1	54.2 [43.9, 64.5]
	Quartile 3	67.9	67.6 [58.1, 75.6]
	Quartile 4	85.6	86 [79.8, 91.4]
Subjects with NSCLC	Quartile 1	27.1	26.5 [17.3, 36.4]
	Quartile 2	46.2	46.9 [35.3, 58.5]
	Quartile 3	55.6	58.8 [45.7, 71.4]
	Quartile 4	78.3	76.9 [66.7, 85.7]

Abbreviations: $Cavg_{TOE}$ = average concentration to time of event; NSCLC = non-small cell lung cancer; PI = prediction interval.
Source: es.analysis.r

Table 5-52: Numerical predictive check of Grade ≥3 neutropenia final model

Population	DXd $Cavg_{TOE}$	Grade ≥3 Neutropenia Rate (%)	
		Observed	Model-predicted (Estimate [90% PI])
All subjects	Quartile 1	11.2	10.2 [7.7, 13]
	Quartile 2	17.1	14.6 [11.4, 17.7]
	Quartile 3	16.1	21.8 [18.3, 25.5]
	Quartile 4	45.7	43.5 [39.3, 48.1]
Subjects with breast cancer	Quartile 1	14.4	10.5 [7, 14]
	Quartile 2	19.4	14.1 [10.1, 18.3]
	Quartile 3	15.5	21.2 [16.4, 26.1]
	Quartile 4	38.5	39.2 [32.2, 45.8]
Subjects with gastric cancer	Quartile 1	11.3	12.4 [5.4, 20]
	Quartile 2	18	16.6 [9.1, 25.4]
	Quartile 3	24.4	26.7 [18.7, 35.4]
	Quartile 4	61.4	55.4 [46.9, 63.7]
Subjects with NSCLC	Quartile 1	1.7	6.8 [1.8, 12.8]
	Quartile 2	8.2	12.3 [5, 20.8]
	Quartile 3	2.2	14.9 [6.8, 23.3]
	Quartile 4	36.6	29.4 [17.8, 41.9]

Abbreviations: $Cavg_{TOE}$ = average concentration to time of event; NSCLC = non-small cell lung cancer; PI = prediction interval.
Source: es.analysis.r

Table 5-64: Grade ≥2 LVEF decrease (ECHO/MUGA) final model parameters

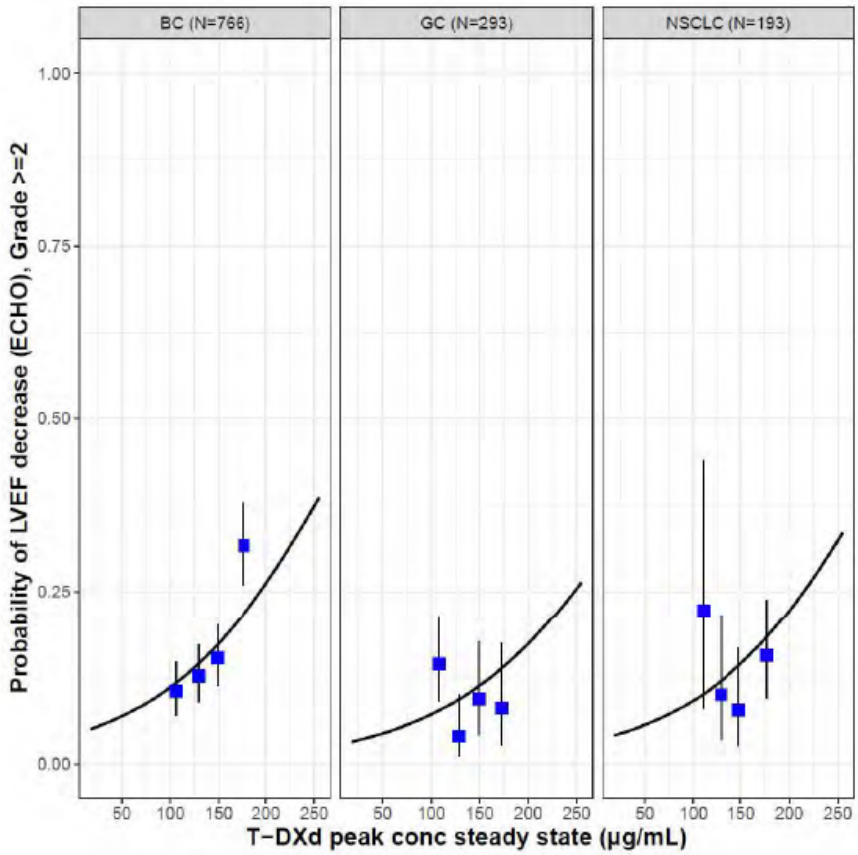
Exposure-Response Model		Parameter	Estimate	Standard Error	RSE (%)
Exposure Metric	Safety Endpoint				
T-DXd peak conc steady state (µg/mL)	Grade ≥2 LVEF decrease (ECHO/MUGA)	Intercept	-2.82	0.427	--
		Slope	0.0106	0.00258	24
		Tumor location GEJ	-1.69	0.756	45
		Tumor location missing	-0.0423	0.265	626
		Non-Asian	-0.306	0.18	59
		Asian not from Japan	-0.702	0.251	36
		Sex Male	-0.633	0.242	38

Abbreviations: ECHO = echocardiogram-based; GEJ = gastroesophageal junction; 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. Missing tumor location covariate had a relatively high RSE but was included in the base model as part of the tumor location covariate.

Source: es.analysis.r

Figure 5-52: Multivariate fit of Grade ≥2 LVEF decrease (ECHO/MUGA) final model stratified by tumor type



Abbreviations: AE = adverse event; BC = breast cancer; CI = confidence interval; Cmax = maximum concentration; ECHO = echocardiogram-based; GC = gastric cancer; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition scan; N = number of subjects; NSCLC = non-small cell lung cancer.

Note: Subjects per group are stratified into exposure quartiles. Points are AE rate per exposure quartile plotted at the median exposure of the quartile. Vertical bars are 90% CIs of the AE rate. The curve is the modeled exposure-response relationship using the multivariate model, averaging across covariate-specific curves for each subject in the group.

Source: es.analysis.r

Table 5-65: Numerical predictive check of Grade ≥2 LVEF decrease (ECHO/MUGA) final model

Population	Exposure Metric	Rate of Grade ≥2 LVEF Decrease (ECHO) (%)	
		Observed	Model-predicted (Estimate [90% PI])
All subjects	Quartile 1	12.2	10.2 [7.6, 13.2]
	Quartile 2	10.7	12.9 [9.9, 15.9]
	Quartile 3	12.5	15.1 [12, 18.6]
	Quartile 4	23.5	20.4 [17, 24.2]
Subjects with breast cancer	Quartile 1	10.4	11 [7.6, 14.9]
	Quartile 2	12.6	14.5 [10.6, 18.9]
	Quartile 3	15.5	17.1 [13.1, 21.9]
	Quartile 4	31.3	23.6 [18.6, 29.1]
Subjects with gastric cancer	Quartile 1	14.4	8.8 [4.4, 13.5]
	Quartile 2	5.3	9 [4.1, 15.1]
	Quartile 3	8.1	9.6 [3.6, 16.7]
	Quartile 4	7.8	11.1 [4.4, 18.9]
Subjects with NSCLC	Quartile 1	22.2	9.1 [0, 23.9]
	Quartile 2	10	11.4 [3.3, 20.9]
	Quartile 3	7.8	14.3 [6.7, 23.4]
	Quartile 4	15.5	19.1 [12, 26.2]

Abbreviations: ECHO = echocardiogram-based; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition scan; NSCLC = non-small cell lung cancer ; PI = prediction interval.
Source: es.analysis.r

ADME characteristics

The absorption, distribution, metabolism, and excretion characteristics of T-DXd are well-characterized based on a series of nonclinical studies using human biomaterials as described in the initial BC application, and based on data from clinical Studies J101, J102, A103, A104, and U201. Serum concentrations of three analytes (T-DXd, total anti-HER2 antibody, and DXd) were measured in the clinical studies to characterize the PK of T-DXd.

Covariate effects on DXd (the cytotoxic moiety) pharmacokinetics

The effect of each covariate included in the final model, including the new study U302, on the Cmin,ss, Cmax,ss, and AUCss of DXd after administration of T-DXd at 5.4 mg/kg Q3W was evaluated by forest plots (**Figure 3.6**). Renal function, measured by creatinine clearance, was not a significant covariate in the PopPK analysis for DXd; however, hepatic function measures (AST and total bilirubin) were significant covariates in the PopPK analysis for DXd. The forest plots show the effects of different values of the covariates for a typical subject, defined in the PopPK analysis as an Asian subject with BC who was administered T-DXd lyophilized powder drug product (Lyo-DP) and who weighed 58 kg with median lab values of AST 28 U/L and total bilirubin 7.4 µmol/L.

The majority of the covariates (baseline AST, baseline bilirubin, race-country, and cancer type) had effects contained within the 0.8 to 1.25 exposure ratio. Subjects with extreme values of body weight (90 kg; 95th percentile) had an approximately 30% higher Cmax,ss and a 32% higher AUCss, respectively, relative to a typical subject with a body weight of 58 kg. This covariate effect on steady-state exposures was only marginally outside the 0.8 to 1.25 exposure ratio interval.

Figure 3.6: Forest Plot of Covariate Effect on the Cmin,ss, Cmax,ss, and AUCss of DXd at Steady State

Covariate	Percentile	Value	Ratio [90% CI]
Body weight (kg)	5th	43	0.874 [0.854, 0.897]
	25th	52	0.948 [0.939, 0.959]
	50th	60	1.01 [1.01, 1.02]
	75th	69	1.08 [1.07, 1.1]
	95th	90	1.22 [1.17, 1.27]
AST (U/L)	5th	15	0.899 [0.876, 0.919]
	25th	20	0.944 [0.93, 0.956]
	50th	26	0.987 [0.982, 0.993]
	75th	37	1.05 [1.04, 1.06]
	95th	77	1.19 [1.15, 1.23]
Total bilirubin (umol/L)	5th	3	0.886 [0.849, 0.915]
	25th	5	0.952 [0.934, 0.966]
	50th	7	0.992 [0.987, 0.997]
	75th	10	1.05 [1.04, 1.06]
	95th	17	1.12 [1.09, 1.16]
Race-country		Non-Asian	1 [0.996, 1]
Cancer type		Gastric cancer	0.929 [0.892, 0.976]
		NSCLC	0.862 [0.816, 0.913]

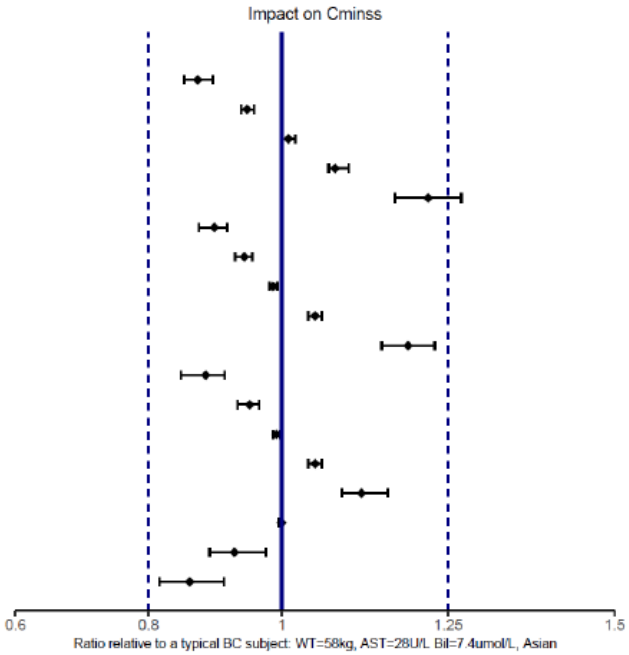
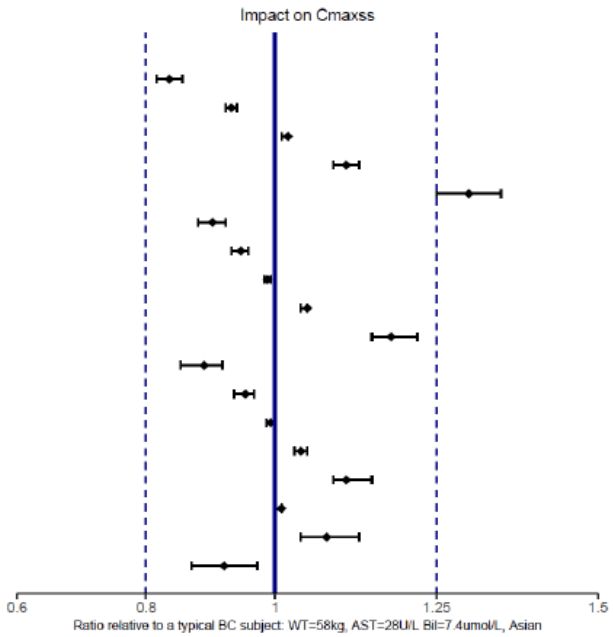
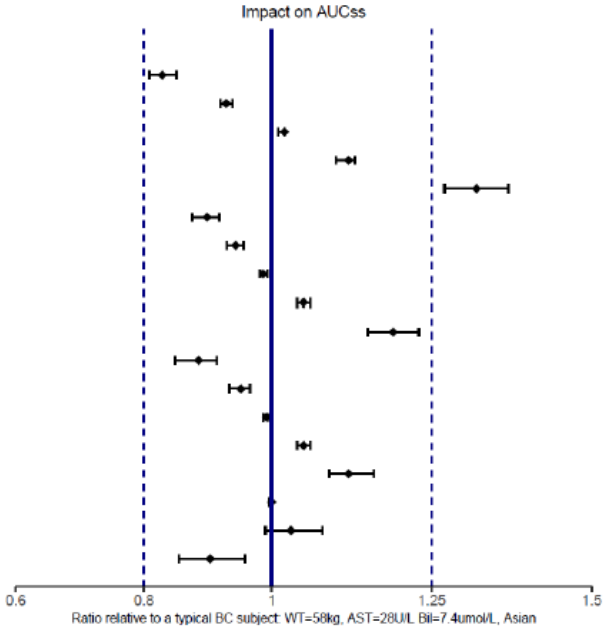


Figure 3.6: Forest Plot of Covariate Effect on the Cmin,ss, Cmax,ss, and AUCss of DXd at Steady State (Continued)

Covariate	Percentile	Value	Ratio [90% CI]
Body weight (kg)	5th	43	0.836 [0.817, 0.857]
	25th	52	0.932 [0.923, 0.941]
	50th	60	1.02 [1.01, 1.02]
	75th	69	1.11 [1.09, 1.13]
	95th	90	1.3 [1.25, 1.35]
AST (U/L)	5th	15	0.903 [0.881, 0.923]
	25th	20	0.947 [0.933, 0.958]
	50th	26	0.988 [0.983, 0.993]
	75th	37	1.05 [1.04, 1.05]
	95th	77	1.18 [1.15, 1.22]
Total bilirubin (umol/L)	5th	3	0.89 [0.854, 0.919]
	25th	5	0.954 [0.937, 0.967]
	50th	7	0.993 [0.987, 0.998]
	75th	10	1.04 [1.03, 1.05]
	95th	17	1.11 [1.09, 1.15]
Race-country		Non-Asian	1.01 [1, 1.01]
Cancer type		Gastric cancer	1.08 [1.04, 1.13]
		NSCLC	0.921 [0.871, 0.973]



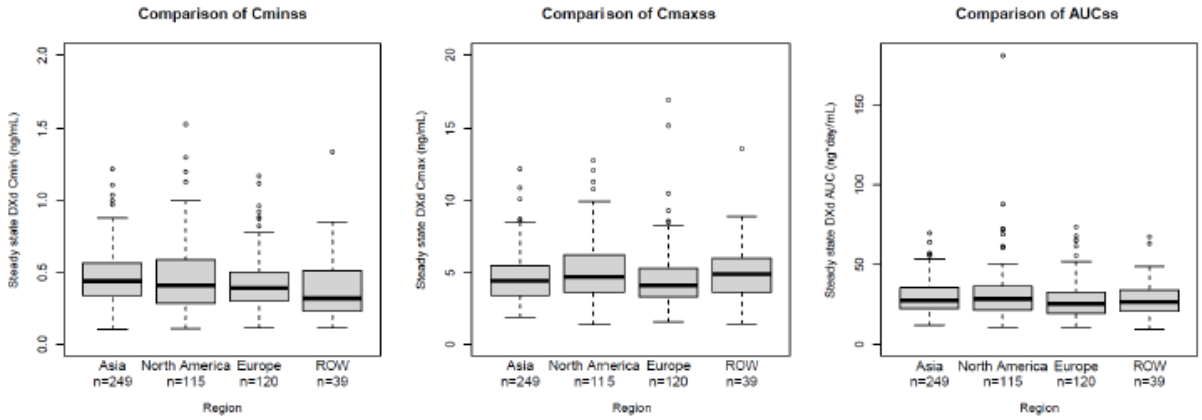
Covariate	Percentile	Value	Ratio [90% CI]
Body weight (kg)	5th	43	0.829 [0.809, 0.851]
	25th	52	0.929 [0.92, 0.939]
	50th	60	1.02 [1.01, 1.02]
	75th	69	1.12 [1.1, 1.13]
	95th	90	1.32 [1.27, 1.37]
AST (U/L)	5th	15	0.899 [0.876, 0.919]
	25th	20	0.944 [0.93, 0.956]
	50th	26	0.987 [0.982, 0.993]
	75th	37	1.05 [1.04, 1.06]
	95th	77	1.19 [1.15, 1.23]
Total bilirubin (umol/L)	5th	3	0.886 [0.849, 0.915]
	25th	5	0.952 [0.934, 0.966]
	50th	7	0.992 [0.987, 0.997]
	75th	10	1.05 [1.04, 1.06]
	95th	17	1.12 [1.09, 1.16]
Race−country		Non−Asian	1 [0.996, 1]
Cancer type		Gastric cancer	1.03 [0.99, 1.08]
		NSCLC	0.904 [0.855, 0.958]



AST = aspartate aminotransferase; AUCss = area under the serum concentration-time curve; BC = breast cancer; Bil = bilirubin; Cmax,ss = maximum serum concentration; Cmin,ss = minimum serum concentration; CI = confidence interval; DXd = released drug; FL-DP 1/2 = frozen liquid drug product 1/2; Lyo-DP = lyophilized powder drug product; NSCLC = non-small cell lung cancer; T-DXd = trastuzumab deruxtecan; WT = body weight.
Note: First and second dashed vertical lines correspond to ratios of 0.8 and 1.25, respectively. The solid vertical line corresponds to a ratio of 1 and represents the typical subject. Points and whiskers represent the estimate and 90% confidence interval, respectively. A typical subject is defined as an Asian subject with BC, body weight 58 kg, total bilirubin 7.4 µmol/L, AST 28 U/L, administered the Lyo-DP T-DXd formulation.
Source: Module 5.3.3.5 Population PK Report PMx012 Figure 4-15

The exposure to DXd at steady state after administration of T-DXd at 5.4 mg/kg Q3W in subjects with BC in each region (Asia, North America, Europe, and ROW) (based on posthoc individual estimates) is shown in **Figure 3.7**. The exposure in subjects with BC was similar between Asia, North America, Europe, and ROW. The geometric mean ratios of the AUCss, Cmax,ss, and Cmin,ss in subjects with BC in North America, Europe, or ROW to those in subjects with BC in Asia were in the range of 0.794 to 1.08.

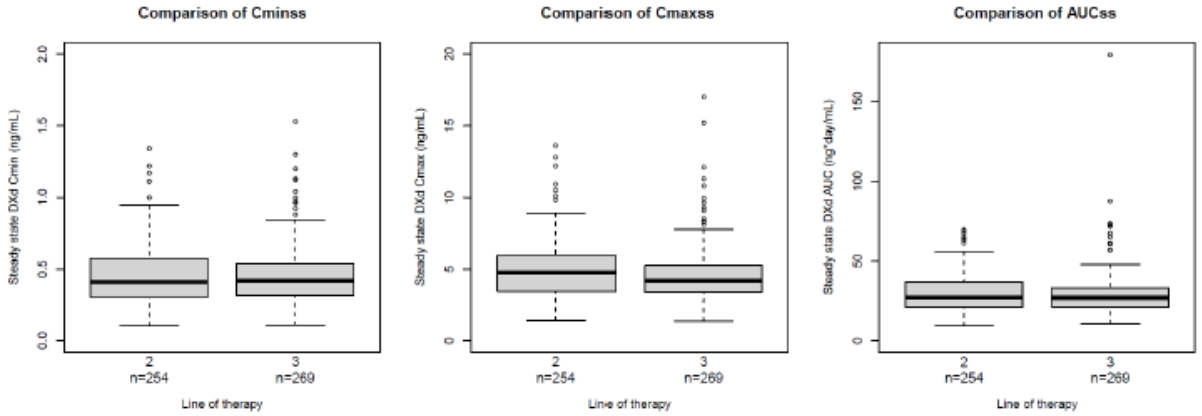
Figure 3.7: Box Plots of Exposure to DXd at Steady State after Administration of DXd at 5.4 mg/kg Q3W in Subjects with Breast Cancer in Each Region (Asia, North America, Europe, and ROW)



AUCss = area under the serum concentration-time curve at steady state; BC = breast cancer; Cmax,ss = maximum serum concentration at steady state; Cmin,ss = minimum serum concentration at steady state; DXd = released drug; n = number of subjects; Q3W = every 3 weeks; ROW = rest of the world.
Note: 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.
Source: Module 5.3.3.5 Population PK Report PMx012 Figure 4-25

The exposure to DXd at steady state after administration of DXd at 5.4 mg/kg Q3W in all subjects with BC by line of therapy (based on posthoc individual estimates) is shown in **Figure 3.9**. The exposure in subjects with BC was similar between second and third line of therapy. The geometric mean ratios of the AUCss, Cmax,ss, and Cmin,ss in subjects with second-line BC to those in subjects with third-line BC were in the range of 0.987 to 1.06.

Figure 3.9: Box Plots of Exposure to DXd at Steady State after Administration of T-DXd at 5.4 mg/kg Q3W in Subjects with Breast Cancer by Line of Therapy



AUCss = area under the serum concentration-time curve at steady state; Cmax,ss = maximum serum concentration at steady state; Cmin,ss = minimum serum concentration at steady state; DXd = released drug; n = number of subjects; Q3W = every 3 weeks; T-DXd = trastuzumab deruxtecan.
Note: 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.
Source: Module 5.3.3.5 Population PK Report PMx012 Figure 4-41

The DXd exposures were compared based on renal or hepatic impairment status for subjects with BC. The exposure to DXd was similar in subjects with renal or hepatic impairment compared to subjects without renal or hepatic impairment.

2.3.3. Pharmacodynamics

Mechanism of action

Trastuzumab deruxtecan (T-DXd) is a human epidermal growth factor receptor 2 (HER2)-targeted antibody linked to topoisomerase I inhibitor molecules (ADC molecule). DXd acts as a cytotoxic payload.

Primary and secondary pharmacology

Study U302

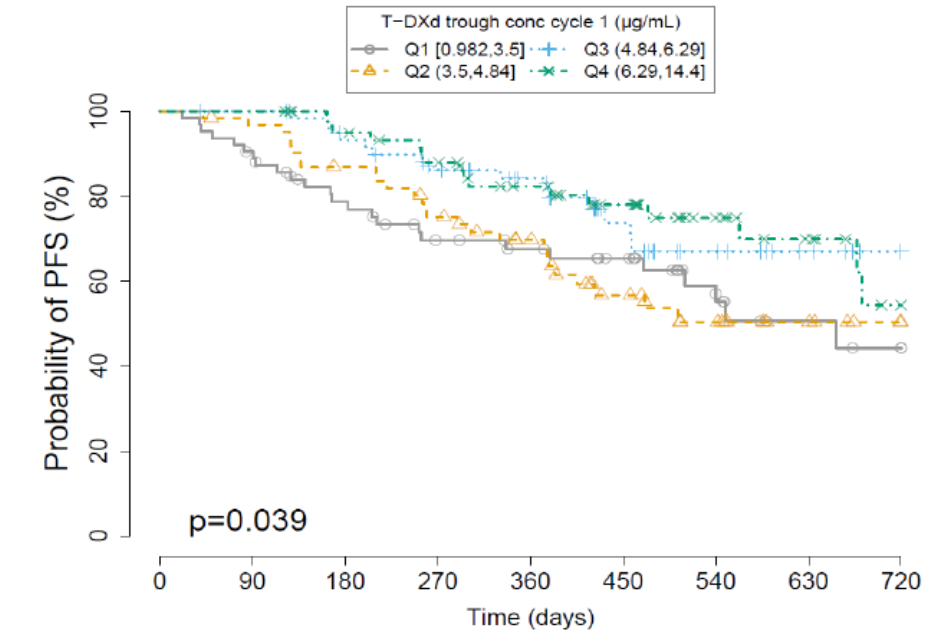
Exposure-efficacy analysis

Data from subjects with HER2-positive BC from Study U302 were used as a data set for the E-R analyses for efficacy. A total of 249 subjects were included. The efficacy endpoints were PFS, OS, and cORR as determined by BICR. The exposure indicators investigated were the AUC, Cmax, and Cmin of T-DXd and DXd in Cycle 1 and at steady state and Cavg during the period up to the development of a respective efficacy event.

Progression free survival (PFS)

In the analysis of U302, a significant E-R relationship was found between PFS and increasing T-DXd exposures (Cmin at Cycle 1) based on Kaplan-Meier curves. **Figure 3.10** shows the exploratory Kaplan-Meier curve for PFS stratified by the interquartile ranges of Cmin at Cycle 1 of T-DXd. The effect of each covariate on PFS as predicted from the E-R relationships is shown in the forest plot of **Figure 3.11**. PFS was statistically significantly longer in subjects with higher T-DXd Cmin at Cycle 1 (P = 0.039). However, these Kaplan-Meier curves have some degree of overlap with crossing lines. The exposure-response shows a shallow trend of relationship; differences in Day 360 PFS probability at the 5th and 95th percentiles of exposure vs. the median exposure were <7%. There were no significant relationships between increasing DXd exposures and PFS.

Figure 3.10: Kaplan-Meier Curve for Progression-Free Survival Stratified by Interquartile Ranges of Exposure: Study U302

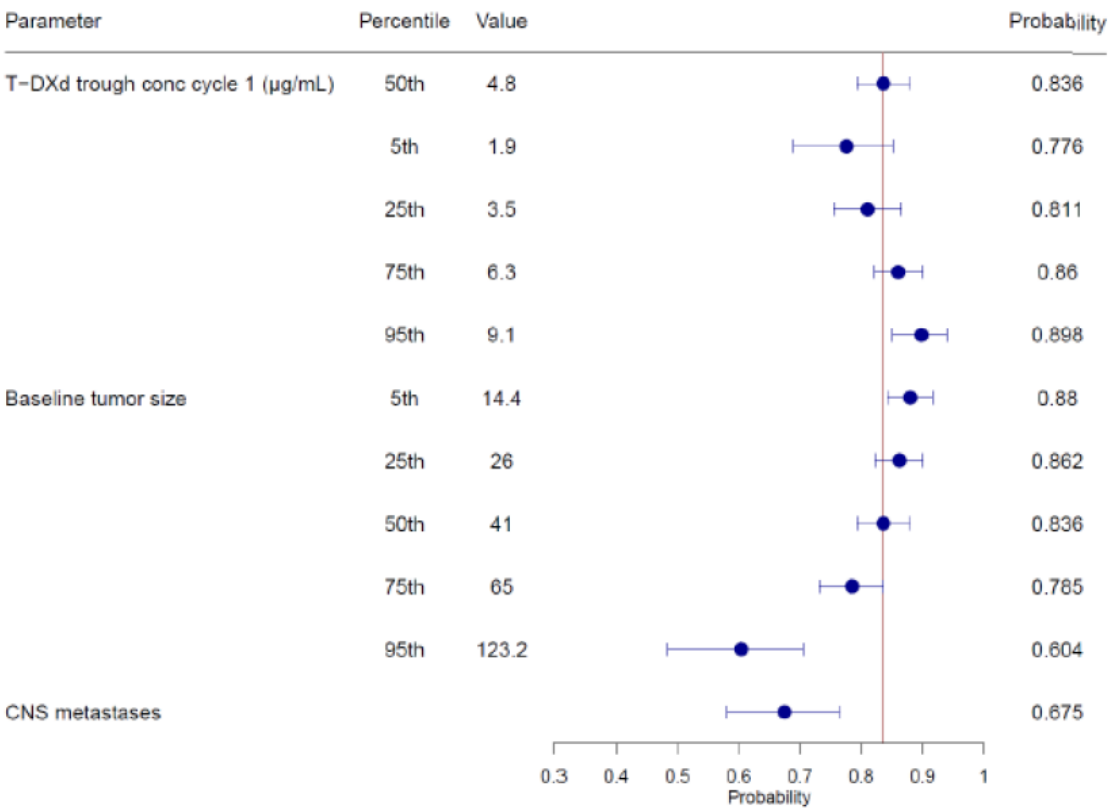


N at risk

Q1	63	57	46	37	33	28	17	10	7
Q2	62	60	53	45	36	22	14	7	2
Q3	62	62	55	49	39	23	15	9	5
Q4	62	62	57	51	42	33	20	13	7

Conc = concentration; N = number of subjects; PFS = progression-free survival; Q = quartile; T-DXd = trastuzumab deruxtecan.
Note: Curves are Kaplan-Meier curves stratified by exposure quartiles. Points are censor times. P-value is for the log-rank test.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx013 Figure 5-1

Figure 3.11: Forest Plot of Progression-Free Survival at Day 360: Study U302

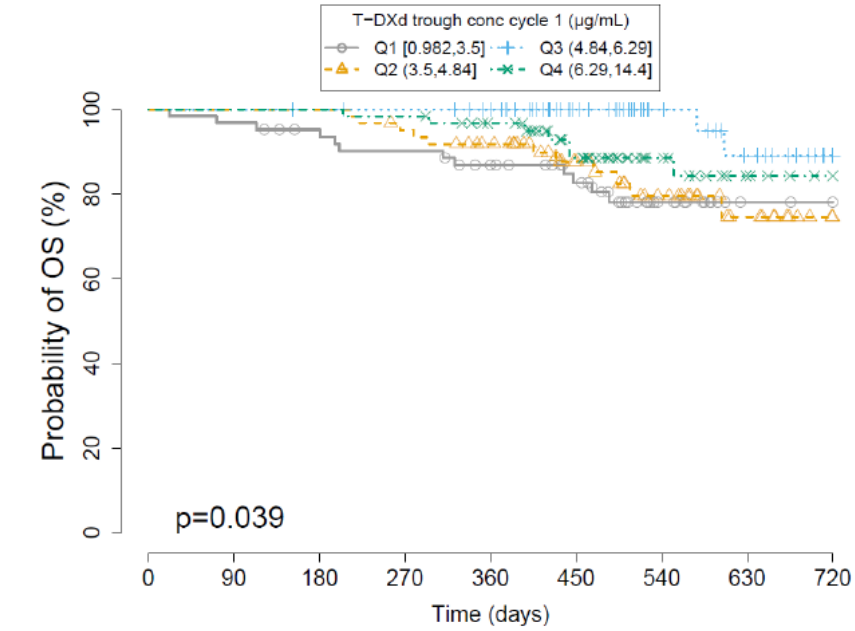


CNS = central nervous system; conc = concentration; T-DXd = trastuzumab deruxtecan.
Note: Dot and horizontal line corresponds to the probability estimate and 90% confidence interval, respectively, for 1000 simulated models incorporating parameter uncertainty. Vertical line corresponds to the model-predicted probability for a typical subject with baseline tumor size of 41 mm, no history of CNS metastases, and indicated median T-DXd exposure for 5.4 mg/kg T-DXd. The CNS metastases parameter indicates the presence of CNS metastases.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx013 Figure 5-4

Overall survival (OS)

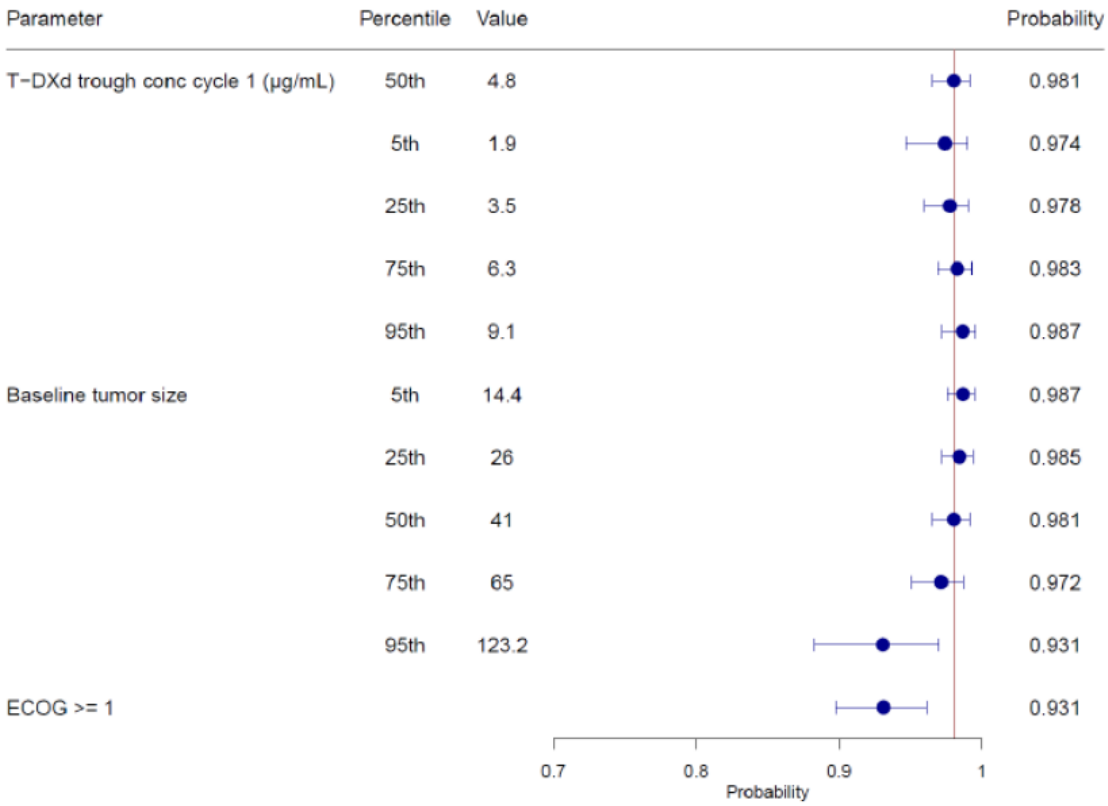
A significant E-R relationship was also found between OS and increasing T-DXd exposures (Cmin at Cycle 1) based on Kaplan-Meier curves. **Figure 3.12** shows an exploratory Kaplan-Meier curve for OS stratified by the interquartile ranges of Cmin of T-DXd at Cycle 1. The effect of each covariate on OS as predicted from the E-R relationships is shown in the forest plot of **Figure 3.13**. However, OS data are immature and these Kaplan-Meier curves have some degree of overlap with crossing lines. There were no significant relationships between increasing DXd exposures and OS.

