21 May 2026
EMADOC-1700519818-3246710
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Enhertu

International non-proprietary name: trastuzumab deruxtecan

Procedure No. EMA/VR/0000293327

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

Abbreviation or special term	Explanation
ADA	anti-drug antibody
AE	adverse event
ASCO	American Society of Clinical Oncology
BC	breast cancer
BICR	blinded independent central review
BLC	biliary tract cancer
BoR	best overall response
BRAF	v-raf murine sarcoma viral oncogene homologue B1
CAP	College of American Pathologists
CBR	clinical benefit rate
CC	cervical cancer
CI	confidence interval
CR	complete response
CRC	colorectal cancer
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTD	common technical document
DCO	data cut-off
DCR	disease control rate
DoR	duration of response
DP-02	DESTINY-PanTumor02 study; D967VC00001
EC	endometrial cancer
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
ER	exposure-response
FAS	Full Analysis Set (intent-to-treat population)
FDA	Food and Drug Administration
GC	gastric cancer
GEJ	gastroesophageal junction
HER2	human epidermal growth factor receptor 2
ICR	Independent Central Review
IHC	immunohistochemistry
ILD	interstitial lung disease
INV	investigator
ISE	integrated summary of efficacy
ISH	in situ hybridization
KM	Kaplan-Meier curve
LV	left ventricular
LVEF	left ventricular ejection fraction
NA	not applicable
NE	not evaluable
NED	no evidence of disease
NSCLC	non-small cell lung cancer

Abbreviation or special term	Explanation
OC	ovarian cancer
ORR	objective response rate
OS	overall survival
PC	pancreatic cancer
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PS	performance status
PT	preferred term
Q3W	every 3 weeks
RAS	rat sarcoma viral oncogenes homologue
RECIST v1.1	Response Evaluation Criteria in Solid Tumours, version 1.1
ROW	rest of world
RP2D	recommended Phase 2 Dose
RSE	Relative Standard Error
SAP	statistical analysis plan
SAE	serious adverse event
SoC	standard of care
SCE	Summary of Clinical Efficacy (CTD Module 2.7.3)
SCP	Summary of Clinical Pharmacology (CTD Module 2.7.2)
SD	stable disease
T-DM1	trastuzumab emtansine
T-DXd	trastuzumab deruxtecan (ENHERTU, DS8201)
TEAE	treatment-emergent adverse event
TTR	time to response
US	United States
VEGF	vascular endothelial growth factor
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Daiichi Sankyo Europe GmbH submitted to the European Medicines Agency on 22 August 2025 an application for a variation.

The following variation was requested:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of adult patients with unresectable or metastatic HER2-positive Immunohistochemistry (IHC3+) solid tumours who have received prior treatment and who have no satisfactory alternative treatment options for Enhertu, based on pooled pop-PK analysis and interim results from study D967VC00001 (DESTINY-PanTumor02); this is a Phase II, Multicenter, Open-label Study to Evaluate the Efficacy and Safety of Trastuzumab Deruxtecan (T-DXd, DS-8201a) for the Treatment of Selected HER2-expressing Tumours; as a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 9.2 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce editorial changes to the PI.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0397/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0397/2024 was not yet completed as some measures were deferred.

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 application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's requests for consideration

Conditional marketing authorisation

The applicant requested consideration of its extension of indication application in accordance with Article 14-a of the Regulation No 726/2004.

Scientific advice

The MAH received Scientific Advice from the CHMP on 10 November 2022 (EMA/SA/0000102946). 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: Thalia Marie Blicher Co-Rapporteur: Peter Mol

Timetable	Actual dates
Submission date	22 Aug 2025
Start of procedure:	13 Sept 2025
CHMP Rapporteur's preliminary assessment report circulated on:	7 Nov 2025
PRAC Rapporteur preliminary assessment report circulated on:	14 Nov 2025
CHMP CoRapporteur's preliminary assessment report circulated on:	19 Nov 2025
PRAC RMP advice and assessment overview adopted by PRAC	27 Nov 2025
Joint Rapporteur's updated assessment report circulated on:	5 Dec 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	11 Dec 2025
MAH's responses submitted to the CHMP on:	17 Feb 2026
CHMP (Co)Rapporteur's preliminary assessment report on the MAH's responses circulated on:	24 Mar 2026
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	25 Mar 2026
PRAC RMP advice and assessment overview adopted by PRAC	10 Apr 2026
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	16 Apr 2026
Request for supplementary information adopted by the CHMP on:	23 Apr 2026
MAH's responses submitted to the CHMP on:	28 Apr 2026
CHMP (Co)Rapporteur's preliminary assessment report on the MAH's responses circulated on:	6 May 2026
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	12 May 2026
CHMP opinion:	21 May 2026
The CHMP adopted a report on similarity of Enhertu with Ayvakyt, Elahere, Ezmekly, Finlee, Hetronifly, Imdylltra, Kimmtrak, Koselugo, Lutathera, Ogsiveo, Ojemda, Onivyde pegylated liposomal, Pemazyre, Qarziba, Qinlock, Romvimza, Spexotras, Tibsovo, Voranigo, Vyloy, Zejula, Zepzelca, Ziihera, and Zynyz (Appendix 1) on:	21 May 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The MAH applied for an extension of indication in patients who harbour an Immunohistochemistry (IHC) 3+ HER2-positive solid tumour, i.e. a histology independent indication.

The applied indication is for the treatment as monotherapy of adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumours who have received prior treatment and who have no satisfactory alternative treatment options.

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

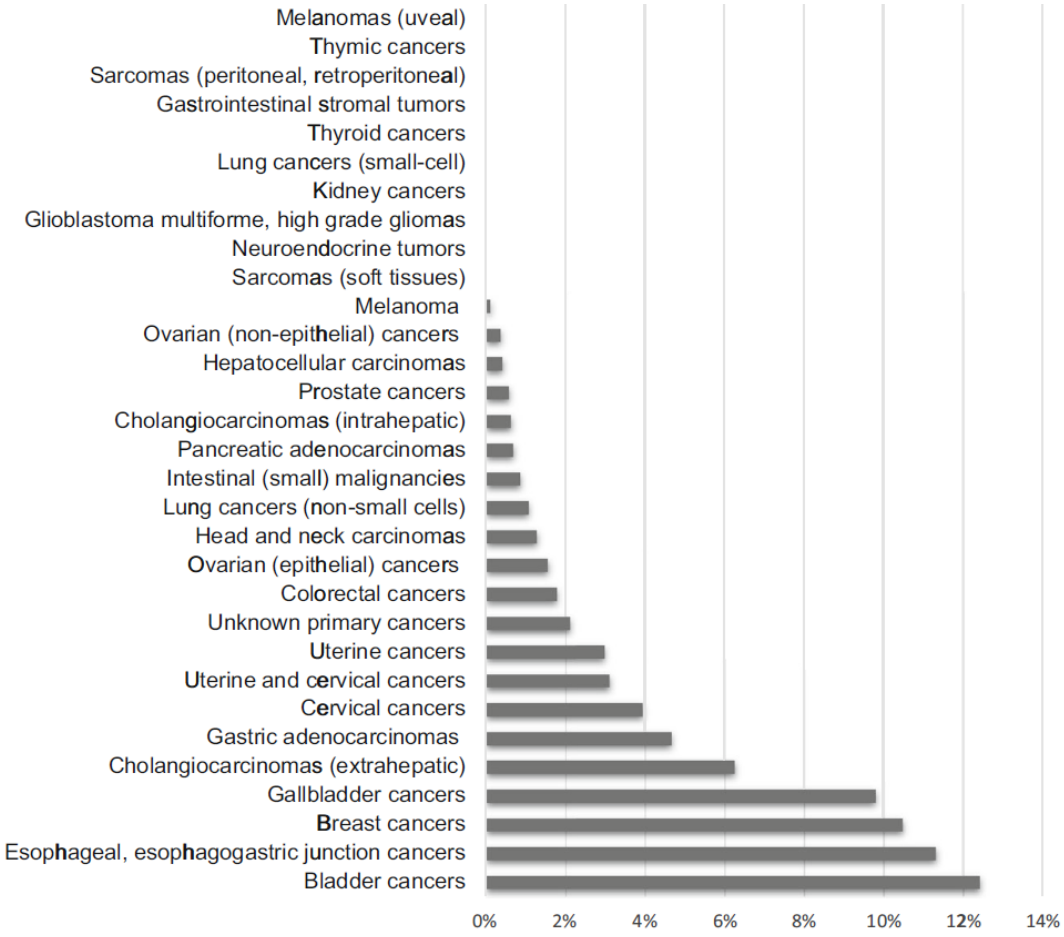
'Other unresectable or metastatic solid tumours

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumours who have received prior treatment and who have no satisfactory treatment options (see sections 4.4 and 5.1; for biomarker-based patient selection, see section 4.2).'

Epidemiology

HER2 (IHC 3+) expression has been observed across diverse solid tumours (Figure 1). Historically, HER2 expression has been defined in breast and GC as IHC 3+, or IHC 2+ with amplification, but HER2-expression, with or without ERBB2 amplification has been described more widely, including in biliary tract cancer, breast, bladder cancer, gastric, endometrial, NSCLC, colorectal cancer, oesophageal cancer, gallbladder cancer, cervical cancer, salivary gland and uterine cancer, but also in cancers of unknown primary, testicular, ovarian, head and neck, pancreatic, small intestinal cancers, and melanoma (Yan et al 2015, Uzunparmak et al 2023).

Figure 1 HER2 positivity across cancers: analysis of 37,992 samples by IHC



IHC3+ was considered HER2 IHC positive

Source: Yan et al 2015

Biologic features

Human epidermal growth factor receptor 2 (HER2) is a proto-oncogene involved in signal transduction pathways leading to tumour cell proliferation, migration, apoptosis, and differentiation. HER2 overexpression/amplification is considered an oncogenic driver across different types of tumours, including breast (Neve *et al* 2001), gastric (Gravalos and Jimeno *et al* 2008) and non-small-cell lung cancer (NSCLC) (Zhao and Xia *et al* 2020), for which anti-HER2 targeted therapies have been approved and are widely used in clinical practice.

Overexpression of HER2 is etiologically linked with tumorigenesis. *In vitro* and transgenic models have shown that HER2 overexpression by itself is potently transforming, and that HER2-driven tumours are dependent on HER2 function (Moasser 2007). Upon overexpression, amplification, or mutation, HER2 can homodimerise or heterodimerise and activate downstream signalling pathways, including mitogen - activated protein kinase (MAPK) and lipid kinase phoshoinositide-3-kinase signalling pathway (PI3K/AKT), leading to enhanced proliferation, invasion or survival phenotypes (Gutierrez and Schiff 2011, Moasser 2007).

Clinical presentation, and prognosis

HER2 overexpression is a well-established prognostic biomarker in multiple solid tumours, often associated with aggressive disease and poorer clinical outcomes. In breast cancer, HER2 positivity

correlates with increased proliferation, higher histological grade, and a greater propensity for metastasis, contributing to unfavourable prognosis (Pegram *et al.*, 2023). In gastric and gastroesophageal cancers, HER2 overexpression is linked to poor survival and adverse clinicopathological features, including serosal invasion, lymph node involvement, advanced stage, and distant metastases. (Jørgensen *et al.*, 2012). Additionally, HER2 alterations —including overexpression and ERBB2 amplification— have been identified in other malignancies such as bladder, uterine, and biliary tract cancers, where they are increasingly recognised as indicators of aggressive tumour biology (Quaquarini *et al.*, 2024).

Management

The management of advanced/metastatic HER2 positive tumours depends on the tumour type/site and the previously used systemic therapies in the neo-/adjuvant setting, as per European Society For Medical Oncology (ESMO) guidelines for the specific tumour site. Upon progression following first-line therapy, patients may be considered for subsequent treatment options tailored to the clinical context—such as local interventions in cases of oligometastatic disease—as well as overall condition of the patient, individual preferences, and the presence of actionable genomic alterations, in alignment with current clinical guidelines. The Table 1 presents the current treatment options for 2L+ therapy of HER2-positive solid tumours enrolled in the clinical studies with Enhertu.

Table 1 Current Standard of Care Treatment for Common Tumour Types

Tumour type	Publication	ESMO recommendation	Treatment regimen (N)	Confirmed ORR, % (95% CI)	Median DoR (95% CI)	Median PFS (95% CI)	Median OS (95% CI)
Biliary tract cancer	Lamarca et al 2021a	Per ESMO guidelines, FOLFOX is the preferred regimen for the treatment of biliary tract cancer following progression after 1L therapy. Biomarker directed therapy is supported, with isocitrate dehydrogenase 1, FGFR, and NTRK inhibitors being treatment options for patients with recurrent disease and associated molecular abnormalities. HER2-directed therapies can be considered in patients with HER2 amplification who lack other therapeutic options (ESMO 2022, Vogel et al 2022).	2 L FOLFOX (N = 81)	5% (NR)	NR	4.0 months (3.2, 5.0)	6.2 months (5.4, 7.6)
Bladder cancer	Rosenberg et al 2019 a	2L and later therapy options include pembrolizumab, enfortumab vedotin and chemotherapy depending on prior therapy in the 1L setting. For biomarker directed therapy erdafitinib recommended for susceptible FGFR3 alterations, no consensus if 2L immune checkpoint inhibitor therapy or erdafitinib should be used preferentially in these patients (ESMO 2021, Powles et al 2022).	2 L enfortumab vedotin (N = 125)	44% (35.1, 53.2)	7.6 months (4.9, 7.5)	5.8 months (4.9, 7.5)	11.7 months (9.1, NR)
	Tagawa et al 2021b		3 L sacituzumab govitecan (N = 113)	27.4% (19.5, 36.6)	7.2 months (4.7, 8.6)	5.4 months (3.5, 7.2)	10.9 months (9.0, 13.8)
	Bellmunt et al 2017a		2 L pembrolizumab (N = 270)	21.1% (16.4, 26.5)	NR	2.1 months (2.0, 2.2)	10.3 months (8.0, 11.8)

Table 1 Current Standard of Care Treatment for Common Tumour Types

Tumour type	Publication	ESMO recommendation	Treatment regimen (N)	Confirmed ORR, % (95% CI)	Median DoR (95% CI)	Median PFS (95% CI)	Median OS (95% CI)
Endometrial cancer	Makker et al 2022a	For 2L and later endometrial carcinoma, ESMO guidelines recommend chemotherapy or biomarker-directed therapies, including lenvatinib/pembrolizumab combination for patients who have failed a previous platinum-based chemotherapy and who are not candidates for curative surgery or radiotherapy. There is no standard of care for 2L chemotherapy. Doxorubicin and weekly paclitaxel are considered the most active therapies. Single-agent immune check point blockade therapy should be considered for MSI-H/mismatch repair deficient tumours. The increasing numbers of patients with exposure to checkpoint inhibitors in the 1L setting further increases the unmet need for novel treatment options in the 2L and later setting (ESMO 2022, Oaknin et al 2022).	2/3 L pembrolizumab + Lenvatinib (N = 411)	31.9% (27.4, 36.6)	14.4 months (NR)	7.2 months (5.7, 7.6)	18.3 months (15.2, 20.5)
Cervical cancer	Weiss et al 1990a	Paclitaxel and cisplatin combined with bevacizumab is preferred 1L regimen in metastatic or recurrent cervical cancer based on the balance between efficacy and toxicity profile. In patients progressing following 1L therapy, different cytostatic agents, including vinorelbine, topotecan, gemcitabine or nanoparticle albumin-bound paclitaxel have been evaluated. However, response rates are low, and DoR is short. Therefore, per ESMO guidelines there is no clear recommendation for the most effective 2L therapy (ESMO 2017, Marth et al 2017).	2 L CTx (carboplatin) (N = 41)	15% (6, 29)	NR	NR	NR
	Chung et al 2019a		2 L+ pembrolizumab (N = 77)	14.3% (7.4, 24.1)	NR	NR	NR
	Oaknin et al 2022, Oaknin et al 2024b		2/3 L ipilimumab + nivolumab (N = 43)	34.9% (NR)	NR	4.7 months (32, 10.0)	19.9 months (7.8, 32.8)

Table 1 Current Standard of Care Treatment for Common Tumour Types

Tumour type	Publication	ESMO recommendation	Treatment regimen (N)	Confirmed ORR, % (95% CI)	Median DoR (95% CI)	Median PFS (95% CI)	Median OS (95% CI)
Ovarian cancer (PRR)	Pujade-Lauraine et al 2014a	After failure on 1L therapy, further platinum-based combination chemotherapy is recommended for patients with recurrent platinum-sensitive disease. For patients requiring rapid response, the combination of platinum-based doublet PLD, gemcitabine, or paclitaxel) with bevacizumab is preferred. Bevacizumab and polymerase (PARP) inhibitors (PARPi) to be continued until disease progression or the next line of treatment. For patients with relapsed disease for whom platinum is not an option (including platinum resistance), single-agent non-platinum options that can be recommended include weekly paclitaxel, PLD, topotecan and gemcitabine (ESMO 2023, González-Martín et al 2023).	2/3 L Non-platinum CTx + bevacizumab (N = 179)	27.3% (NR)	NR	6.7 months (5.7, 7.9)	16.6 months (13.7, 19.0)
Pancreatic cancer	Mita et al 2019a	2L depends on 1L regimens, After FOLFIRINOX treatment, gemcitabine-Nab-paclitaxel (not EMA or FDA approved as second-line therapy) or gemcitabine alone to the patients with ECOG PS 0-1 and a favourable comorbidity profile. In patients with, or who have recovered to, ECOG PS 0-1 and who have been pretreated with a gemcitabine-based regimen, nanoliposomal irinotecan-5FU-LV (EMA and FDA approved in metastatic pancreatic cancer). Biomarker-guided treatments including pembrolizumab (MSI-H/dMMR), larotrectinib or	2 L CTx (gemcitabine + NAb-paclitaxel) (N = 30)	13.3% (5.3, 29.7)	NR	3.8 months (3.3, 4.8)	7.6 months (5.7, 8.6)
	Wang-Gillam A et al 2016c		2L nanoliposomal-IRI + 5FU/LV (N=117)	16% (8.5-22.3)	NR	3.1 months (2.7, 4.2)	6.1 months (4.8, 8.9)

Table 1 Current Standard of Care Treatment for Common Tumour Types

Tumour type	Publication	ESMO recommendation	Treatment regimen (N)	Confirmed ORR, % (95% CI)	Median DoR (95% CI)	Median PFS (95% CI)	Median OS (95% CI)
		entrectinib (NTRK gene fusion-positive) (ESMO 2023, Conroy et al 2023)					
Colorectal cancer	Giantonio et al 2007 b	2L or later therapy depends on the 1L setting and includes oxaliplatin, irinotecan, anti-vascular endothelial growth factor (anti-VEGF) targeted therapies, and (for patients with KRAS/NRAS/BRAF wild-type tumours) biomarker-directed therapy with cetuximab or panitumumab. For BRAF V600E-mutated, pre-treated mCRC patients, encorafenib and cetuximab is recommended. For dMMR/MSI-H tumours progressing after first-line ChT, ipilimumab and nivolumab is recommended (ESMO 2022, Cervantes et al 2023)	2 L bevacizumab + FOLFOX4 (N = 286)	22.7% (NR)	NR	7.3 months (NR)	12.9 months (NR)
	Strickler et al 2022a; Strickler et al 2023 Tucatinib USPI 2023		2 L+ tucatinib + trastuzumab (N = 84)	38% (28, 49)	12.4 months (8.5, 20.5)	8.2 months (4.2, 10.3)	24.1 months (20.3, 36.7)
	Van Custem et al 2012 c		2L FOLFIRI + Aflibercept (N=612)	19.8% (16.4–23.2)	NR	6.9 months (6.51, 7.20)	13.5 months (12.52, 14.95)
Non-small cell lung cancer	Herbst et al 2016 a	2L and later treatment of metastatic NSCLC is determined by previous first-line therapy and whether actionable oncogenic biomarkers are present. If no prior immunotherapy received, immune checkpoint inhibitors are advised as second-line therapy; if immunotherapy was previously given, single-agent chemotherapy or the combination of docetaxel plus ramucirumab is recommended (ESMO 2023, Hendriks et al 2023a).	2 L pembrolizumab 2 mg/kg (N = 344)	18% (14.1, 22.5)	NR	3.9 months (3.1, 4.1)	10.4 months (9.4, 11.9)
	Garon et al 2014 a		2 L ramucirumab + docetaxel (N = 628)	22.9% (19.7, 26.4)	NR	4.5 months (IQR 2.3, 8.3)	10.5 months (IQR 5.1, 21.2)
Breast cancer	Hurvitz et al 2023 a	T-DXd recommend as the preferred second-line therapy after progression on a taxane and trastuzumab (I-A), Included in the treatment options for third line and beyond for HER2 positive	2 L+ T-DXd (N = 261)	79% (73.1, 83.4)	36.6 months (22.4, NE)	28.8 months (22.4, 37.9)	NR (40.5, not estimable)