Figure 3.12: Kaplan-Meier Curve for Overall Survival Stratified by Interquartile Ranges of Exposure: Study U302



CI = confidence interval; N = number of subjects; OS = overall survival; Q = quartile; T-DXd = trastuzumab deruxtecan.
Note: The top plot presents Kaplan-Meier curves by exposure quartiles. P-value in the top plot is for the log-rank test. The bottom four plots present univariate Cox regression fits per exposure quartile. The exposure metric and exposure quartile are indicated in the title of each plot. The solid black line represents the estimated Kaplan-Meier curves. The dashed lines are 95% CIs. The solid blue line represents the estimated Kaplan-Meier curve determined with univariate Cox regression.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx013 Figure 5-5

Figure 3.13: Forest Plot of Overall Survival at Day 360: Study U302

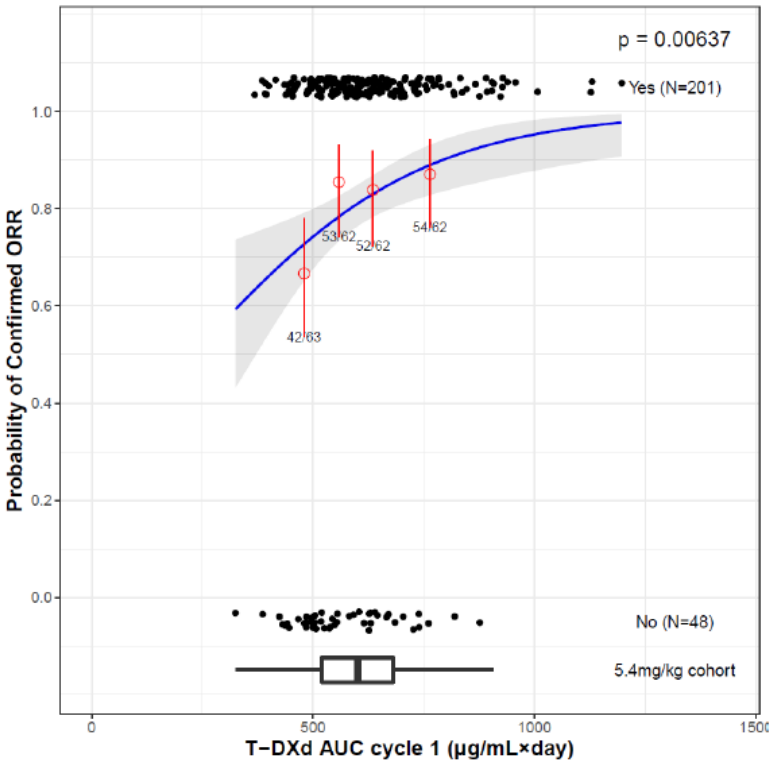


Conc = concentration; ECOG = Eastern Cooperative Oncology Group (performance status); T-DXd = trastuzumab deruxtecan.
Note: Dot and horizontal line corresponds to the probability estimate and 90% confidence interval, respectively, for 1000 simulated models incorporating parameter uncertainty. Vertical line corresponds to the model-predicted probability for a typical subject with baseline ECOG = 0, baseline tumor size of 41 mm, and indicated median T-DXd exposure for 5.4 mg/kg T-DXd.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx013 Figure 5-8

Confirmed ORR (cORR)

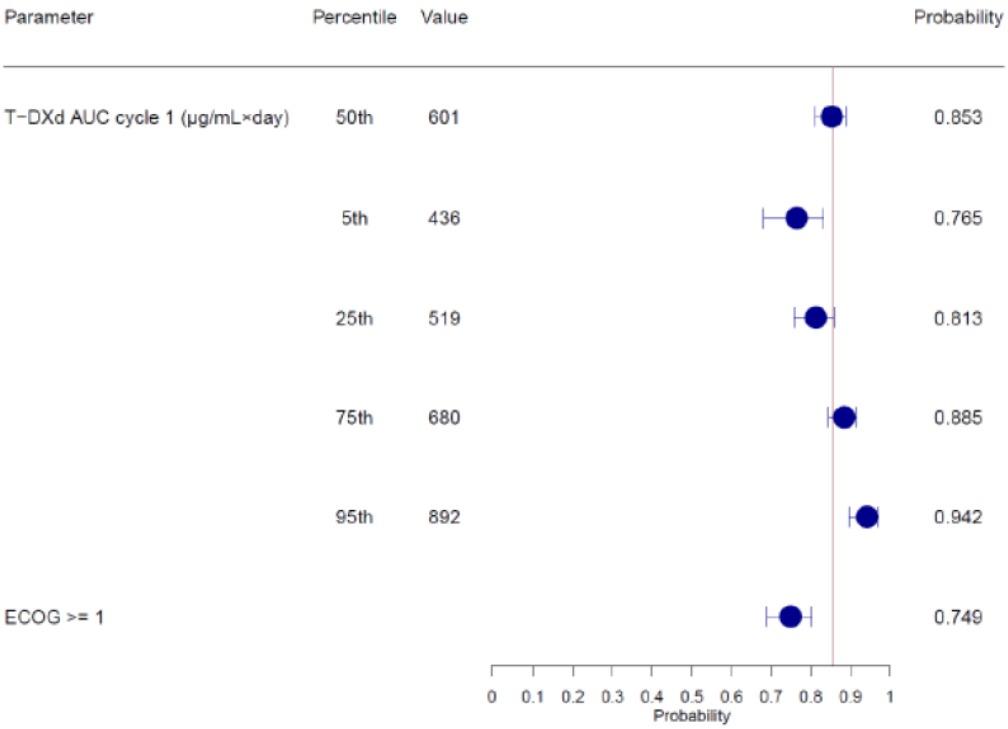
The analysis of cORR confirmed by BICR using univariate logistic regression is shown in **Figure 3.14**. The effect of covariates on cORR, as predicted from the E-R relationships, is shown in the forest plot in **Figure 3.15**. cORR was statistically significantly higher in subjects with higher T-DXd AUC at Cycle 1 (P = 0.00637). However, the differences in cORR at the 5th and 95th exposure percentiles of exposure metrics vs. the median exposure were <9% and the CIs of the cORR probability overlap across different percentiles; in addition, more than half of the patients in the lowest exposure quartiles have ECOG PS values ≥1.

Figure 3.14: Relationship Between Exposure and Confirmed Objective Response Rate: Study U302



AUC = area under the serum concentration-time curve; N = number of subjects; ORR = objective response rate; T-DXd = trastuzumab deruxtecan.
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 6.4 mg/kg dose group; the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx013 Figure 5-10

Figure 3.15: Forest Plot of Confirmed Objective Response Rate



AUC = area under the serum concentration-time curve; ECOG = Eastern Cooperative Oncology Group (performance status); ORR = objective response rate; T-DXd = trastuzumab deruxtecan.
Note: Dot and horizontal line corresponds to the probability estimate and 90% confidence interval, respectively, for 1000 simulated models incorporating parameter uncertainty. Vertical line corresponds to the model-predicted probability for a typical subject with baseline ECOG = 0 and indicated median T-DXd exposure for 5.4 mg/kg T-DXd.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx013 Figure 5-12

Simulated PFS and OS event probabilities and ORR at Day 360 for T-DXd 5.4 mg/kg were comparable across race-country categories and region categories in subjects with BC (**Table 3.7**).

Table 3.7: Simulated Efficacy Endpoints at Day 360 for T-DXd 5.4 mg/kg Q3W in Subjects with Breast Cancer by Race-country and Region

	Endpoint	Subgroup	Observed (%)	Model-predicted Rate (%) Estimate (90% CI)
Race-country	PFS	Asian-Japan	77.1	79.2 (73.4, 84.0)
		Asian Non-Japan	72.0	75.4 (69.7, 80.6)
		Non-Asian	79.6	75.2 (69.5, 80.5)
	OS	Asian-Japan	94.3	97.0 (95.1, 98.4)
		Asian Non-Japan	93.5	93.0 (89.5, 95.7)
		Non-Asian	94.1	93.5 (90.1, 96.3)
	ORR	Asian-Japan	74.3	82.6 (75.1, 88.0)
		Asian Non-Japan	79.3	78.3 (70.2, 85.0)
		Non-Asian	84.5	82.6 (74.7, 88.3)
Region	PFS	North America	73.9	70.4 (58.6, 80.9)
		Europe	83.0	79.3 (74.2, 84.2)
		Asia	73.5	76.2 (71.1, 81.0)
		Rest of the World	75.3	72.0 (64.5, 78.9)
	OS	North America	87.5	91.2 (83.6, 95.7)
		Europe	98.0	96.4 (94.3, 98.1)
		Asia	93.6	93.9 (91.1, 96.3)
		Rest of the World	92.2	91.2 (85.4, 95.5)
	ORR	North America	75.0	83.5 (73.5, 90.4)
		Europe	86.0	83.3 (76.6, 88.9)
		Asia	77.8	79.2 (72.0, 85.7)
		Rest of the World	87.2	81.2 (73.3, 87.5)

CI = confidence interval; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; Q3W = every 3 weeks; T-DXd = trastuzumab deruxtecan.
Note: Modeled efficacy endpoint use all subjects in the indicated subgroup from Study U302. Subjects' numbers were 35, 111, and 103 for Asian-Japan, Asian non-Japan, and non-Asian, respectively and 16, 50, 144, and 39 for North America, Europe, Asia, and rest of the world, respectively.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx013 Table 5-6, 5-10, and 5-15

Exposure-safety analysis

An integrated dataset across nine clinical studies (J101, J102, A103, A104, U201, J202, U204, U205, and U302) including subjects with GC, BC, NSCLC (HER2-mutant and HER2-overexpressing), and other tumours was used in the E-R analyses for key safety endpoints. This analysis is an updated E-R analysis which added Study U302 to 1059 solid tumour patients from eight other studies and included 512 BC subjects.

The E-R analyses for safety were conducted using an integrated dataset across nine studies (J101, J102, A103, A104, U201, J202, U204, U205, and U302) using the following safety endpoints:

- Treatment-emergent adverse events (TEAEs) associated with discontinuation of study drug administration
- TEAEs associated with dose reduction of study drug
- TEAEs associated with interruption of study drug administration
- Grade ≥3 TEAEs
- Serious adverse events (SAEs)
- Any grade and Grade ≥3 (laboratory-defined) anemia, neutrophil count decreased, platelet count decreased

- Grade ≥2 left ventricular ejection fraction (LVEF) decreased
- Any grade and Grade ≥3 drug-related interstitial lung disease (ILD) that was adjudicated by the independent ILD adjudication committee.

E-R analyses for the safety endpoints listed below were performed by logistic regression. In addition, an E-R analysis with the Cox proportional hazards model was performed for any grade and Grade ≥3 drug-related ILD adjudicated by the independent ILD adjudication committee.

The exposure indicators investigated were Cavg in addition to the AUC, Cmax, and Cmin of T-DXd and DXd for Cycle 1 and at steady state.

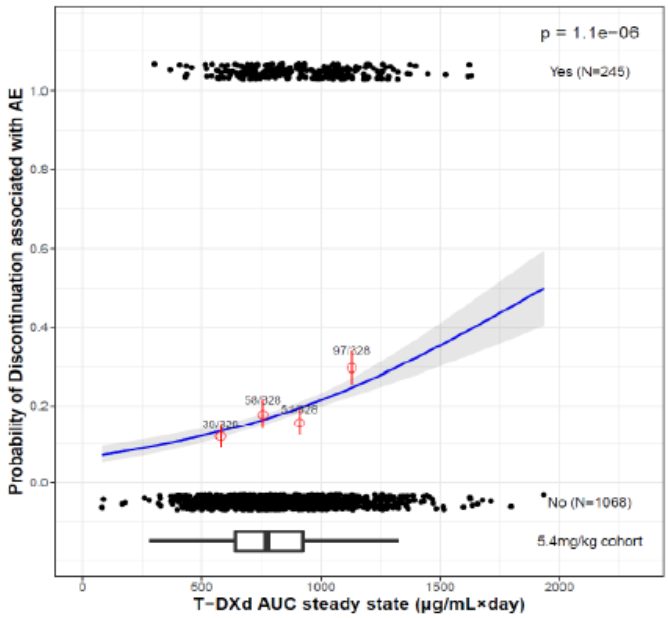
The analysis showed a statistically significant exposure-safety relationship with at least one exposure metric for all evaluated safety endpoints. The most significant exposure indicators were used in the final model. For all safety endpoints, the exposure indicators selected for the final model were the same as the exposure indicators for the E-R analyses for the initial BC application.

Results

E-R safety relationships observed in the current analysis update were consistent with previous ER analyses. T-DXd AUCss was correlated with discontinuation associated with TEAE (P = 1.1 × 10-6); T-DXd Cmax,ss was correlated with Grade ≥2 LVEF decrease (P = 2.27 × 10-5); and DXd Cavg to the event time was correlated with dose reduction associated with TEAE (P = 5.7 × 10-25), Grade ≥3 TEAEs (P = 8.48 × 10-34), SAEs (P = 1.98 × 10-23), hematologic TEAEs (Grade ≥3 anemia [P = 2.3 × 10-22], any grade neutrophil count decreased [P = 4.33 × 10-29]; Grade ≥3 neutrophil count decreased [P = 5.72 × 10-28]; any grade platelet count decreased [P = 3.43 × 10-44], Grade ≥3 platelet count decreased [P = 4.81 × 10-21]).

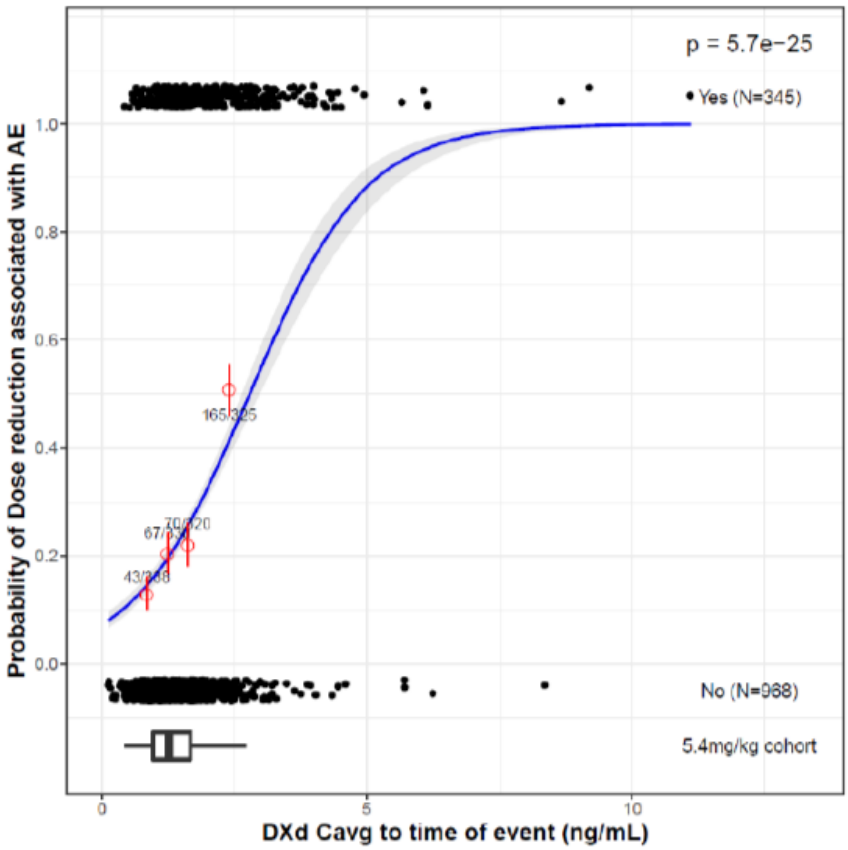
Exposure-safety figures for T-DXd and DXd:

Figure 3.16: Relationship Between Exposure and Adverse Events Associated with Discontinuation of Study Drug



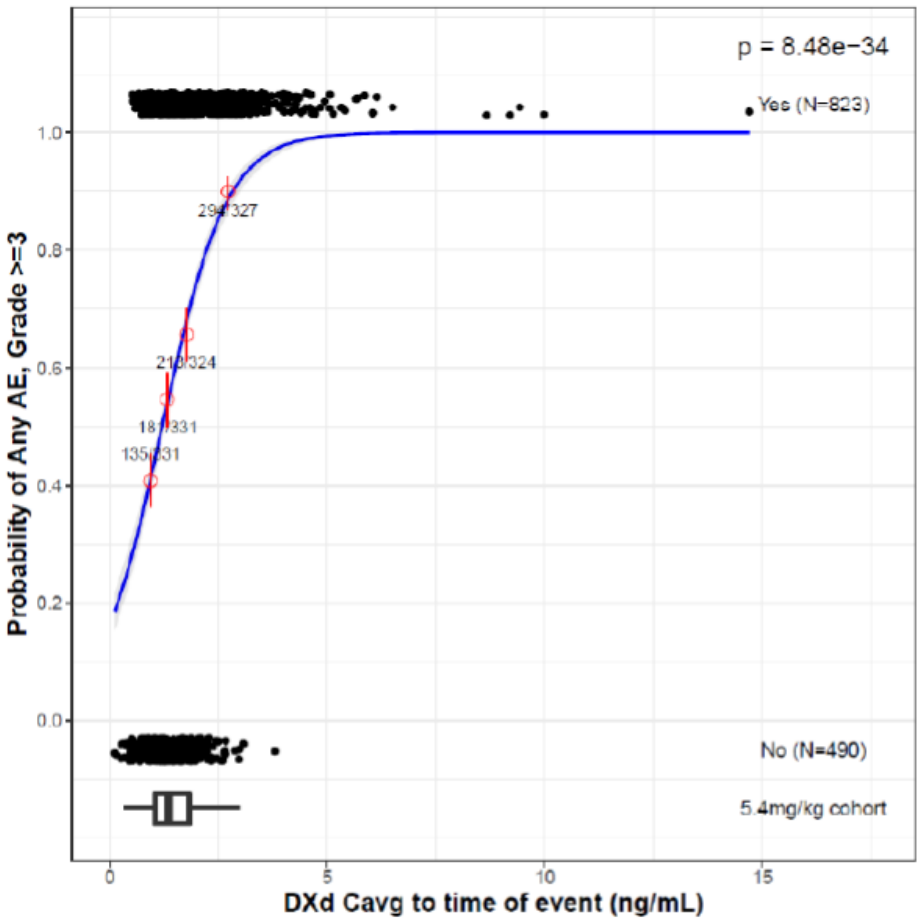
AE = treatment-emergent adverse event; CI = confidence interval; N = number of subjects; T-DXd = trastuzumab deruxtecan.
Note: Plot shows probability of AE versus exposure. Yes and No refer to if subjects experienced or did not experience discontinuation associated with AEs. Subjects are stratified into exposure quartiles. Red points are discontinuation rates per exposure quartile plotted at the median exposure of the quartile. Vertical red bars are 90% CIs of the discontinuation 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. The p-value is for the slope of the logistic regression fit.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx013 Figure 5-14

Figure 3.18: Relationship Between Exposure and Adverse Events Associated with Dose Reduction of Study Drug



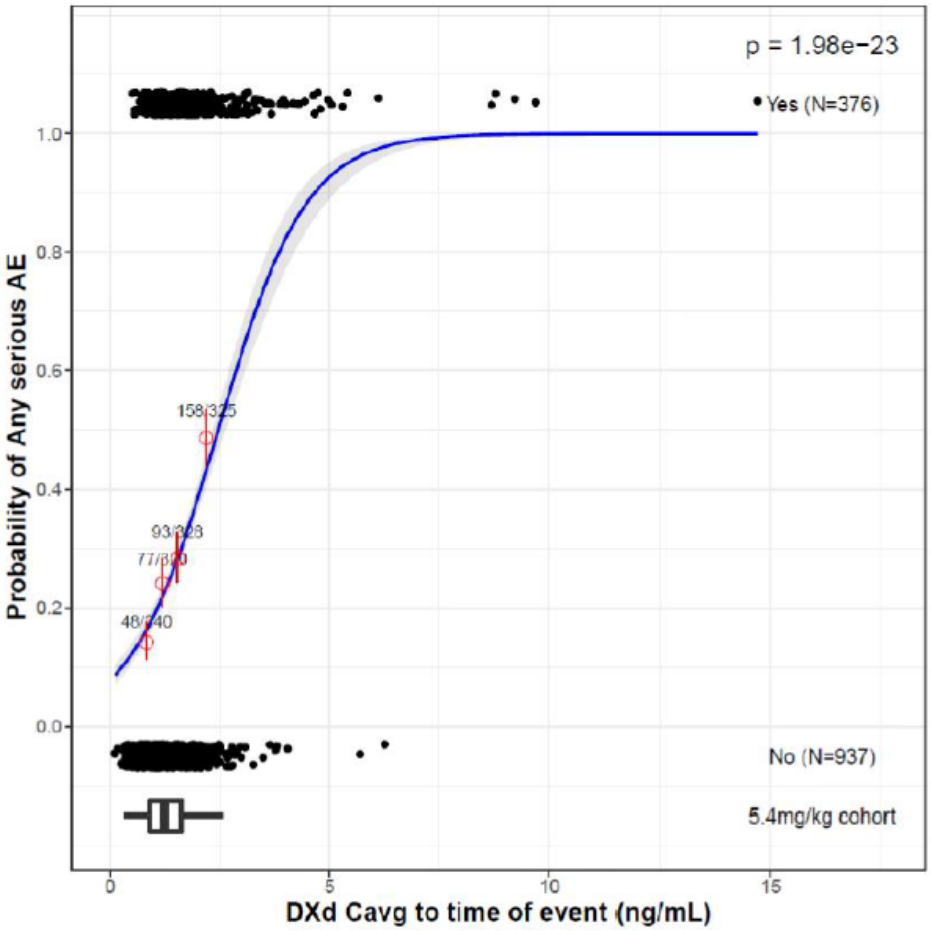
AE = treatment-emergent adverse event; Cavg = average serum concentration; CI = confidence interval; DXd = released drug; N = number of subjects.
Note: Plot shows probability of AE versus exposure. Yes and No refer to if subjects experienced or did not experience dose reductions associated with AEs. Subjects are stratified into exposure quartiles. Red points are dose reduction rates per exposure quartile plotted at the median exposure of the quartile. Vertical red bars are 90% CIs of the dose reduction 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: Module 5.3.3.5 Exposure-Response Analysis Report PMx013 Figure 5-19

Figure 3.20: Relationship Between Exposure and Grade ≥3 Adverse Events



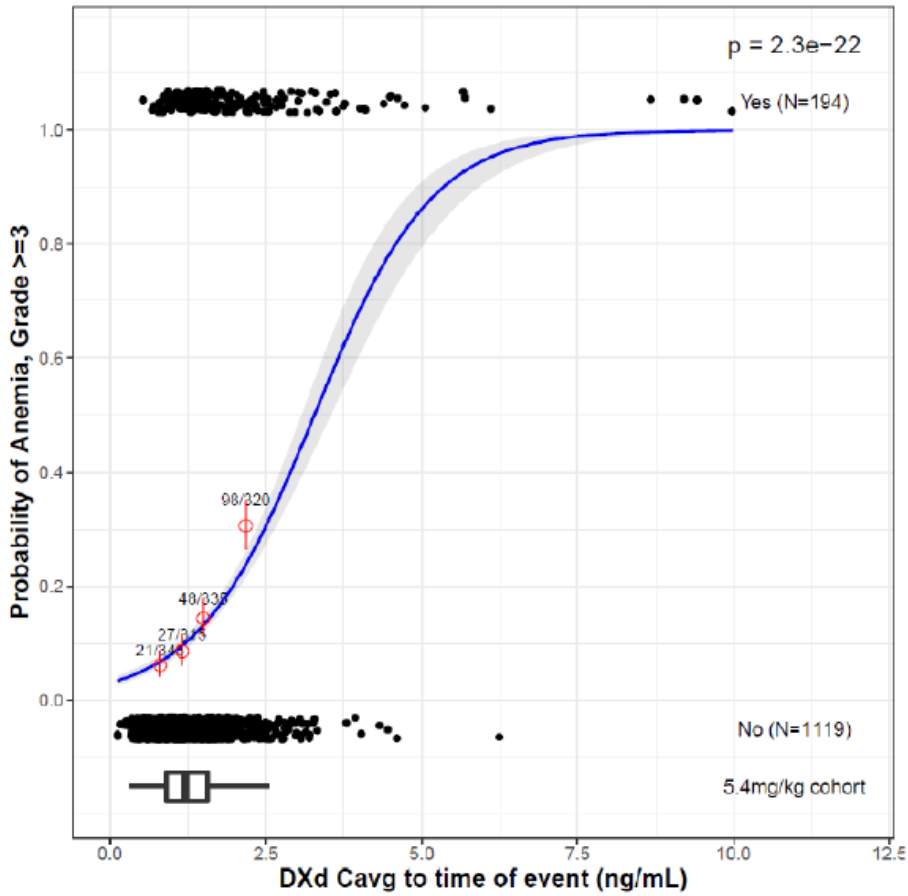
AE = treatment-emergent adverse event; Cavg = average serum concentration; CI = confidence interval; DXd = released drug; N = number of subjects.
Note: Plot shows probability of AE versus exposure. Yes and No refer to if subjects experienced or did not experience Grade ≥3 AEs. Subjects are stratified 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: Module 5.3.3.5 Exposure-Response Analysis Report PMx013 Figure 5-25

Figure 3.22: Relationship Between Exposure and Serious Adverse Events



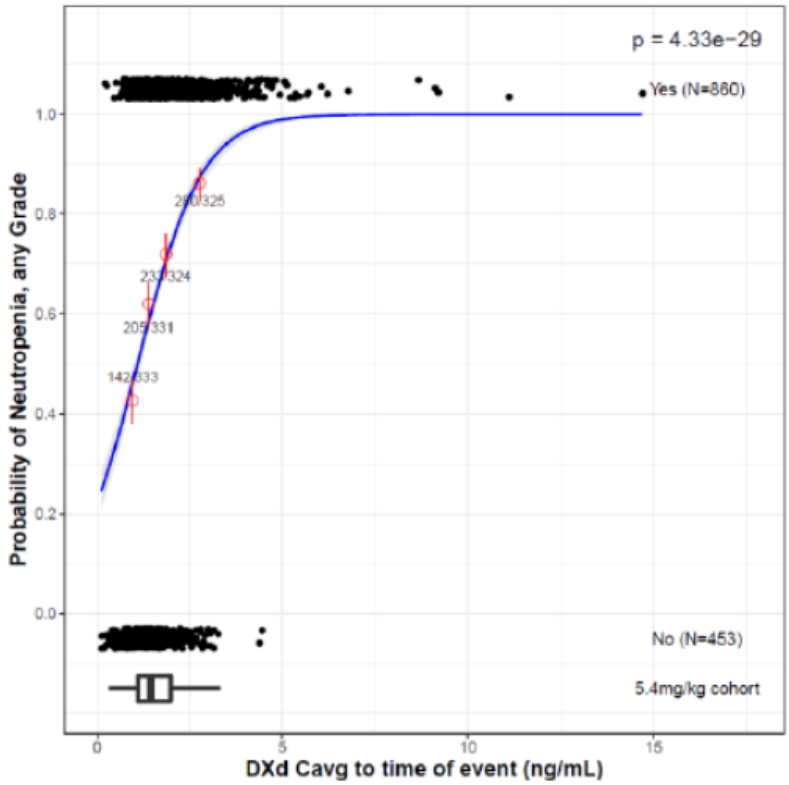
AE = treatment-emergent adverse event; Cavg = average serum concentration; CI = confidence interval; DXd = released drug; N = number of subjects.
Note: Plot shows probability of AE versus exposure. Yes and No refer to if subjects experienced or did not experience serious AEs. Subjects are stratified 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: Module 5.3.3.5 Exposure-Response Analysis Report PMx013 Figure 5-30

Figure 3.24: Relationship Between Exposure and Anemia (Grade ≥3)



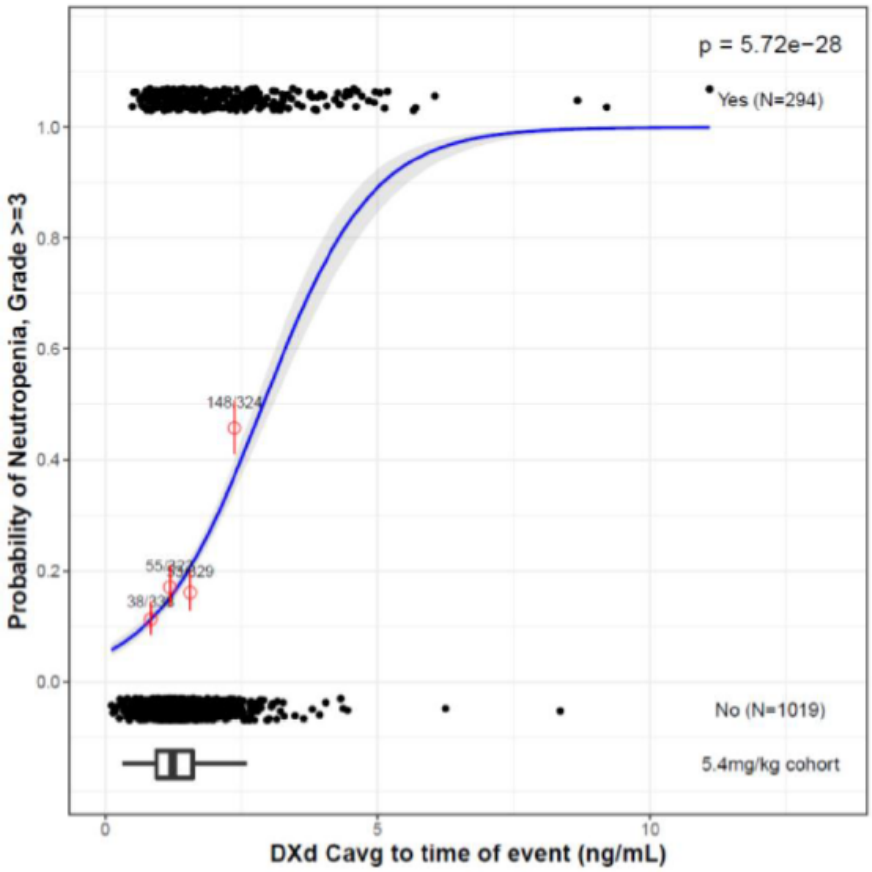
AE = treatment-emergent adverse event; Cavg = average concentration; CI = confidence interval; N = number of subjects.
Note: Plot shows probability of AE versus exposure. Yes and No refer to if subjects experienced or did not experience anemia (laboratory-based). Subjects are stratified into exposure 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: Module 5.3.3.5 Exposure-Response Analysis Report PMx013 Figure 5-35

Figure 3.26: Relationship Between Exposure and Neutrophil Count Decreased (Any Grade)



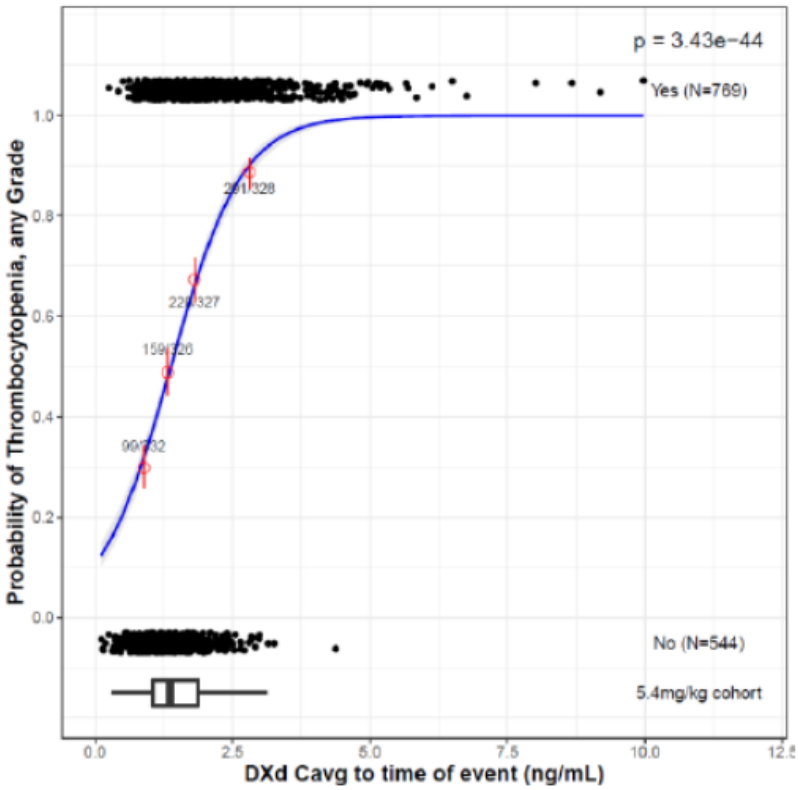
AE = treatment-emergent adverse event; Cavg = average concentration; CI = confidence interval; DXd = released drug; N = number of subjects.
Note: Plot shows probability of AE versus exposure. Yes and No refer to if subjects experienced or did not experience neutropenia (laboratory-based). Subjects are 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: Module 5.3.3.5 Exposure-Response Analysis Report PMx013 Figure 5-40

Figure 3.28: Relationship Between Exposure and Neutrophil Count Decreased (Grade ≥3)



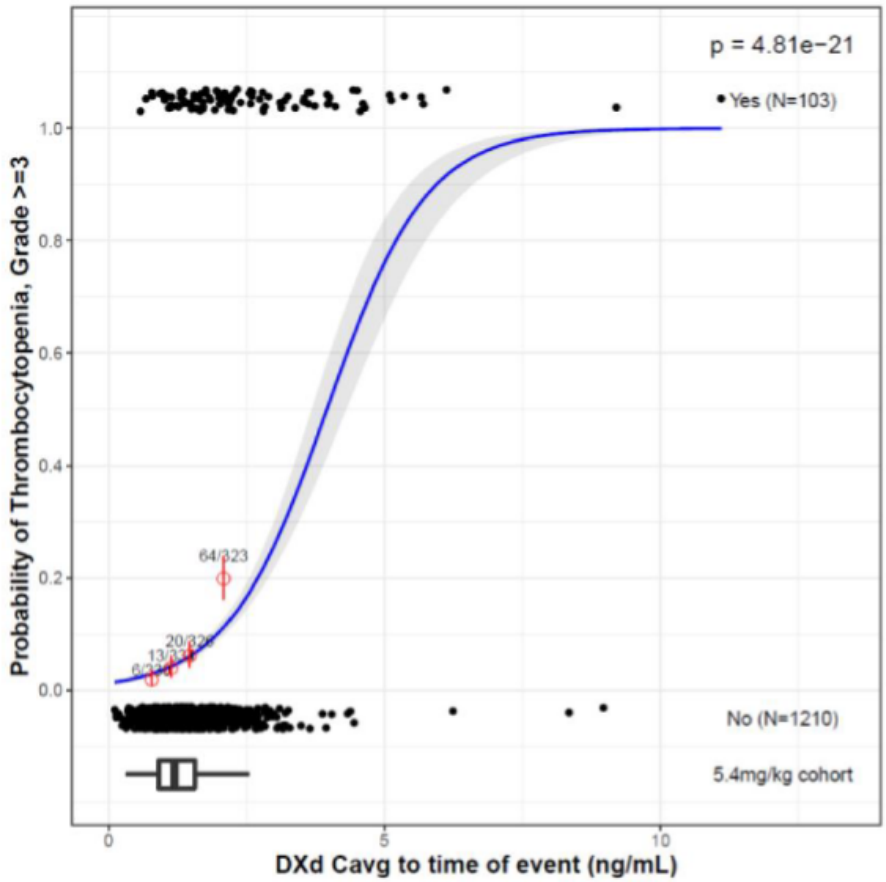
AE = treatment-emergent adverse event; Cavg = average concentration; CI = confidence interval; DXd = released drug; N = number of subjects; T-DXd = trastuzumab deruxtecan.
Note: Plot shows probability of AE versus exposure. Yes and No refer to if subjects experienced or did not experience neutropenia (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 T-DXd dose group. The box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx013 Figure 5-40

Figure 3.30: Relationship Between Exposure and Platelet Count Decreased (Any Grade)



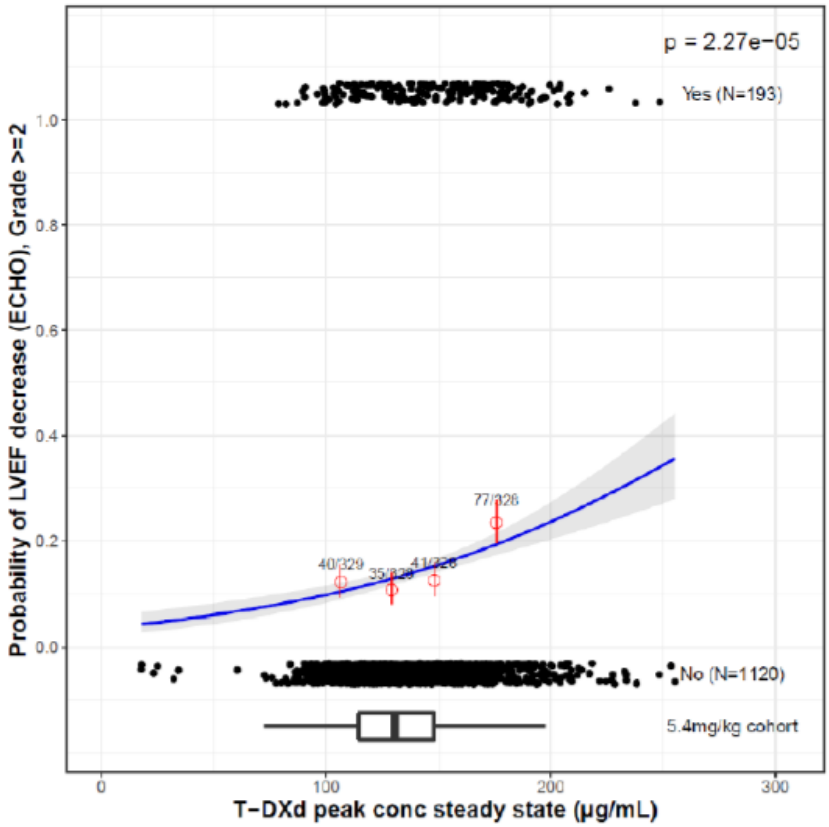
AE = treatment-emergent adverse event; Cavg = average concentration; CI = confidence interval; DXd = released drug; T-DXd = trastuzumab deruxtecan.
Note: Plot shows probability of AE versus exposure. Y es and No refer to if subjects experienced or did not experience thrombocytopenia (laboratory-based). 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 T-DXd dose group; the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx013 Figure 5-45

Figure 3.32: Relationship Between Exposure and Platelet Count Decreased (Grade ≥3)



AE = treatment-emergent adverse event; Cavg = average concentration; CI = confidence interval; DXd = released drug; T-DXd = trastuzumab deruxtecan.
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 T-DXd dose group; the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx013 Figure 5-45

Figure 3.34: Relationship Between Exposure and Decreased LVEF (Grade ≥2)



AE = treatment-emergent adverse event; CI = confidence interval; conc = concentration; ECHO = echocardiogram-based; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition scan; N = number of subjects; T-DXd = trastuzumab deruxtecan.
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 T-DXd dose group; the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx013 Figure 5-50

The exposure in non-Japanese (non-Japanese Asians and non-Asians) was estimated to be similar to the exposure in Japanese subjects based on the PopPK analysis; however, the results of the E-R analyses for safety showed that the final logistic regression model included race-country as a covariate for TEAEs associated with discontinuation of study drug administration, any SAE, hematologic TEAEs, and LVEF decrease. The incidence rate of these TEAEs after administration of 5.4 mg/kg dose in subjects with BC as predicted using the final model were compared across race-country, region, and line of therapy (**Table 3.8**). With respect to all TEAEs, the incidence rate tended to be similar between second- and third-line therapy, and between North American and European subjects.