Table 1 Current Standard of Care Treatment for Common Tumour Types

Tumour type	Publication	ESMO recommendation	Treatment regimen (N)	Confirmed ORR, % (95% CI)	Median DoR (95% CI)	Median PFS (95% CI)	Median OS (95% CI)
		metastatic and advanced BC (ESMO 2021, Gennari et al 2021)					
Gastric cancer	Shitara et al 2020 a	2L treatment for advanced GC includes ramucirumab plus paclitaxel, with ramucirumab monotherapy as an alternative. Where ramucirumab is not available, monotherapy with paclitaxel, docetaxel, or irinotecan, as well as the FOLFIRI regimen, are considered. Continuation of trastuzumab beyond first-line is not advised in HER2-positive cases; however, trastuzumab deruxtecan could be considered as later line of therapy. For patients with MSI-H/dMMR disease, pembrolizumab is recommended as second-line therapy (ESMO 2022, Lordick et al 2022).	3 L+ trastuzumab deruxtecan (N = 125)	51% (42, 61)	11.3 months (5.6, NE)	5.6 months (4.3, 6.9)	12.5 months (9.6, 14.3)

a Recommended by NCCN and ESMO guidelines
b Recommended by NCCN guideline
c Recommended by ESMO guideline

Table 2 Additional table of EMA approved products in the 2nd line setting

Disease/drug	ORR	DOR	Notes
BTC:			
Ziihera	51.6%	14.9 months	IHC3+ HER2, CMA (n=62)
NSCLC: Squamous carcinoma without mutation:			
Afatinib	5.5%	7.29 months	LUX Lung 8, ph 3 study (n=795)
Histology independent:			
Atezolizumab	14%	16.3 months	OAK, ph3 study
Tislelizumab	20.9%	14.7 months	BGB-A317-303, ph 3 study
Bladder cancer:			
Erdafitinib for FGFR3+ disease	35.3%	5.6 months	
Atezolizumab	13.4%	21.7 months	Imgivor211
Endometrial cancer			
Dostarlimab for dMMR/MSI-H	45%	NR	GARNET (n=143)
Cervical cancer:			
Tisotumab vedotin	17.8%	5.3 months	SGNTV-003, ph 3 (n=502)
Cemiplimab	16.4%	16.4 months	Study 1676, ph 3 (n=608)
Ovarian cancer:			
Mirvetuximab soravtansine for platinum resistant disease with FR alpha positive tumour	42.3%	6.7 months	MIRASOL (n=227)
PARP inhibitors for those who have response to re-challenged with platinum and did not receive PARPi before: Olaparib	Not reported	mPFS: 9.2 months	OPINION
Trabectedin+ PLD (pegylated liposomal doxorubicin)	27.6 %	7.4 months (mPFS)	ET743-OVA-301 (n=672)
Pancreatic cancer:			
RET positive disease: Selpercatinib	53.8%	Range 2.50, 52.14 months	SAT (n=18)

Unmet medical need

Despite available standard treatment options for patients with HER-2 positive unresectable locally advanced or metastatic solid tumours, most patients will eventually exhaust their treatment options.

Therefore, better treatments are needed that can improve overall survival and quality of life in patients in this setting.

2.1.2. About the product

Trastuzumab deruxtecan (T DXd, Enhertu) is a HER2-directed ADC composed of a humanised anti-HER2 IgG1 monoclonal antibody with the same amino acid sequence as trastuzumab. It includes a plasma-stable, selectively cleavable linker and topoisomerase I inhibitor payload, (a derivative of exatecan).

Enhertu is conditionally authorised in the EU for the following indications:

Breast cancer

Enhertu as monotherapy is indicated 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. (EMEA/H/C/005124/II/0014)

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic

- hormone receptor (HR)-positive, HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment (EMEA/H/C/005124/II/0048)
- HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy (EMEA/H/C/005124/II/0022)

Non-small cell lung cancer (NSCLC)

Enhertu as monotherapy is indicated for the treatment of adult patients with advanced NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy. (EMEA/H/C/005124/II/0027) – subject to specific obligations

Gastric cancer

Enhertu as monotherapy is indicated for the treatment of adult patients with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen. (EMEA/H/C/005124/II/0012).

Posology and method of administration

Breast cancer, NSCLC, and other unresectable or metastatic solid tumours

The recommended dose of Enhertu is 5.4 mg/kg body weight given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

Table 3 Dose reduction schedule

Dose reduction schedule	Breast cancer, NSCLC, and Other Solid Tumours	Gastric cancer
Recommended starting dose	5.4 mg/kg	6.4 mg/kg
First dose reduction	4.4 mg/kg	5.4 mg/kg
Second dose reduction	3.2 mg/kg	4.4 mg/kg
Requirement for further dose reduction	Discontinue treatment	Discontinue treatment

Type of Application and aspects on development

The MAH requested consideration of its application for an extension of indication of a Conditional Marketing Authorisation in accordance with Article 14-a of Regulation (EC) 726/2004, based on the following criteria:

- The benefit-risk balance is positive, as justified in this application
- It is likely that the applicant will be able to provide comprehensive data:
  Study DP-02 (DESTINY-PanTumor02) is a Phase II, Multicenter, Open-label Study to Evaluate the Efficacy and Safety of Trastuzumab Deruxtecan (T-DXd, DS-8201a) for the Treatment of Selected HER2-expressing Tumours. Part 1 of the study is completed and forms the basis for this submission. Part 2 of DP-02 is ongoing and will evaluate additional cohorts of patients with HER2-expressing tumours, as determined via central testing only, and includes 5 cohorts ((A to E), N=40 / cohort): A) any tumour type that is HER2 IHC 3+ (excluding breast, gastric cancer, and colorectal cancer), B) any tumour type that is HER2 IHC 2+/ISH+ (excluding breast, gastric cancer, and colorectal cancer), C) HER2 IHC 2+ or 1+ endometrial cancer, D) HER2 IHC 2+ or 1+ovarian cancer, and E) HER2 IHC 2+ or 1+ cervical cancer.
  Similar to the data available from Part 1, the primary efficacy endpoint is ORR with DoR as a key secondary endpoint. Final analysis for all Part 2 cohorts, including Cohort A, is planned to be performed approximately 12 months after the last patient is enrolled, respective to each cohort.
  The variability of the different tumour types enrolled as part of the tumour agnostic framework makes it difficult to design a randomized study with a single comparator defined or to design a standardised control arm that is ethically and clinically relevant across the diverse patient population enrolled in the trial. In addition, HER2-positive tumours are relatively rare in many non-breast, non-gastric cancers and inclusion into trials challenging. As a basket trial, targeting multiple tumour types in later lines of treatment, the overall number of HER2-positive patients is small, and subdividing them further into control and experimental groups would reduce statistical power. Recruiting enough patients to populate both the treatment and control arms in a meaningful, balanced way would be challenging. Therefore, in the absence of a randomized control arm and, given the heterogeneity of tumour histologies, additional pan-tumour HER2 IHC3+ data of 40 patients is planned from Part 2A of the DP-02 study.
  Given the prevalence of HER2 overexpression in tumour types outside of breast and gastric cancer is relatively low (Yan *et al* 2015), which is further reduced by the smaller numbers of patients in a pre-treated population, a total of 454 patients is considered a comprehensive dataset to support the proposed indication.
- Unmet medical needs will be addressed, as patients with HER2-expressing advanced or metastatic solid tumours in the 2L and later treatment setting continue to have poorer

outcomes with currently available treatments than patients with less aggressive non-HER2-expressing tumours (Vivaldi *et al* 2020, Morrison *et al* 2006, Slomovitz *et al* 2004, Vermij *et al* 2021, Fuchs *et al* 2007, Shang *et al* 2017, Luo *et al* 2018), Gan *et al* 2021, Laurent-Puig *et al* 2016, Strickler *et al* 2022, Ahcene Diaballah *et al* 2022, Liu *et al* 2010).
Several tissue-agnostic targeted therapies in biomarker-selected populations are approved, including in tumours with microsatellite instability high, deficient mismatch repair, high tumour mutational burden, BRAF V600E, NTRK fusions and RET rearrangements with recent scientific advances globally (Tateo *et al* 2023). However, the majority of patients with HER2 (IHC 3+) expressing or amplified tumours (including ovarian, endometrial, lung, bladder, and BTC) receive standard chemotherapy treatments that are not specifically targeted toward HER2-expressing tumours and thus provide limited clinical benefit. HER2-targeted therapies are limited and currently approved for the treatment of HER2-positive BC, GC, and BTC.
Standard of care therapies in the late line setting include multi agent cytotoxic therapy with toxicities; if there are any residual toxicity from first line therapy then this further limits the therapeutic options in subsequent lines of therapy. In most common tumour types, 2L treatments recommended by ESMO guidelines typically do not report response rates above 35-40%. Furthermore, across less common tumour types, single agent or combination chemotherapy is often the only option, and typically results in more limited efficacy, with ORR less than 30% and an expected mDoR under 6 months. By targeting molecular characterisation and drivers of therapeutic vulnerabilities such as HER2-positive (IHC 3+) across tumour types, T-DXd offers the opportunity to improve therapeutic outcomes for patients. The MAH has also presented a table with responses rates to currently available therapies in second line setting for different tumours and provided cross sectional comparison of ORRs in those tumours for standard of care and Enhertu (not shown) claiming that ORR observed with Enhertu are higher than in Standard of Care (SoC).