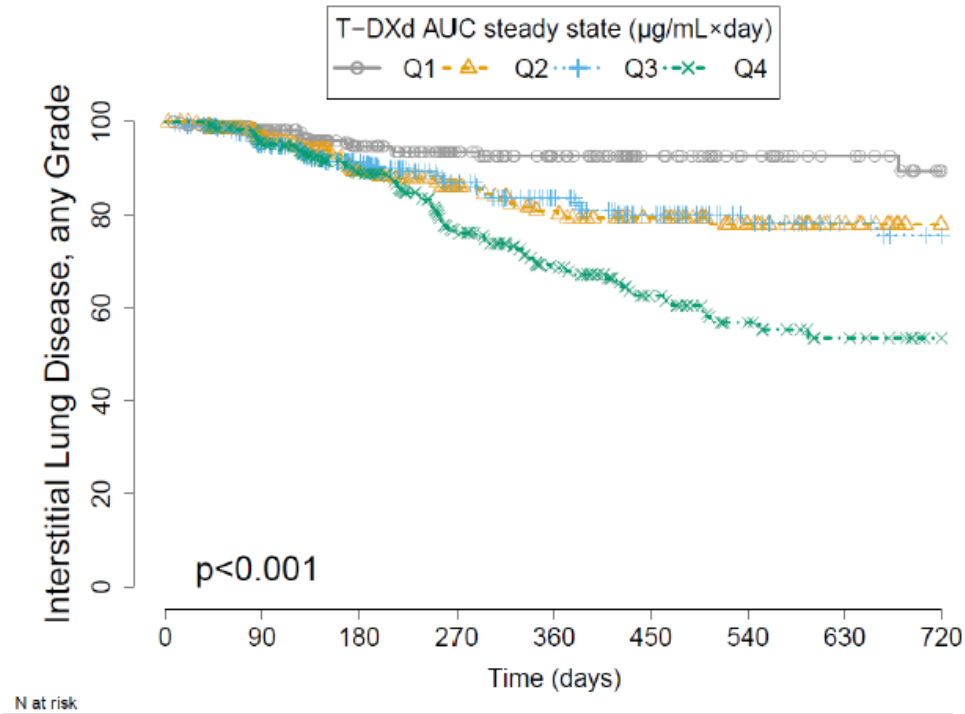
Table 3.8: Incidence Rate of Adverse Events in Subjects with Breast Cancer (5.4 mg/kg Q3W) Predicted in the Final Model (by Race-country, Region, and Line of Therapy)

	Model-Predicted Rate (% [90% CI]), at 5.4 mg/kg Q3W of T-DXd in Breast Cancer Subjects									
	Discon. Associated with TEAE	Dose Reduction Associated with TEAE	Grade ≥3 TEAE	Serious TEAE	Grade ≥3 Anemia	Any Grade Neutropenia	Grade ≥3 Neutropenia	Any Grade Thrombocytopenia	Grade ≥3 Thrombocytopenia	Grade ≥2 LVEF Decrease
Race-country										
Asian-Japan	22.4 (17.8, 27.7)	22.5 (18.1, 27.4)	61.1 (56.9, 65.6)	19.4 (15.7, 23.8)	14.0 (9.9, 18.5)	72.8 (67.3, 77.5)	27.3 (22.5, 32.3)	62.0 (56.8, 67.3)	7.9 (5.9, 10.3)	18.2 (14.7, 21.9)
Asian-Non-Japan	11.1 (7.7, 15.6)	24.5 (20.3, 29.0)	55.3 (50.6, 60.3)	20.7 (16.2, 26.5)	11.3 (7.5, 16.2)	79.9 (74.4, 84.7)	20.0 (15.6, 25.0)	66.5 (60.1, 72.7)	10.5 (7.3, 14.6)	10.3 (7.3, 14.2)
Non-Asian	17.5 (13.3, 22.3)	22.3 (18.1, 27.2)	52.2 (47.5, 57.0)	28.9 (24.2, 34.0)	7.3 (4.9, 10.6)	56.3 (49.5, 62.5)	10.6 (8.2, 13.6)	48.3 (43.1, 53.4)	2.7 (1.7, 4.3)	16.0 (12.9, 19.3)
Region										
Asia	17.9 (13.7, 23.1)	23.4 (19.1, 28.0)	58.6 (54.5, 63.1)	19.8 (15.7, 24.4)	12.6 (8.9, 17.0)	76.4 (71.1, 80.8)	24.6 (20.1, 29.6)	63.3 (57.9, 68.3)	8.9 (6.6, 11.9)	14.9 (11.8, 18.8)
Europe	16.9 (12.7, 22.0)	21.9 (17.5, 26.4)	49.9 (45.1, 55.0)	27.0 (22.5, 31.8)	4.8 (3.0, 7.2)	56.0 (48.6, 62.9)	10.2 (8.0, 13.3)	47.3 (41.4, 53.3)	2.6 (1.7, 4.1)	15.3 (12.4, 18.6)
North America	17.1 (12.9, 22.3)	23.1 (18.4, 28.0)	55.4 (50.3, 60.1)	29.7 (25.0, 35.2)	10.9 (7.2, 15.5)	58.0 (51.2, 64.7)	12.1 (9.1, 15.8)	52.7 (46.9, 58.1)	3.9 (2.4, 6.2)	15.2 (12.3, 18.7)
ROW	16.4 (12.2, 21.1)	22.7 (17.7, 28.7)	50.0 (43.2, 56.9)	26.8 (20.8, 34.0)	5.0 (3.1, 7.7)	55.0 (46.4, 63.2)	10.4 (7.9, 13.8)	44.8 (37.1, 53.4)	2.4 (1.5, 4.0)	17.4 (14.0, 21.8)
Line of Therapy										
Second Line or Above	15.5 (11.9, 20.8)	23.8 (19.5, 27.6)	54.8 (50.9, 59.2)	22.3 (18.5, 26.9)	8.1 (5.7, 12.6)	69.4 (64.0, 74.1)	17.5 (13.9, 21.6)	51.9 (45.9, 57.9)	6.7 (4.9, 9.6)	14.8 (11.2, 18.3)
Third Line or Above	18.7 (14.6, 24.4)	22.7 (17.8, 26.8)	56.6 (53.7, 60.4)	23.9 (20.3, 28.6)	11.7 (8.4, 15.9)	65.9 (60.1, 70.7)	19.0 (15.5, 23.4)	59.6 (54.4, 64.1)	5.9 (4.4, 8.0)	15.6 (12.3, 18.3)

CI = confidence interval; Discon. = discontinuation; Q3W = every 3 weeks; T-DXd = trastuzumab deruxtecan; ROW = rest of the world; TEAE = treatment-emergent adverse events.
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 PMx013 Tables 5-80, 5-81 and 5-82

Figure 3.36 and Figure 3.37 show Kaplan-Meier curves for the time to ILD (any grade and Grade ≥3) for each interquartile range based on an exposure metrics (AUCss of T-DXd for any grade and T-DXd Cmax,ss for Grade ≥3). There was a statistically significant relationship between the exposure to T-DXd (AUCss) and the incidence rate of ILD (any grade) ($P < 0.001$) and between the exposure to T-DXd (Cmax,ss) and the incidence rate of ILD (Grade ≥3) ($P = 0.002$). The incidence rate of ILD (any grade and Grade ≥3) tended to be higher in subjects with higher exposure.

Figure 3.36: Kaplan-Meier Curves for Interstitial Lung Disease (Any Grade) Stratified by Interquartile Ranges of Exposure

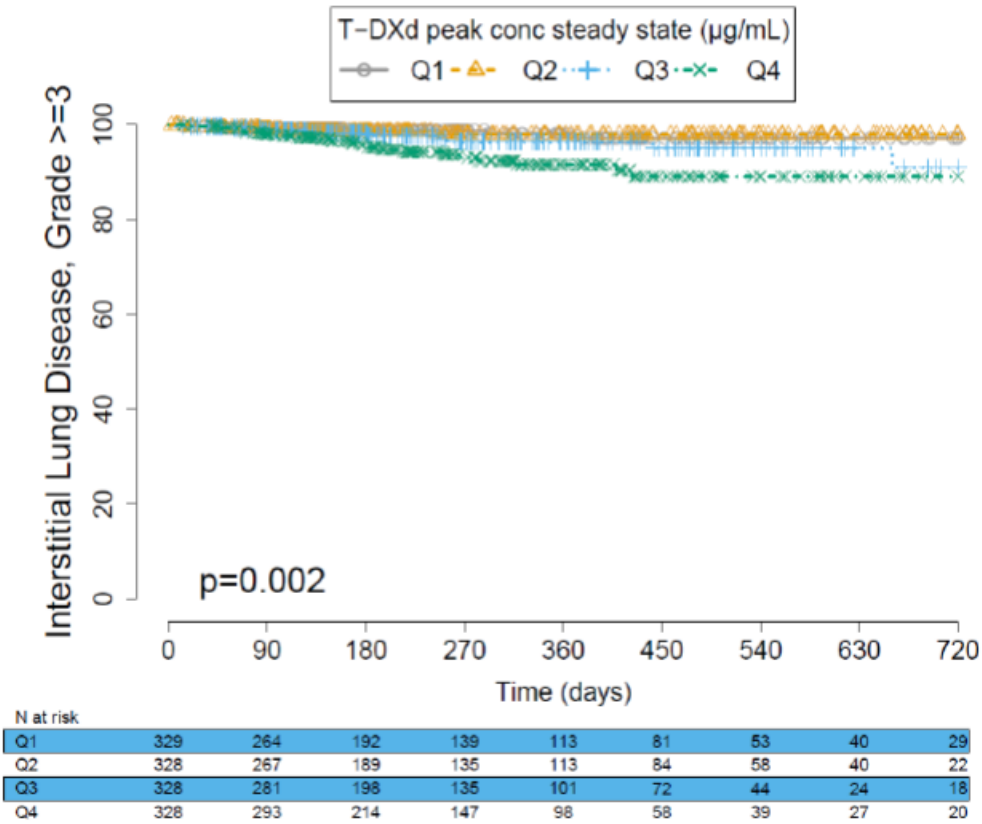


N at risk

Q1	329	241	160	120	96	67	44	34	23
Q2	328	265	184	128	102	77	52	34	19
Q3	328	280	202	136	104	75	46	32	26
Q4	328	292	216	142	99	63	43	29	18

AE = treatment-emergent adverse event; CI = confidence interval; N = number of subjects; Q = quartile; T-DXd = trastuzumab deruxtecan.
Note: Kaplan-Meier curves by exposure quartiles. P-value is for the log-rank test.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx013 Figure 5-56

Figure 3.37: Kaplan-Meier Curves for Interstitial Lung Disease (Grade ≥3) Stratified by Interquartile Ranges of Exposure



AE = treatment-emergent adverse event; CI = confidence interval; N = number of subjects; Q = quartile; T-DXd = trastuzumab deruxtecan.
Note: Kaplan-Meier curves by exposure quartiles. P-value is for the log-rank test.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx013 Figure 5-57

The incidence rate of ILD (any grade and Grade ≥3) at Day 90, Day 180, and Day 360 after the administration of T-DXd at 5.4 mg/kg Q3W in subjects with BC was predicted based on the final model (**Table 3.9**). Any grade ILD rates at Day 360 were approximately 15% in non-Asians, 9% in non-Japan Asians, and 24% in Asian-Japan subjects. Nevertheless Grade ≥3 ILD rates were comparable across race-country category and less than 5% at Day 360.

Table 3.9: Incidence Rate of Model-predicted Interstitial Lung Disease After Administration of T-DXd at 5.4 mg/kg in Subjects with Breast Cancer

Adverse Event	Landmark	Race-Country Category	Model-predicted Rate of ILD Estimate (90% CI)
ILD Any Grade	Day 90	Asian-Japan	4.6 (3.4, 5.8)
		Asian-Non-Japan	1.5 (0.9, 2.2)
		Non-Asian	2.7 (1.9, 3.6)
		Overall	3.0 (2.3, 3.8)
	Day 180	Asian-Japan	11.1 (9.0, 13.3)
		Asian-Non-Japan	3.7 (2.4, 5.3)
		Non-Asian	6.7 (5.1, 8.4)
		Overall	7.4 (6.1, 8.7)
	Day 360	Asian-Japan	24.2 (20.6, 28.1)
		Asian-Non-Japan	8.7 (5.7, 12.1)
		Non-Asian	15.1 (12.4, 18.4)
		Overall	16.5 (14.5, 18.9)
ILD Grade ≥3	Day 90	Asian-Japan	0.7 (0.4, 1.1)
		Asian-Non-Japan	1.0 (0.6, 1.5)
		Non-Asian	1.0 (0.6, 1.5)
		Overall	0.9 (0.5, 1.3)
	Day 180	Asian-Japan	1.5 (0.9, 2.2)
		Asian-Non-Japan	2.0 (1.3, 2.9)
		Non-Asian	2.0 (1.4, 2.8)
		Overall	1.9 (1.3, 2.6)
	Day 360	Asian-Japan	2.8 (2.0, 3.8)
		Asian-Non-Japan	3.7 (2.6, 5.0)
		Non-Asian	3.7 (2.7, 4.8)
		Overall	3.4 (2.5, 4.5)

CI = confidence interval; ILD = interstitial lung disease; T-DXd = trastuzumab deruxtecan.
Note: Modeled safety endpoint rates use all subjects in indicated race-country subgroup. Exposures are dose-normalized to a 5.4 mg/kg T-DXd dose in breast cancer. Subject numbers in breast cancer were 250, 189, 327, and 766 for Asians from Japan, Asians not from Japan, non-Asians, and overall, respectively.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx013 Table C

2.3.4. Discussion on clinical pharmacology

The current application is to seek marketing approval for the use of T-DXd 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. The currently approved and recommended T-DXd dosing regimens for breast cancer is 5.4 mg/kg as an intravenous (IV) infusion once every 3 weeks (Q3W).

The clinical pharmacology profile of T-DXd has been characterized previously in the initial T-DXd marketing application in BC (see Enhertu EPAR). The clinical pharmacology package for the initial BC application included five studies (Studies J101, J102, A103, A104, and U201). The package included in the current application also includes data from four additional studies: Two Phase 2 studies in subjects with HER2-positive advanced GC or gastroesophageal junction (GEJ) adenocarcinoma (Studies J202 and U205), a Phase 2 study in subjects with metastatic HER2-mutant or HER2-overexpressing NSCLC (Study U204), and a Phase 3 study in subjects with HER2-positive BC (Study U302). Data from these nine studies were used in the PopPK and exposure-response (E-R) analyses. In study U302, subjects were randomized in a 1:1 ratio to T-DXd 5.4 mg/kg (261 subjects) or trastuzumab emtansine (T-DM1) (263 subjects). Serum concentrations of T-DXd, total anti-HER2 antibody, and DXd were evaluated and

used for the PopPK and E-R analyses. Due to sparse PK sampling in the study, NCA was not conducted for Study U302.

The bioanalytical methods used for quantification of T-DXd (intact drug), total anti-HER2 antibody (mAb), DXd (released drug) and anti-T-DXd antibodies in serum were conducted using the same methods that were used in the initial BC application. Five new validation reports were submitted with this variation that covered the methods used for bioanalysis conducted in Chinese study U302. The results for DXd obtained at Covance Shanghai for cross-validation QC samples and some bioanalytical reports could not be located. The Applicant was recommended to provide the final bioanalytical reports for study U302 post-authorisation once they are available (PAM-REC).

A previous model developed for T-DXd PK was sequentially added additional data from patients with breast cancer from study U302 (2962 T-DXd and 2968 DXd samples available from 254 BC patients) with re-estimation of parameters. T-DXd PK could be described by a two-compartment model with linear clearance. The production of DXd was modelled by a two-component time-varying release rate from T-DXd. No new covariates were included based on the additional BC data. Parameter estimates of the updated models were compared to the parameters estimates of the previous models for T-DXd and DXd. In general, the additional BC data from U302 improved the precision of model parameters and the parameter estimates were largely comparable across models.

The ADME characteristics of T-DXd are well known. Based on the new popPK modelling with U302 data included, minor and acceptable updates of some PK values have been made in section 5.2 of the SmPC.

The Applicant has provided new analyses on covariates of exposure where the results of study U302 are included. The majority of the covariates had effects contained within the 0.8 to 1.25 exposure ratio. High body weight results in slightly higher exposure. None of the estimated values are considered to have a clinically meaningful impact on DXd PK.

The exposure in subjects with BC was similar between second and third line of therapy. The geometric mean ratios of the AUCss, Cmax,ss, and Cmin,ss in subjects with second-line BC to those in subjects with third-line BC were in the range of 0.987 to 1.06.

No new information regarding drug interaction potential has been provided in the present application.

As regards the PKPD effects in study U302, there is a clear relationship between the cycle 1 trough exposure estimates of T-DXd and the probability of PFS. The probability of PFS, however, was only +/- 7% for the 5^{th} and the 95^{th} percentiles compared with the median exposure. In the KM plot based on exposure quartiles, a statistically significant relationship was found with Q1 and Q2 consistently below Q3 and Q4. There were no significant relationships between increasing DXd exposures and PFS. A significant relationship between cycle 1 T-DXd exposure and cORR was also found. However, the lowest exposure quartile of T-Dxd included subjects with lower body weight, larger baseline tumour sizes, a greater percentage of ECOG ≥1, and a greater percentage of renal and hepatic impairment. Therefore, the univariate analyses are likely to be confounded by poor prognostic factors and co-morbidities. It is acknowledged that patients with poor prognostic factors are overrepresented in the group with lowest exposure quartile for other antibodies in the oncology field (pembrolizumab, nivolumab, ipilimumab) and this hampers robust exposure-efficacy evaluation when only one dose has been used.

The exposure-safety analyses performed with U302 data included in the data set have yielded results that are consistent with the previous analyses. T-DXd AUC,ss is correlated with TEAE mediated discontinuation of study drug and any grade ILD, T-DXd Cmax,ss is correlated with Grade ≥2 LVEF decrease and Grade ≥3 ILD, and DXd Cavg until time of event is correlated with the other TEAEs. The

risk of ILD is associated with higher exposure to T-DXd, and the risk of ILD grade ≥3 is similar between Asians and non-Asians. Finally, modelled TEAE rates were comparable between second or later lines and third or later lines of therapy for 5.4 mg/kg Q3W T-DXd in BC subjects.

2.3.5. Conclusions on clinical pharmacology

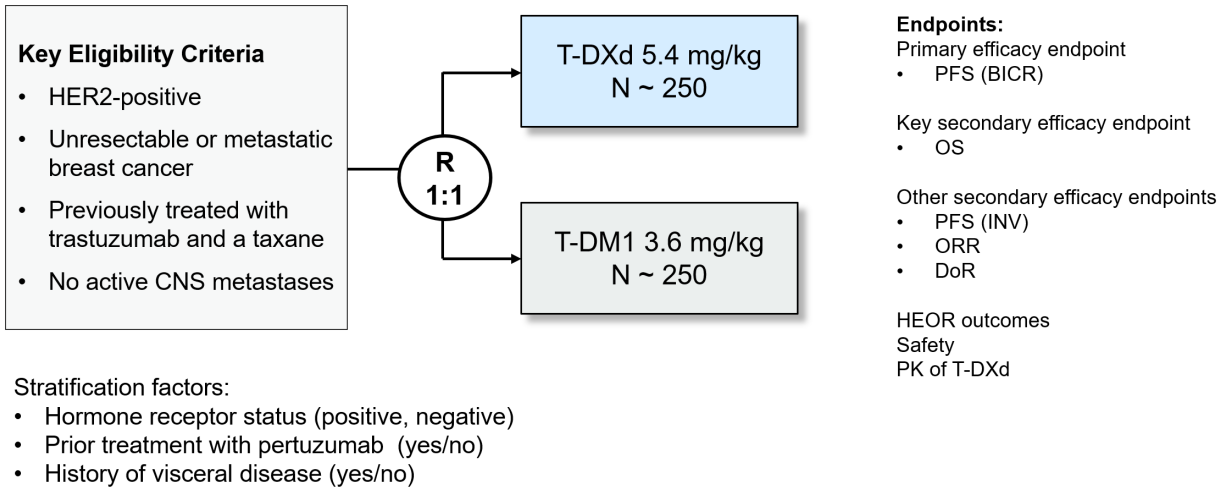
Trastuzumab deruxtecan (T-DXd) is a HER2-targeted antibody and topoisomerase I inhibitor conjugate (ADC molecule) approved for the treatment of unresectable or metastatic HER2-positive breast cancer (T-DXd dose 5.4 mg/kg). The present application concerns approval of T-DXd as 2L monotherapy after at least one prior anti-HER2-based regimen. The pharmacology package included in the current application includes data from a phase 3 study in the intended patient population. Data from the phase 3 study and inclusion of the new PKPD data to the PK model do not change the existing knowledge on T-DXd PKPD in BC patients.

2.4. Clinical efficacy

2.4.1. Main study(ies)

Destiny-Breast03 – Study U302 a Phase 3, multicenter, randomized, open-label, two-arm, active-controlled study was conducted in subjects with unresectable and/or metastatic HER2-positive breast cancer previously treated with trastuzumab and a taxane

Figure 1.1 Study U302 Design



BICR = blinded independent central review; CNS = central nervous system; DoR = duration of response; HEOR = Health Economics and Outcome Research; HER2 = human epidermal growth factor receptor; INV = investigator assessment; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; R = randomization; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan

Methods

Study participants

Inclusion Criteria

Subjects must have satisfied all of the following criteria to be included in the study:

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

2. Was an adult ≥18 years old (followed local regulatory requirements if the legal age of consent for study participation was >18 years old)

3. Had pathologically documented BC that:

a. was unresectable or metastatic.

b. had confirmed HER2-positive expression as determined according to American Society of Clinical Oncology - College of American Pathologists) guidelines evaluated at a central laboratory

c. was previously treated with trastuzumab and taxane in the advanced/metastatic setting or progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including trastuzumab and taxane

4. Had documented radiologic progression (during or after most recent treatment or within 6 months after completing adjuvant therapy).

5. Tumour was HER2 positive, as confirmed by central laboratory assessment of most recent tumour tissue sample available. If archived tissue was not available, a fresh biopsy was required.

6. Presence of at least 1 measurable lesion per modified Response Evaluation Criteria in Solid Tumours (modified RECIST version 1.1 [mRECIST v1.1])

- Brain lesions were considered as non-target lesions only

7. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1

8. Adequate bone marrow function within 14 days before randomization, defined as:

- Absolute neutrophil count ≥1.5 × 109/L (granulocyte colony-stimulating factor [G-CSF] administration was not allowed within 1 week prior to Screening assessment)
- Platelet count ≥100 × 109/L (platelet transfusion was not allowed within 1 week prior to Screening assessment)
- Hemoglobin level ≥9.0 g/dL (red blood cell transfusion was not allowed within 1 week prior to Screening assessment)

9. Adequate renal function within 14 days before randomization, defined as:

- Creatinine clearance (CrCL) ≥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); see Section 17.2 of the clinical study protocol (Appendix 16.1.1).

10. Adequate hepatic function within 14 days before randomization, defined as:

- Total bilirubin ≤1.5 × upper limit of normal (ULN) if no liver metastases or <3 × ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline, and
- Aspartate transaminase (AST)/alanine transaminase (ALT) ≤3 × ULN

11. 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 ≤1.5 × ULN

12. Female subjects of reproductive/childbearing potential were required to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and for at least 7 months after the last dose of study drug. Male subjects were required to inform all potential female partners that they were participating in a clinical trial of a drug that may cause birth defects. Male subjects were required to either avoid intercourse or to agree that they and/or any female partners of reproductive/ childbearing potential used a highly effective form of contraception during and upon completion of the study and for at least 4.5 months after the last dose of T-DXd or 4 months after the last dose of T-DM1.

13. Male subjects were not allowed to freeze or donate sperm throughout the study period beginning at Cycle 1 Day 1 and for at least 4.5 months after the last dose of T-DXd or 4 months after the last dose of T-DM1. Preservation of sperm was to be considered prior to enrollment in this study.

14. Female subjects were not allowed to donate ova or retrieve them for their own use from the time of Screening, throughout the study treatment period, and for at least 7 months after the last dose of study drug.

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

Exclusion Criteria

Subjects who met any of the following criteria were disqualified from entering the study:

1. Prior treatment with an anti-HER2 ADC (such as T-DM1) in the metastatic setting. Prior treatment in the adjuvant/neoadjuvant setting was allowed if progression of disease had not occurred within 12 months of end of adjuvant therapy.

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

a. History of myocardial infarction within 6 months before randomization

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

c. Troponin levels consistent with myocardial infarction, as defined according to the manufacturer of the troponin test, within 28 days prior to randomization

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

e. Left ventricular (LV) dysfunction <50% within 28 days prior to randomization

3. Had a history of (noninfectious) ILD/pneumonitis that required steroids, had current ILD/pneumonitis, or had suspected ILD/pneumonitis that could not be ruled out by imaging at Screening

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

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

5. Had a history of severe hypersensitivity reactions to either the drug substances or inactive ingredients in the drug product.

6. Had a history of severe hypersensitivity reactions to other mAbs.

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

8. Social, familial, or geographical factors that would have interfered with study participation or follow-up.

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

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

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

12. Unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade $\leq$1 or returned to baseline levels. Subjects with chronic Grade 2 toxicities (eg, Grade 2 chemotherapy-induced neuropathy) were eligible at the discretion of the investigator after consultation with the Sponsor Medical Monitor or designee.

13. Therapeutic radiation therapy or major surgery within 4 weeks before randomization or palliative stereotactic radiation therapy within 2 weeks before randomization

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

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

16. Was pregnant, breastfeeding, or planning to become pregnant.

17. Subject had an immediate family member among the study site personnel working for the investigator or Sponsor personnel.

18. Was otherwise considered inappropriate for the study by the investigator.

19. Prior participation in a study involving an ADC produced by Daiichi Sankyo.

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

Treatments

T-DXd for injection was administered iv at starting dose of 5.4 mg/kg Q3W.

The comparator drug, T-DM1, used for injection was a lyophilized powder in single-use vials. The starting dose of T-DM1 was 3.6 mg/kg Q3W.

Objectives

Primary Objective

The primary objective was to compare the PFS benefit of T-DXd to T-DM1 in subjects with HER2-positive, unresectable and/or metastatic BC previously treated with trastuzumab and taxane.

Key Secondary Objective

The key secondary objective was to compare the OS benefit of T-DXd to T-DM1.

Other Secondary Objectives

To evaluate efficacy of T-DXd compared to T-DM1 on the following:

- Confirmed ORR
- Duration of response (DoR)
- PFS based on investigator assessment

To further determine the pharmacokinetics (PK) of T-DXd

To further evaluate the safety of T-DXd compared to T-DM1

To evaluate the Health Economic and Outcomes Research (HEOR) endpoints for T-DXd compared to T-DM1.

Exploratory Objectives

To evaluate the efficacy of T-DXd compared to T-DM1 on clinical benefit rate (CBR) and PFS on the next line of therapy (PFS2)

To evaluate the potential biomarkers of response/resistance (eg, serum HER2-extracellular domain [HER2ECD])

To evaluate the exposure-response relationships for the efficacy and safety endpoints

Outcomes/endpoints

Primary Efficacy Endpoint: PFS Based on BICR

The primary efficacy endpoint was PFS based on BICR assessment using RECIST v1.1. PFS was defined as the time from the date of randomization to the earliest date of the first documented tumour progression or death due to any cause. If a subject was alive with no objective documentation of radiographic disease progression by the analysis data cut-off (DCO) date, PFS was censored at the last adequate tumour evaluation date before the DCO. Discontinuation associated with disease progression without supportive evidence satisfying RECIST v1.1 progression criteria were not considered as PFS events.

Secondary Efficacy Endpoints

The key secondary efficacy endpoint was OS, defined as the time from the date of randomization to the date of death due to any cause. If there was no death reported for a subject before the DCO for OS analysis, OS was censored at the date of last contact at which s/he was known to be alive.

Other secondary efficacy endpoints included:

- PFS based on investigator assessment (INV)
- Objective response rate (ORR) based on BICR and INV. ORR was defined as the proportion of subjects with best overall response of complete response (CR) or partial response (PR) according to RECIST v1.1 criteria. Confirmation of CR or PR was required.
- Duration of response (DoR) based on BICR and INV. DoR was defined as the time from the date of the first documented objective response (CR or PR) to the date of the first documentation of disease progression or death due to any cause for subjects with a confirmed CR or PR.

Exploratory Efficacy Endpoints

Exploratory efficacy endpoints included:

- Time to response (TTR) based on BICR. TTR was defined as the time from the date of randomization to the date of the first documentation of objective response (CR or PR). Time to response was measured for responding subjects only.
- Best percent change in the sum of diameters (SoD) of measurable tumours based on BICR.
- Clinical benefit rate (CBR) based on BICR. CBR was defined as the sum of the CR rate, PR rate, and the rate of stable disease lasting more than 6 months.
- PFS on next-line treatment (PFS2) based on INV. PFS2 was defined as the time from date of randomization to the first documented progression on next line therapy or death due to any cause, whichever occurred first. Next line therapy was defined as the first new systemic antineoplastic therapy initiated after discontinuation of study treatment regardless of the reason for end of treatment.

Health Economics and Outcome Research Endpoints

- The impact of treatment on HRQoL was assessed based on changes from baseline over time in the EORTC QLQ-C30 questionnaire, the EORTC QLQ-BR45 questionnaire, and the EQ-5D-5L questionnaire. Hospitalization-related endpoints were also evaluated (see DS8201-A-U302 CSR Appendix 16.1.1 Protocol Version 6.0 Section 10.1).

The primary patient reported outcome (PRO) variable of interest was the global health status/global quality of life (QoL) scale score of the EORTC QLQ-C30. Secondary PRO variables of interest were physical functioning, emotional functioning, and social functioning subscale scores of the EORTC QLQ-C30, the BC symptoms scale of the EORTC QLQ-BR45, and the index score of the EQ-5D-5L.

Sample size

The study is planned with a group sequential design, which includes an interim assessment for PFS using a Haybittle-Peto stopping boundary. Assuming a median PFS of 9.6 months in the T-DM1 arm based on the results of the EMILIA study, it is hypothesized that treatment with trastuzumab deruxtecan will result in a HR of 0.7, a 30% reduction in the hazard rate of PFS (disease progression or death) that would correspond to a 43% improvement in median PFS from 9.6 months in the T-DM1 arm to 13.7 months in the trastuzumab deruxtecan arm under the exponential model assumption.

A total of approximately 500 subjects will be randomized (250 subjects to trastuzumab deruxtecan and 250 subjects to T-DM1). An interim analysis that allows the study to declare superiority of the primary efficacy endpoint is planned after approximately 234 (70%) of the targeted PFS events are documented. The final PFS analysis will occur after approximately 335 PFS events have been documented, if superiority is not demonstrated at the interim analysis.

With 335 PFS events, the study will have approximately 90.4% power to detect an HR of 0.70 in PFS at an overall 2-sided significance level of 0.05 to reject the null hypothesis (HR =1) using a log-rank test and a 2-look group sequential design with Haybittle-Peto efficacy boundary.

OS will be compared between the 2 treatment groups, provided that the test of the primary endpoint PFS is statistically significant at either interim analysis or final analysis. Assuming a median OS of 29.9 months in the T-DM1 arm based on the results of the EMILIA study, it is hypothesized that treatment with trastuzumab deruxtecan will result in a hazard ratio of 0.7 in OS that would correspond to a 43% improvement in median OS from 29.9 months in the T-DM1 arm to 42.7 months in the trastuzumab deruxtecan arm under the exponential model assumption.

With 250 OS events, the study will have approximately 80% power (conditional on PFS being significant) to detect a HR of 0.70 in OS at an overall 2-sided significance level of 0.05 to reject the null hypothesis (HR =1) using a log-rank test and a 3-look group sequential design with Lan- DeMets alpha spending function with O'Brien-Fleming efficacy boundary2, 3. If the true hazard ratio is 0.7, it is estimated that approximately 96 (38.4%) and 153 (61.2%) of the targeted OS events will be documented at the timing of the 2 OS interim analyses (when PFS IA and FA are performed).

Randomisation

The target sample size of approximately 500 subjects was randomized in a 1:1 ratio into 2 treatment groups (DS-8201a versus T-DM1). Randomization was stratified by:

- Hormone receptor status (positive, negative)
- Prior treatment with pertuzumab (yes, no)
- History of visceral disease (yes, no)

Blinding (masking)

This is an open label study.

Statistical methods

Analysis Sets for efficacy

The full analysis set (FAS) will include all subjects randomized into the study. The full analysis set will be the primary analysis set for all efficacy analysis. Following the intent-to-treat principle, subjects will be analysed according to the treatments and strata they were assigned at randomization.

Primary efficacy endpoint PFS by BICR

The primary efficacy analysis will be the comparison of the distribution of PFS between the two treatment groups using a stratified log-rank test, with strata being the same as the randomization stratification factors from IXRS. The survival distribution of PFS will be estimated using the Kaplan-Meier (K-M) method for each treatment group and the results will be presented graphically by treatment group.

The treatment effect hazard ratio (HR) of PFS and its two-sided 95% CI will be estimated using stratified Cox proportional hazards regression model with the same stratification factors as the randomization stratification factors taken from IXRS.

Censoring rules for PFS

Event or censoring for primary PFS analyses will be as follows:

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) for no baseline or no post-baseline 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")

* 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.

Source SAP page 49/282

Supportive and sensitivity analyses for PFS

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

Sensitivity analyses of the primary efficacy endpoint will be performed to assess the impact of censoring rules used for the primary efficacy analysis:

- Using the BICR PFS data on the full analysis set, and including PFS events whenever they occurred, i.e. not censoring for missing 2 consecutive tumour assessments.
- Using the BICR PFS data on the full analysis set, but censoring for new anti-cancer therapy. In such cases, the censoring date would be the date of last evaluable tumour assessment prior to anti-cancer therapy (other than study drug).

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

Key secondary efficacy endpoint OS

Overall survival will be compared between the 2 treatment groups, using a stratified log-rank test stratified by the randomization stratification factors as recorded by IXRS. The survival distribution of OS will be estimated by Kaplan-Meier method and results will be presented graphically. The treatment effect hazard ratio (HR) and its 95%CI will be 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 is no death reported for a subject before the data cut-off for OS analysis, OS will be censored at the last contact date at which the subject is known to be alive.

Other efficacy endpoints: ORR

ORR (based on BICR and investigator assessment) will be 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 will be summarized and the 95%CI will be calculated using continuity correction. The Cochran-Mantel-Haenszel test stratified by the randomization stratification factors per IXRS will be used to compare ORR at two-sided significance level of 0.05.

As a supportive analysis, ORR will also be summarized by using the investigator review of tumour data.

Interim Analyses

An interim analysis of PFS for superiority is planned after approximately 234 PFS events per BICR (70% of target total of 335) have been documented. If the study continues to the final PFS analysis, the final PFS analysis will be performed when approximately 335 PFS events have been documented. A group sequential design, utilizing 2-look Haybittle-Peto stop boundary will be used to construct the efficacy stopping boundaries with an overall 2-sided significance level of 0.05.

Up to two interim analyses and a final analysis of OS are planned, provided PFS is statistically significant. The first OS interim analysis is planned at time of the PFS interim analysis, and the second OS interim analysis is planned at time of the final PFS analysis.

Approximately 96 and 153 of the planned 250 OS events (38.4% and 61.2% of information fractions) will be expected to be documented by time of the first and the second OS interim analyses, respectively. Final OS analysis is planned after approximately 250 OS events have been documented. A group sequential design, utilizing 3-look Lan-DeMets alpha spending function with O'Brien -Fleming stop boundary, will be used to construct the efficacy stopping boundaries with an overall 2-sided significance level of 0.05. OS will be hierarchically tested in the following way:

1. The first potential OS analysis will be at the time of the PFS interim analysis after 96 expected deaths. If PFS is statistically significant at this stage, OS will also be tested. If OS is not statistically significant at this stage, the second OS interim analysis will be planned after 153 deaths. If OS is not statistically significant at the second interim analysis, a final analysis is planned after 250 deaths have been recorded.

2. If PFS is not statistically significant at the time of the interim analysis of PFS, then OS will not be tested at the time of the interim analysis of PFS. If PFS is statistically significant at the time of the final analysis, then OS will also be tested. In terms of alpha spending, this analysis will be performed as if the first analysis of OS had occurred at the PFS interim analysis. If OS is not statistically significant at this stage, further testing will be carried out when a total of 250 deaths have been recorded.

3. If PFS is not statistically significant after the final analysis for PFS is performed, then OS will not be tested.

Multiple Comparisons/Multiplicity

There are two potential sources of multiplicity:

• Multiplicity arising due to testing two endpoints PFS and OS

• Multiplicity arising due to the group sequential design

To address the first multiplicity issue, the primary efficacy endpoint, PFS, and the key secondary efficacy endpoint, OS, will be tested hierarchically to maintain the overall two-sided type-I error rate to 0.05 or less.

A group sequential design, utilizing 2-look Haybittle-Peto boundary will be used to control the type I error rate for the primary efficacy analysis PFS. A group sequential design, utilizing 3-look Lan-DeMets alpha spending function with O'Brien-Fleming boundary, will be used to construct the efficacy stopping boundaries for OS.

The type I error rate will be controlled by using a Lan-DeMets alpha spending function with O'Brien-Fleming boundary for OS independent of the Haybittle-Peto boundary used for PFS. This guarantees

the protection of the overall significance level across the 2 hypotheses and the repeated testing of the OS hypotheses in the interim and the final analyses.

Revisions to the SAP

The original version of the SAP is dated 28 Sep 2020. The SAP was updated three times (latest version 24 June 2021) as summarised below:

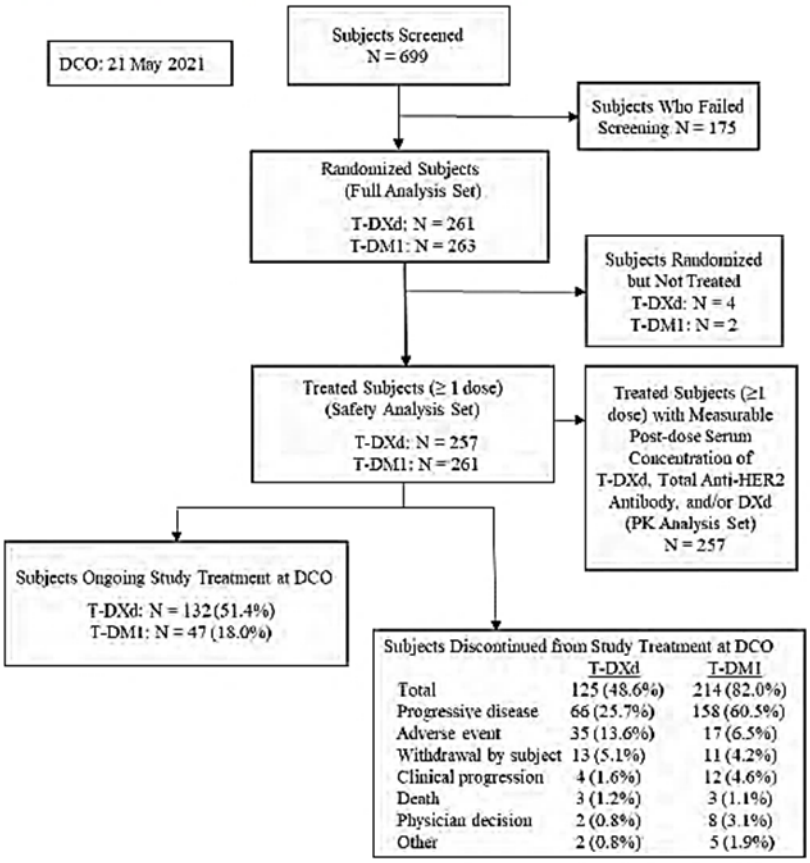
DOCUMENT REVISION HISTORY		
Document Version	**Document Date**	**Reason for Revision**
V1.0	28 SEP 2020	Original Version
V1.1	29 OCT 2020	Included details for analysis and analytic conventions
V1.2	29 APR 2021	Updated analytic conventions for PFS2, ECOG, and HEOR. Updated subgroup analyses. Added imputation rules for incomplete death date. Updated COVID-19 related analyses. Included summary of exposure-adjusted incidence rate of TEAEs and additional LVEF analysis. Deleted Biomarker endpoint examples that will not be analyzed Updated text for clarifications/consistency.
V1.3	24JUN2021	Updated text for clarifications/consistency Updated the details of BOR evaluation to incorporate the cases for subjects with tumor scan performed but no identified disease/lesion at baseline

An addendum was added 31 Aug 2021 to implement minor changes in the definition of the per protocol set and in the QoL variables.