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.
  HER2 aberrant tumours, including overexpression, have been associated with poor prognosis and patient outcomes across multiple tumour types. In later-line treatment settings, there is no universally accepted SoC for HER2-positive tumours. Limited treatment options exist for the majority of tumour types with recurrent HER2-positive disease with treatments mainly consisting of standard chemotherapy, untargeted toward tumorigenic biomarkers, such as HER2, and are associated with high toxicities. Current treatment options for these patients, focused after failure on standard therapies, provide limited clinical benefit. In addition, patients in later lines often have reduced performance status, organ function or cumulative toxicities from prior treatments, which may make many regimens intolerable.
  T-DXd is the first tissue-agnostic therapy for patients with HER2-positive (IHC 3+) tumours that demonstrates consistent and clinically meaningful confirmed ORR with durable response in this patient population. Compared to current treatments across multiple HER2-positive (IHC 3+) tumour types, T-DXd demonstrates durable, high response rates leading to clinically meaningful survival outcomes. The safety and tolerability profile of T-DXd is well established; supported by pivotal safety data from patients with IHC 3+ solid tumours at 2 doses (T-DXd 5.4 mg/kg (N=347) and T-DXd 6.4 mg/kg (N=68)) and supporting safety data, pooled from patients in various tumour types and IHC expression levels (T-DXd 5.4 mg/kg (N=3057) and T-DXd 6.4 mg/kg (N=889). This demonstrates that T-DXd 5.4 mg/kg is generally well tolerated, demonstrates an acceptable and generally

manageable safety profile in the intended patient population and has a safety profile comparable to the established safety profile for T-DXd.

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

See Table 6 for the Tabular overview of clinical studies.

The Applicant received Scientific Advice on the development of Trastuzumab deruxtecan for the treatment of adult patients with unresectable or metastatic HER2-expressing (IHC 2+/IHC 3+) solid tumours that have progressed following prior treatment or who have no satisfactory alternative treatment options from the CHMP on 10/11/2022 (EMA/SA/0000102946). The Scientific Advice pertained to the following clinical aspects:

- The adequacy of the DP-02 study to support an approval for T-DXd in the treatment of adult patients with unresectable or metastatic HER2-expressing solid tumours that have progressed following prior treatment or who have no satisfactory alternative treatment options, in particular with regards to number of tumour types included, patient population and safety data pooling approach
- The companion diagnostic strategy to the use of existing HER2 IHC tests, which are CE marked for breast/gastric cancer, in advance of a device CE-certified for a histology independent indication being available.

2.1.4. General comments on compliance with GCP

The MAH states that the study DP-02 was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation/GCP, applicable regulatory requirements.

To date there have been one Regulatory Authority site inspection conducted on the pivotal study DP-02.

Table 4 Details of inspections conducted by regulatory authorities

Study number	Inspection date	Regulatory agency
D967VC00001 (DESTINY-PanTumor02, DP-02) Site: Dr Funda Meric-Bernstam	29 Jan – 1 Feb 2024	FDA

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

2.2.1.1. Solid Tumour Prevalence

Due to the practicalities of considering all possible solid tumours, a conservative approach was used; where it is assumed that all existing indications are also captured under the HER2-positive

solid tumours prevalence, where a broad prevalence estimate is utilised. To this end the prevalence of all cancers was taken as a worst-case estimate of the potential patient population eligible for treatment with T-DXd. The Globocan database estimates Denmark to be the European Member State with the highest prevalence of cancer; 1-year prevalence of all cancers is 698.9 per 100 000 (Globocan 2022[1]). The conservative worst-case F_{pen} was considered to be 0.00699.

2.2.1.2. Maximum daily dose

The maximum daily dose is calculated based on the maximum recommended dose which can be taken in one day (6.4 mg/kg for gastric cancer) and the average weight of a European adult (6.4 mg/kg × 70.8 kg). A reduction is applied to this maximum daily dose based on the percentage of total dose representing the active drug (2.5%); equivalent to 11.3 mg per day.

2.2.1.3. Combined Prevalence and Posology refinement

Using a market penetration of 0.699% and the dose regimen of 1 treatment every 21 days, the resulting overall refined Fpen is calculated as follows:

$$F_{PEN\text{-}refined} = \frac{0.00699 \times 1 \times 17.4}{365}$$

$$F_{PEN\text{-}refined} = \frac{0.122}{365} = 0.000333$$

$$PEC_{Surfacewater} = \frac{DOSEai \times Fpen}{WASTEWinhab \times DILUTION}$$

where;

DOSEai = maximum daily dose consumed per inhabitant = 11.3 mg inh^{-1} d^{-1}

Fpen-refined = 0.000333 (F_{pen} refined for cancer prevalence and posology)

WASTEWinhab = amount of wastewater per inhabitant per day = 200 L inh^{-1} d^{-1}

DILUTION = dilution factor = 10

$$PEC_{surfacewater} = \frac{11.3 \times 0.000333}{200 \times 10}$$

$$PEC_{surfacewater} = 188 \times 10^{-6}\ mg/L$$

$$\boldsymbol{PEC_{surfacewater} = 1.88 \times 10^{-3}\ \mu g/L}$$

The overall refined $PEC_{surfacewater}$ is below the PEC action limit (0.01 µg/L) for triggering a full Phase II ERA.

[1] Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2024). Global Cancer Observatory: Cancer Today (version 1.1). Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.who.int/today

Table 5 Summary of main study results: Phase I

Substance (INN/Invented Name):	MAAA-1181a (drug part of trastuzumab deruxtecan)		
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential-log Kow	OECD 107	1.92 at pH 5 1.80 at pH 7 1.28 at pH 9	Potential PBT: N

Phase I			
Parameter	Value	Unit	Conclusion
$PEC_{sw\ default,}$ F_{pen} = 0.01	0.0565	µg/L	
$PEC_{sw,\ refined}$ (based on prevalence and treatment regime) F_{pen} = 0.000333 (refined)	0.00188	µg/L	≥ 0.01 threshold: N
Other concerns (e.g. chemical class)			N

2.2.2. Discussion on non-clinical aspects

The MAH submitted an updated Environmental risk assessment (ERA) report in support of the variation application for Enhertu concerning the addition of a new therapeutic indication of the treatment of adult patients with unresectable or metastatic HER2-positive (ICH3+) solid tumours.

According to the Phase I Risk assessment for trastuzumab deruxtecan (T-DXd), the Predicted environmental concentration in surface water (PEC_{SW}) was re-evaluated by refinement of the market penetration factor (F_{PEN}). The F_{PEN} was refined based on posology and prevalence, whereby a histology independent indication was proposed addressing all approved indications, i.e. the prevalence of all cancers was taken as an estimate of the potential patient population eligible for treatment with T-DXd. Prevalence data were sourced from Globocan (2022) for countries of the European Union. This is considered a conservative approach and the data used were the most recent. Hence, the prevalence and posology based F_{PEN} refinement and the resulting PEC_{SW} value of 0.00188 is acceptable. It is agreed that the action limit of 0.01 µg/L was not reached and no further Risk assessment is warranted. For the PBT/vPvB screening, the MAH provided log D_{OW} values which were already assessed as part of the initial authorisation, with the conclusion that no further PBT/vPvB assessment is required. This is agreed with.

The MAH proposal for labelling and risk mitigation measures noted in the package leaflet are agreed with. Labelling in section 6.6 of the Summary of Product Characteristics (SmPC) is considered in line with the revised ERA guideline (EMEA/CHMP/SWP/4447/00 Rev.1, 2024).

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of trastuzumab deruxtecan.

- Considering the above data, trastuzumab deruxtecan should be used according to the precautions stated in the SmPC in order to minimize any potential risks to the environment.

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

Table 6 Clinical Studies for T DXd in Previously Treated HER2-expressing Solid Tumours Supporting a histology independent IHC 3+ Indication

Phase and status of study	Study number (Name)	Objective(s) of study	Study design and type of control	Investigational drug and dose regimen	Study population	DCO	Regions
Multi-tumor							
Phase II Ongoing	D967VC00001 (DESTINY-PanTumor02, DP-02)	To evaluate the efficacy and safety of T-DXd for the treatment of selected HER2-expressing tumours	Open-label Nonrandomized, multi-cohort, multicenter, single-arm	T-DXd 5.4 mg/kg IV infusion Q3W	HER2-expressing advanced solid tumours across 7 tumour cohorts	10 Oct 2024	North America, Europe and Asia-Pacific
Lung Cancer							
Phase II Completed	DS8201-A-U204 (DESTINY-Lung01, DL-01)	To investigate the efficacy and safety of T-DXd in subjects with HER2-overexpressing or HER2-mutated advanced NSCLC	Open-label, multicenter, Nonrandomized, single-arm	T-DXd 5.4 mg/kg or 6.4 mg/kg IV infusion Q3W	HER2-overexpressing or -mutated advanced NSCLC	03 Dec 2021	North America, Japan, and Europe
Colorectal Cancer							
Phase II Completed	DS8201-A-U207 (DESTINY-CRC02, DC-02)	To evaluate the efficacy, safety, and PK of T-DXd in patients with HER2-overexpressing locally advanced, unresectable, or metastatic colorectal cancer	multicenter, randomized, uncontrolled, 2-arm, parallel In the first stage, participants were planned to be randomized 1:1 with 2 doses of T-DXd. After Stage 1 enrolment was complete, all further eligible participants were planned to be registered to T-DXd administered IV in Stage 2	T-DXd 5.4 mg/kg or 6.4 mg/kg IV infusion Q3W	HER2-overexpressing locally advanced or metastatic colorectal cancer	01 Nov 2022	US, Asia-Pacific, and Europe

2.3.2. Pharmacokinetics

Bioanalytical Methods

Pharmacokinetics

Serum concentrations of T-DXd, total anti-HER2 antibody, and DXd (the drug component of the ADC) were measured by using previously reported validated bioanalytical methods. The conducted bioanalysis in the DP-02 study fulfilled the regulatory criteria for performance of standard curve, QC samples, ISR samples and samples were analysed within verified stability window.

Immunogenicity

The immunogenicity assessment for anti-T-DXd antibodies in serum was conducted by using the previously reported validated methods, updated for the relevant patient population. ADA-positive samples were further analysed for NAb detection against T-DXd.

Evaluation and qualification of models

PK data analysis

For PopPK analysis, R Project for Statistical Computing (version 4.0.2. or higher) was used to carry out minor modifications to the analysis dataset, exploratory analysis, diagnostic graphics, post-processing of NONMEM (version 7.5.0 or higher) and STAN (version 18.0 or higher) analysis results and statistical analysis. The first-order condition estimation approximation (FOCE) was used as estimation method. The HMC NUTS was used as a sampling method in the STAN analysis.