Results

Participant flow

Figure 7.1: Subject Disposition (All Screened Subjects)



DCO = data cut-off; DXd = released drug; HER2 = human epidermal growth factor receptor 2
PK = pharmacokinetic; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan
Source: Table 14.1.1.1

Table 3. Reasons for Screen Failure in Study DS8201-A-U302

Parameter	Number of subjects
Screen failure	175
Failed to meet inclusion/exclusion criteria	153 (87.4)
Ex04 (Spinal cord compression or clinically active central nervous system metastases)	44 (25.1)
In05 (HER2-positive by central lab)	22 (12.6)
In06 (≥1 measurable lesion)	20 (11.4)
In03 (BC that was unresectable or metastatic, HER2-positive, and previously treated with trastuzumab and taxane)	17 (9.7)
Adverse event	1 (0.6)
Withdrawal by subject	8 (4.6)
Physician decision	3 (1.7)

Parameter	Number of subjects
Screen failure	175
Failed to meet inclusion/exclusion criteria	153 (87.4)
Ex04 (Spinal cord compression or clinically active central nervous system metastases)	44 (25.1)
In05 (HER2-positive by central lab)	22 (12.6)
In06 (≥1 measurable lesion)	20 (11.4)
In03 (BC that was unresectable or metastatic, HER2-positive, and previously treated with trastuzumab and taxane)	17 (9.7)
Lost to follow-up	1 (0.6)
Other	9 (5.1)

BC = breast cancer; HER2 = human epidermal growth factor receptor 2
Data cut-off date: 21 May 2021
Source: Appendix 1, Table 6a; Module 5.3.5.1 DS-8201-A-U302 CSR Listing 16.2.2.1

A total of 699 subjects were screened and 524 subjects were randomized. Six subjects were randomized but not treated: 2 subjects failed screening but were randomized in error (T-DXd and T-DM1), 2 subjects did not meet eligibility criteria (T-DXd), 1 was withdrawn by the investigator (T-DXd), and 1 subject withdrew consent (T-DM1).

Recruitment

From 9 August 2018 to the DCO date of 21 May 2021, 524 subjects were randomized at 118 study sites in 14 countries: Australia (14 subjects), Belgium (5), Brazil (63), Canada (2), China (65), France (38), Hong Kong (21), Italy (25), Japan (68), Republic of Korea (84), Spain (25), Taiwan (71), United Kingdom (11), United States (32). Median duration of follow (study duration) as of DCO of 21 May 2021: 15.9 months (range: 0, 32.7).

Conduct of the study

After the initial release (v1.0, 23 March 2018), the study protocol was amended 5 times. A summary of changes for all versions of the protocol is available in Appendix 16.1.1. Key changes in each amendment were as shown below.

Amendment 1 (Version 2.0, 20 Jun 2018, Before the First Subject Signed an ICF)

- Clarified that TEAEs were graded according to NCI CTCAE v5.0.
- Updated to indicate starting dose of T-DXd was to be 5.4 mg/kg.
- Clarified that if study treatment was delayed more than 4 weeks from the planned date of administration, the subject was to be withdrawn from study treatment (not withdrawn from the study).
- Updated text to reflect that the 160 mg per vial dosage was not being supplied.
- Updated the IV study drug infusion time after the initial infusion to a minimum of 30 minutes.
- Updated criteria for dose modification and definitions of grades to match NCICTCAE v5.0.
- Clarified language regarding timing of obtaining signed and dated written consent.

- Deleted requirement for HEOR assessments at Screening.
- Specified that a positive urine pregnancy test result must have been confirmed immediately using a serum test, with a confirmed negative test result within 72 hours prior to drug administration.
- Clarified that a subject's first dose/Cycle 1 Day 1 should have occurred within 7 days after the date the subject was randomized.
- Added a PK blood sample to be collected for subjects with suspected ILD/pneumonitis, if feasible.
- Revised to reflect mRECIST v1.1 criteria and overall response table used in the Independent Review Charter.

Amendment 2 (Version 3.0, 08 Mar 2019, Before the First Subject Signed an ICF)

- Clarified the primary objective.
- Updated the secondary efficacy objective and endpoint of CBR to be an exploratory objective.
- Updated the secondary objective and endpoint to be confirmed ORR.
- Updated the screening period assessment from within 14 days of starting study treatment to within 14 days before randomization.
- Added text specifying ECGs would be performed prior to blood draws.
- Updated ECGs to allow a 3-day window before the first dose in each Cycle.
- Added the HEOR outcomes, EORTC QLQ-C30 and EORTC QLQ-BR45, and EQ-5D-5L questionnaires to procedures completed at Cycle 2 Day 1 and clarified that HEOR outcomes would be assessed every 2 cycles after Cycle 4.
- Clarified that secondary analyses would be performed at the time of the primary PFS analysis.
- Added confirmation of complete response and partial response
- Added AESI wording to reflect the latest T-DXd safety profile.
- Included enhanced data collection details for LV dysfunction.
- Clarified that the AESIs ILD/pneumonitis targeted questionnaire was to be collected for only the T-DM1 arm and clarified that AESI infusion-related reaction information was to be collected through narrative forms.

Amendment 3 (Version 4.0, 26 Apr 2019, During the Course of the Study)

- Amended the ILD monitoring plan to include that pulmonary function tests and pulse oximetry should be conducted, and arterial blood gas examinations should be conducted as clinically indicated, when evaluating potential ILD events.

Amendment 4 (Version 5.0, 23 Apr 2020, During the Course of the Study)

- Updated the exploratory endpoints to remove duration of SD and time to hospitalization.
- Updated the risks and benefits for study subjects to reflect the current Investigator Brochure.
- Updated Inclusion Criterion #11 and blood chemistry coagulation tests to specify either partial thromboplastin or activated partial thromboplastin time.

- Added Inclusion Criterion #15 to include a washout period for chloroquine and hydroxychloroquine.
- Prohibited the use of chloroquine and hydroxychloroquine during the treatment period.
- 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.
- Updated the guidelines on monitoring and management of ILD.
- Specified the analysis of the NAb assay for samples confirmed to be ADA positive.
- Updated AESI language to remove QT prolongation.
- Clarified the PTs that are submitted to the ILD Adjudication Committee.
- Removed infusion-related reaction from the AESI section.
- Added an interim analysis for PFS and additional OS analyses.
- Updated the secondary objective/endpoint of OS to be a key secondary efficacy objective/endpoint.
- Removed the Response Evaluable Analysis Set.
- Clarified the efficacy exploratory subgroup analyses.

Amendment 5 (Version 6.0, 25 Sep 2020, During the Course of the Study)

- Updated the exploratory objectives and exploratory efficacy endpoints subsections.
- Added COVID-19 serology testing.
- Added conditions for collecting PK samples from subjects treated with chloroquine or hydroxychloroquine.
- Added an exploratory endpoint of PFS2 based on investigator assessment.
- Updated the efficacy boundary for the interim analysis for PFS.

In the table below, the number of subjects who consented to each protocol version are presented.

Table. Protocol Version that Subjects Signed Informed Consent Under (Full Analysis Set)

Protocol version	**T-DXd (N = 261)**	**T-DM1 (N = 263)**	**Total (N = 524)**
	n (%)		
1.0	2 (0.8)	1 (0.4)	3 (0.6)
2.0	167 (64.0)	167 (63.5)	334 (63.7)
3.0	3 (1.1)	1 (0.4)	4 (0.8)
4.0	88 (33.7)	94 (35.7)	182 (34.7)
5.0	1 (0.4)	0	1 (0.2)

T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan

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, 4 subjects were temporarily transferred to another existing study site that was different from the site at which the subject originally enrolled. In such cases, the transfer was initiated by the Sponsor. Study activities, including drug dispensing and dosing for each subject, were performed per protocol at the transfer site. All documentation and data entry, however, was maintained by the site at which the subject was originally enrolled, and the investigator at the site at which the subject was originally enrolled maintained oversight of the subject throughout the subject's participation in this study, including during the transfer period. All 4 transferred subjects returned to the site at which they originally enrolled when the facility reopened for subject visits.

Modification of study procedures as a result of the COVID-19 pandemic was generally not necessary. The following modifications were permitted by the protocol:

- Screening and on-treatment safety laboratory tests were performed locally and the data were transmitted to the Sponsor and retained in the site's medical record.
- ECGs were performed and read locally, with values recorded in the eCRF.
- Tumour imaging assessments were performed locally and read locally and results were recorded in the eCRF.
- PRO were administered on paper (and, in some cases, via phone) and results were recorded on the eCRF.
- Dose interruptions were limited by protocol to 49 days after last dose date, unless permission for a subject to remain on study was granted. Because of pandemic-related disruptions, some sites were closed to subject access, leading to delays in dosing. A dosing extension request form was created to document such delays, which required sites to document the nature of the disruption to access as well as proof of continued benefit from treatment. Seven subjects required such dosing extensions during the course of the study, with a maximum dosing extension of 25 days.

Changes in Monitoring/Oversight

Risk-based/remote monitoring activities initiated at the beginning of the study continued during the COVID-19 pandemic; however, 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 database lock, site data verification could not be completed in 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 data review and data cleaning activities were conducted over the course of the study.

Table 7.8: Major Protocol Deviations (Full Analysis Set)

Category of Deviation	Number (%) of Subjects		
	T-DXd (N = 261)	T-DM1 (N = 263)	Total (N = 524)
Subjects with any major protocol deviation	26 (10.0)	22 (8.4)	48 (9.2)
Related to COVID-19	1 (0.4)	1 (0.4)	2 (0.4)
Study procedures criteria	9 (3.4)	2 (0.8)	11 (2.1)
Related to COVID-19	1 (0.4)	1 (0.4)	2 (0.4)
Investigational product compliance	6 (2.3)	1 (0.4)	7 (1.3)
Eligibility criteria	5 (1.9)	8 (3.0)	13 (2.5)
Informed consent	3 (1.1)	6 (2.3)	9 (1.7)
Concomitant medication	2 (0.8)	1 (0.4)	3 (0.6)
Laboratory assessment criteria (results out of window)	1 (0.4)	2 (0.8)	3 (0.6)
Efficacy criteria	1 (0.4)	0	1 (0.2)
Serious adverse event reporting	0	3 (1.1)	3 (0.6)

COVID-19 = coronavirus disease 2019; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan
For each category and deviation, subjects were counted only once, regardless of the number of events in that category of deviation.
Results are presented in descending order of frequency in the T-DXd arm.
Data cut-off date: 21 May 2021
Source: Table 14.1.1.2

Baseline data

Table 3.2 Demographic and Baseline Disease Characteristics (Full Analysis Set)

Parameter	T-DXd (N=261)	T-DM1 (N=263)
Age (years)		
Mean (Std Dev)	54.5 (11.11)	54.2 (11.84)
Median (Min, Max)	54.3 (27.9, 83.1)	54.2 (20.2, 83.0)
Age group (years)		
<65	212 (81.2)	206 (78.3)
≥65	49 (18.8)	57 (21.7)
<75	253 (96.9)	255 (97.0)
≥75	8 (3.1)	8 (3.0)
Sex		
Female	260 (99.6)	262 (99.6)
Male	1 (0.4)	1 (0.4)
Region[a]		
Asia	149 (57.1)	160 (60.8)
Europe	54 (20.7)	50 (19.0)
North America	17 (6.5)	17 (6.5)
Rest of the world	41 (15.7)	36 (13.7)

Parameter	T-DXd (N=261)	T-DM1 (N=263)
Line of prior systemic therapy in metastatic setting		
0	1 (0.4)	1 (0.4)
1	108 (41.4)	102 (38.8)
2	60 (23.0)	64 (24.3)
3	44 (16.9)	45 (17.1)
4	15 (5.7)	23 (8.7)
≥5	33 (12.6)	28 (10.6)
Stratification factors[b]		
Hormone receptors[b]		
Positive	131 (50.2)	134 (51.0)
Negative	130 (49.8)	129 (49.0)
Prior treatment with pertuzumab[b]		
Yes	156 (59.8)	158 (60.1)
No	105 (40.2)	105 (39.9)
Prior history of visceral disease[b]		
Yes	184 (70.5)	185 (70.3)
No	77 (29.5)	78 (29.7)
Reported History of CNS metastases		
Yes	62 (23.8)	52 (19.8)
No	199 (76.2)	211 (80.2)
HER2 expression (IHC) by central laboratory		
0	0	0
1+	1 (0.4)	0
2+	25 (9.6)	30 (11.4)
3+	234 (89.7)	232 (88.2)
Not evaluable	1 (0.4)	1 (0.4)
Not examined	0	0
HER2 gene amplification (ISH) - Central		
Amplified	24 (9.2)	29 (11.0)
Non-Amplified	2 (0.8)	2 (0.8)
Not Evaluable	0	0
Missing	235 (90.0)	232 (88.2)
Subgroups		
Hormone receptor - derived, based on local laboratory[c]		
Positive	133 (51.0)	139 (52.9)
Negative	126 (48.3)	122 (46.4)

Parameter	T-DXd (N=261)	T-DM1 (N=263)
Indeterminate	1 (0.4)	1 (0.4)
Missing	1 (0.4)	1 (0.4)
Estrogen receptors (local laboratory)		
Positive	129 (49.4)	132 (50.2)
Negative	130 (49.8)	128 (48.7)
Indeterminate	1 (0.4)	2 (0.8)
Missing	1 (0.4)	1 (0.4)
Progesterone receptors (local laboratory)		
Positive	81 (31.0)	92 (35.0)
Negative	177 (67.8)	168 (63.9)
Indeterminate	2 (0.8)	1 (0.4)
Missing	1 (0.4)	2 (0.8)
Prior pertuzumab - derived[d]		
Yes	162 (62.1)	158 (60.1)
No	99 (37.9)	105 (39.9)
Lines of prior systemic therapy excluding hormone therapies		
<3	188 (72.0)	191 (72.6)
≥3	73 (28.0)	72 (27.4)
Baseline visceral disease[e]		
Yes	195 (74.7)	189 (71.9)
No	66 (25.3)	74 (28.1)
Baseline CNS metastases		
Yes	43 (16.5)	39 (14.8)
No	218 (83.5)	224 (85.2)
Renal function at baseline[f]		
Within normal range[g]	134 (51.3)	131 (49.8)
Mild impairment[g]	96 (36.8)	105 (39.9)
Moderate impairment[g]	27 (10.3)	25 (9.5)
Severe impairment[g]	0	0
End stage renal disease[g]	0	0
Missing	4 (1.5)	2 (0.8)
Hepatic function at baseline		
Within normal range	208 (79.7)	212 (80.6)
Mild impairment	49 (18.8)	49 (18.6)
Moderate impairment	0	0
Severe impairment	0	0

Parameter	T-DXd (N=261)	T-DM1 (N=263)
Missing	4 (1.5)	2 (0.8)
ECOG PS		
0	154 (59.0)	175 (66.5)
1	106 (40.6)	87 (33.1)
Missing	1 (0.4)	1 (0.4)

CrCL = creatinine clearance; 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; IXRS = interactive web/voice response system; Max = maximum; Min = minimum; SAP = statistical analysis plan; Std Dev = standard deviation; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan

[a] Asia = China, Hong Kong, Japan, Republic of Korea, Taiwan; Europe = Belgium, France, Italy, Spain, United Kingdom; North America = United States, Canada; Rest of the World = Australia, Brazil.

[b] Based on IXRS

[c] Derived from locally determined estrogen and progesterone receptors. Hormone receptor: positive = estrogen receptor-positive and/or progesterone receptor-positive; negative = estrogen receptor-negative and progesterone receptor-negative; indeterminate = (neither estrogen receptor- nor progesterone receptor-positive) and (estrogen receptor-indeterminate or progesterone receptor-indeterminate) based on estrogen receptors and progesterone receptors reported from EDC.

[d] Derived based on prior cancer systemic therapy.

[e] Baseline visceral disease was determined with any target or non-target tumour in the lesion locations specified in the SAP. Baseline was defined as the last non-missing value taken before the first dose of study drug.

[f] Within normal range, mild, and moderate impairment are presented for subgroup analyses.

[g] Within normal range = CrCL ≥90 mL/min; mild impairment = CrCL ≥60 mL/min, <90 mL/min; moderate impairment = CrCL ≥30 mL/min, <60 mL/min; severe impairment (CrCL ≥15 mL/min, <30 mL/min); end stage = CrCL <15 mL/min. (see DS8201-A-U302 Appendix 16.1.9 SAP Section 7.2.1.5). No subject had end-stage renal disease.

Data cut-off date: 21 May 2021

Source: DS8201-A-U302 CSR Table 14.1.2.1.1 and Table 14.1.3.2

Table 7.5: Breast Cancer History (Full Analysis Set)

Parameter	Number (%) of Subjects		
	T-DXd (N = 261)	T-DM1 (N = 263)	Total (N = 524)
Time from initial histological diagnosis to study treatment (months)			
n	257	261	518
Mean (std dev)	59.5 (56.52)	57.3 (55.79)	58.4 (56.11)
Median	38.8	40.7	39.6
Minimum, Maximum	4, 346	5, 325	4, 346
HER2 expression (IHC) - Local			
0	1 (0.4)	0	1 (0.2)
1+	3 (1.1)	1 (0.4)	4 (0.8)
2+	30 (11.5)	39 (14.8)	69 (13.2)
3+	223 (85.4)	221 (84.0)	444 (84.7)
Not evaluable	1 (0.4)	0	1 (0.2)
Not examined	1 (0.4)	1 (0.4)	2 (0.4)
HER2 gene amplification (ISH) - Local			
Positive	80 (30.7)	79 (30.0)	159 (30.3)
Equivocal	0	3 (1.1)	3 (0.6)
Negative	0	3 (1.1)	3 (0.6)
Examined but not evaluable	1 (0.4)	0	1 (0.2)

HER2 = human epidermal growth factor receptor 2; IHC = immunochemistry; ISH = in situ hybridization; std dev = standard deviation; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan

Data cut-off date: 21 May 2021

Source: Table 14.1.3.1

Table 7.6: Prior Breast Cancer Systemic Therapy (Full Analysis Set)

Parameter	T-DXd (N = 261)	T-DM1 (N = 263)	Total (N = 524)
Any prior systemic cancer therapy, n (%)			
Yes	260 (99.6)	262 (99.6)	522 (99.6)
No [a]	1 (0.4)	1 (0.4)	2 (0.4)
Number of regimens, n (%)			
0 [a]	1 (0.4)	1 (0.4)	2 (0.4)
1	63 (24.1)	63 (24.0)	126 (24.0)
2	50 (19.2)	62 (23.6)	112 (21.4)
3	51 (19.5)	42 (16.0)	93 (17.7)
4	33 (12.6)	31 (11.8)	64 (12.2)
≥5	63 (24.1)	64 (24.3)	127 (24.2)
n	261	263	524
Mean (std dev)	3.3 (2.33)	3.2 (2.32)	3.3 (2.33)
Median	3.0	3.0	3.0
Minimum, Maximum	0, 17	0, 15	0, 17
Lines of prior systemic therapy in metastatic setting, n (%)			
0 [a]	1 (0.4)	1 (0.4)	2 (0.4)
1	108 (41.4)	102 (38.8)	210 (40.1)
2	60 (23.0)	64 (24.3)	124 (23.7)
3	44 (16.9)	45 (17.1)	89 (17.0)
4	15 (5.7)	23 (8.7)	38 (7.3)
≥5	33 (12.6)	28 (10.6)	61 (11.6)

Parameter	T-DXd (N = 261)	T-DM1 (N = 263)	Total (N = 524)
n	261	263	524
Mean (std dev)	2.4 (1.95)	2.5 (2.04)	2.5 (1.99)
Median	2.0	2.0	2.0
Minimum, Maximum	0, 16	0, 15	0, 16
Intent of prior breast cancer therapy in metastatic setting,[b] n (%)			
Neoadjuvant	73 (28.0)	65 (24.7)	138 (26.3)
Adjuvant	123 (47.1)	120 (45.6)	243 (46.4)
Locally advanced	19 (7.3)	19 (7.2)	38 (7.3)
Metastatic	233 (89.3)	224 (85.2)	457 (87.2)
Preventive	1 (0.4)	6 (2.3)	7 (1.3)
Maintenance	27 (10.3)	30 (11.4)	57 (10.9)
Other	9 (3.4)	10 (3.8)	19 (3.6)
Intent of prior cancer systemic therapy: trastuzumab,[c,d] n (%)			
Neoadjuvant	45 (17.3)	45 (17.2)	90 (17.2)
Adjuvant	78 (30.0)	77 (29.4)	155 (29.7)
Locally advanced	16 (6.2)	14 (5.3)	30 (5.7)
Metastatic	222 (85.4)	218 (83.2)	440 (84.3)
Preventive	0	0	0
Maintenance	17 (6.5)	16 (6.1)	33 (6.3)
Other	2 (0.8)	3 (1.1)	5 (1.0)

std dev = standard deviation; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan
[a] The prior cancer systemic therapy case report form pages were not completed for 2 subjects who were mistakenly randomized but not treated.
[b] Subjects may have been treated with more than 1 type of therapy.
[c] Percentages are based on the number of subjects with the corresponding prior cancer systemic therapy.
[d] Percentages are based on the number of subjects who received trastuzumab as prior cancer systemic therapy.
Data cut-off date: 21 May 2021
Source: Table 14.1.3.2

Table 7.7: Prior Breast Cancer Systemic Therapy in the Metastatic Setting – Not Including Hormone Therapy (Full Analysis Set)

Parameter	T-DXd (N = 261)	T-DM1 (N = 263)	Total (N = 524)
Lines of prior systemic therapy in metastatic setting, not including hormone therapy, n (%)			
0	2 (0.8)	3 (1.1)	5 (1.0)
1	130 (49.8)	123 (46.8)	253 (48.3)
2	56 (21.5)	65 (24.7)	121 (23.1)
3	35 (13.4)	35 (13.3)	70 (13.4)
4	15 (5.7)	19 (7.2)	34 (6.5)
≥5	23 (8.8)	18 (6.8)	41 (7.8)
Mean (std dev)	2.2 (1.85)	2.1 (1.69)	2.1 (1.77)
Median	1.0	2.0	2.0
Minimum, Maximum	0, 16	0, 14	0, 16

std dev = standard deviation; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan
Data cut-off date: 21 May 2021
Source: Module 5.3.5.3, Table 1

Numbers analysed

The Applicant presents data from 524 HER2-positive breast cancer patients from the pivotal study U302: 261 patients in the T-DXd arm and 263 patients in the T-DM1 arm.

Outcomes and estimation

Primary endpoint – PFS by BICR

Table 3.3 Progression-free Survival per Blinded Independent Central Review (Full Analysis Set)

Parameter	T-DXd (N=261)	T-DM1 (N=263)
Subjects (%) with events	87 (33.3)	158 (60.1)
Progressive disease	80 (30.7)	152 (57.8)
Death	7 (2.7)	6 (2.3)
Subjects (%) without events (censored)	174 (66.7)	105 (39.9)
No baseline evaluable tumour assessment	1 (0.4)	0
No post-baseline tumour assessment	3 (1.1)	7 (2.7)
Event after missing 2 consecutive assessments	8 (3.1)	12 (4.6)
Lost to follow-up	0	0
Withdrew consent	7 (2.7)	6 (2.3)
Ongoing without event	128 (49.0)	49 (18.6)
Adequate tumour assessment no longer available	27 (10.3)	31 (11.8)
Median PFS (95% CI), months[a]	NE (18.5, NE)	6.8 (5.6, 8.2)
Stratified log-rank test *P*-value[b]	<0.000001[c]	
Stratified Cox proportional hazards model[b]		
Hazard ratio (95% CI)	0.2840 (0.2165, 0.3727)	

CI = confidence interval; HR = hazard ratio; IXRS = interactive web/voice response system; NE = not estimable; PFS = progression-free survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan

PFS was defined as the time from the date of randomization to the date of the first radiographic disease progression or death due to any cause, whichever came first.

[a] Median PFS is from Kaplan-Meier analysis. Confidence interval for median is computed using the Brookmeyer-Crowley method.

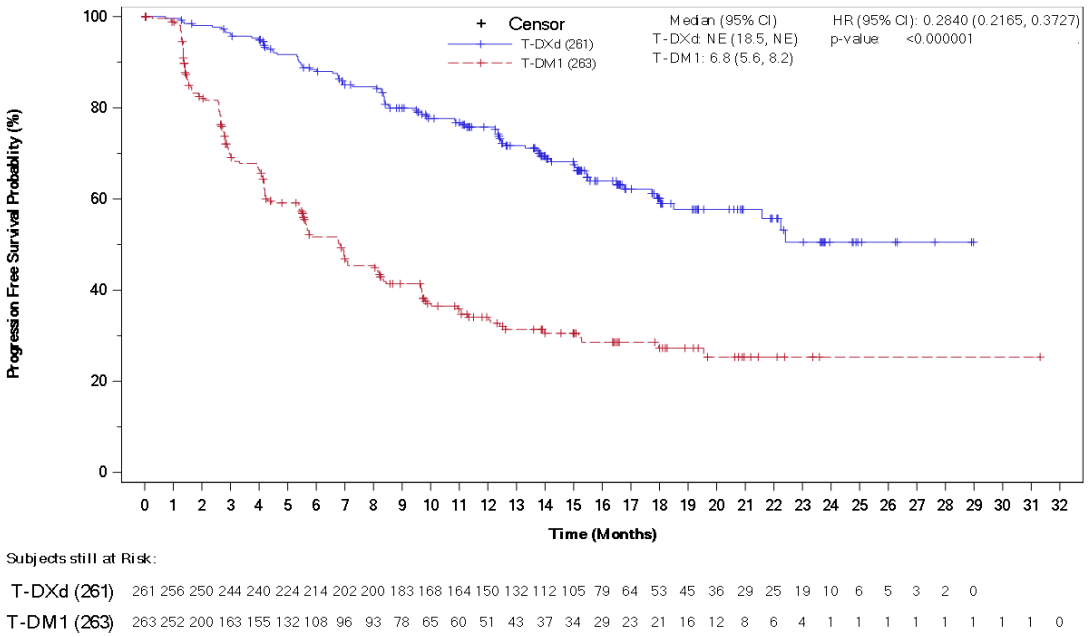
[b] Two-sided *P*-value from stratified log-rank test and HR and 95% CI from stratified Cox proportional hazards model with stratification factors: hormone receptor status, prior treatment with pertuzumab, and history of visceral disease, as defined by IXRS.

[c] The actual *P*-value is 7.8×10^{-22}.

Data cut-off date: 21 May 2021

Source: DS8201-A-U302 CSR Table 14.2.1.1

Figure 3.1 Kaplan-Meier Plot of Progression-free Survival by Blinded Independent Central Review (Full Analysis Set)



CI = confidence interval; HR = hazard ratio; NE = not estimable; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan
Stratified Cox proportional hazards model for hazard ratio and stratified log-rank test for the *P*-value.
The actual *P*-value is 7.8×10^{-22}.
Data cut-off date: 21 May 2021
Source: DS8201-A-U302 CSR Figure 14.2.1.1

Table 3.4 Overview of Progression-free Survival per Blinded Independent Central Review Using Different Analysis Methods

Type of Analysis	Number of Subjects With Events	Median PFS (95% CI), month	Hazard Ratio (95% CI)	Log-rank test *P*-value (2-sided)
Full Analysis Set				
T-DXd	87/261	NE (18.5, NE)	0.2840 (0.2165, 0.3727)	<0.000001[a]
T-DM1	158/263	6.8 (5.6, 8.2)		
Unstratified log-rank and unstratified Cox proportional hazard model				
T-DXd	87/261	NE (18.5, NE)	0.3052 (0.2341, 0.3980)	<0.000001[b]
T-DM1	158/263	6.8 (5.6, 8.2)		
Per-protocol Analysis Set				
T-DXd	86/253	NE (18.5, NE)	0.2798 (0.2128, 0.3679)	<0.000001[c]
T-DM1	156/249	6.8 (5.5, 8.1)		
Effect of not censoring for missing 2 consecutive assessments				
T-DXd	95/261	22.2 (17.9, NE)	0.2946 (0.2273, 0.3820)	<0.000001[d]
T-DM1	171/263	6.9 (5.6, 8.3)		
Effect of censoring for new anti-cancer therapy[e]				
T-DXd	83/261	NE (21.6, NE)	0.2684 (0.2038, 0.3535)	<0.000001[f]
T-DM1	156/263	6.8 (5.5, 8.1)		
Effect of back-dating PFS[g]				
T-DXd	95/261	22.2 (18.0, NE)	0.2881 (0.2222, 0.3736)	<0.000001[h]
T-DM1	171/263	5.8 (5.4, 7.0)		

CI = confidence interval; NE = not estimable; PFS = progression-free survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan
[a] The actual *P*-value is 7.8×10^{-22}.
[b] The actual *P*-value is 2.5×10^{-20}.
[c] The actual *P*-value is 4.6×10^{-22}.
[d] The actual *P*-value is 2.3×10^{-22}.
[e] For subjects who received new anti-cancer therapy, the censoring date was the date of the last evaluable tumour assessment prior to start of anti-cancer therapy.
[f] The actual *P*-value is 2.5×10^{-23}.
[g] PFS event time was backdated in the case that PFS event occurred after the subject missed 1 or more tumour assessments. In such cases, the PFS event date was considered to be 6 weeks after the last evaluable tumour assessment that occurred prior to progression/death.
[h] The actual *P*-value is 4.6×10^{-23}.
Data cut-off date: 21 May 2021
Source: DS8201-A-U302 CSR Tables 14.2.1.1, 14.2.1.2.1, 14.2.1.2.2, 14.2.1.2.3, 14.2.1.2.4, and 14.2.1.2.8

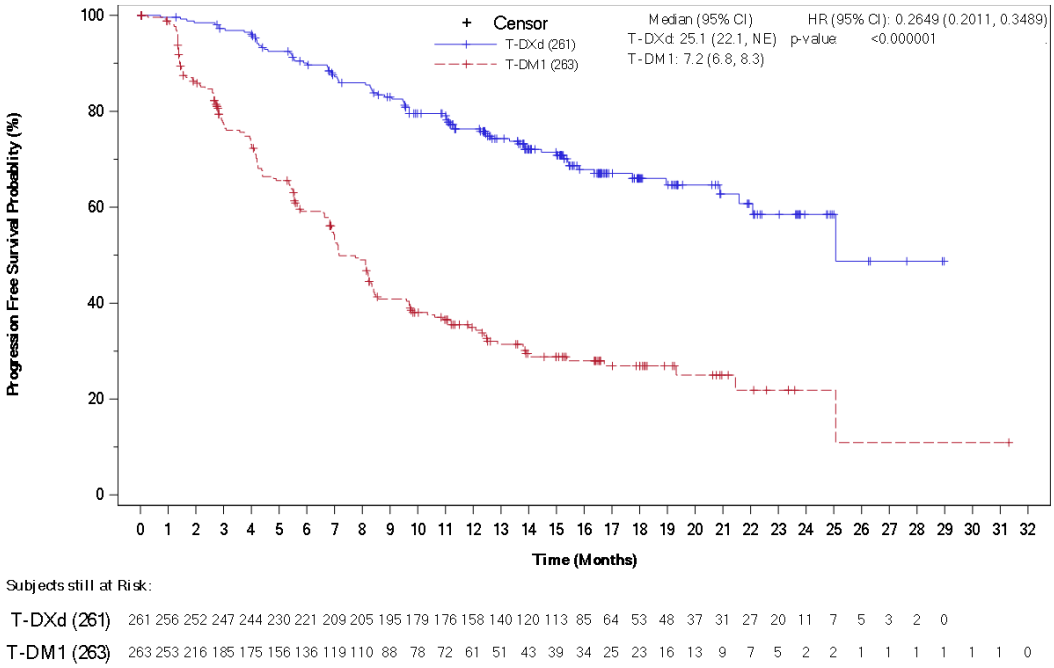
Secondary endpoint – PFS by INV

Table 3.5 Progression-free Survival per Investigator Assessment (Full Analysis Set)

Parameter	T-DXd (N=261)	T-DM1 (N=263)
Subjects (%) with events	78 (29.9)	168 (63.9)
Progressive disease	71 (27.2)	161 (61.2)
Death	7 (2.7)	7 (2.7)
Subjects (%) without events (censored)	183 (70.1)	95 (36.1)
No baseline evaluable tumour assessment	1 (0.4)	1 (0.4)
No post-baseline tumour assessment	3 (1.1)	4 (1.5)
Event after missing 2 consecutive assessments	9 (3.4)	6 (2.3)
Lost to follow-up	0	0
Withdrew consent	7 (2.7)	7 (2.7)
Ongoing without event	139 (53.3)	56 (21.3)
Adequate tumour assessment no longer available	24 (9.2)	21 (8.0)
Median PFS (95% CI), months[a]	25.1 (22.1, NE)	7.2 (6.8, 8.3)
Stratified log-rank test p-value[b]	<0.000001[c]	
Stratified Cox proportional hazards model[b]		
Hazard ratio (95% CI)	0.2649 (0.2011, 0.3489)	

CI = confidence interval; HR = hazard ratio; IXRS = interactive web/voice response system; NE = not estimable; PFS = progression-free survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan
PFS was defined as the time from the date of randomization to the date of the first radiographic disease progression or death due to any cause, whichever came first.
[a] Median PFS is from Kaplan-Meier analysis. Confidence interval for median is computed using the Brookmeyer-Crowley method.
[b] Two-sided *P*-value from stratified log-rank test and HR and 95% CI from stratified Cox proportional hazards model with stratification factors: hormone receptor status, prior treatment with pertuzumab, and history of visceral disease, as defined by IXRS.
[c] The actual *P*-value is 6.5×10^{-24}.
Data cut-off date: 21 May 2021
Source: DS8201-A-U302 CSR Table 14.2.1.2.7

Figure 3.2 Kaplan-Meier Plot of Progression-free Survival by Investigator Assessment (Full Analysis Set)



CI = confidence interval; HR = hazard ratio; NE = not estimable; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan
Stratified Cox proportional hazards model for hazard ratio and stratified log-rank test for the *P*-value.
The actual P-value is 6.5×10^{-24}.
Data cut-off: 21 May 2021
Source: DS8201-A-U302 CSR Figure 14.2.2.4

Table 3.6 Concordance Analysis of Progression-free Survival Between Investigator and Blinded Independent Central Review Assessments (Full Analysis Set)

Treatment Arm	PFS Result by INV	Number (%) of Subjects With PFS Result by BICR			Total	Concordance Rate
		Death	PD	Censored		
T-DXd (N = 261)	Death	6 (85.7)	1 (14.3)	0	7	81.99
	PD	1 (1.4)	51 (71.8)	19 (26.8)	71	
	Censored	0	28 (15.3)	155 (84.7)	183	
	Total	7	80	174	261	
T-DM1 (N = 263)	Death	6 (85.7)	1 (14.3)	0	7	78.71
	PD	0	128 (79.5)	33 (20.5)	161	
	Censored	0	23 (24.2)	72 (75.8)	95	
	Total	6	152	105	263	

BICR = blinded independent central review; INV = investigator; PD = progressive disease; PFS = progression-free survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan
Percentages were based on row total.
Concordance (%) rate between BICR-assessed and investigator-assessed PFS status (event vs. censored) was calculated as 100 × (N – [subjects with discord between sources for event vs. censored]) / N.
Data cut-off date: 21 May 2021
Source: DS8201-A-U302 CSR Table 14.2.5.1

A sensitivity analysis was performed in which subjects with both BICR- and investigator-assessed PFS as events were counted as events, with the earliest of the two being defined as the event. Results of this sensitivity analysis showed a PFS HR of 0.28 (95%CI: 0.22, 0.36).