ERES analysis dataset preparation and statistical analysis were performed using Statistical Analysis Software (SAS version 9.4) and R Project for Statistical Computing, Version 4.0.2 or higher. The ERES analysis was performed using R Project for Statistical Computing version 4.0.2. or higher.

PopPK modelling

The primary purpose of this analysis is to update an established monotherapy population pharmacokinetic (PopPK) model for both T-DXd and DXd based on multiple new clinical trial data including various tumour types. This new monotherapy PopPK model is developed to characterise pharmacokinetics across a broad base of tumour types and to support key exposure metrics for exposure-response modelling.

In this analysis, previously developed PopPK model for T-DXd was updated by including new PK data from Study DP-02 and the PK data of five additional Studies (D967YC00001 [DESTINY-Lung 03, DL03], D7811C00001 [DESTINY-Lung 05, DL05], D9676C00002 [DESTINY-Gastric06, DG06], D9670C00001 [DESTINY-Breast06, DB06] and monotherapy modules [Modules 0 and 7] of D967JC00001 [DESTINY-Breast07, DB07]) to describe the serum concentration-time profiles of T-DXd and its payload DXd in patients with various tumour types.

In the T-DXd data, 302 (0.699%) post-dose below the lower limit of quantification (BLQ) samples were excluded, resulting in the T-DXd dataset including 39247 T-DXd serum PK samples from 3576 patients. In the DXd data, 91 (0.213%) post-dose BLQ samples were excluded, resulting in the DXd dataset including 39019 DXd serum PK samples from 3576 patients. Data that are BLQ were excluded from the estimation of the model parameters (M1-method) but retained in the NONMEM dataset and are used in the exploratory analysis. In total, 256 samples out of 78275 (representing ~0.3 % of the total number of samples) were considered outliers (|CWRES|>5) and were excluded from the data, ensuring that no patient was entirely removed from the dataset.

The previously developed popPK model was used as a starting point for the current model development. The PK data for T-DXd were described using a two-compartment model with linear elimination, while DXd was described by a one-compartment model, with time-varying release of drug from T-DXd.

During the development of the T-DXd monotherapy PopPK model, certain covariates related to tumour type (specifically, CRC and NSCLC on VcT-DXd) were removed from the previous model, as they were no longer found to be statistically significant. The overall model structure remained unchanged from the prior T-DXd model. Baseline albumin, Japanese, tumour size at baseline, body weight and tumour type (gastric cancer (GC) and CRC) were found as statistically significant covariates on CLT-DXd. Body weight, sex and tumour type (GC) had a statistically significant impact on the central V1T-DXd. Additionally, Japanese was included as a covariate on V2T-DXd. Regarding the DXd monotherapy PopPK model, certain covariates related to tumour type (specifically, GC on CLDXd, and other tumour types on V3DXd) were removed from the previous model, as they were no longer found to be statistically significant. The overall model structure remained unchanged from the prior DXd model. Ritonavir coadministration, itraconazole coadministration, AST, baseline bilirubin, body weight and tumour type (NSCLC, CRC and Others) were found as statistically significant covariates on CLDXd. Age, formulation, tumour type (NSCLC and CRC) and non-Asian had a statistically significant impact on the V3DXd. Tumour size at baseline was not available in two studies (DL03 and monotherapy DB07) and had 7.52% of missing values overall.

The parameter estimates for the final T-DXd model are reported in Table 7.

Table 7 T-DXd Population PK Model Parameter Estimates

Parameter	Estimate	RSE (%)	95% CI	Shrinkage (%)	Unit
T-DXd Population Parameter					
CL (T-DXd)	19.3	0.668	[19.0 ; 19.5]	-	mL/h
V1 (T-DXd)	2813	0.398	[2790 ; 2830]	-	mL
Q (T-DXd)	7.80	1.05	[7.64 ; 7.96]	-	mL/h
V2 (T-DXd)	6000	1.71	[5800 ; 6200]	-	mL
T-DXd Covariates					
Albumin on CL (T-DXd)	-0.431	8.83	[-0.505 ; -0.356]	-	-
Japanese on CL (T-DXd)	-0.118	9.97	[-0.140 ; -0.0945]	-	-
Tumour Size at Baseline on CL (T-DXd)	0.0622	11.3	[0.0484 ;0.0760]	-	-
Body weight on CL (T-DXd)	0.401	6.14	[0.353 ; 0.450]	-	-
Sex on V1 (T-DXd)	0.132	7.97	[0.111 ; 0.153]	-	-
Body Weight on V1 (T-DXd)	0.453	3.46	[0.422 ; 0.484]	-	-
Japanese on V2 (T-DXd)	-0.165	18.4	[-0.224 ; -0.105]	-	-
GC on CL (T-DXd)	0.146	13.3	[0.108 ; 0.184]	-	-

Parameter	Estimate	RSE (%)	95% CI	Shrinkage (%)	Unit
CRC on CL (T-DXd)	0.114	21.4	[0.0665 ; 0.162]	-	-
GC on V1 (T-DXd)	0.125	11.4	[0.0968 ; 0.152]	-	-
T-DXd Interindividual Variability					
ETA CL (T-DXd)	27.7	1.06	[27.7 ; 27.7]	11.6	%
CORR ETA CL-V1 (T-DXd)	0.472	3.51	[0.439 ; 0.504]	-	-
ETA V1 (T-DXd)	17.2	0.927	[17.2 ; 17.2]	10.7	%
ETA Q (T-DXd)	27.9	3.88	[27.9 ; 28.0]	51.5	%
ETA V2 (T-DXd)	66.5	2.58	[66.5 ; 66.6]	31.4	%
T-DXd Residual Variability					
Proportional Res.Error (T-DXd)	19.4	0.171	[19.4 ; 19.4]	10.2	%
Additive Res.Error (T-DXd)	0.905	1.77	[0.873 ; 0.936]	10.2	µg/mL

T-DXd and DXd were modelled separately. The parameter estimates for the final DXd model are reported in Table 8 (as T-DXd estimates are fixed to the value of Table 7 only the DXd parameter values are presented in Table 8 to reduce repetition).

Table 8 T-DXd and DXd Population PK Model Parameter Estimates

Parameter	Estimate	RSE (%)	95% CI	Shrinkage (%)	Unit	Fixed
DXd Population Parameter						
CL (DXd)	18.4	1.88	[17.7 ; 19.1]	-	L/h	FALSE
KREL (DXd)	0.0197	1.84	[0.0190 ; 0.0204]	-	h^-1	FALSE
FPC1 (DXd)	0.716	0.734	[0.706 ; 0.726]	-	-	FALSE
FPC1 (DXd)	-0.153	2.36	[-0.160 ; -0.145]	-	-	FALSE
DXd Covariates						
Ritonavir Combination on CL (DXd)	-0.113	15.5	[-0.148 ; -0.0789]	-	-	FALSE
Itraconazole Combination on CL (DXd)	-0.112	19.4	[-0.155 ; -0.0697]	-	-	FALSE
AST on CL (DXd)	-0.196	7.51	[-0.225 ; -0.167]	-	-	FALSE
Bilirubin on CL (DXd)	-0.150	9.68	[-0.178 ; -0.121]	-	-	FALSE
Body Weight on CL (DXd)	0.266	13.7	[0.195 ; 0.338]	-	-	FALSE
Age on V3 (DXd)	0.537	8.85	[0.444 ; 0.631]	-	-	FALSE
Formulation on V3 (DXd)	0.553	10.9	[0.435 ; 0.672]	-	-	FALSE
NSCLC on V3 (DXd)	-0.306	8.83	[-0.359 ; -0.253]	-	-	FALSE
Others on CL (DXd)	-0.171	13.4	[-0.216 ; -0.126]	-	-	FALSE
Non-Asian on V3 (DXd)	-0.203	8.41	[-0.237 ; -0.170]	-	-	FALSE
DXd Interindividual Variability						
ETA CL (DXd)	29.3	3.00	[29.3 ; 29.3]	36.8	%	FALSE
ETA V3 (DXd)	49.6	1.59	[49.6 ; 49.6]	20.6	%	FALSE

Parameter	Estimate	RSE (%)	95% CI	Shrinkage (%)	Unit	Fixed
ETA KREL (DXd)	32.6	2.71	[32.6 ; 32.7]	26.9	%	FALSE
ETA FPC1 (DXd)	76.0	2.62	[76.0 ; 76.1]	30.0	%	FALSE
DXd Residual Variability						
Proportional Res.Error (DXd)	30.7	0.278	[30.7 ; 30.7]	10.6	%	FALSE

GOF plots are presented in Figure 2 (CWRES distribution plots not included).

Figure 2 Final Model – Goodness of Fit Plots

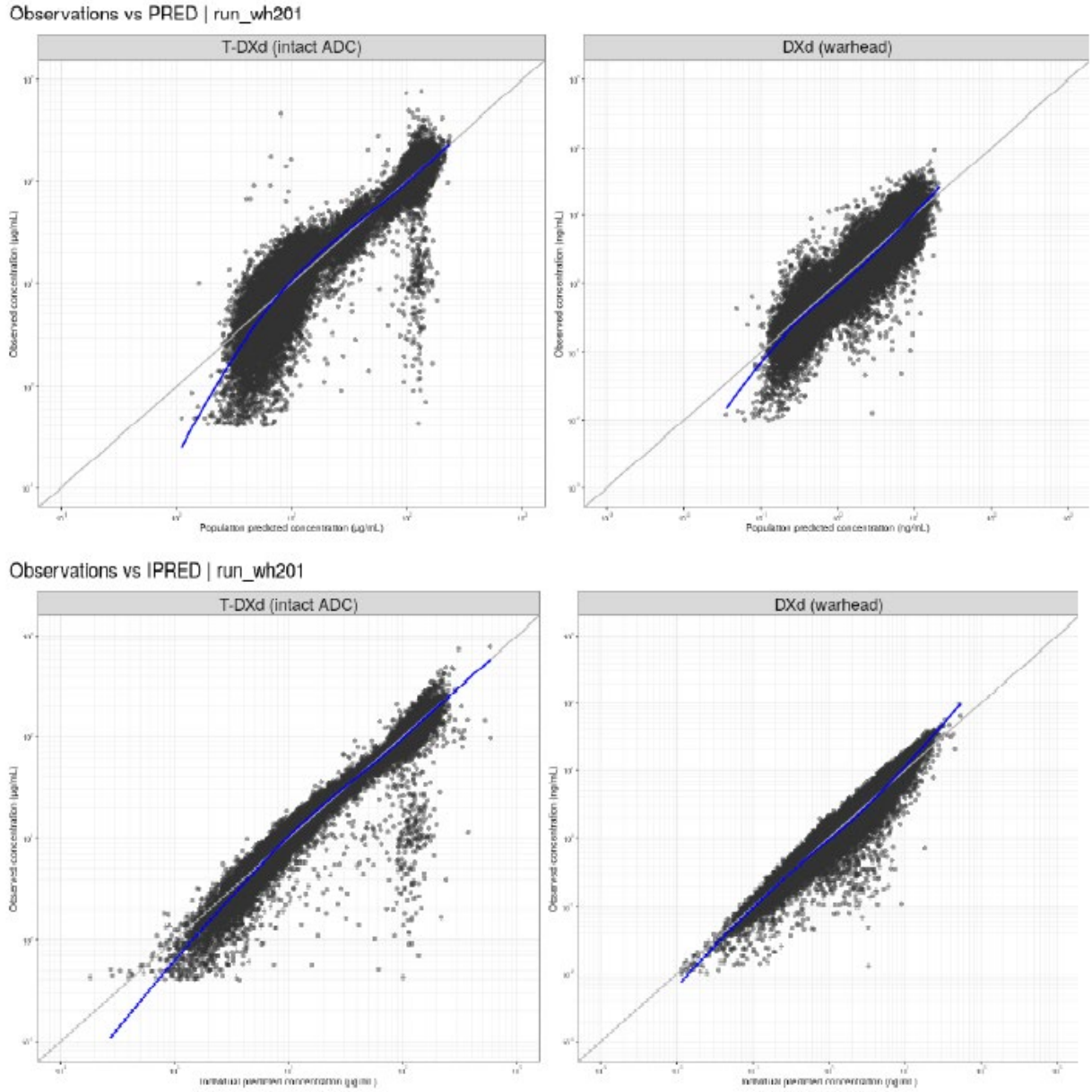
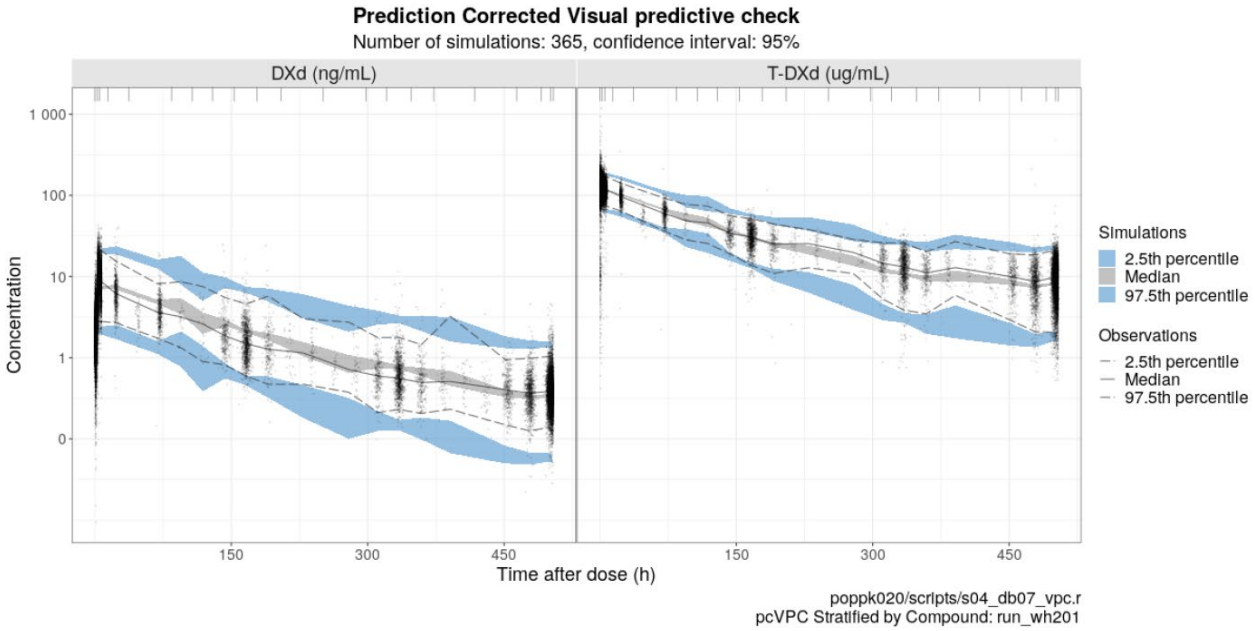


Figure 3 pcVPC of the Final Model vs Time after Dose – Overall



2.3.2.1. Pharmacokinetics in the target population

In the pivotal studies DP-02, PK of the ADC T-DXd, total anti-HER2 antibody, and the topoisomerase I inhibitor DXd were investigated by sparse sampling. NCA was not conducted and PK parameters were estimated post hoc. by PopPK model. In the supportive studies DL-01 and DC-02 PK was investigated by rich sampling in cycle 1 and sparse sampling in later cycles. PK parameters were estimated with both NCA analysis and PopPK analysis.

Study DP-02 – PK

The study design of DP-02 is described in section 2.4.2. . The PK Analysis Set included 267 patients who received at least one dose of T-DXd and had any measurable concentrations of T-DXd, DXd, and/or total anti-HER2 antibody after first dose. The concentration profile of T-DXd was similar to that of the total anti-HER2 antibody. DXd exposure was lower than either T-DXd or total anti-HER2 antibody exposure. Concentration levels were consistent with concentration levels observed in other indications dosed at 5.4 mg/kg Q3W.

Table 9 Summary of Serum Concentrations (PK Analysis Set)

Nominal time	Concentration of T-DXd (µg/mL) (Mean, SD)	Concentration of DXd (ng/mL) (Mean, SD)	Concentration of total antibody (µg/mL) (Mean, SD)
Cycle 1: 15 mins post-infusion	110.248, 32.174	5.923, 6.190	113.409, 29.584
Cycle 1: 5 hours post-infusion	103.768, 27.125	13.703, 9.221	106.129, 27.369
Cycle 2: pre-infusion	3.429, 2.127	0.239, 0.185	5.313, 4.423
Cycle 4: pre-infusion	9.133, 19.432	0.405, 0.456	13.437, 21.685
Cycle 4: 15 mins post-infusion	112.044, 37.597	2.184, 1.249	121.347, 44.414

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The gmean AUC,ss and gmean Cmax,ss of T-DXd and DXd for the IHC3+ patients included in DP-02, stratified according to cancer type estimated by PopPK are provided in Table 10 and Table 11.

Table 10 Summary of Post-hoc T-DXd AUC_{ss} (µg × hr/mL) in Patients with IHC 3+ Solid Tumours Included in DP-02 Study Stratified by Tumour Type

Tumour type	Median	Mean	SD	CV (%)	Geometric Mean
Cohort 1: Biliary Tract Cancer (n = 22)	15678.24	16376.94	4726.82	28.86	15689.57
Cohort 2: Bladder n = 27)	15257.95	15345.52	2833.93	18.47	15086.51
Cohort 3: Cervical Cancer (n = 10)	17060.4	17539.17	5504.19	31.38	16826.89
Cohort 4: Endometrial Cancer (n = 16)	17841.35	17431.36	4622.76	26.52	16811.43
Cohort 5: Ovarian Cancer (n = 15)	13836.74	14911.77	3718.01	24.93	14485.85
Cohort 6: Pancreatic Cancer (n = 5)	9479.78	10114.9	1144.29	11.31	10066.42
Cohort 7: Rare Tumours (n = 16)	16088.7	17157.01	4982.5	29.04	16478.29

Table 11 Summary of Post-hoc T-DXd Cmax,ss (µg/mL) in Patients with IHC 3+ Solid Tumours Included in DP-02 Study Stratified by Tumour Type

Tumour type	Median	Mean	SD	CV (%)	Geometric Mean
Cohort 1: Biliary Tract Cancer (n = 22)	119.98	121.11	26.59	21.96	118.25
Cohort 2: Bladder Cancer (n = 27)	112.68	116.72	16.91	14.49	115.59
Cohort 3: Cervical Cancer (n = 10)	129.84	136.3	34.89	25.6	132.92
Cohort 4: Endometrial Cancer (n = 16)	131.85	133.97	25.21	18.82	131.57
Cohort 5: Ovarian Cancer (n = 15)	116.81	115.8	24.74	21.36	113.29
Cohort 6: Pancreatic Cancer (n = 5)	87.2	88.68	4.34	4.89	88.6
Cohort 7: Rare Tumours (n = 16)	117.46	120.79	25.89	21.43	118.1

Study DL-01 (DS8201-A-U204) – PK

The study design of DL-01 is described in section 2.4.3.1. . Study DL-01, including PK has previously been submitted and assessed, see EPAR (EMEA/H/C/005124/II/0027). Across both treatment groups (Stage 1 and 2), the PK parameters for T-DXd and total anti-HER2 antibody were similar. The exposure of DXd was lower than the exposure of T-DXd. There was a dose-related increase in mean PK exposure parameters (Cmax and AUC through 21 days post-dose [AUC21d]) across the 5.4 mg/kg and 6.4 mg/kg treatment groups. Selected Cycle 1 mean PK-data (SD) of T-DXd (Cohort 1a, 5.4 mg/kg, N =41): AUC21d = 573.43 (140.35) µg*d/mL, Cmax 135.21 (40.371) µg/mL.

The gmean AUC,ss and gmean Cmax,ss of T-DXd and DXd for the IHC3+ in patients included in DL-01 were estimated post hoc. by PopPK are provided in Table 12 and Table 13.