Table xxx. Sensitivity Analysis of Progression-free Survival Based on BICR – Set 1 (Full Analysis Set)

Progression-free Survival Analyses	T-DXd (N = 261)	T-DM1 (N = 263)
Subjects with events, n (%)		
Progressive disease including imputed PD	100 (38.3)	185 (70.3)
Death	6 (2.3)	6 (2.3)
Median PFS, months (95% CI)[a]	21.6 (16.5, NE)	5.5 (4.2, 6.8)
Stratified Cox hazard ratio (95% CI)[b]	0.2773 (0.2166, 0.3550)	

BICR = Blinded Independent Central Review; CI = confidence interval; IXRS = Interactive Web/Voice Response System; KM = Kaplan-Meier; PD = progressive disease; PFS = progression-free survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan

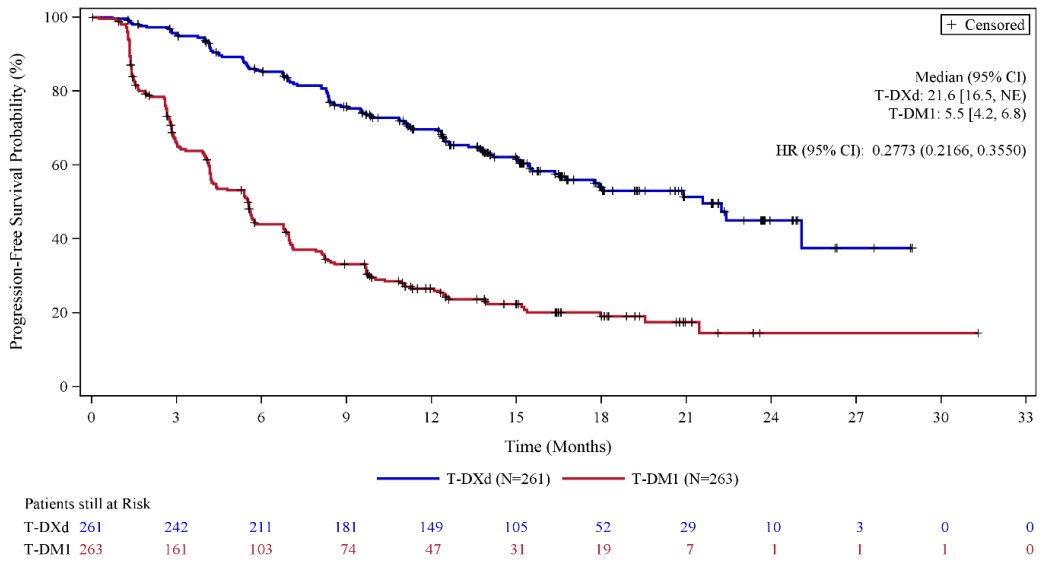
Data cut-off date: 21 May 2021

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

[b] Hazard ratio and 95% CI are from the stratified Cox proportional hazards model with stratification factors: hormone receptor status, prior treatment with pertuzumab, and history of visceral disease, as defined by the IXRS.

PFS was 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 came first. Subjects who had BICR- and investigator-assessed PFS events were counted as events. The event date was the BICR-assessed PFS date or the investigator-assessed PFS date, whichever occurred first. Source: Appendix 1 Table 4

Figure xxx. Kaplan-Meier Plot of Sensitivity Analysis of Progression-free Survival Based on BICR – Set 1 (Full Analysis Set)



BICR = Blinded Independent Central Review; CI = confidence interval; HR = hazard ratio; PFS = progression-free survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan

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. Subjects who had BICR- and investigator-assessed PFS events are counted as events, and the event date is the BICR-assessed PFS date or the investigator-assessed PFS date whichever occurs first.

Stratified Cox proportional hazard model for hazard ratio. Source: Appendix 1 Figure 1

Secondary endpoint – OS

Table 3.7 Overall Survival (Full Analysis Set)

Parameter	T-DXd (N=261)	T-DM1 (N=263)
Subjects with events (deaths), n (%)	33 (12.6)	53 (20.2)

Parameter	T-DXd (N=261)	T-DM1 (N=263)
Subjects without events (censored), n (%)	228 (87.4)	210 (79.8)
Alive	215 (82.4)	192 (73.0)
Lost to follow-up	13 (5.0)	18 (6.8)
Median OS (months)[a]	NE	NE
95% CI	(NE, NE)	(NE, NE)
Stratified log-rank *P*-value[b]	0.007172	
Stratified Cox hazards ratio (95% CI)[b]	0.5546 (0.3587, 0.8576)	
OS rate at 3 months[c]	99.2	96.9
95% CI	(96.9, 99.8)	(93.9, 98.4)
OS rate at 6 months[c]	98.4	94.5
95% CI	(95.9, 99.4)	(90.9, 96.7)
OS rate at 9 months[c]	96.1	91.3
95% CI	(92.8, 97.9)	(87.1, 94.2)
OS rate at 12 months[c]	94.1	85.9
95% CI	(90.3, 96.4)	(80.9, 89.7)
OS rate at 18 months[c]	85.7	76.5
95% CI	(79.8, 90.0)	(69.8, 81.8)
OS rate at 24 months[c]	80.8	73.7
95% CI	(73.0, 86.6)	(66.1, 79.9)

CI = confidence interval; DCO = data cut-off; IXRS = interactive web/voice response system; OS = overall survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan

Overall survival 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.

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

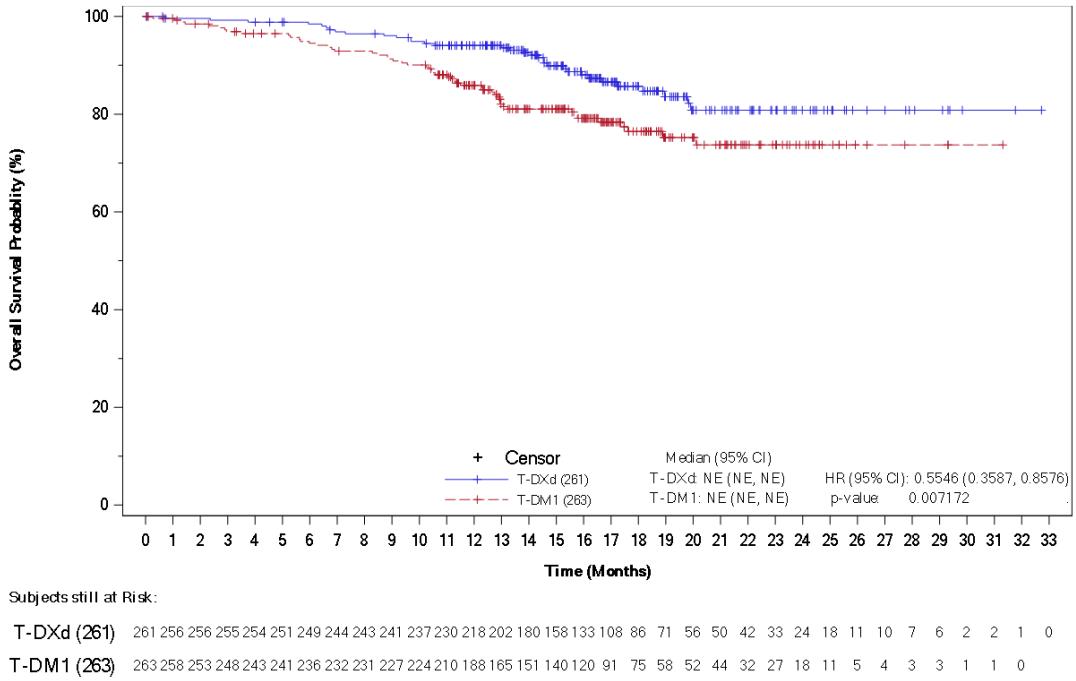
[b] Two-sided *P*-value from stratified log-rank test and hazard ratio and 95% CI from stratified Cox proportional hazards model with stratification factors: hormone receptor status, prior treatment with pertuzumab, and history of visceral disease based on IXRS.

[c] Estimate and CI for OS rate at the specified time point are from Kaplan-Meier analysis.

Data cut-off date: 21 May 2021

Source: DS8201-A-U302 CSR Table 14.2.2.1

Figure 3.4 Kaplan-Meier Plot of Overall Survival (Full Analysis Set)



CI = confidence interval; HR = hazard ratio; NE = not estimable; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan
Stratified Cox proportional hazards model for hazard ratio and stratified log-rank test for *P*-value.
Data cut-off: 21 May 2021
Source: DS8201-A-U302 CSR Figure 14.2.2.1

Other secondary endpoints: BOR, ORR DOR and CBR

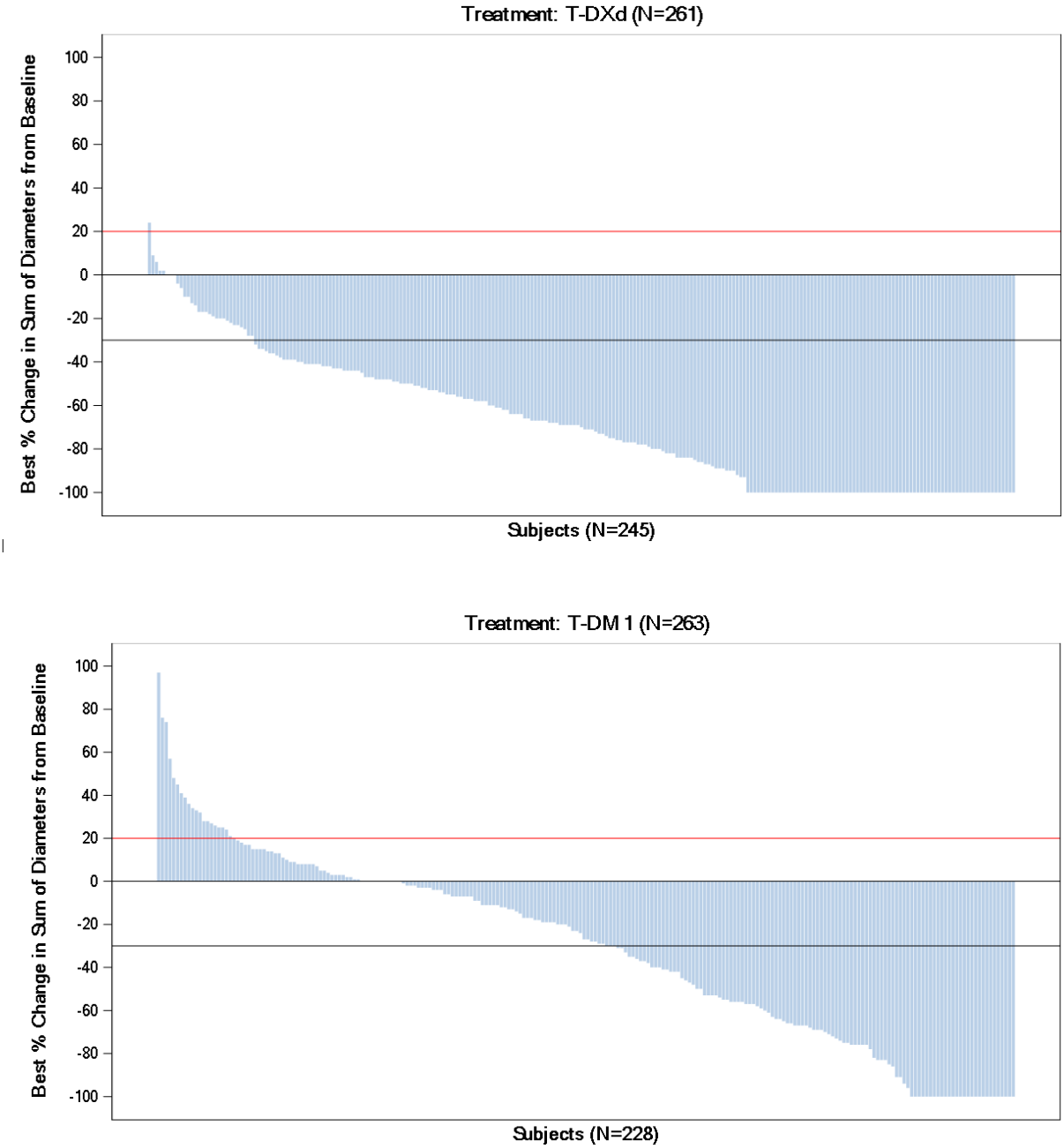
Table 3.8 Best Overall Response, Objective Response Rate, and Clinical Benefit Rate Based on Blinded Independent Central Review (Full Analysis Set)

Parameter	T-DXd (N=261)	T-DM1 (N=263)
Best overall response, n (%)		
Complete response	42 (16.1)	23 (8.7)
Partial response	166 (63.6)	67 (25.5)
Stable disease	44 (16.9)	112 (42.6)
Progressive disease	3 (1.1)	46 (17.5)
Not evaluable	6 (2.3)	15 (5.7)
Confirmed ORR[a]		
n (%)	208 (79.7)	90 (34.2)
95% CI[b]	(74.3, 84.4)	(28.5, 40.3)
P-value (stratified analysis)[c]	<0.0001	
Clinical benefit rate, n (%)[d]	233 (89.3)	120 (45.6)
95% CI[b]	(84.9, 92.8)	(39.5, 51.9)

CI = confidence interval; CR = complete response; IXRS = interactive web/voice response system; ORR = objective response rate; PR = partial response; SD = stable disease; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan
[a] ORR = CR + PR
[b] Based on Clopper-Pearson method for single proportion.
[c] 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

[d] defined as CR + PR + SD >6 months
Data cut-off date: 21 May 2021
Source: DS8201-A-U302 CSR Table 14.2.3.1.1

Figure 3.5 Waterfall Plot of Best Percent Change from Baseline in Sum of Diameters of Target Lesions in Each Treatment Arm (Full Analysis Set)



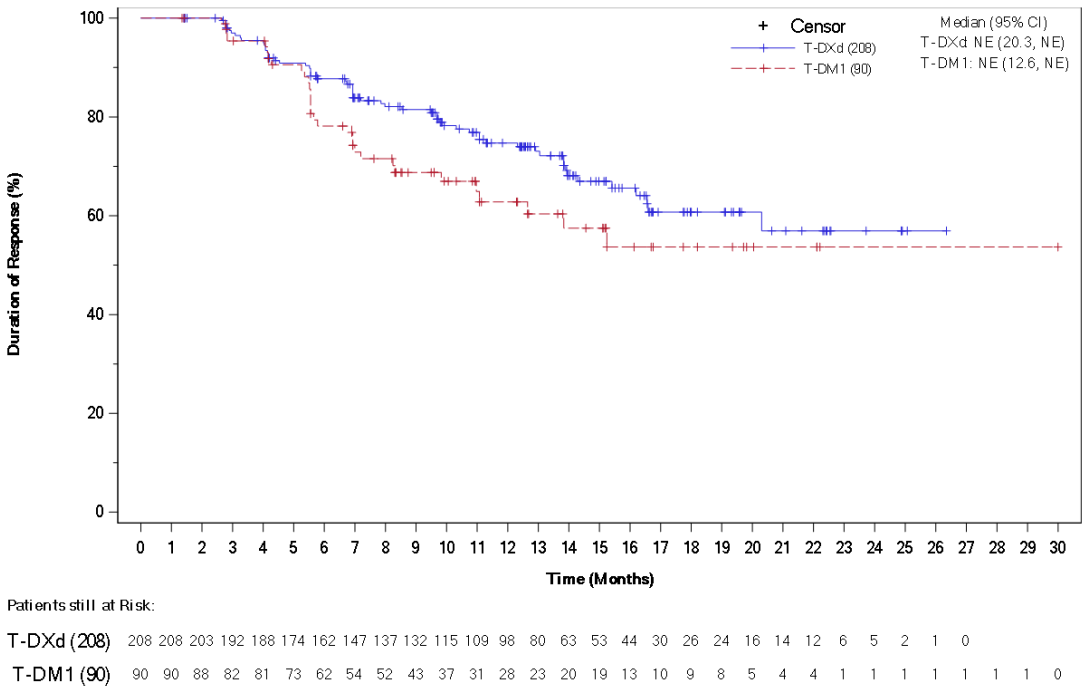
Baseline was defined as the last measurement taken before the randomization date.
For each subject, the best (minimum) percent change from baseline in the sum of diameters for all target lesions is represented by a vertical line.
Only subjects with measurable disease at baseline and at least 1 post-baseline are included in the waterfall graphs.
Data cut-off: 21 May 2021
Source: DS8201-A-U302 CSR Figure 14.2.4.1

Table 3.9 Duration of Response Based on Blinded Independent Central Review (Full Analysis Set)

Parameter	T-DXd (N=261)	T-DM1 (N=263)
Subjects with CR or PR, n	208	90
Subjects with events,[a] n (%)	58 (27.9)	31 (34.4)
Progressive disease	55 (26.4)	31 (34.4)
Death	3 (1.4)	0
Subjects without events (censored),[a] n (%)	150 (72.1)	59 (65.6)
Event after missing 2 consecutive assessments	6 (2.9)	4 (4.4)
Lost to follow-up	0	0
Withdrew consent	6 (2.9)	2 (2.2)
Ongoing without event	119 (57.2)	39 (43.3)
Adequate tumour assessment no longer available	19 (9.1)	14 (15.6)
Median confirmed DoR (months) (95% CI)[b]	NE (20.3, NE)	NE (12.6, NE)

CI = confidence interval; CR = complete response; DoR = duration of response; PR = partial response; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan
[a] Percentage was calculated using number of subjects with CR/PR
[b] Median is from Kaplan-Meier estimate. Confidence interval for median is computed using the Brookmeyer-Crowley method.
Data cut-off date: 21 May 2021
Source: DS8201-A-U302 CSR Table 14.2.3.2

Figure 3.6 Kaplan-Meier Plot of Duration of Response Based on Blinded Independent Central Review - All Responders (Full Analysis Set)



CI = confidence interval; CR = complete response; NE = not estimable; PR = partial response; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan
All responders included all subjects with a best overall response of CR or PR
Data cut-off: 21 May 2021
Source: DS8201-A-U302 CSR Figure 14.2.3.2.1

Exploratory endpoint – Patient-related outcomes (PRO)

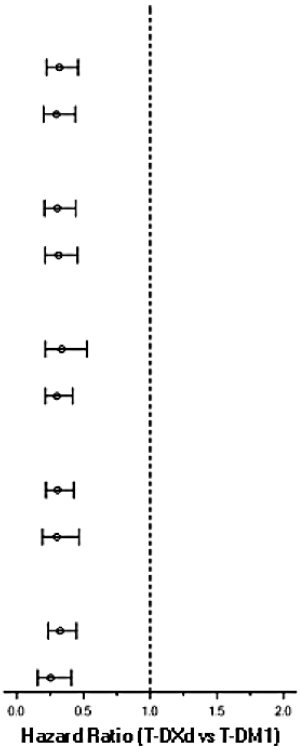
The following PRO questionnaires were summarized by treatment arm: EORTC QLQ-C30, EORTC QLQ-BR45, and EQ-5D-5L.

The PRO completion compliance rate was high at baseline (97%) and diminished during follow-up (about 83-87% at Cycle 3 and below 50% at C21 in the T-DXd arm and at C9 in the T-DM1 arm). Evaluation of PRO variables showed that the QoL of patients in the T DXd arm was either maintained or numerically improved on treatment compared with patients in the T DM1 arm.

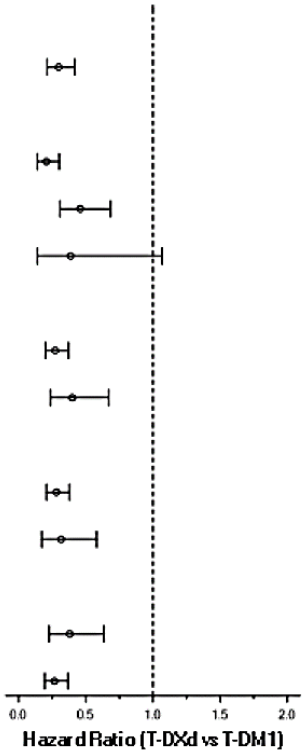
Ancillary analyses

Figure 8.3: Forest Plot of Treatment Comparison for Progression-free Survival Based on Blinded Independent Central Review, by Subgroup (Full Analysis Set)

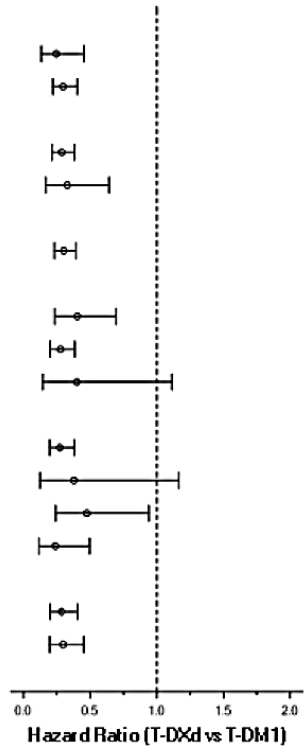
Subgroup	Number of Events T-DXd	T-DM1	Median Survival (Months, 95% CI) T-DXd	T-DM1	Hazard Ratio (95% CI)
Hormone Receptor Status					
Positive (n=272)	46/133	84/139	22.4 [17.7, NE]	6.9 [4.2, 9.8]	0.3191 [0.2217, 0.4594]
Negative (n=248)	41/126	73/122	NE [18.0, NE]	6.8 [5.4, 8.3]	0.2965 [0.2008, 0.4378]
Estrogen Receptors					
Positive (n=261)	43/129	80/132	22.4 [17.7, NE]	5.8 [4.2, 9.8]	0.3035 [0.2084, 0.4420]
Negative (n=258)	44/130	76/128	NE [18.0, NE]	6.8 [5.4, 8.3]	0.3127 [0.2143, 0.4562]
Progesterone Receptors					
Positive (n=173)	31/81	56/92	22.4 [14.1, NE]	5.6 [3.2, 8.0]	0.3360 [0.2153, 0.5244]
Negative (n=345)	56/177	100/168	NE [21.6, NE]	7.1 [5.7, 9.7]	0.2999 [0.2151, 0.4181]
Prior Treatment with Pertuzumab					
Yes (n=320)	57/162	98/158	NE [18.5, NE]	6.8 [5.4, 8.3]	0.3050 [0.2185, 0.4257]
No (n=204)	30/99	60/105	NE [16.5, NE]	7.0 [4.2, 9.7]	0.2999 [0.1924, 0.4675]
Lns. of Pr. Sys. Thpy. not Inc. Horm. Thpy					
< 3 lines (n=379)	60/188	107/191	NE [21.6, NE]	8.2 [6.8, 10.0]	0.3242 [0.2354, 0.4465]
>= 3 lines (n=145)	27/73	51/72	22.2 [15.4, NE]	4.3 [2.9, 5.7]	0.2531 [0.1563, 0.4097]



Subgroup	Number of T-DXd	Events T-DM1	Median Survival (Months, 95% CI) T-DXd	T-DM1	Hazard Ratio (95% CI)
Lns. of Sys. Thpy. Pr. to Part. Trt.					
< 3 lines (n=308)	54/156	95/152	NE [18.5, NE]	6.8 [5.4, 8.3]	0.2975 [0.2115, 0.4186]
Renal Impairment at Baseline					
Within Normal Range (n=265)	40/134	88/131	NE [21.6, NE]	5.4 [4.1, 6.8]	0.2057 [0.1399, 0.3026]
Mild Impairment (n=201)	41/96	60/105	17.9 [14.1, NE]	8.3 [5.7, 11.1]	0.4586 [0.3072, 0.6847]
Moderate Impairment (n=52)	6/27	10/25	NE [16.5, NE]	15.2 [5.7, NE]	0.3864 [0.1398, 1.0679]
Hepatic Impairment					
Within Normal Range (n=420)	62/208	123/212	NE [21.6, NE]	7.0 [5.7, 9.7]	0.2722 [0.1994, 0.3716]
Mild Impairment (n=98)	25/49	35/49	16.5 [9.7, NE]	3.0 [1.9, 6.8]	0.3988 [0.2373, 0.6701]
Baseline Visceral Disease					
Yes (n=384)	72/195	123/189	22.2 [16.5, NE]	5.7 [4.2, 7.0]	0.2806 [0.2083, 0.3779]
No (n=140)	15/66	35/74	NE [NE, NE]	11.3 [6.8, NE]	0.3157 [0.1718, 0.5804]
History of CNS Metastases					
Yes (n=114)	31/62	31/52	15.0 [12.6, 22.2]	5.7 [2.9, 7.1]	0.3796 [0.2267, 0.6357]
No (n=410)	56/199	127/211	NE [22.4, NE]	7.0 [5.5, 9.7]	0.2665 [0.1939, 0.3665]



Subgroup	Number of T-DXd	Events T-DM1	Median Survival (Months, 95% CI) T-DXd	T-DM1	Hazard Ratio (95% CI)
Baseline CNS Metastases					
Yes (n=82)	22/43	27/39	15.0 [12.5, 22.2]	3.0 [2.8, 5.8]	0.2465 [0.1341, 0.4529]
No (n=442)	65/218	131/224	NE [22.4, NE]	7.1 [5.6, 9.7]	0.2971 [0.2199, 0.4014]
Age					
<65 (n=418)	75/212	128/206	22.4 [17.9, NE]	5.8 [4.2, 7.1]	0.2862 [0.2138, 0.3832]
>=65 (n=106)	12/49	30/57	NE [NE, NE]	11.3 [5.6, 19.5]	0.3278 [0.1673, 0.6424]
Age					
<75 (n=508)	85/253	156/255	NE [18.5, NE]	6.8 [5.5, 8.1]	0.3023 [0.2312, 0.3952]
Race					
White (n=143)	21/71	34/72	NE [17.7, NE]	10.0 [5.6, NE]	0.4030 [0.2333, 0.6962]
Asian (n=314)	56/152	110/162	NE [16.5, NE]	5.6 [4.1, 7.0]	0.2775 [0.1998, 0.3853]
Other (n=48)	7/28	8/20	NE [15.0, NE]	18.0 [5.4, NE]	0.4004 [0.1439, 1.1139]
Region					
Asia (n=309)	54/149	108/160	NE [16.8, NE]	5.6 [4.1, 6.9]	0.2724 [0.1951, 0.3801]
North America (n=34)	7/17	8/17	22.2 [8.3, NE]	12.1 [2.8, NE]	0.3778 [0.1226, 1.1639]
Europe (n=104)	15/54	19/50	NE [17.7, NE]	18.0 [10.0, NE]	0.4750 [0.2402, 0.9394]
Rest of World (n=77)	11/41	23/36	NE [15.1, NE]	6.8 [4.2, 9.7]	0.2391 [0.1156, 0.4948]
ECOG PS					
0 (n=329)	46/154	103/175	NE [22.2, NE]	7.0 [5.5, 9.7]	0.2853 [0.2007, 0.4056]
1 (n=193)	41/106	55/87	17.7 [15.0, NE]	5.7 [4.0, 8.2]	0.2969 [0.1956, 0.4507]



CI = confidence interval; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; NE = not estimable; T-DM1 (trastuzumab emtansine); T-DXd (trastuzumab deruxtecan)
Lns. Of Pr. Sys. Thpy. Not Inc. Horm. Thpy. = Lines of prior systemic therapy not including hormone therapy

Lns. Of Sys. Thpy. Pr. To Pert. Trt. = Lines of systemic therapy prior to pertuzumab treatment
Subgroup values were derived from baseline.
Hazard ratio is from the unstratified Cox proportional hazard model.
Data cut-off date: 21 May 2021
Source: Figure 14.2.1.3.1

Table 12 Progression-free Survival by Setting for Prior Trastuzumab Based on Blinded Independent Central Review (Full Analysis Set)

	Trastuzumab in the Metastatic Setting[c]		Trastuzumab in the (Neo)Adjuvant Setting[d]	
Progression-free Survival Analyses	**T-DXd (N = 235)**	**T-DM1 (N = 228)**	**T-DXd (N = 25)**	**T-DM1 (N = 32)**
Subjects with events, n (%)	80 (34.0)	136 (59.6)	7 (28.0)	22 (68.8)
Median PFS, months (95% CI)[a]	NE (18.0, NE)	6.8 (5.6, 8.3)	NE (13.3, NE)	6.8 (2.8, 9.7)
Stratified Cox hazard ratio (95% CI)[b]	0.3164 (0.2391, 0.4188)		0.1993 (0.0832, 0.4775)	

CI = confidence interval; IXRS = Interactive Web/Voice Response System; KM = Kaplan-Meier; NE = not estimable; PFS = progression-free survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan
PFS was 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 came first.
[a] Median PFS is from the KM analysis. The CI for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from the unstratified Cox proportional hazards model with treatment as the only covariate.
[c] Includes subjects who received a prior systemic trastuzumab therapy intended for "locally advanced"/"metastatic" or "other" (palliative).
[d] Includes subjects who received a prior systemic trastuzumab therapy intended for "neo-adjuvant", "adjuvant", or "maintenance" with PD within 6 months since the end of the therapy if the end of therapy date and PD date are present after imputation but did not receive any prior systemic trastuzumab therapy for "locally advanced"/"metastatic" or "other" (palliative).
Data cut-off date: 21 May 2021

Efficacy according to de-novo metastatic vs recurrent metastatic disease

Table 2: Analysis of Progression-free Survival Based on BICR by Disease Status (Full Analysis Set)

	T-DXd (N = 261)			T-DM1 (N = 263)			T-DXd vs T-DM1
Subgroup	**n**	**No. of Events (%)**	**Median PFS (95% CI)[a] (months)**	**n**	**No. of Events (%)**	**Median PFS (95% CI)[a] (months)**	**Hazard Ratio (95% CI)[b]**
De-novo metastatic cancer	93	34 (36.6)	22.4 (15.0, NE)	104	65 (62.5)	5.8 (4.2, 8.1)	0.3483 (0.2291, 0.5295)
Recurrent unresectable/metastatic cancer	168	53 (31.5)	NE (18.5, NE)	159	93 (58.5)	7.0 (5.4, 9.7)	0.2788 (0.1977, 0.3934)

CI = confidence Interval; NE = not estimable; PFS = progression-free survival; SAP = statistical analysis plan; T-DM1 = trastuzumab emtansine; T-DXd = transtuzumab deruxtecan
De-novo metastatic cancer is defined as Stage IV at initial diagnosis.
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. For each arm, the denominator for percentages is the number of subjects in each subgroup in the Full Analysis Set.
[a] Median PFS is from Kaplan-Meier analysis. CI for median was computed by using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate.
Source: Appendix 1 Table 8b

Table 3: Analysis of Overall Survival by Disease Status (Full Analysis Set)

	T-DXd (N = 261)			T-DM1 (N = 263)			T-DXd vs T-DM1
Subgroup	**n**	**No. of Events (%)**	**Median OS (95% CI)[a] (months)**	**n**	**No. of Events (%)**	**Median OS (95% CI)[a] (months)**	**Hazard Ratio (95% CI)[b]**
De-novo metastatic cancer	93	12 (12.9)	NE (NE, NE)	104	24 (23.1)	NE (NE, NE)	0.5182 (0.2591, 1.0366)
Recurrent unresectable/metastatic cancer	168	21 (12.5)	NE (NE, NE)	159	29 (18.2)	NE (NE, NE)	0.6160 (0.3512, 1.0804)

CI = confidence Interval; NE = not estimable; OS = overall survival; T-DM1 = trastuzumab emtansine; T-DXd = transtuzumab deruxtecan
De-novo metastatic cancer is defined as Stage IV at initial diagnosis.
OS is defined as the time from the date of randomisation to the date of death from any cause. If there is no death reported for a subject before the data cut-off for OS analysis, OS will be censored at the last contact date at which the subject is known to be alive. For each arm, the denominator for percentages is the number of subjects in each subgroup in the Full Analysis Set.
[a] Median OS is from Kaplan-Meier analysis. CI for median was computed by using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate.
Source: Appendix 1 Table 8c

Efficacy according to prior lines of anti-HER2 therapy

Table 7 Analysis of Progression-free Survival – Based on BICR by Lines of Anti-HER2 Prior Therapy (Full Analysis Set)

	T-DXd (N = 261)			T-DM1 (N = 263)			T-DXd vs T-DM1
Subgroup	n	No. of Events (%)	Median PFS (95% CI) [a] (months)	n	No. of Events (%)	Median PFS (95% CI)[a] (months)	Hazard Ratio (95% CI)[b]
Lines of Prior Anti-HER2 Therapy							
1	193	64 (33.2)	NE (18.5, NE)	197	115 (58.4)	8.0 (5.7, 9.7)	0.3285 (0.2409, 0.4479)
≥2	66	23 (34.8)	22.2 NE)	63	43 (68.3)	4.2 (2.8, 5.7)	0.2257 (0.1341, 0.3799)
1 or 2	241	80 (33.2)	NE (18.5, NE)	239	143 (59.8)	7.0 (5.6, 8.4)	0.3079 (0.2332, 0.4064)
≥3	18	7 (38.9)	15.4 (8.3, NE)	21	15 (71.4)	4.3 (2.0, 7.1)	0.2058 (0.0777, 0.5451)

CI = confidence interval; HER2 = human epidermal growth factor receptor 2; NE = not estimable; PFS = progression-free survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan

Data cut-off date: 21 May 2021

a Median PFS 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.

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. Subgroup values are as defined at baseline.

Efficacy according to trastuzumab in the metastatic or (neo)adjuvant setting

The median PFS was NE for subjects who had received prior trastuzumab in the metastatic setting and for subjects who had received prior trastuzumab in the (neo)adjuvant setting but not in the metastatic setting. For T-DM1, the median PFS was 6.8 months for subjects with prior trastuzumab in the metastatic setting and for subjects with prior trastuzumab in the (neo)adjuvant setting but not in the metastatic setting.

Table 3. Progression-free Survival by Setting for Prior Trastuzumab Based on Blinded Independent Central Review (Full Analysis Set)

	Trastuzumab in the Metastatic Setting[c]		Trastuzumab in the (Neo)Adjuvant Setting[d]	
Progression-free Survival Analyses	T-DXd (N = 235)	T-DM1 (N = 228)	T-DXd (N = 25)	T-DM1 (N = 32)
Subjects with events, n (%)	80 (34.0)	136 (59.6)	7 (28.0)	22 (68.8)
Median PFS, months (95% CI)[a]	NE (18.0, NE)	6.8 (5.6, 8.3)	NE (13.3, NE)	6.8 (2.8, 9.7)
Stratified Cox hazard ratio (95% CI)[b]	0.3164 (0.2391, 0.4188)		0.1993 (0.0832, 0.4775)	

CI = confidence interval; IXRS = Interactive Web/Voice Response System; KM = Kaplan-Meier; NE = not estimable; PFS = progression-free survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan

PFS was 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 came first.

[a] Median PFS is from the KM analysis. The CI for median was computed using the Brookmeyer-Crowley method.

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

[c] Includes subjects who received a prior systemic trastuzumab therapy intended for "locally advanced"/"metastatic" or "other" (palliative).

[d] Includes subjects who received a prior systemic trastuzumab therapy intended for "neo-adjuvant", "adjuvant", or "maintenance" with PD within 6 months since the end of the therapy if the end of therapy date and PD date are present after imputation but did not receive any prior systemic trastuzumab therapy for "locally advanced"/"metastatic" or "other" (palliative).

Data cut-off date: 21 May 2021.

Summary of main study

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 1. Summary of Efficacy for trial Destiny Breast03 (Study U302)

Title: A Phase 3, Multicenter, Randomized, Open-label, Active-controlled Study of Trastuzumab Deruxtecan, an Anti-HER2-antibody Drug Conjugate, versus Trastuzumab Emtansine (T-DM1) for HER2-positive, Unresectable and/or Metastatic Breast Cancer Subjects Previously Treated with Trastuzumab and Taxane			
Study identifier	DS8201-A-U302		
Design	Randomised, 2-arm, phase 3, open-label, multicenter study		
	Duration of main phase:		Treatment continued until disease, withdrawal of consent, or until progression or unacceptable toxicity.
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Not applicable
Hypothesis	Superiority: Significant benefit for PFS		
Treatments groups	T-DXd		Trastuzumab deruxtecan iv 5.4 mg/kg every 3 weeks (Q3W), number randomized: 261 patients
	T-DM1		Trastuzumab emtansine iv 3.6 mg/kg every 3 weeks (Q3W), number randomized: 263 patients
Endpoints and definitions	Primary endpoint	PFS by BICR	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
Database lock	DCO 21 May 2021		

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat: Primary analysis			
Descriptive statistics and estimate variability	Treatment group	T-DXd (N=261)	T-DM1 (N=263)	
	Patients with events	87 (33.3%)	158 (60.1%)	

	PFS by BICR (Months)	NE	6.8
	95% CI	18.5; NE	5.6; 8.2
	OS (Months)	NE	NE
	95% CI	NE; NE	NE; NE
	PFS by INV (Months) 95% CI	25.1 22.1; NE	7.2 6.8; 8.3
	Confirmed ORR	208 (79.7%)	90 (34.2%)
	95% CI	74.3; 84.4	28.5; 40.3
Effect estimate per comparison	Primary endpoint: PFS by BICR	Comparison groups	T-DXd vs T-DM1
		Hazard ratio	0.28
		95%CI	0.22; 0.37
		P-value	<0.000001*
	Secondary endpoint: OS	Comparison groups	T-DXd vs T-DM1
		Hazard ratio	0.55
		95%CI	0.36; 0.86
		P-value	NA
	Secondary endpoint: PFS by INV	Comparison groups	T-DXd vs T-DM1
		Hazard ratio	0.26
		95%CI	0.20; 0.35
		P-value	<0.000001**
	Secondary endpoint: Confirmed ORR	Comparison groups	T-DXd vs T-DM1
		Stratified P-value	<0.0001
Notes	* The actual *P*-value is 7.8×10^{-22} ** The actual *P*-value is 6.5×10^{-24}		

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy assessment of the applied extension of indication is based on the pivotal study Destiny breast03 or Study U302, which is a phase 3 randomised open-label two-arm study comparing trastuzumab deruxtecan (T-DXd) head to head with the current SOC in the 2L setting, i.e. trastuzumab emtansine (T-DM1). The applied extension of indication is for the 2L setting of HER2-positive metastatic breast cancer after the established 1L use of a taxane and pertuzumab + trastuzumab. Patients were recruited from 118 study sites in 14 countries and the median study duration was 15.9 months at the DCO of 21 May 2021. 524 patients were randomized 1:1 to the two treatment arms and this is an acceptable sample size. The pivotal study was fully recruited in approximately 2 years and 9 months and a relevant fraction of the patients has been recruited from an EU like population (~33%). The presented data are from the prespecified interim analysis (IA) for superiority of the primary efficacy endpoint of blinded independent central review (BICR)-assessed progression-free survival (PFS). The differences in toxicity management between the treatment arms are acknowledged and the

open-label design can be acceptable as the main efficacy endpoints were assessed blinded and included overall survival. It will, however, hamper the interpretation of quality of life parameters as discussed below.