Table 12 Summary of Post-hoc T-DXd Exposure Parameters in DL-01 in Patients with IHC 3+ Lung Cancer Receiving 5.4 mg/kg and 6.4 mg/kg (Population PK Analysis)

	5.4 mg/kg T-DXd DL-01 Lung Cancer (n = 17)		6.4 mg/kg T-DXd DL-01 Lung Cancer (n = 10)	
Parameter	**AUCss (µg × hr/mL)**	**Cmax (µg/mL)**	**AUCss (µg × hr/mL)**	**Cmax (µg/mL)**
Mean	17463.82	136.5	23139.46	163.94
Std Dev	4273.76	23.54	8867.01	25.7
%CV	24.47	17.24	38.32	15.68
Median	17618.4	136.72	21142.58	162.06
Geometric Mean	16952.31	134.48	22036.54	162.07

Table 13 Summary of Post-hoc DXd Exposure Parameters in DL-01 in Patients with IHC 3+ Lung Cancer Receiving 5.4 mg/kg and 6.4 mg/kg (Population PK Analysis)

	5.4 mg/kg T-DXd DL-01 Lung Cancer (n = 17)		6.4 mg/kg T-DXd DL-01 Lung Cancer (n = 10)	
Parameter	**AUCss (ng × hr/mL)**	**Cmax (ng/mL)**	**AUCss (ng × hr/mL)**	**Cmax (ng/mL)**
Mean	672.32	5.1	785.89	5.64
Std Dev	156.75	1.21	161.01	1.4
%CV	23.31	23.77	20.49	24.77
Median	684.21	5.09	713.6	5.76
Geometric Mean	654.42	4.96	772.31	5.46

Study DC-02 (DS8201-A-U207) – PK

The study design of DC-02 is described in section 2.4.3.2. . In each cohort, the PK parameters for T-DXd and total anti-HER2 antibody were similar. The exposure of DXd was lower than the exposure of T-DXd. On a molar basis, the T-DXd Cmax was approximately 200-fold higher than that for DXd. The exposure of T-DXd (Table 14), total anti-HER2 antibody, and DXd were similar

between HER2-overexpressing mCRC patients (Cohort A) and low HER2-expressing mCRC patients (Cohorts B and C). The gmean AUC,ss and gmean Cmax,ss of T-DXd and DXd for the IHC3+ in patients included in DC-02 were estimated post hoc. by PopPK are provided in Table 15 and Table 16.

Table 14 Summary of T-DXd Pharmacokinetic Parameters (Pharmacokinetic Analysis Set)

Treatment Group Statistics	Cmax (µg/mL)	Tmax (h)a	AUClast (µg*d/mL)	AUC21d (µg*d/mL)	AUCinf (µg*d/mL)	L (mL/d/kg)	Vss (mL/kg)	t1/2 (d)
T-DXd 5.4 mg/kg Q3W Stage 1								
n	41	41	41	38	30	30	30	30
Mean	120.25	4.78	554.06	552.78	581.78	10.26	57.20	4.96
StdDev	30.657	1.5, 529.5	189.362	188.415	193.377	3.266	12.875	1.243
T-DXd 5.4 mg/kg Q3W Stage 2								
n	41	41	41	37	34	34	34	34
Mean	138.10	1.80	591.52	627.21	645.01	9.20	52.25	4.82
StdDev	41.597	0.9, 162.8	225.923	188.356	193.577	3.005	14.480	1.220
T-DXd 5.4 mg/kg Q3W Total								
n	82	82	82	75	64	64	64	64
Mean	129.17	2.09	572.79	589.50	615.37	9.70	54.57	4.89
StdDev	37.406	0.9, 529.5	208.011	190.822	194.558	3.150	13.868	1.223
T-DXd 6.4 mg/kg Q3W Stage 1								
n	39	39	39	35	31	31	31	31
Mean	149.95	4.78	706.36	734.26	805.49	8.48	54.22	5.55
StdDev	24.050	1.5, 6.9	227.492	189.293	192.037	2.429	10.279	1.007

AUC21d = area under the serum concentration-time curve up to 21 days; AUCinf = area under the serum concentration-time curve up to infinity; AUClast = area under the serum concentration-time curve up to the last quantifiable time; CL = total body clearance; Cmax = maximum serum concentration; Q3W = every 3 weeks; StdDev = standard deviation; t1/2 = terminal elimination half-life; T-DXd = trastuzumab deruxtecan; Tmax = time to reach maximum serum concentration; Vss = volume of distribution at steady state [a] Median (min, max) is shown for Tmax. Mean = Median, StdDev = Range, for Tmax. Data cut-off: 01 Nov 2022

Table 15 Summary of Post-hoc T-DXd Exposure Parameters in DC-02 in Patients with IHC 3+ Colorectal Cancer Receiving 5.4 mg/kg and 6.4 mg/kg (Population PK Analysis)

	5.4 mg/kg T-DXd DC-02 Colorectal Cancer (n = 64)		6.4 mg/kg T-DXd DC-02 Colorectal Cancer (n = 34)	
Parameter	**AUCss (µg × hr/mL)**	**Cmax (µg/mL)**	**AUCss (µg × hr/mL)**	**Cmax (µg/mL)**

Table 15 Summary of Post-hoc T-DXd Exposure Parameters in DC-02 in Patients with IHC 3+ Colorectal Cancer Receiving 5.4 mg/kg and 6.4 mg/kg (Population PK Analysis)

	5.4 mg/kg T-DXd DC-02 Colorectal Cancer (n = 64)		6.4 mg/kg T-DXd DC-02 Colorectal Cancer (n = 34)	
Mean	16290.7	130.78	20861.79	153.13
Std Dev	4600.89	24.42	5586.09	22.1
%CV	28.24	18.67	26.78	14.43
Median	16071.62	125.56	20693.38	153.39
Geometric Mean	15665.46	128.57	20048.43	151.53

Table 16 Summary of Post-hoc DXd Exposure Parameters in DC-02 in Patient with IHC 3+ Colorectal Cancer Receiving 5.4 mg/kg and 6.4 mg/kg (Population PK Analysis)

	5.4 mg/kg T-DXd DC-02 Colorectal Cancer (n = 64)		6.4 mg/kg T-DXd DC-02 Colorectal Cancer (n = 34)	
Parameter	AUCss (ng × hr/mL)	Cmax (ng/mL)	AUCss (ng × hr/mL)	Cmax (ng/mL)
Mean	813.03	6.07	1098.39	7.59
Std Dev	590.21	3.38	647.92	4.09
%CV	72.59	55.61	58.99	53.92
Median	734.42	5.45	850.29	6.25
Geometric Mean	714.21	5.44	973.39	6.8

Population-PK estimated exposure parameters for total population

Steady-state PK parameters of T-DXd and DXd in in patients with metastatic BC, NSCLC, or HER2-positive (IHC 3+) Solid Tumours was estimated with updated population PK model, see Table 17 and **Table 18**

Table 17 Summary of Post-hoc T-DXd Exposure Parameters in Patients with Metastatic BC, NSCLC, or HER2-positive (IHC 3+) Solid Tumours Receiving 5.4 mg/kg (Population PK Analysis)

	5.4 mg/kg T-DXd (N = 2567)	
Parameter	**AUCss (µg × hr/mL)**	**Cmax (µg/mL)**
Mean	18531	133.5
Std Dev	6362	29
%CV	34.33	21.73
Median	17866	130.1
Geometric Mean	17734	130.8

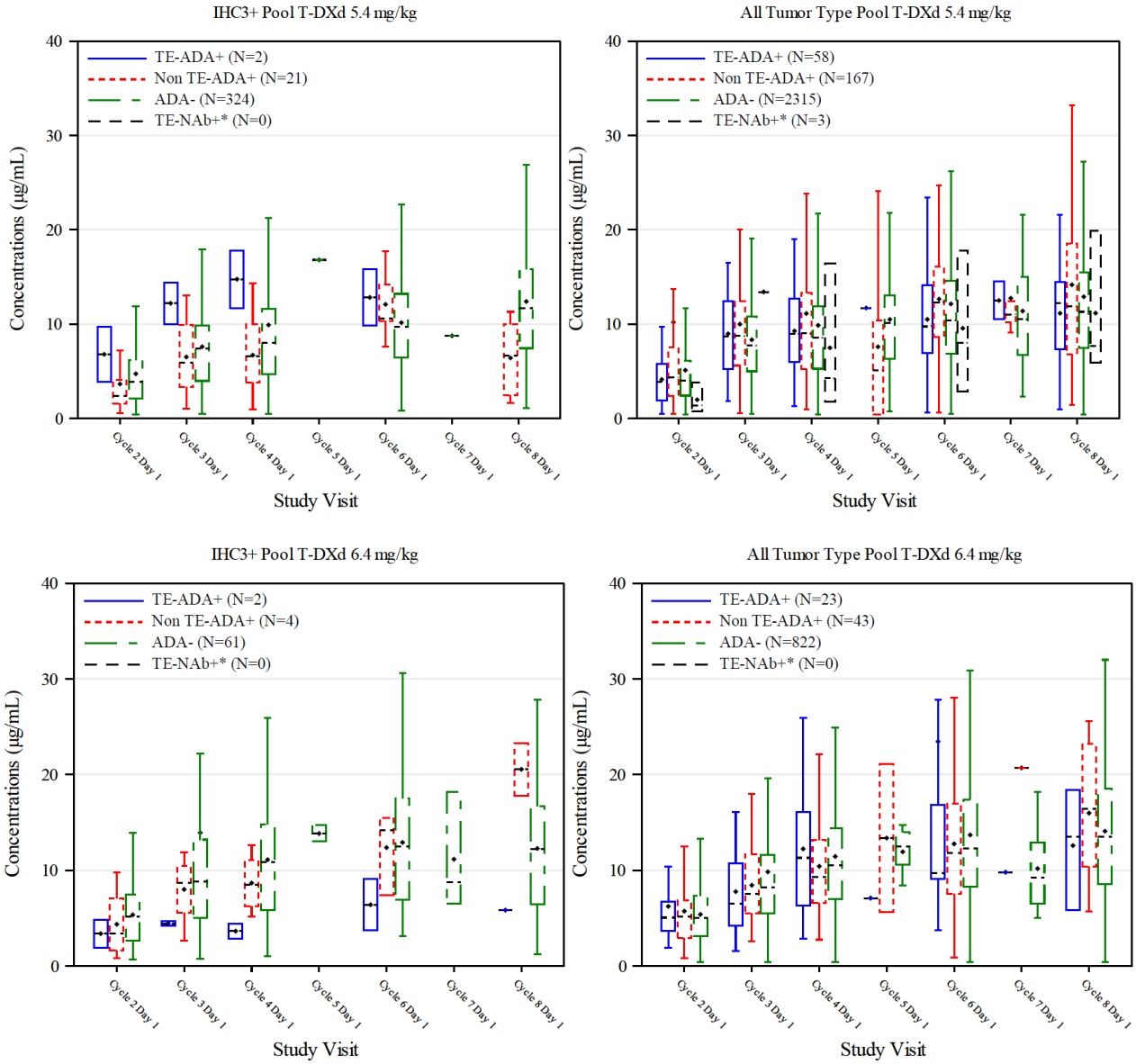
Table 18 Summary of Post-hoc DXd Exposure Parameters in Patients with Metastatic BC, NSCLC, or HER2-positive (IHC 3+) Solid Tumours Receiving 5.4 mg/kg and 6.4 mg/kg of T-DXd (Population PK Analysis)