The primary endpoint was PFS as assessed by BICR using RECIST v1.1 with overall survival (OS) as key secondary endpoint. Other secondary endpoints were PFS as assessed by investigator, confirmed objective response rate (ORR; by BICR and investigator), and duration of response (DOR; by BICR and investigator). The primary and secondary endpoints are acceptable and established in the current setting. Exploratory efficacy endpoints included amongst others time to response by BICR, clinical benefit rate (CBR; sum of CR, PR and stable disease lasting more than 6 months), and PFS on next-line treatment by investigator (PFS2). Health-related quality of life (HRQoL) was assessed with established questionnaires (EORTC quality of life QLQ-C30 (primary patient reported outcome [PRO], QLQ-BR45, EQ-5D-5L). It is uncertain whether the HRQoL outcomes should be viewed as secondary endpoints (clinical overview) or exploratory (study protocol). No formal statistical testing was planned as recommended in the scientific advice, including handling of missing data, and the open-label design limits the interpretation of HRQoL outcomes. Overall, this precludes a claim on PRO in the SmPC.

It should be noted that T-DXd 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.

Baseline characteristics showed that the median age was ~54 years with ~80% of the patients being less than 65 years old and ~18% of the patients were ≥65 years, which is considered reflective of the patient population. Two male patients were included, one in each treatment arm, which is acceptable since breast cancer is rare in men. Moreover, the results from the pivotal trial is considered extrapolatable to men with HER2-positive metastatic breast cancer in line with previous EMA decisions for HER2-targeted treatments (e.g. trastuzumab). The low number of patients older than 75 years is already reflected in section 4.2 of the SmPC.

Most patients were Asian (57.1% and 60.8%, respectively) or European (20.7% and 19%), so the Asian population dominated the study population, but the fraction of European patients is considered acceptable for interpretation of the study results in an EU context.

The study population was heavily pre-treated, and many patients had at least 2 prior lines of therapy in the metastatic setting. If endocrine therapy is excluded, the majority of the patients had less than 3 prior systemic therapies (~72%), which is more than what was the minimum required by the inclusion criteria and what has been reflected in the current target population for the applied indication, i.e. second-line treatment in the metastatic setting. Therefore, the MAH was asked to justify the applicability of the study results for the applied indication. It is agreed that the PFS and OS results are clinically relevantly improved regardless of number of prior lines of therapy, number of lines of anti-HER2 based therapy and this is encouraging. Although part of the included patient population was more heavily pre-treated than expected, the results from the study population are still considered applicable to the targeted patient population.

Most patients were of ECOG PS 0 (59% and 66.5%) or 1 (40.6% and 33.1%); HER2 expression on ICH of 3+ (85.4% and 84.0%) and approximately half of the patients had hormone receptor (HR)-positive tumours, while a third of the tumours were Progesterone receptor positive, which reflects the target population. Prior pertuzumab was given in ~60% of the patients and the majority of patients had a history of visceral metastases (70.5% and 70.3%). Hence, for these three chosen stratification factors, the patients were equally distributed between arms and, except for prior pertuzumab, the study

population is considered to reflect the targeted patient population. However, the fraction of patients treated with pertuzumab is considered lower than what would be expected in a European population. Relatively few patients had CNS metastases at baseline (16.5% and 14.8%), probably due to the strict inclusion criteria regarding stability and no use of corticosteroids and lower than would be expected of the incidence of CNS metastases in the patient population with HER2+ MBC eligible for a 2L+ systemic treatment.

Efficacy data and additional analyses

The primary endpoint was met and the primary analysis of **PFS by BICR** showed a statistically significant and clinically relevant improvement from 6.8 months (95%CI: 5.6, 8.2) with T-DM1 to not reached (95%CI: 18.5, NE) with T-DXd, HR 0.28 (95%CI: 0.22, 0.37). The data is partly mature with 33.3% events in the active T-DXd arm and 60.1% events in the control arm, but the KM curves separate early and stay separated, so further updates are considered unlikely to change the study result significantly due to the high number of events in the control arm. Patients were censored in 66.7% in the T-DXd arm and 39.9% of the T-DM1 arm. The main reason for censoring was ongoing without event (49.0% and 18.6%, respectively), although also more than 10% in both arms was censored for "adequate tumour assessment no longer available" as the last tumour scan was more than 14 weeks before DCO. Other reasons for censoring occurred in less than 5%. The sensitivity analyses provided support the primary analysis of PFS by BICR.

Initially, the PFS analysis was planned when approximately 331 events had been observed, with 90% power to detect an HR of 0.70 in PFS using a log-rank test and a 2-look group sequential design with O'Brien-Fleming efficacy boundary (2-sided p-value 0.05). This was based on an estimated median PFS of 13.7 months with T-DXd vs. 9.6 months for T-DM1. An IA of PFS was added based on emergent data from study U201, to be conducted earlier after approximately 234 events (70% information fraction). To ensure that the study would be declared positive on a highly clinically relevant magnitude of benefit, the efficacy boundaries were changed to the more stringent Haybittle-Peto efficacy boundary with a 2-sided p value of 0.000204 or less.

The performance of the control arm is lower than the median PFS reported in patients on T-DM1 in the EMILIA study (T-DM1 vs capecitabine and lapatinib, median PFS 9.6 months), but is considered in line with the PFS observed with T-DM1 alone after the THP regimen (Taxane + trastuzumab + pertuzumab), as observed in the KATE2 study (T-DM1 + atezolizumab vs T DM1 + placebo, median PFS of 6.8 months). Moreover, the study population in the Destiny breast03 is heavily pre-treated and the majority had previously been treated with pertuzumab, which was not the case in the EMILIA study. Hence, the performance of the control arm is considered acceptable in this context.

The key secondary endpoint was **overall survival** and OS data are not mature at the time the first IA with only 12.2% events with T-DXd and 20.2% events in the control arm after 15.9 months of follow up. Hence, the median OS was not reached in either of the treatment arms and was not statistically significantly improved although the KM curves for OS visually separate and a detriment in OS is not likely. Considering that the targeted patient population are likely to receive further lines of treatment, this OS result is considered sufficient for the current procedure, but the MAH has committed to submit the results from the upcoming OS analyses from the pivotal study U302 post-authorization as a recommendation.

At the time the IA for PFS was added, OS was designated as key secondary endpoint. Two IA were planned, at the time of primary PFS analysis if significant and at about 153 OS events. With 250 OS events (final analysis), the study will have approximately 80% power to detect a HR of 0.70 in OS (2-sided p-value 0.05) using a log-rank test and a 3-look group sequential design with Lan-DeMets alpha

spending function with O'Brien-Fleming efficacy boundary. Median OS was assumed to increase from 29.9 months with T-DM1 to 42.7 months with T-DXd under the exponential model assumption. The methodology is acceptable; however, it should be noted that at the time of the currently provided DCO, the study did not meet the pre-specified number of OS events needed to achieve sufficient power (estimated 96 targeted OS events), despite the recommendations made during the scientific advice.

After the initial release (March 2018), the study protocol was amended 5 times. The main changes were with amendment 4 (April 2020) and amendment 5 (September 2020) were the above described interim analysis for PFS with updated efficacy boundary and changes in the OS analyses were added.

PFS by investigator also showed a statistically significant and clinically relevant improvement from 7.2 months (95%CI: 6.8; 8.3) with T-DM1 to 25.1 months (95%CI: 22.1, NE) with T-DXd, HR 0.26 (95%CI: 0.20, 0.35). Median duration of PFS follow-up was 15.5 months and 13.9 months in the investigational and control arm, respectively. The data is again partly mature with 29.9% events in the active T-DXd arm and 63.9% events in the control arm. The KM curves also separates early and stay separated and the overall concordance rate of PFS between INV and BICR was 81.99% in the T-DXd arm and 78.71% in the T-DM1 arm, which is acceptable in the context of the open-label design. Due to discrepancies between PFS per BICR and investigator assessment, a sensitivity analysis was requested counting the earliest occurrence as event independent of assessment method. The results of this analysis showed consistent results with the primary analysis.

ORR by BICR is clinically and statistically significantly improved from 34.2% in the control arm to 79.7% with T-DXd. The improvement was observed for both complete and partial response (CR and PR), i.e. the CR was improved from 8.7% to 16.1%, while the PR was improved from 25.5% to 63.6% with T-DXd. It is noted that very few patients progressed on treatment with T-DXd (1.1%) and the induced responses were durable, although median DOR was not reached in either arm, the median DoR was NE (95%CI: 20.3, NE) in the T-DXd arm vs. NE (95%CI: 12.6, NE) in the T-DM1 arm. However, the DoR data is not mature, with 27.9% and 34.4% events in each arm, respectively, so the MAH is asked to provide updated confirmed ORR and DoR, if possible, but these are not yet available. The Applicant proposes to submit updated clinical efficacy data at the time of the next OS analysis (currently projected for 3Q2022) post-authorisation and this is acceptable.

Subgroup analyses of the primary endpoint (PFS by BICR) supported a benefit of T-DXd compared with T-DM1 for important pre-specified subgroups above for all point estimates including prior pertuzumab therapy, hormone receptor status, presence of stable brain metastases, presence of visceral disease, prior lines of systemic therapies, and across geographic regions. Although not predefined, additional subgroup analyses were requested and they all support the primary analysis.

Patient-reported outcomes - The PRO completion compliance rate was high at baseline (97%) and diminished during follow-up (about 83-87%% at Cycle 3 and below 50% at C21 in the T-DXd arm and at C9 in the T-DM1 arm). Evaluation of PRO variables showed that the QoL of subjects in the T-DXd arm was either maintained or numerically improved on treatment compared with subjects in the T-DM1 arm. Although it is reassuring that there seems to be no detriment on QoL in patients treated with T-DXd compared to T-DM1 and numerical increases in QoL may support the beneficial effect of T-DXd, the lack of preplanned/defined analysis of PRO outcomes and the open-label study design preclude firm conclusions. In addition, by not reaching statistical significance for the key secondary endpoint OS, all other endpoints lower in hierarchy are considered to be descriptive. Therefore, QoL of life data are not reflected in the SmPC.

Regarding the wording of the indication, the MAH proposes to not specifically mention that patients had received prior trastuzumab and taxane therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy as was defined in the inclusion

criteria and included in the wording of the indication for T-DM1 (see section 1.3 of the assessment report). The text proposal for the indication to treat patients who have received a prior anti-HER2-based regimen can, however, be agreed. First of all, the standard SOC for first-line treatment is well known and constitutes the combination of trastuzumab, pertuzumab and a taxane chemotherapy. In less fit patients, a less toxic or no chemotherapeutic agents may be considered (Gennari et al., Annals of Oncology, 2021). Based on the mechanism of action of T-DXd, there are no concerns regarding differential safety or efficacy of T-DXd monotherapy in second line after a first-line therapy with a less toxic or no chemotherapeutic backbone. Also, the ESMO guidelines recommended that patients with metastatic recurrence within 6-12 months of receiving adjuvant trastuzumab-pertuzumab should continue to second-line therapy (Gennari et al., Annals of Oncology, 2021).

2.4.3. Conclusions on the clinical efficacy

The results from the pivotal Study U302 show a statistically significant and clinically relevant increase in PFS from median of 6.8 months with T-DM1 treatment to a median of not reached with T-DXd treatment (95%CI: 18.5, NE) in patients with HER2-positive, unresectable and/or metastatic breast cancer previously treated with trastuzumab and taxane. The key secondary endpoint OS was immature, but there was no sign of a detriment. Other secondary endpoints were supportive of a benefit of T-DXd treatment over T-DM1 treatment. Final efficacy data from the pivotal U302 study were recommended to be provided post-approval (PAM-REC).

2.5. Clinical safety

Introduction

The primary data on clinical safety of trastuzumab deruxtecan (T-DXd) are based on data from the T-DXd arm (N=257) and the T-DM1 arm (N=261) of Study U302. Moreover, data for subjects with HER2-positive BC who received T-DXd 5.4 mg/kg in Study J101 and Study U201 were pooled with those from Study U302 to form the "HER2-positive BC T-DXd 5.4 mg/kg Pool" (N=491). In addition, the data for patients with any tumour type who received T-DXd ≥ 5.4 mg/kg in the completed studies were included in the "All Tumour Types T-DXd ≥5.4 mg/kg Pool" (N=1219).

Table 1.2 Summary of Studies Included in Data Presentations

Evaluation	Drug / Dose	Number of Subjects Treated
Primary analysis Subjects with HER2-positive BC from Study U302	T-DXd 5.4 mg/kg T-DM1	T-DXd: 257 T-DM1: 261
HER2-positive BC T-DXd 5.4 mg/kg Pool Multi-study pool of subjects with HER2-positive BC who received T-DXd 5.4 mg/kg	T-DXd 5.4 mg/kg	491 Study U302: 257 Study U201: 184 Study J101: 50
All Tumour Types T-DXd ≥5.4 mg/kg Pool Multi-study pool of subjects with any tumour type who received T-DXd ≥5.4 mg/kg	T-DXd 5.4 mg/kg	573 Study U302: 257 Study U201: 184 Study J101: 91 Study U204: 41
	T-DXd 6.4 mg/kg	619 Study U201: 48 Study J101: 183 Study J202: 169

		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-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan Source: Module 5.3.5.3 SCS SAP v1.2

Patient exposure

Table 1.3 Summary of Exposure (Safety Analysis Set)

Parameter	**Study U302**		**HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)**
	T-DXd (N = 257)	**T-DM1 (N = 261)**	
Treatment duration (months) [a]			
Mean (Std Dev)	13.67 (6.292)	8.02 (6.026)	12.89 (7.235)
Median	14.26	6.90	12.65
Minimum, maximum	0.7, 29.8	0.7, 25.1	0.7, 37.1
Treatment duration (month categories), n (%) [a]			
0 to ≤3	8 (3.1)	67 (25.7)	43 (8.8)
>3 to ≤6	32 (12.5)	53 (20.3)	67 (13.6)
>6 to ≤9	28 (10.9)	53 (20.3)	65 (13.2)
>9 to ≤12	27 (10.5)	25 (9.6)	54 (11.0)
>12 to ≤18	102 (39.7)	40 (15.3)	135 (27.5)
>18 to ≤24	46 (17.9)	19 (7.3)	97 (19.8)
>24	14 (5.4)	4 (1.5)	30 (6.1)
Total patient-years of exposure [b]	292.9	174.5	527.3
Cumulative dose level (mg/kg) [c]			
Mean (Std Dev)	97.40 (44.534)	39.49 (29.326)	91.11 (50.664)
Median	101.67	33.47	89.75
Minimum, maximum	5.4, 216.8	3.6, 136.2	5.3, 225
Number of cycles			
Mean (Std Dev)	18.7 (8.54)	11.3 (8.48)	17.6 (9.80)
Median	20.0	10.0	17.0
Minimum, maximum	1, 40	1, 36	1, 45
Dose intensity (mg/kg/3 weeks) [d]			
Mean (Std Dev)	4.97 (0.561)	3.44 (0.303)	4.97 (0.588)
Median	5.17	3.56	5.20
Minimum, maximum	2.8, 5.8	2.2, 3.8	2.5, 5.8

Parameter	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Relative dose intensity (%) [e]			
Mean (Std Dev)	99.86 (1.725)	99.92 (1.567)	96.12 (8.885)
Median	100.00	100.00	99.58
Minimum, maximum	92.7, 107.6	94.2, 107.1	46.1, 107.6
Relative dose intensity categories, n (%) [e]			
≥90%	257 (100)	261 (100)	427 (87.0)
<90% to ≥80%	0	0	31 (6.3)
<80% to ≥60%	0	0	26 (5.3)
<60%	0	0	7 (1.4)

BC = breast cancer; CSR = clinical study report; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; SAP = Statistical Analysis Plan; Std Dev = standard deviation; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan

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

1 month = 365.25/12 = 30.44 days

[a] Treatment duration (months) = (date of the last dose – date of the first dose +21)/30.44

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

[c] Cumulative dose level = sum of the actual dose level received (mg/kg)

[d] Dose intensity (mg/kg/3 weeks) = cumulative dose level (mg/kg) / (duration of treatment [days]/21)

[e] Relative dose intensity (%) derivation/definition for each study followed the study convention specified in the SAP for each CSR.

Source: Module 5.3.5.3 SCS Table 1.1.3

Adverse events

At the time of DCO, 51.4% and 18.0% of patients were on treatment with T-DXd and T-DM1, respectively. The main reasons for treatment discontinuation were progressive disease (25.7% and 60.5% for T-DXd and T-DM1, respectively) and discontinuations due to adverse events (13.6% and 7.3% for T-DXd and T-DM1, respectively) (see also Figure 7.1 in the efficacy section).

Table 2.2 Overview of Treatment-emergent Adverse Events (Safety Analysis Set)

Parameter	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Subjects with any TEAE	256 (99.6)	249 (95.4)	489 (99.6)
TEAEs with CTCAE ≥Grade 3 [a]	134 (52.1)	126 (48.3)	270 (55.0)
Serious TEAEs	49 (19.1)	47 (18.0)	111 (22.6)
TEAEs associated with study drug interruption	113 (44.0)	61 (23.4)	210 (42.8)
TEAEs associated with dose reduction	55 (21.4)	33 (12.6)	104 (21.2)
TEAEs associated with study drug discontinuation	35 (13.6)	19 (7.3)	77 (15.7)
TEAEs associated with an outcome of death [b]	5 (1.9)	5 (1.9)	18 (3.7)

Parameter	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Drug-related TEAE [c]	252 (98.1)	226 (86.6)	485 (98.8)
TEAE with CTCAE ≥Grade 3 [a]	116 (45.1)	104 (39.8)	231 (47.0)
Serious TEAEs	28 (10.9)	16 (6.1)	59 (12.0)
TEAE associated with study drug interruption	91 (35.4)	34 (13.0)	166 (33.8)
TEAE associated with dose reduction	55 (21.4)	33 (12.6)	98 (20.0)
TEAE associated with study drug discontinuation	33 (12.8)	13 (5.0)	72 (14.7)
TEAE associated with an outcome of death	0	0	4 (0.8)

AE = adverse event; BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event
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 outcome of death, refer to.
[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 2.3 Treatment-emergent Adverse Events Reported in at Least 10% of Subjects in Either Treatment Arm of Study U302, by Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA Preferred Term/ Grouped Term [a]	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Subjects with any TEAE	256 (99.6)	249 (95.4)	489 (99.6)
Nausea	195 (75.9)	79 (30.3)	382 (77.8)
Vomiting	126 (49.0)	26 (10.0)	243 (49.5)
Fatigue [a]	126 (49.0)	90 (34.5)	278 (56.6)
Neutropenia [a]	110 (42.8)	31 (11.9)	187 (38.1)
Alopecia	95 (37.0)	8 (3.1)	203 (41.3)
Constipation	88 (34.2)	51 (19.5)	171 (34.8)
Anemia [a]	84 (32.7)	45 (17.2)	164 (33.4)
Leukopenia [a]	78 (30.4)	22 (8.4)	128 (26.1)
Decreased appetite	75 (29.2)	44 (16.9)	158 (32.2)
Diarrhoea	75 (29.2)	18 (6.9)	150 (30.5)
Aspartate aminotransferase increased	66 (25.7)	105 (40.2)	106 (21.6)
Thrombocytopenia [a]	66 (25.7)	139 (53.3)	121 (24.6)
Alanine aminotransferase increased	56 (21.8)	77 (29.5)	82 (16.7)
Headache [a]	56 (21.8)	42 (16.1)	105 (21.4)

MedDRA Preferred Term/ Grouped Term [a]	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Abdominal pain [a]	54 (21.0)	20 (7.7)	103 (21.0)
Stomatitis [a]	50 (19.5)	14 (5.4)	88 (17.9)
Weight decreased	43 (16.7)	16 (6.1)	63 (12.8)
Upper respiratory tract infection [a]	37 (14.4)	23 (8.8)	87 (17.7)
Blood alkaline phosphatase increased	35 (13.6)	30 (11.5)	51 (10.4)
Hypokalaemia	33 (12.8)	26 (10.0)	64 (13.0)
Dizziness	32 (12.5)	22 (8.4)	58 (11.8)
Dyspepsia	29 (11.3)	16 (6.1)	65 (13.2)
Epistaxis	29 (11.3)	42 (16.1)	63 (12.8)
Lymphopenia [a]	29 (11.3)	9 (3.4)	58 (11.8)
Cough	27 (10.5)	26 (10.0)	83 (16.9)
Pyrexia	27 (10.5)	39 (14.9)	54 (11.0)
Interstitial lung disease [b]	27 (10.5)	5 (1.9)	62 (12.6)
Rash [a]	20 (7.8)	27 (10.3)	54 (11.0)
Blood lactate dehydrogenase increased	17 (6.6)	35 (13.4)	25 (5.1)

BC = breast cancer; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities, Version 23.0; N = total number of treated subjects; PT = preferred term; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event
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 once for each of the different PTs/grouped terms.
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
[a] The PTs included in each grouped term are listed in Table 2.1.
[b] Interstitial lung disease includes events that were adjudicated as drug-related ILD.
Source: Module 5.3.5.3 SCS Tables 1.2.1.3, 1.2.2.1, 1.2.4.1

Grade ≥ 3 AEs

Table 2.5 Treatment-emergent Adverse Events of at Least CTCAE Grade 3 Reported in at Least 5% of Subjects in Either Treatment Arm of Study U302, by Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA Preferred Term/ Grouped Term [a]	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Subjects with any TEAE ≥Grade 3	134 (52.1)	126 (48.3)	270 (55.0)
Neutropenia [a]	49 (19.1)	8 (3.1)	96 (19.6)
Anemia [a]	19 (7.4)	15 (5.7)	40 (8.1)
Thrombocytopenia [a]	19 (7.4)	67 (25.7)	30 (6.1)
Nausea	17 (6.6)	1 (0.4)	33 (6.7)
Leukopenia [a]	17 (6.6)	1 (0.4)	32 (6.5)
Fatigue [a]	15 (5.8)	2 (0.8)	32 (6.5)

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events; HER2 = human epidermal growth factor receptor 2; MedDRA = Medical Dictionary for Regulatory Activities, Version 23.0; N = total number of treated subjects; PT = preferred term; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event
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 once for each of the different PTs/grouped terms.
[a] The PTs included in each grouped term are listed in Table 2.1.
Source: Module 5.3.5.3 SCS Tables 1.2.1.5, 1.2.2.1

Treatment-related AEs – ADRs

Table 2.4 Drug-related Treatment-emergent Adverse Events Reported in at Least 10% of Subjects in Either Treatment Arm of Study U302, by Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA Preferred Term/ Grouped Term [a]	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Subjects with any drug-related TEAE	252 (98.1)	226 (86.6)	485 (98.8)
Nausea	187 (72.8)	72 (27.6)	368 (74.9)
Fatigue [a]	115 (44.7)	77 (29.5)	253 (51.5)
Vomiting	113 (44.0)	15 (5.7)	214 (43.6)
Neutropenia [a]	110 (42.8)	29 (11.1)	183 (37.3)
Alopecia	93 (36.2)	6 (2.3)	198 (40.3)
Anemia [a]	78 (30.4)	37 (14.2)	145 (29.5)
Leukopenia [a]	77 (30.0)	20 (7.7)	125 (25.5)
Decreased appetite	67 (26.1)	33 (12.6)	143 (29.1)
Thrombocytopenia [a]	64 (24.9)	135 (51.7)	117 (23.8)
Diarrhoea	61 (23.7)	10 (3.8)	120 (24.4)
Aspartate aminotransferase increased	60 (23.3)	97 (37.2)	96 (19.6)
Constipation	58 (22.6)	25 (9.6)	103 (21.0)
Alanine aminotransferase increased	50 (19.5)	71 (27.2)	72 (14.7)
Stomatitis [a]	43 (16.7)	12 (4.6)	80 (16.3)
Abdominal pain [a]	34 (13.2)	11 (4.2)	60 (12.2)
Weight decreased	33 (12.8)	11 (4.2)	46 (9.4)
Interstitial lung disease [b]	27 (10.5)	5 (1.9)	62 (12.6)
Blood alkaline phosphatase increased	25 (9.7)	29 (11.1)	36 (7.3)
Blood lactate dehydrogenase increased	14 (5.4)	27 (10.3)	19 (3.9)

BC = breast cancer; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities, Version 23.0; N = total number of subjects in the study or pool; PT = preferred term; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event
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 once for each of the different PTs/grouped terms.
If relationship was missing, the event was considered to be related to the drug.
[a] The PTs included in each grouped term are listed in Table 2.1.
[b] Interstitial lung disease includes events that were adjudicated as drug-related ILD.
Source: Module 5.3.5.3 SCS Tables 1.2.1.4, 1.2.2.2, 1.2.5.1

Grade ≥ 3 ADRs

Table 2.24 Common Adverse Drug Reactions Reported in ≥10% of Subjects with Any Event or ≥2% of Subjects with Events of Grade 3 or 4 in the T-DXd Arm, by MedDRA System Organ Class and Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA System Organ Class Preferred Term/ Grouped Term [a]	Number (%) of Subjects					
	Study U302				HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)	
	T-DXd (N = 257)		T-DM1 (N = 261)			
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Blood and lymphatic system disorders						
Neutropenia [a]	110 (42.8)	49 (19.1)	31 (11.9)	8 (3.1)	187 (38.1)	96 (19.6)
Anemia [a]	84 (32.7)	19 (7.4)	45 (17.2)	15 (5.7)	164 (33.4)	40 (8.1)
Leukopenia [a]	78 (30.4)	17 (6.6)	22 (8.4)	1 (0.4)	128 (26.1)	32 (6.5)
Thrombocytopenia [a]	66 (25.7)	19 (7.4)	139 (53.3)	67 (25.7)	121 (24.6)	30 (6.1)
Lymphopenia [a]	29 (11.3)	10 (3.9)	9 (3.4)	3 (1.1)	58 (11.8)	24 (4.9)
Gastrointestinal disorders						
Nausea	195 (75.9)	17 (6.6)	79 (30.3)	1 (0.4)	382 (77.8)	33 (6.7)
Vomiting	126 (49.0)	4 (1.6)	26 (10.0)	2 (0.8)	243 (49.5)	14 (2.9)
Constipation	88 (34.2)	0	51 (19.5)	0	171 (34.8)	1 (0.2)
Diarrhoea	75 (29.2)	3 (1.2)	18 (6.9)	1 (0.4)	150 (30.5)	9 (1.8)
Abdominal pain [a]	54 (21.0)	2 (0.8)	20 (7.7)	1 (0.4)	103 (21.0)	5 (1.0)
Stomatitis [a]	51 (19.8)	2 (0.8)	14 (5.4)	0	89 (18.1)	5 (1.0)
Dyspepsia	29 (11.3)	0	16 (6.1)	0	65 (13.2)	0
General disorders and administration site conditions						
Fatigue [a]	127 (49.4)	15 (5.8)	91 (34.9)	2 (0.8)	280 (57.0)	32 (6.5)
Hepatobiliary disorders						
Transaminases increased	81 (31.5)	6 (2.3)	121 (46.4)	20 (7.7)	130 (26.5)	14 (2.9)
Investigations						
Weight decreased	43 (16.7)	3 (1.2)	16 (6.1)	1 (0.4)	63 (12.8)	3 (0.6)
Blood alkaline phosphatase increased	35 (13.6)	1 (0.4)	30 (11.5)	0	51 (10.4)	3 (0.6)
Metabolism and nutrition disorders						
Decreased appetite	75 (29.2)	4 (1.6)	44 (16.9)	1 (0.4)	158 (32.2)	7 (1.4)
Hypokalemia	33 (12.8)	9 (3.5)	26 (10.0)	2 (0.8)	64 (13.0)	17 (3.5)
Musculoskeletal and Connective Tissue Disorders						
Musculoskeletal pain	80 (31.1)	3 (1.2)	66 (25.3)	1 (0.4)	139 (28.3)	4 (0.8)
Nervous System Disorders						
Headache	56 (21.8)	1 (0.4)	42 (16.1)	0	105 (21.4)	1 (0.2)
Dizziness	32 (12.5)	1 (0.4)	22 (8.4)	0	58 (11.8)	1 (0.2)
Respiratory, thoracic and mediastinal disorders						

MedDRA System Organ Class Preferred Term/ Grouped Term [a]	Number (%) of Subjects					
	Study U302				HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)	
	T-DXd (N = 257)		T-DM1 (N = 261)			
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Epistaxis	29 (11.3)	0	42 (16.1)	1 (0.4)	63 (12.8)	0
Cough	27 (10.5)	1 (0.4)	26 (10.0)	0	83 (16.9)	1 (0.2)
Interstitial lung disease [b]	27 (10.5)	2 (0.8)	5 (1.9)	0	62 (12.6)	3 (0.6)
Skin and subcutaneous tissue disorders						
Alopecia	95 (37.0)	1 (0.4)	8 (3.1)	0	203 (41.3)	2 (0.4)

ADR = adverse drug reaction; BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities, Version 23.0; N = total number of treated subjects; PT = preferred term; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan

No Grade 5 ADRs were reported in either treatment arm.

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

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

[b] Interstitial lung disease includes events that were adjudicated as drug-related ILD. Source: Module 5.3.5.3 Table 2.22

Table 2.15: Overview of Selected Treatment-emergent Adverse Events, by Preferred Term/Grouped Term (Safety Analysis Set)

Selected TEAE (MedDRA Preferred Term/ Grouped Term [a])	Number (%) of Subjects											
	Overall		≥Grade 3		SAE		Study Drug Discontinuation		Dose Reduction		Study Drug Interruption	
	T-DXd (N=257)	T-DM1 (N=261)	T-DXd (N=257)	T-DM1 (N=261)	T-DXd (N=257)	T-DM1 (N=261)	T-DXd (N=257)	T-DM1 (N=261)	T-DXd (N=257)	T-DM1 (N=261)	T-DXd (N=257)	T-DM1 (N=261)
Nausea	195 (75.9)	79 (30.3)	17 (6.6)	1 (0.4)	2 (0.8)	0	0	0	16 (6.2)	1 (0.4)	8 (3.1)	0
Fatigue [a]	126 (49.0)	90 (34.5)	15 (5.8)	2 (0.8)	0	1 (0.4)	1 (0.4)	0	8 (3.1)	4 (1.5)	11 (4.3)	5 (1.9)
Vomiting	126 (49.0)	26 (10.0)	4 (1.6)	2 (0.8)	5 (1.9)	2 (0.8)	1 (0.4)	0	3 (1.2)	1 (0.4)	2 (0.8)	1 (0.4)
Neutropenia [a]	110 (42.8)	31 (11.9)	49 (19.1)	8 (3.1)	0	0	1 (0.4)	0	9 (3.5)	1 (0.4)	43 (16.7)	5 (1.9)
Constipation	88 (34.2)	51 (19.5)	0	0	1 (0.4)	1 (0.4)	0	0	0	0	0	0
Anemia [a]	84 (32.7)	45 (17.2)	19 (7.4)	15 (5.7)	2 (0.8)	3 (1.1)	0	0	1 (0.4)	0	9 (3.5)	7 (2.7)
Leukopenia [a]	78 (30.4)	22 (8.4)	17 (6.6)	1 (0.4)	0	0	0	0	1 (0.4)	0	13 (5.1)	0
Decreased appetite	75 (29.2)	44 (16.9)	4 (1.6)	1 (0.4)	1 (0.4)	0	0	0	2 (0.8)	0	3 (1.2)	2 (0.8)
Diarrhoea	75 (29.2)	18 (6.9)	3 (1.2)	1 (0.4)	0	1 (0.4)	0	0	2 (0.8)	0	2 (0.8)	0
Thrombocytopenia [a]	66 (25.7)	139 (53.3)	19 (7.4)	67 (25.7)	0	3 (1.1)	2 (0.8)	7 (2.7)	5 (1.9)	11 (4.2)	11 (4.3)	6 (2.3)
Headache [a]	56 (21.8)	42 (16.1)	1 (0.4)	0	0	0	0	0	1 (0.4)	0	0	0
Abdominal pain [a]	54 (21.0)	20 (7.7)	2 (0.8)	1 (0.4)	1 (0.4)	1 (0.4)	0	0	1 (0.4)	0	3 (1.2)	0
Stomatitis [a]	50 (19.5)	14 (5.4)	2 (0.8)	0	0	0	0	0	1 (0.4)	0	1 (0.4)	0
Upper respiratory tract infection [a]	37 (14.4)	23 (8.8)	1 (0.4)	0	1 (0.4)	0	0	0	0	0	3 (1.2)	1 (0.4)
Lymphopenia [a]	29 (11.3)	9 (3.4)	10 (3.9)	3 (1.1)	0	0	0	0	0	0	1 (0.4)	0
Rash [a]	20 (7.8)	27 (10.3)	0	0	0	0	0	0	0	0	0	0
Febrile neutropenia	2 (0.8)	0	2 (0.8)	0	2 (0.8)	0	0	0	1 (0.4)	0	1 (0.4)	0

MedDRA = Medical Dictionary for Regulatory Activities, Version 23.0; N = total number of treated subjects; PT = preferred term; SAE = serious adverse event; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event

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

PTs/grouped terms are sorted by decreasing incidence in the overall column for the T-DXd arm.

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 once for each of the different PTs/grouped terms.

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

Source: Module 5.3.5.3 SCS Tables 1.2.2.1, 1.2.2.3, 1.2.2.4, 1.2.2.5, 1.2.2.6

Adverse events of special interest – ILD and Left ventricular dysfunction

Table 2.19 Selected Preferred Terms in Adverse Events of Special Interest

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 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 23.0; PT = preferred term; SMQ = Standardised MedDRA Query

Table 2.20 ILD Events by Adjudicated Outcome and Adjudicated Grade (Safety Analysis Set)

Adjudicated Outcome/ CTCAE Grade Reported by Adjudication Committee [a]	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Subjects with any event of potential ILD	36 (14.0)	5 (1.9)	81 (16.5)
Subjects with any event adjudicated as ILD	28 (10.9)	5 (1.9)	66 (13.4)
Grade 1	7 (2.7)	4 (1.5)	14 (2.9)
Grade 2	17 (6.6)	1 (0.4)	39 (7.9)
Grade 3	2 (0.8)	0	3 (0.6)
Grade 4	1 (0.4)	0	1 (0.2)
Grade 5	1 (0.4)	0	9 (1.8)
≥Grade 3	4 (1.6)	0	13 (2.6)
Subjects with any event adjudicated as drug-related ILD	27 (10.5)	5 (1.9)	62 (12.6)
Grade 1	7 (2.7)	4 (1.5)	14 (2.9)
Grade 2	18 (7.0)	1 (0.4)	38 (7.7)
Grade 3	2 (0.8)	0	3 (0.6)
Grade 4	0	0	0
Grade 5	0	0	7 (1.4)
≥Grade 3	2 (0.8)	0	10 (2.0)
Subjects with any event adjudicated as not drug-related ILD	1 (0.4)	0	4 (0.8)

Adjudicated Outcome/ CTCAE Grade Reported by Adjudication Committee [a]	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Grade 1	0	0	0
Grade 2	0	0	2 (0.4)
Grade 3	0	0	0
Grade 4	0	0	0
Grade 5	1 (0.4)	0	2 (0.4)
≥Grade 3	1 (0.4)	0	2 (0.4)

AC = Adjudication Committee; BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities, Version 23.0; N = total number of treated subjects; PT = preferred term; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event
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 2.21 Overview of Adjudicated Drug-related ILD Events (Safety Analysis Set)

Adjudicated Outcome / CTCAE Grade Reported by Adjudication Committee	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Subjects with any event adjudicated as drug-related ILD	27 (10.5)	5 (1.9)	62 (12.6)
ILD CTCAE ≥Grade 3 [a]	2 (0.8)	0	10 (2.0)
Serious ILD	6 (2.3)	1 (0.4)	19 (3.9)
ILD associated with study drug discontinuation	21 (8.2)	3 (1.1)	46 (9.4)
ILD associated with study drug interruption	7 (2.7)	1 (0.4)	13 (2.6)
ILD associated with dose reduction	2 (0.8)	0	6 (1.2)
ILD associated with an outcome of death [b]	0	0	7 (1.4)

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; N = total number of treated subjects; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event
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] Adjudicated drug-related ILD associated with an outcome of 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 2.22 Outcome of Events Adjudicated as Drug-related ILD (Safety Analysis Set)

Outcome of Event	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Subjects with any TEAE adjudicated as drug-related ILD	27 (10.5)	5 (1.9)	62 (12.6)
Recovered/Resolved	15 (55.6)	4 (80.0)	29 (46.8)
Not recovered/Not resolved	8 (29.6)	0	19 (30.6) [a]
Recovering/Resolving	2 (7.4)	0	3 (4.8)
Recovered/Resolved with sequelae	2 (7.4)	0	3 (4.8)
Fatal	0	1 (20.0)	6 (9.7)
Missing/Unknown	0	0	1 (1.6)

BC = breast cancer; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; N = total number of treated subjects; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event

Outcomes are sorted by decreasing incidence in the T-DXd arm.

Percentage for each outcome was calculated using the number of subjects with adjudicated drug-related ILD as the denominator.

[a] The Study U201 eCRF had the option of "ongoing" as an outcome; 1 (1.6%) subject had an event of adjudicated drug-related ILD with this outcome. Source: Module 5.3.5.3 SCS Tables 1.2.4.1, 1.2.5.4

Table 2.23 Summary of LVEF Decrease, Based on Laboratory Data (Safety Analysis Set)

Parameter	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Subjects with worst LVEF CTCAE grade post-baseline, n (%)			
Non-missing n [a]	252	238	471
Grade 2	34 (13.5)	24 (10.1)	76 (16.1)
Subjects with LVEF measurement since worst grade, n (%)	26	17	59
Recovered from worst grade to ≥90% of baseline, n (%) [b,c]	20 (76.9)	12 (70.6)	45 (76.3)
Grade 3	1 (0.4)	1 (0.4)	1 (0.2)
Subjects with LVEF measurement since worst grade, n (%)	1	1	1
Recovered from worst grade to ≥90% of baseline, n (%) [b,c]	0	0	0
LVEF measurements at baseline			
n	257	261	491
Mean (Std Dev)	64.6 (6.36)	63.9 (6.24)	64.3 (6.52)
Median	65.0	65.0	64.0
Minimum, maximum	50, 86	50, 80	50, 86
40% to 49%	0	0	0
20% to 39%	0	0	0

Parameter	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
<20%	0	0	0
Lowest LVEF measurement post-baseline			
n	252	238	471
Mean (Std Dev)	61.0 (5.45)	62.2 (6.23)	60.5 (5.64)
Median	60.0	62.0	60.0
Minimum, maximum	40, 76	40, 79	40, 76
40% to 49%	3 (1.2)	2 (0.8)	9 (1.8)
20% to 39%	0	0	0
<20%	0	0	0
Maximum LVEF decrease from baseline			
n	252	238	471
Mean (Std Dev)	-3.6 (5.07)	-1.8 (5.93)	-3.9 (5.12)
Median	-3.0	-2.0	-3.0
Minimum, maximum	-20, 11	-20, 15	-20, 11
10% to 19% decrease in absolute value	32 (12.5)	23 (8.8)	71 (14.5)
≥20% decrease in absolute value	1 (0.4)	1 (0.4)	1 (0.2)
Highest LVEF measurement post-baseline			
n	252	238	471
Mean (Std Dev)	68.3 (6.08)	67.1 (6.21)	67.5 (6.31)
Median	69.0	67.0	67.0
Minimum, maximum	53, 84	50, 83	50, 84
Maximum LVEF increase from baseline			
n	252	238	471
Mean (Std Dev)	3.7 (5.77)	3.1 (6.01)	3.2 (5.63)
Median	3.0	2.0	3.0
Minimum, maximum	-16, 21	-15, 22	-16, 21
10% to 19% increase in absolute value	37 (14.4)	34 (13.0)	63 (12.8)
≥20% increase in absolute value	1 (0.4)	1 (0.4)	1 (0.2)

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events; HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; N = total number of subjects treated; Std Dev = standard deviation; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan

LVEF was defined as follows: Grade 2 = resting LVEF of ≥40% to <50%, or a 10% to <20% decrease from baseline; Grade 3 = resting LVEF of ≥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 2.11 Treatment-emergent Serious Adverse Events Reported in at Least 1% of Subjects in Either Treatment Arm of Study U302, by Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA Preferred Term/ Grouped Term [a]	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Any subject with a treatment-emergent SAE	49 (19.1)	47 (18.0)	111 (22.6)
Interstitial lung disease [b]	6 (2.3)	1 (0.4)	19 (3.9)
Vomiting	5 (1.9)	2 (0.8)	9 (1.8)
Pneumonia	4 (1.6)	5 (1.9)	10 (2.0)
Pyrexia	4 (1.6)	0	4 (0.8)
Disease progression	3 (1.2)	1 (0.4)	5 (1.0)
Urinary tract infection	3 (1.2)	1 (0.4)	5 (1.0)
Anemia [a]	2 (0.8)	3 (1.1)	5 (1.0)
Thrombocytopenia [a]	0	3 (1.1)	1 (0.2)

BC = breast cancer; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities, Version 23.0; N = total number of treated subjects; PT = preferred term; SAE = serious adverse event; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
PTs/grouped terms are sorted by decreasing incidence in the T-DXd arm. 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 once for each of the different PTs/grouped terms.
[a] The PTs included in each grouped term are listed in Table 2.1.
[b] Interstitial lung disease includes events that were adjudicated as drug-related ILD.
Source: Module 5.3.5.3 SCS Tables 1.2.1.8, 1.2.2.3, 1.2.4.2

Table 2.9 Primary Cause of Any Deaths and On-treatment Deaths (Safety Analysis Set)

Primary Cause of Death	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Any death	33 (12.8)	53 (20.3)	112 (22.8)
Disease progression	25 (9.7)	36 (13.8)	80 (16.3)
Adverse event	2 (0.8)	4 (1.5)	10 (2.0)
Other	2 (0.8) [a]	5 (1.9) [b]	9 (1.8)
Unknown	4 (1.6)	8 (3.1)	13 (2.6)
On-treatment death [c]	6 (2.3)	5 (1.9)	16 (3.3)
Disease progression	4 (1.6)	3 (1.1)	8 (1.6)
Adverse event	1 (0.4) [d]	2 (0.8) [e]	6 (1.2)
Other	0	0	1 (0.2)

Primary Cause of Death	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Unknown	1 (0.4) [f]	0	1 (0.2)

BC = breast cancer; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan

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

[a] Includes Subject No(Other: sepsis) and Subject No(Other: pneumonia).

[b] Includes Subject No(Other: encephalic death), Subject No(Other: myocardial infarction), Subject No. (Other: shortness of breath), Subject No. (Other: chest infection), and Subject No. (Other: disease progression brain metastases)

[c] On-treatment death was defined as any death that occurred from the date of the first dose up to 28 days (for Study J101) or up to 47 days (for Study U302 and Study U201) after the last dose of study drug.

[d] Adverse event of COVID-19 was considered to be the primary cause of death for Subject No.

[e] Includes Subject No. (COVID-19) and Subject No. (acute kidney injury).

[f] Subject No. had a Grade 5 TEAE of sudden death but an unknown primary cause of on-treatment death.

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

Table 2.10 Treatment-emergent Adverse Events Associated with an Outcome of Death, by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Any subject with a TEAE associated with an outcome of death	5 (1.9)	5 (1.9)	18 (3.7)
Disease progression	3 (1.2)	1 (0.4)	5 (1.0)
COVID-19	1 (0.4)	1 (0.4)	1 (0.2)
Sudden death	1 (0.4)	0	1 (0.2)
Acute kidney injury	0	1 (0.4)	1 (0.2)
Hepatic failure	0	1 (0.4)	0
Pulmonary embolism	0	1 (0.4)	0
Respiratory failure	0	0	3 (0.6)
Pneumonitis	0	0	2 (0.4)
Acute hepatic failure	0	0	1 (0.2)
Acute respiratory failure	0	0	1 (0.2)
General physical health deterioration	0	0	1 (0.2)
Lymphangitis	0	0	1 (0.2)
Pneumonia	0	0	1 (0.2)
Shock haemorrhagic	0	0	1 (0.2)

BC = breast cancer; HER2 = human epidermal growth factor receptor 2; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of treated subjects; PT = preferred term; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event

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.

PTs are sorted by decreasing incidence in the T-DXd arm.

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.

Source: Module 5.3.5.3 SCS Table 1.2.1.16

Laboratory findings

Table 3.1 Summary of Shifts from Baseline to Worst Post-baseline CTCAE Grade in Anemia (Hemoglobin Decrease) (Safety Analysis Set)

Treatment Arm/ Pool	Baseline CTCAE Grade	Number (%) of Subjects with Worst Post-baseline CTCAE Grade					
		Normal	1	2	3	4	Total
Study U302 T-DXd (N = 257)	Normal	49 (19.1)	**85 (33.1)**	**33 (12.8)**	**10 (3.9)**	0	177 (68.9)
	1	1 (0.4)	37 (14.4)	**29 (11.3)**	**6 (2.3)**	0	73 (28.4)
	2	0	1 (0.4)	5 (1.9)	**1 (0.4)**	0	7 (2.7)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	50 (19.5)	123 (47.9)	67 (26.1)	17 (6.6)	0	257 (100)
Study U302 T-DM1 (N = 259)	Normal	120 (46.3)	**54 (20.8)**	**10 (3.9)**	**2 (0.8)**	0	186 (71.8)
	1	6 (2.3)	27 (10.4)	**19 (7.3)**	**11 (4.2)**	0	63 (24.3)
	2	0	0	6 (2.3)	**3 (1.2)**	0	9 (3.5)
	3	0	0	1 (0.4)	0	0	1 (0.4)
	4	0	0	0	0	0	0
	Total	126 (48.6)	81 (31.3)	36 (13.9)	16 (6.2)	0	259 (100)
HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 489)	Normal	72 (14.7)	**165 (33.7)**	**60 (12.3)**	**16 (3.3)**	0	313 (64.0)
	1	1 (0.2)	61 (12.5)	**70 (14.3)**	**13 (2.7)**	0	145 (29.7)
	2	0	1 (0.2)	19 (3.9)	**9 (1.8)**	0	29 (5.9)
	3	0	0	2 (0.4)	0	0	2 (0.4)
	4	0	0	0	0	0	0
	Total	73 (14.9)	227 (46.4)	151 (30.9)	38 (7.8)	0	489 (100)

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan
For each group, percentages were based on the number of subjects in the Safety Analysis Set who had a baseline and at least 1 post-baseline assessment.
Baseline value was defined as the last non-missing value prior to the first dose of study drug.
Bolded values represent worsening from baseline.
Source: Module 5.3.5.3 SCS Table 1.3.1.1

Table 3.2 Summary of Shifts (Decrease) from Baseline to Worst Post-baseline CTCAE Grade in Platelet Count (Safety Analysis Set)

Treatment Arm/ Pool	Baseline CTCAE Grade	Number (%) of Subjects with Worst Post-baseline CTCAE Grade					
		Normal	1	2	3	4	Total
Study U302 T-DXd (N = 257)	Normal	119 (46.3)	**97 (37.7)**	**16 (6.2)**	**14 (5.4)**	**3 (1.2)**	249 (96.9)
	1	0	4 (1.6)	**2 (0.8)**	**2 (0.8)**	0	8 (3.1)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	119 (46.3)	101 (39.3)	18 (7.0)	16 (6.2)	3 (1.2)	257 (100)
	Normal	52 (20.1)	**79 (30.5)**	**63 (24.3)**	**51 (19.7)**	**6 (2.3)**	251 (96.9)
	1	0	3 (1.2)	0	**4 (1.5)**	**1 (0.4)**	8 (3.1)

Treatment Arm/ Pool	Baseline CTCAE Grade	Number (%) of Subjects with Worst Post-baseline CTCAE Grade					
		Normal	1	2	3	4	Total
Study U302 T-DM1 (N = 259)	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	52 (20.1)	82 (31.7)	63 (24.3)	55 (21.2)	7 (2.7)	259 (100)
HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 488)	Normal	216 (44.3)	**165 (33.8)**	**29 (5.9)**	**20 (4.1)**	**3 (0.6)**	433 (88.7)
	1	2 (0.4)	30 (6.1)	**16 (3.3)**	**6 (1.2)**	0	54 (11.1)
	2	1 (0.2)	0	0	0	0	1 (0.2)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	219 (44.9)	195 (40.0)	45 (9.2)	26 (5.3)	3 (0.6)	488 (100)

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan

For each group, percentages were based on the number of subjects in the Safety Analysis Set who had a baseline and at least 1 post-baseline assessment.

Baseline value was defined as the last non-missing value prior to the first dose of study drug.

Bolded values represent worsening from baseline.

Source: Module 5.3.5.3 SCS Table 1.3.1.1

Table 3.3 Summary of Shifts (Decrease) from Baseline to Worst Post-baseline CTCAE Grade in Neutrophil Count (Safety Analysis Set)

Treatment Arm/ Pool	Baseline CTCAE Grade	Number (%) of Subjects with Worst Post-baseline CTCAE Grade					
		Normal	1	2	3	4	Total
Study U302 T-DXd (N = 257)	Normal	76 (29.6)	**56 (21.8)**	**72 (28.0)**	**30 (11.7)**	**1 (0.4)**	235 (91.4)
	1	0	2 (0.8)	**6 (2.3)**	**9 (3.5)**	**2 (0.8)**	19 (7.4)
	2	0	0	0	**3 (1.2)**	0	3 (1.2)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	76 (29.6)	58 (22.6)	78 (30.4)	42 (16.3)	3 (1.2)	257 (100)
Study U302 T-DM1 (N = 259)	Normal	167 (64.5)	**34 (13.1)**	**24 (9.3)**	**5 (1.9)**	0	230 (88.8)
	1	3 (1.2)	10 (3.9)	**13 (5.0)**	**1 (0.4)**	0	27 (10.4)
	2	0	0	2 (0.8)	0	0	2 (0.8)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	170 (65.6)	44 (17.0)	39 (15.1)	6 (2.3)	0	259 (100)
HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 488)	Normal	150 (30.7)	**91 (18.6)**	**141 (28.9)**	**61 (12.5)**	**3 (0.6)**	446 (91.4)
	1	0	4 (0.8)	**12 (2.5)**	**15 (3.1)**	**4 (0.8)**	35 (7.2)
	2	1 (0.2)	1 (0.2)	0	**3 (0.6)**	0	5 (1.0)
	3	0	2 (0.4)	0	0	0	2 (0.4)
	4	0	0	0	0	0	0
	Total	151 (30.9)	98 (20.1)	153 (31.4)	79 (16.2)	7 (1.4)	488 (100)

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, v5.0; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan

For each group, percentages were based on the number of subjects in the Safety Analysis Set who had a baseline and at least 1 post-baseline assessment.
Baseline value was defined as the last non-missing value prior to the first dose of study drug.
Bolded values represent worsening from baseline.
Source: Module 5.3.5.3 SCS Table 1.3.1.1

Blood chemistry

Table 3.5 Summary of Shifts (Increase) from Baseline to Worst Post-baseline CTCAE Grade in Serum Creatinine (Safety Analysis Set)

Treatment Arm/ Pool	Baseline CTCAE Grade	Number (%) of Subjects with Worst Post-baseline CTCAE Grade					
		Normal	1	2	3	4	Total
Study U302 T-DXd (N = 257)	Normal	206 (80.2)	**30 (11.7)**	**8 (3.1)**	0	**1 (0.4)**	245 (95.3)
	1	1 (0.4)	7 (2.7)	0	**1 (0.4)**	0	9 (3.5)
	2	0	1 (0.4)	2 (0.8)	0	0	3 (1.2)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	207 (80.5)	38 (14.8)	10 (3.9)	1 (0.4)	1 (0.4)	257 (100)
Study U302 T-DM1 (N = 259)	Normal	230 (88.8)	**14 (5.4)**	**5 (1.9)**	0	0	249 (96.1)
	1	2 (0.8)	6 (2.3)	**1 (0.4)**	**1 (0.4)**	0	10 (3.9)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	232 (89.6)	20 (7.7)	6 (2.3)	1 (0.4)	0	259 (100)
HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)	Normal	392 (79.8)	**70 (14.3)**	**12 (2.4)**	0	**1 (0.2)**	475 (96.7)
	1	1 (0.2)	11 (2.2)	0	**1 (0.2)**	0	13 (2.6)
	2	0	1 (0.2)	2 (0.4)	0	0	3 (0.6)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	393 (80.0)	82 (16.7)	14 (2.9)	1 (0.2)	1 (0.2)	491 (100)

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, v5.0; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan
For each group, percentages were based on the number of subjects in the Safety Analysis Set who had a baseline and at least 1 post-baseline assessment.
Baseline value was defined as the last non-missing value prior to the first dose of study drug.
Bolded values represent worsening from baseline. Source: Module 5.3.5.3 SCS Table 1.3.1.2

Table 3.7 Summary of Shifts (Decrease) from Baseline to Worst Post-Baseline CTCAE Grade in Potassium (Safety Analysis Set)

Treatment Arm/ Pool	Baseline CTCAE Grade	Number (%) of Subjects with Worst Post-baseline CTCAE Grade					
		Normal	1	2	3	4	Total
Study U302 T-DXd (N = 257)	Normal	161 (62.6)	**78 (30.4)**	0	**7 (2.7)**	**2 (0.8)**	248 (96.5)
	1	1 (0.4)	4 (1.6)	0	**2 (0.8)**	**1 (0.4)**	8 (3.1)
	2	0	0	0	0	0	0
	3	0	0	0	1 (0.4)	0	1 (0.4)
	4	0	0	0	0	0	0
	Total	162 (63.0)	82 (31.9)	0	10 (3.9)	3 (1.2)	257 (100)

Treatment Arm/ Pool	Baseline CTCAE Grade	Number (%) of Subjects with Worst Post-baseline CTCAE Grade					
		Normal	1	2	3	4	Total
Study U302 T-DM1 (N = 259)	Normal	154 (59.5)	**98 (37.8)**	0	**4 (1.5)**	0	256 (98.8)
	1	1 (0.4)	2 (0.8)	0	0	0	3 (1.2)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	155 (59.8)	100 (38.6)	0	4 (1.5)	0	259 (100)
HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 487)	Normal	317 (65.1)	**78 (16.0)**	**60 (12.3)**	**14 (2.9)**	**2 (0.4)**	471 (96.7)
	1	1 (0.2)	4 (0.8)	0	**2 (0.4)**	**1 (0.2)**	8 (1.6)
	2	0	0	5 (1.0)	**2 (0.4)**	0	7 (1.4)
	3	0	0	0	1 (0.2)	0	1 (0.2)
	4	0	0	0	0	0	0
	Total	318 (65.3)	82 (16.8)	65 (13.3)	19 (3.9)	3 (0.6)	487 (100)

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, v5.0; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan

For each group, percentages were based on the number of subjects in the Safety Analysis Set who had a baseline and at least 1 post-baseline assessment.

Baseline value was defined as the last non-missing value prior to the first dose of study drug.

Bolded values represent worsening from baseline. Source: Module 5.3.5.3 SCS Table 1.3.1.2

Table 3.8 Hepatic Function Abnormalities (Safety Analysis Set)

Hepatic Parameter	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Alanine aminotransferase (ALT)			
Non-missing n [a]	257	259	489
Baseline ≥ULN	36 (14.0)	32 (12.4)	77 (15.7)
Maximum post-baseline value			
≥3 × ULN	21 (8.2)	44 (17.0)	29 (5.9)
≥5 × ULN	5 (1.9)	18 (6.9)	6 (1.2)
≥8 × ULN	0	7 (2.7)	1 (0.2)
≥10 × ULN	0	4 (1.5)	1 (0.2)
≥20 × ULN	0	0	0
Aspartate aminotransferase (AST)			
Non-missing n [a]	257	259	489
Baseline ≥ULN	54 (21.0)	49 (18.9)	156 (31.9)
Maximum post-baseline value			
≥3 × ULN	18 (7.0)	70 (27.0)	31 (6.3)
≥5 × ULN	5 (1.9)	19 (7.3)	8 (1.6)
≥8 × ULN	2 (0.8)	7 (2.7)	3 (0.6)

Hepatic Parameter	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
≥10 × ULN	1 (0.4)	4 (1.5)	2 (0.4)
≥20 × ULN	0	0	1 (0.2)
ALT or AST			
Non-missing n [a]	257	259	489
Baseline ≥ULN	62 (24.1)	60 (23.2)	167 (34.2)
Maximum post-baseline value			
≥3 × ULN	30 (11.7)	76 (29.3)	48 (9.8)
≥5 × ULN	9 (3.5)	26 (10.0)	12 (2.5)
≥8 × ULN	2 (0.8)	11 (4.2)	3 (0.6)
≥10 × ULN	1 (0.4)	8 (3.1)	2 (0.4)
≥20 × ULN	0	0	1 (0.2)
Total bilirubin (TBL)			
Non-missing n [a]	257	259	491
Baseline ≥ULN	4 (1.6)	3 (1.2)	11 (2.2)
Maximum post-baseline value			
≥1.5 × ULN	16 (6.2)	9 (3.5)	30 (6.1)
≥2 × ULN	7 (2.7)	1 (0.4)	11 (2.2)
≥3 × ULN	1 (0.4)	0	2 (0.4)
Alkaline phosphatase (ALP)			
Non-missing n [a]	257	259	491
Baseline ≥ULN	47 (18.3)	37 (14.3)	132 (26.9)
Maximum post-baseline value			
≥1.5 × ULN	88 (34.2)	72 (27.8)	180 (36.7)
≥2 × ULN	45 (17.5)	36 (13.9)	94 (19.1)
Concurrent TBL elevation with ALT or AST elevation [b]			
Non-missing n [a]	257	259	489
ALT or AST ≥3 × ULN and TBL ≥2 × ULN	3 (1.2)	1 (0.4)	4 (0.8)
Concurrent TBL elevation with ALT or AST elevation and ALP <2 x ULN [b]			
Non-missing n [a]	257	259	489
ALT or AST ≥3 × ULN and TBL ≥2 × ULN and ALP <2 × ULN	3 (1.2)	1 (0.4)	4 (0.8)

BC = breast cancer; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; 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

ECG

Table 4.1 Summary of QTcF Intervals (Safety Analysis Set)

QTcF Interval	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Non-missing n [a]	257	252	491
New >470 ms (female) or >450 ms (male) [b]	25 (9.7)	20 (7.9)	49 (10.0)
New >480 ms [b]	13 (5.1)	14 (5.6)	28 (5.7)
New >500 ms [b]	5 (1.9)	8 (3.2)	8 (1.6)
>30 ms increase from baseline [c]	94 (36.6)	67 (26.6)	146 (29.7)
>60 ms increase from baseline [c]	15 (5.8)	13 (5.2)	24 (4.9)

BC = breast cancer; ECG = electrocardiogram; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; ms = millisecond; QTcF = QT interval corrected for heart rate using Fridericia's correction formula; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan
Percentages were calculated using the non-missing n as the denominator.
[a] Non-missing n is the number of subjects with both baseline and post-baseline data.
[b] A new ECG abnormality was defined as an abnormal ECG finding post-baseline that was not present at baseline.
[c] The baseline value was defined as the last non-missing value before first dose of study drug. If multiple ECG measurements were taken at baseline, the average of all baseline values was used as the baseline value. Source: Module 5.3.5.3 SCS Table 1.3.3

Immunogenicity

Infusion-related reactions occurred infrequently (n=6). Immunogenicity was low with a total of 4 subjects (1.6%) having the treatment-emergent ADAs. None had an event of IRR.

Safety in special populations

Intrinsic factors

Table 5.1 Overall Summary of Treatment-emergent Adverse Events by Age Group (Safety Analysis Set)

Parameter	Number (%) of Subjects					
	Age Group <65 years			Age Group ≥65 years		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 382)	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 109)
	T-DXd (N = 209)	T-DM1 (N = 204)		T-DXd (N = 48)	T-DM1 (N = 57)	
Duration of treatment (months)						
Median	14.45	6.87	12.99	12.61	8.28	12.02

Minimum, maximum	1.4, 29.8	0.7, 25.1	0.7, 37.1	0.7, 26.0	0.7, 25.1	0.7, 29.5
Subjects with any TEAE	208 (99.5)	194 (95.1)	380 (99.5)	48 (100)	55 (96.5)	109 (100)
TEAEs with worst CTCAE ≥Grade 3 [a]	102 (48.8)	93 (45.6)	198 (51.8)	32 (66.7)	33 (57.9)	72 (66.1)
Serious TEAEs	31 (14.8)	26 (12.7)	74 (19.4)	18 (37.5)	21 (36.8)	37 (33.9)
TEAEs associated with study drug discontinuation	26 (12.4)	11 (5.4)	55 (14.4)	9 (18.8)	8 (14.0)	22 (20.2)
TEAEs associated with dose reduction	46 (22.0)	20 (9.8)	79 (20.7)	9 (18.8)	13 (22.8)	25 (22.9)
TEAEs associated with study drug interruption	88 (42.1)	42 (20.6)	157 (41.1)	25 (52.1)	19 (33.3)	53 (48.6)
TEAEs associated with an outcome of death [b]	2 (1.0)	4 (2.0)	11 (2.9)	3 (6.3)	1 (1.8)	7 (6.4)
Subjects with any drug-related TEAE [c]	205 (98.1)	177 (86.8)	377 (98.7)	47 (97.9)	49 (86.0)	108 (99.1)
Drug-related TEAEs with worst CTCAE ≥Grade 3 [c]	89 (42.6)	77 (37.7)	171 (44.8)	27 (56.3)	27 (47.4)	60 (55.0)
Drug-related serious TEAEs	18 (8.6)	8 (3.9)	41 (10.7)	10 (20.8)	8 (14.0)	18 (16.5)
Drug-related TEAEs associated with study drug discontinuation	24 (11.5)	7 (3.4)	51 (13.4)	9 (18.8)	6 (10.5)	21 (19.3)
Drug-related TEAEs associated with dose reduction	46 (22.0)	20 (9.8)	78 (20.4)	9 (18.8)	13 (22.8)	20 (18.3)
Drug-related TEAEs associated with study drug interruption	69 (33.0)	23 (11.3)	121 (31.7)	22 (45.8)	11 (19.3)	45 (41.3)
Drug-related TEAEs associated with an outcome of death [b]	0	0	3 (0.8)	0	0	1 (0.9)

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, v5.0; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event

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

Age in years is 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 outcome of death, refer to Table .

[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

Sex

The number of male subjects (1 in the T-DXd arm and 1 in the T-DM1 arm) was too small to allow for meaningful comparison between males and females.

Race

Table 5.2: Overall Summary of Treatment-emergent Adverse Events by Race (Safety Analysis Set)

Parameter	Number (%) of Subjects								
	White			Asian			Other		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 190)	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 246)	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 51)
	T-DXd (N = 71)	T-DM1 (N = 71)		T-DXd (N = 149)	T-DM1 (N = 161)		T-DXd (N = 37)	T-DM1 (N = 29)	
Duration of treatment (months)									
Median	14.29	7.82	11.76	13.27	5.62	12.68	15.44	8.90	15.18
Minimum, maximum	1.4, 27.8	0.7, 21.9	0.7, 29.5	0.7, 29.8	0.7, 25.1	0.7, 37.1	4.1, 24.9	0.7, 19.5	2.8, 24.9
Subjects with any TEAE	71 (100)	69 (97.2)	189 (99.5)	148 (99.3)	152 (94.4)	245 (99.6)	37 (100)	28 (96.6)	51 (100)
TEAEs with worst CTCAE ≥Grade 3 [a]	34 (47.9)	28 (39.4)	109 (57.4)	80 (53.7)	85 (52.8)	130 (52.8)	20 (54.1)	13 (44.8)	28 (54.9)
Serious TEAEs	13 (18.3)	12 (16.9)	51 (26.8)	27 (18.1)	31 (19.3)	47 (19.1)	9 (24.3)	4 (13.8)	11 (21.6)
TEAEs associated with study drug discontinuation	6 (8.5)	5 (7.0)	23 (12.1)	22 (14.8)	13 (8.1)	42 (17.1)	7 (18.9)	1 (3.4)	12 (23.5)
TEAEs associated with study drug interruption	32 (45.1)	19 (26.8)	77 (40.5)	67 (45.0)	35 (21.7)	110 (44.7)	14 (37.8)	7 (24.1)	20 (39.2)
TEAEs associated with dose reduction	13 (18.3)	4 (5.6)	39 (20.5)	35 (23.5)	26 (16.1)	53 (21.5)	7 (18.9)	3 (10.3)	10 (19.6)
TEAEs associated with an outcome of death [b]	3 (4.2)	2 (2.8)	14 (7.4)	2 (1.3)	2 (1.2)	4 (1.6)	0	1 (3.4)	0
Subjects with any drug-related TEAE [c]	69 (97.2)	58 (81.7)	187 (98.4)	146 (98.0)	142 (88.2)	243 (98.8)	37 (100)	26 (89.7)	51 (100)
Drug-related TEAEs with worst CTCAE ≥Grade 3 [c]	29 (40.8)	20 (28.2)	87 (45.8)	70 (47.0)	75 (46.6)	117 (47.6)	17 (45.9)	9 (31.0)	25 (49.0)
Drug-related serious TEAEs	6 (8.5)	4 (5.6)	22 (11.6)	15 (10.1)	11 (6.8)	27 (11.0)	7 (18.9)	1 (3.4)	9 (17.6)
Drug-related TEAEs associated with study drug discontinuation	6 (8.5)	3 (4.2)	21 (11.1)	20 (13.4)	10 (6.2)	39 (15.9)	7 (18.9)	0	12 (23.5)
Drug-related TEAEs associated with study drug interruption	20 (28.2)	10 (14.1)	52 (27.4)	59 (39.6)	20 (12.4)	93 (37.8)	12 (32.4)	4 (13.8)	18 (35.3)
Drug-related TEAEs associated with dose reduction	13 (18.3)	4 (5.6)	33 (17.4)	35 (23.5)	26 (16.1)	53 (21.5)	7 (18.9)	3 (10.3)	10 (19.6)
Drug-related TEAEs associated with an outcome of death [b]	0	0	3 (1.6)	0	0	1 (0.4)	0	0	0

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, v5.0; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event

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 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 1.4.2, 1.4.3

Table 1 Treatment-emergent Adverse Events Associated with Outcome of Death in White and Asian Subjects in the T-DXd 5.4 mg/kg BC Pool (Safety Analysis Set)

Parameter	Number (%) of Subjects	
	White Subjects (N =190)	Asian Subjects (N = 246)
Subjects with any TEAE with outcome of death	**14 (7.4)**	**4 (1.6)**
Disease progression	3 (1.6)	2 (0.8)
Pneumonitis	2 (1.1)	0
Respiratory failure	2 (1.1)	1 (0.4)
Acute hepatic failure	1 (0.5)	0
Acute kidney injury	1 (0.5)	0
Acute respiratory failure	1 (0.5)	0
COVID-19	1 (0.5)	0
General physical health deterioration	1 (0.5)	0
Lymphangitis	1 (0.5)	0
Pneumonia	1 (0.5)	0
Shock haemorrhagic	1 (0.5)	0
Sudden death	0	1 (0.4)
Subjects with any drug-related TEAEs associated with death	3 (1.6)	1 (0.4)
Pneumonitis	2 (1.1)	0
Respiratory failure	1 (0.5)	1 (0.4)

BC = breast cancer; COVID-19 = coronavirus disease 2019; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event Source: Appendix 2 Table 1

ECOG PS

Table 5.3: Overall Summary of Treatment-emergent Adverse Events by ECOG Performance Status (Safety Analysis Set)

Parameter	Number (%) of Subjects					
	ECOG Performance Status 0			ECOG Performance Status 1		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 287)	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 203)
	T-DXd (N = 152)	T-DM1 (N = 174)		T-DXd (N = 105)	T-DM1 (N = 87)	
Duration of treatment (months)						
Median	14.82	7.08	13.83	12.42	5.72	11.07
Minimum, maximum	1.4, 29.8	0.7, 25.1	0.7, 30.0	0.7, 26.7	0.7, 20.3	0.7, 37.1
Subjects with any TEAE	151 (99.3)	165 (94.8)	285 (99.3)	105 (100)	84 (96.6)	203 (100)
TEAEs with worst CTCAE ≥Grade 3 [a]	74 (48.7)	78 (44.8)	149 (51.9)	60 (57.1)	48 (55.2)	120 (59.1)
Serious TEAEs	25 (16.4)	23 (13.2)	52 (18.1)	24 (22.9)	24 (27.6)	58 (28.6)
TEAEs associated with study drug discontinuation	19 (12.5)	11 (6.3)	46 (16.0)	16 (15.2)	8 (9.2)	31 (15.3)
TEAEs associated with dose reduction	31 (20.4)	20 (11.5)	52 (18.1)	24 (22.9)	13 (14.9)	52 (25.6)
TEAEs associated with study drug interruption	67 (44.1)	43 (24.7)	119 (41.5)	46 (43.8)	18 (20.7)	91 (44.8)
TEAEs associated with an outcome of death [b]	2 (1.3)	3 (1.7)	7 (2.4)	3 (2.9)	2 (2.3)	10 (4.9)
Subjects with any drug-related TEAE [c]	151 (99.3)	151 (86.8)	285 (99.3)	101 (96.2)	75 (86.2)	199 (98.0)
Drug-related TEAEs with worst CTCAE ≥Grade 3 [a]	67 (44.1)	69 (39.7)	132 (46.0)	49 (46.7)	35 (40.2)	98 (48.3)
Drug-related serious TEAEs	15 (9.9)	10 (5.7)	31 (10.8)	13 (12.4)	6 (6.9)	28 (13.8)
Drug-related TEAEs associated with study drug discontinuation	18 (11.8)	9 (5.2)	45 (15.7)	15 (14.3)	4 (4.6)	27 (13.3)
Drug-related TEAEs associated with dose reduction	31 (20.4)	20 (11.5)	50 (17.4)	24 (22.9)	13 (14.9)	48 (23.6)
Drug-related TEAEs associated with study drug interruption	67 (44.1)	43 (24.7)	119 (41.5)	33 (31.4)	8 (9.2)	67 (33.0)
Drug-related TEAEs associated with an outcome of death [b]	0	0	3 (1.0)	0	0	1 (0.5)

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, v5.0; ECOG = Eastern Cooperative Oncology Group; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; SAE = serious adverse event; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event

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 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

Renal function at baseline

Table 5.4: Overall Summary of Treatment-emergent Adverse Events by Baseline Renal Function (Safety Analysis Set)

Parameter	Number (%) of Subjects								
	Normal Renal Function			Mild Renal Impairment			Moderate Renal Impairment		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 243)	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 183)	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 59)
	T-DXd (N=134)	T-DM1 (N=131)		T-DXd (N=96)	T-DM1 (N=105)		T-DXd (N=27)	T-DM1 (N=22)	
Duration of treatment (months)									
Median	15.54	5.78	14.29	12.47	7.56	11.99	11.04	8.28	8.25
Minimum, maximum	1.4, 29.8	0.7, 22.5	0.7, 30.0	0.7, 29.7	0.7, 25.1	0.7, 37.1	3.4, 24.6	0.7, 24.8	0.7, 26.4
Subjects with any TEAE	134 (100.0)	125 (95.4)	246 (99.6)	96 (100.0)	99 (94.3)	187 (100.0)	26 (96.3)	25 (100.0)	55 (98.2)
TEAEs with worst CTCAE ≥Grade 3 [a]	66 (49.3)	58 (44.3)	131 (53.0)	55 (57.3)	52 (49.5)	109 (58.3)	13 (48.1)	16 (64.0)	29 (51.8)
Serious TEAEs	22 (16.4)	14 (10.7)	55 (22.3)	17 (17.7)	24 (22.9)	38 (20.3)	10 (37.0)	9 (36.0)	18 (32.1)
TEAEs associated with study drug discontinuation	16 (11.9)	4 (3.1)	34 (13.8)	11 (11.5)	11 (10.5)	26 (13.9)	8 (29.6)	4 (16.0)	16 (28.6)
TEAEs associated with dose reduction	30 (22.4)	12 (9.2)	51 (20.6)	19 (19.8)	16 (15.2)	39 (20.9)	6 (22.2)	5 (20.0)	14 (25.0)
TEAEs associated with study drug interruption	56 (41.8)	27 (20.6)	104 (42.1)	44 (45.8)	23 (21.9)	82 (43.9)	13 (48.1)	11 (44.0)	23 (41.1)
TEAEs associated with an outcome of death [b]	2 (1.5)	2 (1.5)	9 (3.6)	3 (3.1)	2 (1.9)	7 (3.7)	0	1 (4.0)	2 (3.6)
Subjects with any drug-related TEAE [c]	132 (98.5)	114 (87.0)	244 (98.8)	95 (99.0)	88 (83.8)	186 (99.5)	25 (92.6)	24 (96.0)	54 (96.4)
Drug-related TEAEs with worst CTCAE ≥Grade 3 [a]	55 (41.0)	46 (35.1)	111 (44.9)	49 (51.0)	44 (41.9)	93 (49.7)	12 (44.4)	14 (56.0)	26 (46.4)
Drug-related serious TEAEs	14 (10.4)	2 (1.5)	35 (14.2)	7 (7.3)	12 (11.4)	14 (7.5)	7 (25.9)	2 (8.0)	10 (17.9)
Drug-related TEAEs associated with study drug discontinuation	15 (11.2)	3 (2.3)	31 (12.6)	10 (10.4)	8 (7.6)	25 (13.4)	8 (29.6)	2 (8.0)	15 (26.8)
Drug-related TEAEs associated with dose reduction	30 (22.4)	12 (9.2)	50 (20.2)	19 (19.8)	16 (15.2)	36 (19.3)	6 (22.2)	5 (20.0)	12 (21.4)
Drug-related TEAEs associated with study drug interruption	44 (32.8)	12 (9.2)	83 (33.6)	36 (37.5)	16 (15.2)	63 (33.7)	11 (40.7)	6 (24.0)	19 (33.9)
Drug-related TEAEs associated with an outcome of death [b]	0	0	3 (1.2)	0	0	0	0	0	1 (1.8)

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, v5.0; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event

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 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

Hepatic function at baseline

Table 5.5: Overall Summary of Treatment-emergent Adverse Events by Baseline Hepatic Function (Safety Analysis Set)

Parameter	Number (%) of Subjects					
	Normal Hepatic Function			Mild Hepatic Impairment		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 340)	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 148)
	T-DXd (N = 208)	T-DM1 (N = 212)		T-DXd (N = 49)	T-DM1 (N = 49)	
Duration of treatment (months)						
Median	14.49	7.15	13.52	12.65	3.48	10.46
Minimum, maximum	1.4, 29.8	0.7, 25.1	0.7, 37.1	0.7, 26.2	0.7, 25.1	0.7, 26.3
Subjects with any TEAE	207 (99.5)	202 (95.3)	338 (99.4)	49 (100)	47 (95.9)	148 (100)
TEAEs with worst CTCAE ≥Grade 3 [a]	99 (47.6)	102 (48.1)	182 (53.5)	35 (71.4)	24 (49.0)	85 (57.4)
Serious TEAEs	32 (15.4)	34 (16.0)	70 (20.6)	17 (34.7)	13 (26.5)	40 (27.0)
TEAEs associated with study drug discontinuation	27 (13.0)	16 (7.5)	55 (16.2)	8 (16.3)	3 (6.1)	21 (14.2)
TEAEs associated with dose reduction	41 (19.7)	30 (14.2)	71 (20.9)	14 (28.6)	3 (6.1)	31 (20.9)
TEAEs associated with study drug interruption	85 (40.9)	49 (23.1)	146 (42.9)	28 (57.1)	12 (24.5)	63 (42.6)
TEAEs associated with an outcome of death [b]	3 (1.4)	3 (1.4)	11 (3.2)	2 (4.1)	2 (4.1)	7 (4.7)
Subjects with any drug-related TEAE [c]	204 (98.1)	184 (86.8)	335 (98.5)	48 (98.0)	42 (85.7)	147 (99.3)
Drug-related TEAEs with worst CTCAE ≥Grade 3 [a]	84 (40.4)	86 (40.6)	155 (45.6)	32 (65.3)	18 (36.7)	73 (49.3)
Drug-related serious TEAEs	17 (8.2)	13 (6.1)	37 (10.9)	11 (22.4)	3 (6.1)	22 (14.9)
Drug-related TEAEs associated with study drug discontinuation	25 (12.0)	11 (5.2)	51 (15.0)	8 (16.3)	2 (4.1)	20 (13.5)
Drug-related TEAEs associated with dose reduction	41 (19.7)	30 (14.2)	66 (19.4)	14 (28.6)	3 (6.1)	30 (20.3)
Drug-related TEAEs associated with study drug interruption	66 (31.7)	26 (12.3)	111 (32.6)	25 (51.0)	8 (16.3)	54 (36.5)
Drug-related TEAEs associated with an outcome of death [b]	0	0	4 (2.1)	0	0	0

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, v5.0; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event

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 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

Country and region

Table 5.6: Overall Summary of Treatment-emergent Adverse Events by Country (Safety Analysis Set)

Parameter	Number (%) of Subjects					
	Japan			Non-Japan		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 87)	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 404)
	T-DXd (N = 36)	T-DM1 (N = 31)		T-DXd (N = 221)	T-DM1 (N = 230)	
Duration of treatment (months)						
Median	13.57	7.06	12.16	14.39	6.90	12.65
Minimum, maximum	2.1, 29.8	1.3, 25.1	0.7, 37.1	0.7, 27.8	0.7, 25.1	0.7, 29.5
Subjects with any TEAE	36 (100)	29 (93.5)	87 (100)	220 (99.5)	220 (95.7)	402 (99.5)
TEAEs with worst CTCAE ≥Grade 3 [a]	18 (50.0)	15 (48.4)	46 (52.9)	116 (52.5)	111 (48.3)	224 (55.4)
Serious TEAEs	5 (13.9)	10 (32.3)	15 (17.2)	44 (19.9)	37 (16.1)	96 (23.8)
TEAEs associated with study drug discontinuation	8 (22.2)	4 (12.9)	23 (26.4)	27 (12.2)	15 (6.5)	54 (13.4)
TEAEs associated with dose reduction	9 (25.0)	8 (25.8)	16 (18.4)	46 (20.8)	25 (10.9)	88 (21.8)
TEAEs associated with study drug interruption	20 (55.6)	12 (38.7)	47 (54.0)	93 (42.1)	49 (21.3)	163 (40.3)
TEAEs associated with an outcome of death [b]	0	0	1 (1.1)	5 (2.3)	5 (2.2)	17 (4.2)
Subjects with any drug-related TEAE [c]	36 (100)	29 (93.5)	87 (100)	216 (97.7)	197 (85.7)	398 (98.5)
Drug-related TEAEs with worst CTCAE ≥Grade 3 [a]	17 (47.2)	15 (48.4)	43 (49.4)	99 (44.8)	89 (38.7)	188 (46.5)
Drug-related serious TEAEs	4 (11.1)	6 (19.4)	9 (10.3)	24 (10.9)	10 (4.3)	50 (12.4)
Drug-related TEAEs associated with study drug discontinuation	7 (19.4)	4 (12.9)	21 (24.1)	26 (11.8)	9 (3.9)	51 (12.6)
Drug-related TEAEs associated with dose reduction	9 (25.0)	8 (25.8)	16 (18.4)	46 (20.8)	25 (10.9)	82 (20.3)
Drug-related TEAEs associated with study drug interruption	18 (50.0)	7 (22.6)	39 (44.8)	73 (33.0)	27 (11.7)	127 (31.4)
Drug-related TEAEs associated with an outcome of death [b]	0	0	0	0	0	4 (1.0)

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, v5.0; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event

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

Parameter	Number (%) of Subjects								
	Asia			Europe			Rest of World [a]		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 231)	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 120)	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 41)
	T-DXd (N = 147)	T-DM1 (N = 159)		T-DXd (N = 52)	T-DM1 (N = 49)		T-DXd (N = 41)	T-DM1 (N = 36)	
Duration of treatment (months)									
Median	13.27	5.52	13.07	15.62	8.97	12.55	14.75	8.15	14.75
Minimum, maximum	0.7, 29.8	0.7, 25.1	0.7, 37.1	3.4, 24.9	0.7, 21.9	0.7, 26.3	1.4, 25.1	0.7, 21.5	1.4, 25.1
Subjects with any TEAE	146 (99.3)	150 (94.3)	230 (99.6)	52 (100)	46 (93.9)	119 (99.2)	41 (100)	36 (100)	41 (100)
TEAEs with worst CTCAE ≥Grade 3 [b]	79 (53.7)	84 (52.8)	125 (54.1)	25 (48.1)	21 (42.9)	68 (56.7)	21 (51.2)	18 (50.0)	21 (51.2)
Serious TEAEs	27 (18.4)	31 (19.5)	43 (18.6)	11 (21.2)	7 (14.3)	37 (30.8)	10 (24.4)	8 (22.2)	10 (24.4)
TEAEs associated with study drug discontinuation	22 (15.0)	13 (8.2)	42 (18.2)	6 (11.5)	3 (6.1)	17 (14.2)	6 (14.6)	2 (5.6)	6 (14.6)
TEAEs associated with dose reduction	35 (23.8)	26 (16.4)	50 (21.6)	11 (21.2)	7 (14.3)	24 (20.0)	6 (14.6)	0	6 (14.6)
TEAEs associated with study drug interruption	66 (44.9)	34 (21.4)	106 (45.9)	20 (38.5)	14 (28.6)	51 (42.5)	16 (39.0)	11 (30.6)	16 (39.0)
TEAEs associated with an outcome of death [c]	2 (1.4)	2 (1.3)	3 (1.3)	0	0	7 (5.8)	2 (4.9)	3 (8.3)	2 (4.9)
Subjects with any drug-related TEAE [d]	144 (98.0)	140 (88.1)	228 (98.7)	52 (100)	40 (81.6)	119 (99.2)	40 (97.6)	32 (88.9)	40 (97.6)
Drug-related TEAEs with worst CTCAE ≥Grade 3 [b]	69 (46.9)	74 (46.5)	112 (48.5)	24 (46.2)	15 (30.6)	57 (47.5)	15 (36.6)	13 (36.1)	15 (36.6)
Drug-related serious TEAEs	15 (10.2)	11 (6.9)	25 (10.8)	9 (17.3)	3 (6.1)	21 (17.5)	3 (7.3)	2 (5.6)	3 (7.3)
Drug-related TEAEs associated with study drug discontinuation	20 (13.6)	10 (6.3)	39 (16.9)	6 (11.5)	2 (4.1)	16 (13.3)	6 (14.6)	0	6 (14.6)
Drug-related TEAEs associated with dose reduction	35 (23.8)	26 (16.4)	50 (21.6)	11 (21.2)	7 (14.3)	22 (18.3)	6 (14.6)	0	6 (14.6)
Drug-related TEAEs associated with study drug interruption	58 (39.5)	19 (11.9)	91 (39.4)	15 (28.8)	8 (16.3)	38 (31.7)	11 (26.8)	6 (16.7)	11 (26.8)
Drug-related TEAEs associated with an outcome of death [c]	0	0	0	0	0	2 (1.7)	0	0	0

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, v5.0; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event

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

[a] Rest of World included the following countries: Australia and Brazil

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

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

[d] 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 interactions with strong cytochrome P450 (CYP)3A and organic anion transporting polypeptide (OATP)1B inhibitors were observed in a dedicated drug-drug interaction study (DS8201-A-A104) with ritonavir and itraconazole in subjects with BC (see Enhertu EPAR). No new information on drug interactions is available since the time of Study DS8201-A-A104 (DCO of 26 Sep 2018).

Discontinuation due to adverse events

Table 2.2 Overview of Treatment-emergent Adverse Events (Safety Analysis Set)

Parameter	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Subjects with any TEAE	256 (99.6)	249 (95.4)	489 (99.6)
TEAEs with CTCAE ≥Grade 3 [a]	134 (52.1)	126 (48.3)	270 (55.0)
Serious TEAEs	49 (19.1)	47 (18.0)	111 (22.6)
TEAEs associated with study drug interruption	113 (44.0)	61 (23.4)	210 (42.8)
TEAEs associated with dose reduction	55 (21.4)	33 (12.6)	104 (21.2)
TEAEs associated with study drug discontinuation	35 (13.6)	19 (7.3)	77 (15.7)
TEAEs associated with an outcome of death [b]	5 (1.9)	5 (1.9)	18 (3.7)
Drug-related TEAE [c]	252 (98.1)	226 (86.6)	485 (98.8)
TEAE with CTCAE ≥Grade 3 [a]	116 (45.1)	104 (39.8)	231 (47.0)
Serious TEAEs	28 (10.9)	16 (6.1)	59 (12.0)
TEAE associated with study drug interruption	91 (35.4)	34 (13.0)	166 (33.8)
TEAE associated with dose reduction	55 (21.4)	33 (12.6)	98 (20.0)
TEAE associated with study drug discontinuation	33 (12.8)	13 (5.0)	72 (14.7)
TEAE associated with an outcome of death	0	0	4 (0.8)

AE = adverse event; BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event

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 outcome of death, refer to Table .

[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 2.12 Treatment-emergent Adverse Events Associated with Study Drug Discontinuation in at Least 1% of Subjects in Either Treatment Arm of Study U302, by Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA Preferred Term/ Grouped Term	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool [b] (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Any subject with TEAE associated with study drug discontinuation	35 (13.6)	19 (7.3)	77 (15.7)
Interstitial lung disease [a]	21 (8.2)	3 (1.1)	46 (9.4)
Pneumonia [b]	3 (1.2)	1 (0.4)	4 (0.8)
Thrombocytopenia [c]	2 (0.8)	7 (2.7)	5 (1.0)

BC = breast cancer; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities, Version 23.0; N = total number of treated subjects; PT = preferred term; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event

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 once for each of the different PTs/grouped terms.

PTs/grouped terms are sorted by decreasing incidence in the T-DXd arm.
[a] ILD includes events that were adjudicated as drug-related ILD. Per protocol, discontinuation was required for any subject with ≥Grade 2 ILD in Study U302. Study U201 and Study J101 used different criteria 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)
[b] Includes 1 subject in the T-DXd arm who had a PT of pneumonia that was adjudicated as drug-related ILD. This subject is counted under both ILD and pneumonia.
[c] Includes PTs of thrombocytopenia and platelet count decreased. Source: Module 5.3.5.3 SCS Tables 1.2.1.10, 1.2.2.4, 1.2.4.3

Table 2.13 Treatment-emergent Adverse Events Associated with Dose Reduction Reported in at Least 1% of Subjects in Either Treatment Arm of Study U302, by Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA Preferred Term/ Grouped Term [a]	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Any subject with TEAE associated with dose reduction	55 (21.4)	33 (12.6)	104 (21.2)
Nausea	16 (6.2)	1 (0.4)	25 (5.1)
Neutropenia [a]	9 (3.5)	1 (0.4)	16 (3.3)
Fatigue [a]	8 (3.1)	4 (1.5)	17 (3.5)
Thrombocytopenia [a]	5 (1.9)	11 (4.2)	7 (1.4)
Alanine aminotransferase increased	3 (1.2)	7 (2.7)	4 (0.8)
Vomiting	3 (1.2)	1 (0.4)	6 (1.2)
Aspartate aminotransferase increased	1 (0.4)	7 (2.7)	2 (0.4)

BC = breast cancer; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities, Version 23.0; N = total number of treated subjects; PT = preferred term; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
PTs/grouped terms are sorted by decreasing incidence in the T-DXd arm.
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 once for each of the different PTs/grouped terms.
[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 2.14 Treatment-emergent Adverse Events Associated with Study Drug Interruption Reported in at Least 1% of Subjects in Either Treatment Arm of Study U302, by Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA Preferred Term/ Grouped Term [a]	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Any subject with a TEAE associated with study drug interruption	113 (44.0)	61 (23.4)	210 (42.8)
Neutropenia [a]	43 (16.7)	5 (1.9)	78 (15.9)
Leukopenia [a]	13 (5.1)	0	21 (4.3)
Fatigue [a]	11 (4.3)	5 (1.9)	18 (3.7)
Thrombocytopenia [a]	11 (4.3)	6 (2.3)	18 (3.7)
Anemia [a]	9 (3.5)	7 (2.7)	17 (3.5)
Nausea	8 (3.1)	0	12 (2.4)
Pneumonia	8 (3.1)	3 (1.1)	11 (2.2)
Interstitial lung disease [b]	7 (2.7)	1 (0.4)	13 (2.6)
Dyspnoea	5 (1.9)	0	8 (1.6)

MedDRA Preferred Term/ Grouped Term [a]	Number (%) of Subjects		
	Study U302		HER2-positive BC T-DXd 5.4 mg/kg Pool (N = 491)
	T-DXd (N = 257)	T-DM1 (N = 261)	
Pyrexia	5 (1.9)	1 (0.4)	8 (1.6)
COVID-19	4 (1.6)	3 (1.1)	4 (0.8)
Abdominal pain [a]	3 (1.2)	0	3 (0.6)
Cellulitis	3 (1.2)	0	6 (1.2)
Decreased appetite	3 (1.2)	2 (0.8)	3 (0.6)
Dizziness	3 (1.2)	0	3 (0.6)
Upper respiratory tract infection [a]	3 (1.2)	1 (0.4)	11 (2.2)
Urinary tract infection	3 (1.2)	0	3 (0.6)
Aspartate aminotransferase increased	2 (0.8)	3 (1.1)	2 (0.4)

BC = breast cancer; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities, Version 23.0; N = total number of treated subjects; PT = preferred term; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event
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 once for each of the different PTs/grouped terms.
PTs/grouped terms are sorted by decreasing incidence 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 drug-related ILD. Source: Module 5.3.5.3 SCS Tables 1.2.1.12, 1.2.2.6, 1.2.4.5

Post marketing experience

Initial approval of T-DXd was granted by the United States Food and Drug Administration (US FDA) under accelerated approval on 20 Dec 2019 for the treatment of adults with unresectable or metastatic HER2-positive BC who have received 2 or more prior anti-HER2-based regimens in the metastatic setting.

As of 01 Sep 2021, T-DXd has been authorized for sale in the US, Japan, EU, Great Britain, Israel, and Canada for the treatment of HER2-positive BC and, in some countries, for the treatment of HER2-positive gastric cancer (GC) as well.

The first 3 Periodic Benefit Risk Evaluation Reports (PBRERs) covered the reporting periods 20 Dec 2019 through 19 Jun 2020, 20 Jun 2020 through 19 Dec 2020, and 20 Dec 2020 through 19 Jun 2021. There were no new safety findings based on spontaneous cases received during the period. For the purpose of this procedure, a periodic output was generated from the global safety database from 20 Jun 2021 through 01 Sep 2021. Based on review of data from 20 Dec 2019 through 01 Sep 2021, no new safety findings have been identified from spontaneous reports during the post-marketing period. The reported events were generally consistent with the known safety profile of T-DXd.

2.5.1. Discussion on clinical safety

Safety data has been provided for 1219 patients that received trastuzumab deruxtecan (T-DXd) ≥5.4 mg/kg across five completed clinical trials in various tumour types. Most patients received 6.4 mg/kg (n=619), followed by 5.4 mg/kg (n=573). The safety populations of interest are patients from the pivotal study Destiny Breast03 or U302 (n=257 who received trastuzumab deruxtecan (T-DXd)) and the HER2-positive BC T-DXd 5.4 mg/kg Pool (n=491, named BC pool). 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 in study U302 and the BC pool are 14 and 12 months, respectively. A total of 78% of the patients in the BC pool, which includes the T-DXd-treated patients from study U302, had exposure of T-DXd for more than 6 months and 53% were exposed for more than 12 months, which is acceptable and considered a relevant exposure for the safety assessment.

Almost all of the patients experienced at least one **adverse event** (AE) in the pivotal study U302 and in the HER2-positive breast cancer pool (BC pool), the most frequently observed adverse events were nausea (77.8%), fatigue (56.6%), vomiting (49.5%), and neutropenia (38.1%). Alopecia was much more frequent with T-DXd compared to T-DM1 (41.3% vs 3.1%), which is considered an important AE that has impact on quality of life-measures in the targeted patient population.

Treatment-related AE's (ADR's) with T-DXd were also nausea (74.9%), fatigue (51.5%), vomiting (43.6%), and neutropenia (37.3%) of almost the same incidences. Additional haematological toxicity was also very common, such as anaemia (29.5%), leukopenia (25.5%), and thrombocytopenia (23.8%). Gastrointestinal toxicity was markedly increased with T-DXd vs T-DM1, and besides vomiting (43.6% vs 5.7%), ADR's of decreased appetite (29.1% vs 12.6%), diarrhoea (24.4% vs 3.8%) and constipation (21% vs 9.6%) were clinically significantly more commonly observed. Most commonly TEAEs by PT (>30%) for T-DM1 were (in decreasing order) thrombocytopenia, aspartate aminotransferase (ASAT) increased, fatigue and nausea. Thrombocytopenia and ASAT increased were also reported at a ≥10% higher incidence compared to T-DXd. These are in line with that reported in the SmPC.

As previously shown in the later line setting, most haematological and GI events for T-DXd were grade 1 or 2. No subject in either treatment arm had an event of major bleeding within 14 days of the onset of ≥Grade 3 thrombocytopenia. Of note, the % of unresolved events for thrombocytopenia was 33% and substantial higher than for TDM-1 (11%). As the time to onset of first event of thrombocytopenia was also substantial longer (131 days vs 8 days), resolution of events may increase with longer follow-up. The percentage of unresolved events did not notably change with an additional 3 months follow-up, and a longer follow-up could be needed. Nevertheless, it is reassuring that there were no major bleedings associated with thrombocytopenia and dose modifications were few. Most events were manageable with established treatment guidelines and dose modifications. Adequate statements are presented throughout the SmPC.

Grade ≥3 AE's in the T-DXd arm of pivotal study U302 and the BC pool, respectively, were: neutropenia (19.1% and 19.6%) and anaemia (7.4% and 8.1%). The most common grade ≥3 AEs with T-DM1 were thrombocytopenia (25.7%) and anaemia (5.7%), while thrombocytopenia of high grade was rare with T-DXd (6.1%), so the toxicity profiles of these two HER2-targeting ADCs are considered clinically significantly different. **Treatment-related grade ≥3 events** observed in more than 5% of the patients treated with T-DXd were neutropenia, anaemia, leukopenia, thrombocytopenia, nausea, and fatigue; while grade ≥3 ADR's observed in more than 5% of the patients treated with T-DM1 in the control arm were anaemia, thrombocytopenia and transaminases increased. Hence, more high-grade toxicity was observed with T-DXd.

Adverse events of special interest includes **ILD/pneumonitis**, which is an important identified risk with trastuzumab deruxtecan. This event was commonly observed with T-DXd in the BC pool (13.4%), and these events were most often of grade 2 (7.9%). The majority of these events were assessed to be treatment-related (12.6%) and often led to treatment discontinuation (9.4%). Nearly half of the events were resolved (46.8%) at DCO, but a third (30.6%) was not resolved and there were 6 fatal cases (9.7%) of ILD/pneumonitis. Overall, the risk of ILD/pneumonitis is considered of clinical interest, but the risks of high-grade events and need for discontinuations have not changed significantly with the added safety data from the pivotal U302 study. The ADR of ILD/pneumonitis

continues to be the greatest risk of the treatment with T-DXd and therefore the warning in section 4.4 is endorsed. However, the risk and management of ILD/pneumonitis is adequately described in the SmPC. In addition, information is included in the RMP and educational material. **Left ventricular dysfunction** is considered an important identified risk based on what is known for trastuzumab. The incidences of grade 2 decrease of LVEF (13.5% and 16.1%) or grade 3 decrease of LVEF (0.4% and 0.2%) 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. All events except one with T-DXd were resolved at DCO and appropriate guidance is provided in the SmPC, so decrease in LVEF is considered manageable.

In the BC pool, 22.8% of the patients had died, most commonly due to disease progression (16.3%) and rarely due to an adverse event (2%) or other/unknown reasons (1.8%/2.6%). The narratives for the patients who died from other causes in the pivotal study are agreed. The overall incidence of deaths due to adverse events are acceptable for this non-curative treatment setting and considering the underlying metastatic breast cancer. Deaths due to ADR's are sufficiently reflected in the SmPC.

Serious adverse events (SAEs) were observed in 22.6% of the patients in the BC pool, which is similar to the SAE's observed in the T-DXd arm (19.1%) and the T-DM1 arm (18%). The most commonly observed were interstitial lung disease (ILD) in 3.9%, pneumonia (2%), and vomiting (1.8%). This is in line with the severe toxicity observed in the pivotal study U302. Overall, the rate of SAE's with trastuzumab deruxtecan is acceptable and comparable to the incidence observed with T-DM1.

The overall **discontinuation rate** due to AEs in the BC pool was 15.7%, and of these, 14.7% of the patients discontinued due to treatment-related AEs. Most common AEs leading to discontinuation were ILD/pneumonitis (9.4%), which reflects the known safety profile of trastuzumab deruxtecan. Otherwise, 4 and 5 patients, respectively, discontinued treatment due to pneumonia and thrombocytopenia in the BC pool, which means that the known haematological toxicity rarely led to discontinuations, which is reassuring. More patients discontinued T-DM1 due to thrombocytopenia (2.7%) than those in the T-DXd arm (1%), but the rate of ILD was markedly lower in the T-DM1 arm (7.3%). A numerically higher proportion of patients in the T-DXd arm had adverse events associated with dose reduction compared with the T-DM1 arm, mostly gastrointestinal or hematologic events. Drug interruptions, mainly due to hematological events also occurred more frequently. Overall, the rate of drug interruptions and discontinuations is acceptable for the proposed extension of indication and targeted patient population.

Laboratory findings were in line with the reported AEs.

Vital signs: A notable part of the patients had post-baseline systolic BP values of ≤90 mmHg with a decrease from baseline of ≥20 mmHg (13.6%) or a post-baseline diastolic BP values of ≤50 mmHg with a decrease from baseline of ≥15 mmHg (16.3%), and frequencies were higher than for T-DM1. However, the frequency of the AE hypotension (PT hypotension/blood pressure decreased) was overall low and comparable for T-DXd (2.3%) and T-DM1 (1.9%) and considered not-related to study treatment by the investigator. Further, use of antihypertensive medications might have been a confounding factor and it is acceptable not to consider hypotension as an ADR.

Interactions – extrinsic/intrinsic factors: In the pivotal study, 48 patients (19%) were ≥65 years and 7 were ≥75 years of age. A higher incidence of adverse events ≥grade 3, SAEs, and TEAEs associated with study drug interruption were observed with T-DXd, indicating a lower tolerability. Within the BC pool a ≥10% increase was seen for thrombocytopenia (33.0% vs 22.3%) and ILD (21.1% vs. 10.2%) in elderly (≥65 years, n=109). The increase in ILD by age appears to be explained by increased renal

impairment in the elderly population. The current statement on limited data in subjects ≥75 years of age in section 4.2 and in section 4.8 is still considered relevant.

As previously shown, drug-related ILD increased with increasing severity of renal impairment. Further SAEs and drug discontinuations due to AEs was highest in patients with moderate renal impairment. Patients with severe renal impairment were excluded from the study. Adequate statements are included in section 4.2, 4.4. and 5.2.

At enrollment, 19.1% of the patients in the T-DXd arm had mild hepatic impairment whereas patients with moderate or severe hepatic impairment were excluded. Appropriate statements are included in section 4.2 and 4.4 of the SmPC. Notably, patients with mild hepatic impairment showed higher frequencies of TEAEs, ≥Grade 3, and SAEs, as well as TEAEs associated with drug interruption. This was not observed before in the later line setting. It is reassuring that PK data did not show a relationship between hepatic impairment and exposure, therefore the finding might be related to other factors such as presence of comorbidities and a limited number of patients. Further information on use in patients with moderate impairment will become available in due time (see RMP).

No new safety signals/ADRs were identified based on the BC safety pool or the all-tumour safety pool. The frequencies of the all-tumour safety pool were used for categorization of ADRs in section 4.8 SmPC (N = 1,219), which included patients treated with a higher dose of 6.4 mg/kg. A trend towards higher frequency of ≥Grade 3 TEAEs, SAEs and discontinuations is seen for the all tumour safety pool, whereas frequencies of TEAEs reported in ≥10% of patients were in the same order of magnitude for the all tumour and BC safety pool.

2.5.2. Conclusions on clinical safety

The MAH has provided safety data from ~500 patients with HER2-positive breast cancer, who have had relevant exposure to the approved dose of trastuzumab deruxtecan (5.4 mg/kg iv Q3W) and there were no clinically significant changes of the known safety profile nor any new safety findings. The safety profile of T-DXd was compared head to head with T-DM1 in the second-line metastatic treatment setting and the toxicities observed with T-DXd are considered clinically significantly different from those observed with T-DM1 and tolerability of T-DXd appears lower; however, they remain acceptable and manageable. ILD/pneumonitis is still the greatest risk in the treatment with trastuzumab deruxtecan, but this is adequately reflected in the SmPC.

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 1.3 is acceptable.

The CHMP endorsed the Risk Management Plan version 1.3 with the following content:

Safety concerns

Table 1 : 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 2 : 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 authorization: None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances: None				
Category 3 - Required additional pharmacovigilance activities				
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 3: 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. 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 Recommendations for monitoring of left ventricular dysfunction are included in SmPC Section 4.4. Dose modification guidance for managing the risk of left ventricular dysfunction is included in SmPC Section 4.2. Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire Additional pharmacovigilance activities: None
Important Potential Risks		
Embryo-foetal toxicity	Routine risk minimisation measures: SmPC Section 4.4 SmPC Section 4.6 Patient Information Leaflet Section 2 Recommendations for pregnancy monitoring and contraception usage are included in SmPC Section 4.4 and SmPC Section 4.6. Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Product confusion-related medication error	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 6.6	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Pack and vials: specific livery for ENHERTU on the packaging and specific colours for vial cap and bottle to distinguish from other trastuzumab containing products Additional risk minimisation activities: HCP Guide	Additional pharmacovigilance activities: None
Missing Information		
Use in patients with moderate or severe hepatic impairment	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 5.2 Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Review of data from ongoing clinical studies Additional pharmacovigilance activities: Analysis of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies
Long-term safety	Routine risk minimisation measures: None Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

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

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 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

The current extension of indication for trastuzumab deruxtecan (T-DXd) is 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.

3.1.2. Available therapies and unmet medical need

T-DM1 is the recommended 2L treatment for HER2+ MBC. In the EMILIA study, treatment with T-DM1 improved the disease outcomes compared with treatment with lapatinib plus capecitabine, with an ORR by ICR of 43.6% (95%CI: 38.6, 48.6) in the T-DM1 arm versus (vs.) 30.8% (95%CI: 26.3, 35.7) in the control arm; a median PFS of 9.6 months vs. 6.4 months (HR 0.65 [95%CI: 0.55, 0.77), respectively; and a median OS of 30.9 months vs. 25.1 months (HR 0.68 [95%CI: 0.55, 0.85]), respectively. In the HER2CLIMB study, the addition of tucatinib to the trastuzumab plus capecitabine combination improved median PFS from 5.6 months to 7.8 months (HR: 0.54) and median OS from 17.4 months to 21.9 months (HR: 0.66), which led to an approval in the EU for the 2L+ setting, so this treatment regimen is mostly considered indicated in the relevant second-line setting in patients who have brain metastases, and if not, T-DM1 is generally the preferred option.

The limited duration of efficacy of the current standard of car in the second-line metastatic setting represents an unmet medical need, which might be addressed by newer agents that provide longer PFS. In general, there is a need for more efficacious HER2-targeted treatment regimens.

3.1.3. Main clinical studies

The single pivotal study Destiny breast03 –also known as Study U302– is a phase 3 randomised open-label two-arm study comparing trastuzumab deruxtecan (T-DXd) head to head with the current SOC in the 2L setting, trastuzumab emtansine (T-DM1).

3.2. Favourable effects

The presented data are from the prespecified interim analysis (IA) for superiority of the primary efficacy endpoint of blinded independent central review (BICR)-assessed progression-free survival (PFS) at data cut-off (DCO) date of 21 May 2021.

After a median follow-up for PFS of 15.5 months in the T-DXd arm and 13.9 months in the T-DM1 arm, the primary endpoint was met and the primary analysis of **PFS by BICR** showed an improvement from 6.8 months (95%CI: 5.6, 8.2) with T-DM1 to not reached (95%CI: 18.5, NE) with T-DXd, HR 0.28 (95%CI: 0.22, 0.37). Sensitivity analyses, PFS by investigator, and subgroup analyses were all in support of the primary PFS analysis.

The key secondary endpoint was **overall survival** and OS data are not mature at the time the first IA with only 12.2% events with T-DXd and 20.2% events in the control arm after 15.9 months of follow up. The stratified HR was 0.55 (95%CI: 0.36-0.86), with a p-value of 0.007172 that did not cross the prespecified boundary. Median OS was NE in both arms.

PFS by investigator also showed an improvement from 7.2 months (95%CI: 6.8; 8.3) with T-DM1 to 25.1 months (95%CI: 22.1, NE) with T-DXd, HR 0.26 (95%CI: 0.20, 0.35).

Other exploratory endpoints were supportive of a benefit for T-DXd. **ORR by BICR** is improved from 34.2% in the control arm to 79.7% with T-DXd. The improvement was observed for both complete and partial response (CR and PR), i.e. the CR was improved from 8.7% to 16.1%, while the PR was improved from 25.5% to 63.6% with T-DXd. Median **DOR** was not reached in either arm, the median DoR was NE (95%CI: 20.3, NE) in the T-DXd arm vs. NE (95%CI: 12.6, NE) in the T-DM1 arm.

3.3. Uncertainties and limitations about favourable effects

PFS results are based on an interim analysis, which potentially induces overestimation of the treatment effect. Although this is not expected to affect the clinically relevant gain in PFS, final efficacy data from the pivotal U302 study is recommended to be provided post-approval (PAM-REC).

The median OS was not reached in either of the treatment arms and was not statistically significantly improved, although the KM curves for OS visually separate. Considering that the targeted patient population is likely to receive further lines of treatment, this OS result is considered sufficient for the current procedure. The MAH is recommended to provide the final OS results from study U302 post-authorisation (PAM-REC).

It is noted that very few patients progressed on treatment with T-DXd (1.1%) and the induced responses were durable, although median DOR was not reached in either arm. However, the DoR data is not mature, with 27.9% and 34.4% events in each arm, respectively. As updated confirmed ORR and DoR were not available during the procedure, the Applicant is recommended to submit updated clinical efficacy data at the time of the next OS analysis (currently projected 3Q2022) post-authorisation, together with the results from the respective OS analysis (PAM-REC).

3.4. Unfavourable effects

Almost all of the patients experienced at least one **adverse event** (AE) in the pivotal study U302 and most of these were treatment-related. In the HER2-positive breast cancer pool, the most frequently observed events were nausea (77.8%), fatigue (56.6%), vomiting (49.5%), and neutropenia (38.1%). **Treatment-related AE's** (ADR's) with T-DXd were also nausea (74.9%), fatigue (51.5%), vomiting (43.6%), and neutropenia (37.3%) of almost the same incidences. Additional haematological toxicity was also very common, such as anaemia (29.5%), leukopenia (25.5%), and thrombocytopenia (23.8%). Gastrointestinal toxicity was markedly increased with T-DXd vs T-DM1, and besides vomiting (43.6% vs 5.7%), ADR's of decreased appetite (29.1% vs 12.6%), diarrhoea (24.4% vs 3.8%) and constipation (21% vs 9.6%) were clinically significantly more commonly observed. Alopecia was much more frequent with T-DXd compared to T-DM1 (41.3% vs 3.1%).

Grade 3 AEs in the BC pool were neutropenia (19.6%) and anaemia (8.1%). **Treatment-related grade ≥3 events** observed in more than 5% of the patients treated with T-DXd were neutropenia, anaemia, leukopenia, thrombocytopenia, nausea, and fatigue.

Adverse events of special interest of main clinical interest includes ILD/pneumonitis and in the HER2-positive breast cancer pool, 13.4% of the patients had an ILD/pneumonitis event and these events were most often of grade 2 (7.9%). The majority of these events were assessed to be treatment-related (12.6%) and often led to treatment discontinuation (9.4%). Nearly half of the events were resolved (46.8%) at DCO, but a third (30.6%) was not resolved and there were 6 fatal cases (9.7%) of ILD/pneumonitis. Left ventricular dysfunction is considered an important identified risk

based on what is known for trastuzumab. The incidences of grade 2 decrease of LVEF (13.5% and 16.1%) or grade 3 decrease of LVEF (0.4% and 0.2%) 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. All events except one with T-DXd were resolved at DCO.

Overall, 22.8% of the patients had **died**, most commonly due to disease progression (16.3%) and rarely due to an adverse event (2%) or other/unknown reasons (1.8%/2.6%). The narratives for the patients who died from other causes in the pivotal study are agreed.

S**erious adverse events** (SAE's) were most commonly pertaining to ILD/pneumonitis (3.9%), pneumonia (2%), and vomiting (1.8%) in both the BC pool and this is in line with the severe toxicity observed in the pivotal study U302.

The overall **discontinuation rate** due to AEs in the BC pool was 15.7%, and of these, 14.7% of the patients discontinued due to treatment-related AEs. Most common AEs leading to discontinuation was ILD/pneumonitis in the BC pool (9.4%).

Tolerability of T-DXd was lower than for T-DM1 which resulted in about twice as high number of drug discontinuations and dose interruptions/reductions. SAEs and ≥grade 3 events were reported in the same order of magnitude. The safety profile of T-DM1 is mainly characterized by thrombocytopenia (53.3%), and an increase of transaminases (AST increased: 40.2%, ALT increased: 29.5%), which is in line with what is presented in the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

Risk of ILD in patients with a history of noninfectious ILD/pneumonitis that required steroids is unknown as these were excluded from the trials. Proposed mitigating strategies for ILD (section 4.2 and 4.4 SmPC, aRMM) are considered adequate to reduce the risk of severe/fatal ILD for these patients.

No safety data are available in patients with severe renal impairment. This is reflected in the SmPC.

Safety data in patients >75 years are limited. This is reflected in the SmPC.

No safety data are available in patients with moderate/severe hepatic impairment whereas the safety profile may be different as the drug is primarily hepatically eliminated. A PK and safety study in patients with moderate hepatic impairment is included in the RMP as post-authorisation commitment (see RMP).

3.6. Effects Table

Table 2. Effects Table for Enhertu (T-DXd) for unresectable or metastatic HER2-positive BC who had received an anti-HER2-based regimen in the first-line metastatic setting (data cut-off: 21 May 2021)

Effect	Short description	Unit	Treatment T-DXd N= 257	Control T-DM1 N=261	Uncertainties / Strength of evidence	Ref
Favourable Effects						
PFS by BICR	Progression-free survival	Median in months (95%CI)	NE (18.5; NE)	6.8 (5.6; 8.2)	Strengths: RCT, blinded review Uncertainties: Based	

Effect	Short description	Unit	Treatment T-DXd N= 257	Control T-DM1 N=261	Uncertainties / Strength of evidence	Ref
		% events / Hazard ratio	33.3% vs 60.1%, HR 0.28 (0.22; 0.37)		on IA	
OS	Overall survival	Median in months (95%CI)	NE (NE-NE)	NE (NE-NE)	Strengths: RCT Uncertainties: Immaturity	
		% events / Hazard ratio	12.6% vs 20.2% events, HR 0.55 (NS)			
ORR by BICR	Overall response rate	%	79.7	34.2		
DOR by BICR	Duration of response	Months	NE (20.3; NE)	NE 12.6; NE)	27.9% vs 34.4% events	
Unfavourable Effects						
Any AEs		%	99.6	95.4		
Grade ≥3 AEs		%	52.1	48.3		
SAEs		%	19.1	18.0		
AEs leading to discontinuation		%	13.6	7.3		
AEs associated with death		%	1.9	1.9		
ILD/pneumonitis		%	10.5	1.9	21/27 patients, discontinue treatment	

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

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The primary endpoint of the pivotal trial is PFS by BICR, which is a clinically relevant endpoint for this non-curative setting and acceptable for a single randomised phase 3 study. The efficacy of trastuzumab deruxtecan (T-DXd) compared to T-DM1 in the proposed second-line setting after one anti-HER2-based regimen is considered clinically meaningful, since the primary endpoint of PFS by BICR was markedly prolonged from 6.8 months to NE (with the lower bound of the 95% CI being 18.5 months). As the treatment effect is so strong, the potential overestimation of the PFS results due to the interim analysis is considered to be limited. Updated PFS results will be provided post-marketing with the planned second interim analysis (PAM-REC). Results from the key secondary endpoint OS are immature. A detriment in OS is considered unlikely. Other secondary endpoints were supportive of a benefit of T-DXd treatment over T-DM1 treatment. Response rate (ORR) and duration of response (DoR) were also clinically significantly improved, with a more than doubling of the ORR from 34.2% to 79.2%. These key efficacy results are observed after 15.9 months of follow-up. Moreover, since there

were a high number of PFS events in the control arm (~60%), the overall results are unlikely to change significantly with updated data.

The safety profile of T-DXd was not changed with added safety data from the pivotal study U302 and the main reported adverse events of trastuzumab deruxtecan are still haematological and gastrointestinal toxicities, which were rarely of high grade and manageable by routine clinical practice guidelines and GI and haematological events are known side effects of topoisomerase inhibitors. The major safety concern remains to be the risk of ILD/pneumonitis (10.5%), which frequently led to drug discontinuation. It is reassuring that most events recovered and no new grade 4 or grade 5 (fatal) events occurred, likely due to enhanced awareness. When early recognized, low grade ILD/pneumonitis is manageable with dose modification and corticosteroid treatment in line with established clinical treatment guidelines (see section 4.2 and 4.4 of the SmPC).

Overall, the safety profile of T-DXd is considered worse compared to T-DM1 and differences are not entirely explained by the difference in exposure time. Still, this is outweighed by the gain in efficacy.

3.7.2. Balance of benefits and risks

The reported gain in PFS is clinically relevant and considered to outweigh the risks. It can be concluded that the benefit-risk balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Enhertu for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer, who have received one prior anti HER2 based regimen 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 for Enhertu to include treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted.

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.

Additional risk minimisation measures

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).

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 II-0014'

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