	5.4 mg/kg T-DXd (N = 2567)	
Parameter	AUCss (ng × hr/mL)	Cmax (ng/mL)
Mean	807	5.6
Std Dev	394	2.6
%CV	48.85	46.57
Median	718	5.1
Geometric Mean	737	5.1

Impact of Immunogenicity on Pharmacokinetics

The assessment of T-DXd immunogenicity and the potential effect of ADA on PK was based on 4 pooled datasets (see section 8.3). The box plots of T-DXd exposure (Ctrough) by ADA status from C2D1 to C8D1 shows that there was no apparent effect of ADA on the PK of T-DXd, see Figure 4. Across all time points, T-DXd Ctrough in patients with TE-ADA+ status are similar to those with ADA- status. Moreover, the impact of T-DXd ADA on the PK of T-DXd has been previously evaluated in a PopPK model and found not to be a significant covariate.

Figure 4 Box Plots of T-DXd Ctrough by Visit and ADA Status and by Pools (Immunogenicity Analysis Set)

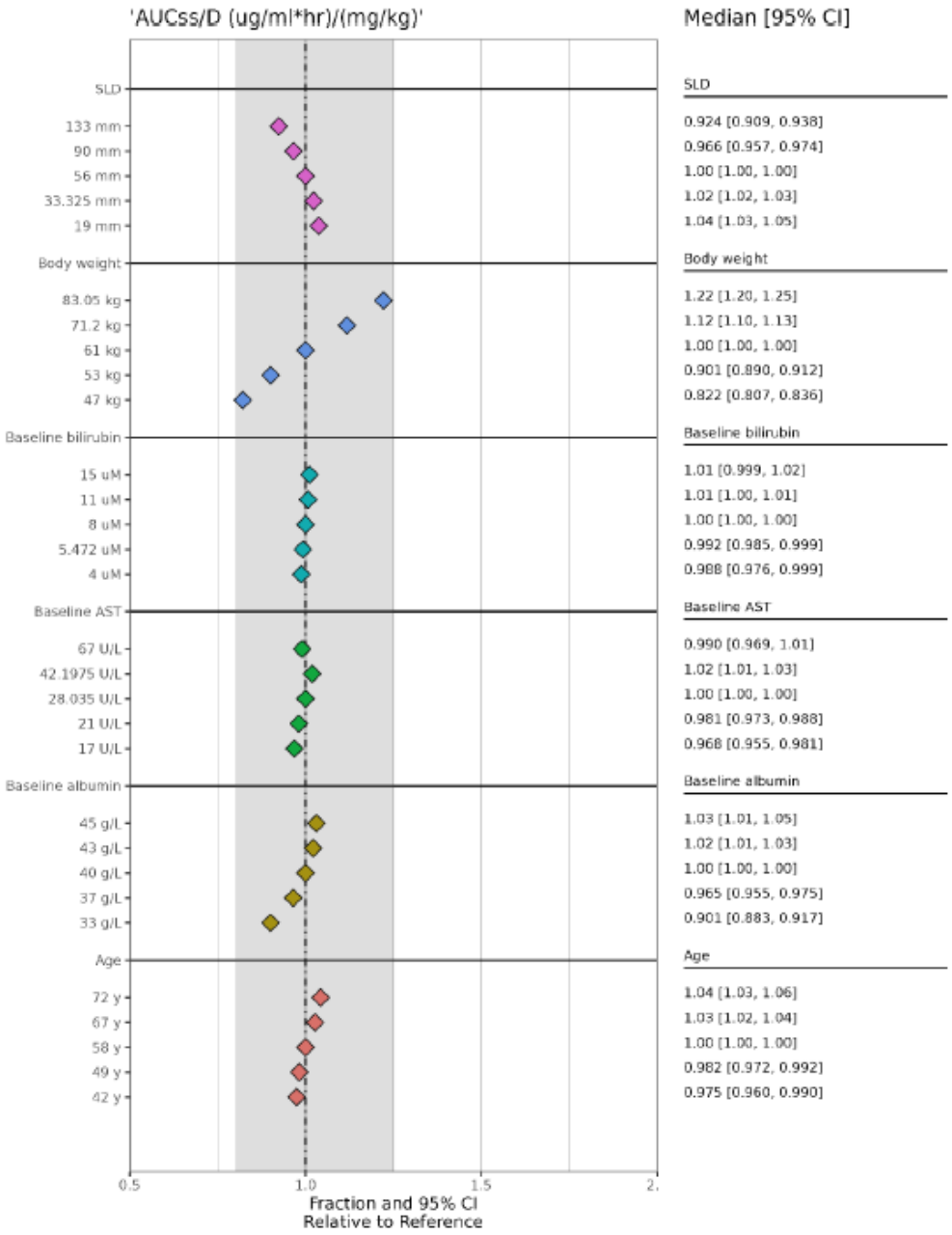


Boxplot = median (dotted line), arithmetic mean (diamond), and 1.5*IQR (spindles)
* nAb test results not available for DP-01, DB-01, DB-07, and DL-03.

Special populations

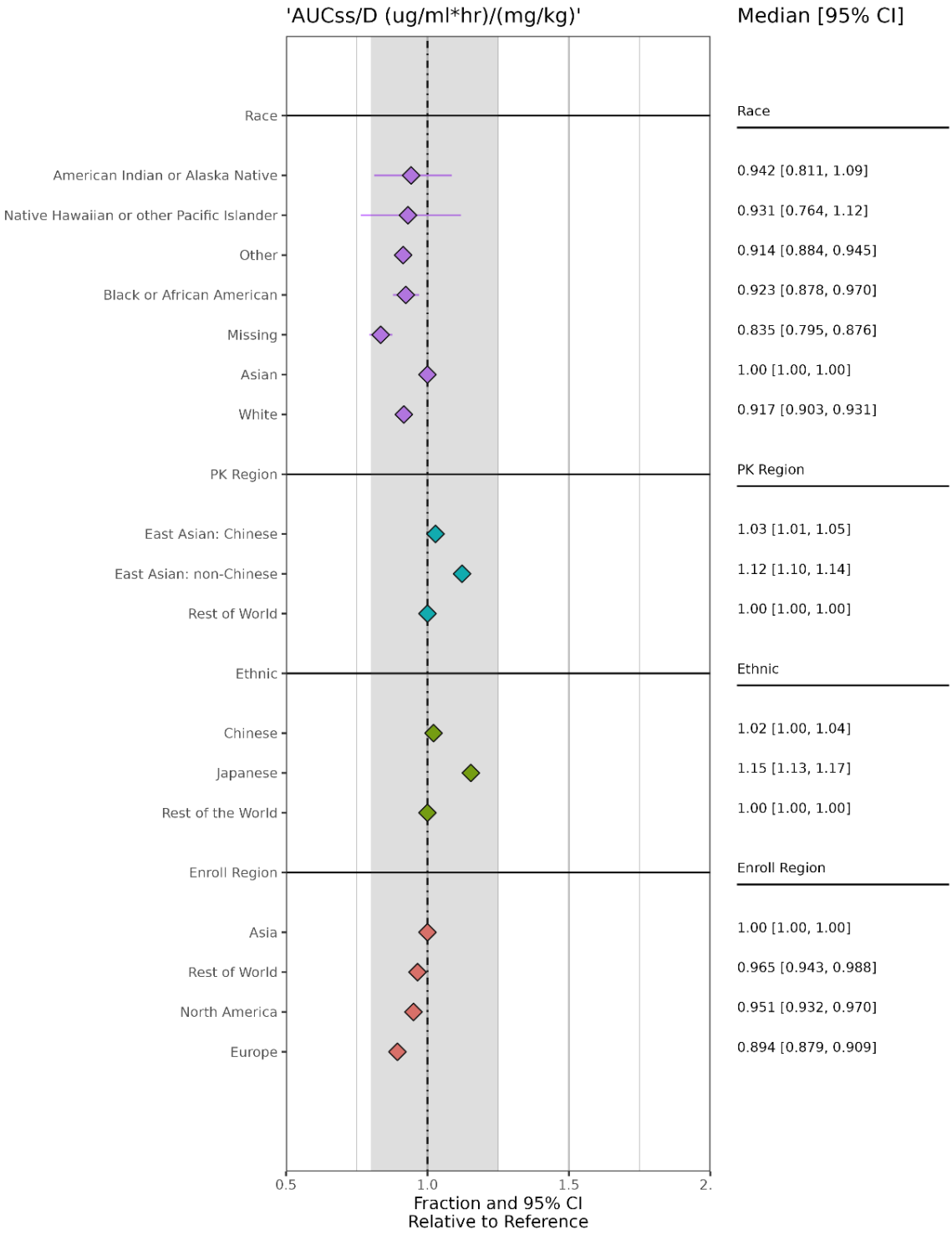
The impact of intrinsic and extrinsic factors on the PK of T-Dxd and DXd was reinvestigated with the updated population PK model. The impact of continuous and categorical covariates on dose normalized systemic exposure AUCss was evaluated for T-DXd and DXd(not shown), see forest plots in Figure 5, Figure 6 and Figure 7. Overall, none of the investigated covariates had a clinically meaningful effect on AUCss/D exposure for either T-DXd or DXd. For T-DXd, all subgroup median AUCss/D values were within the bioequivalence range of 80% to 125%.

Figure 5 Covariate Effects Plot of Continuous Covariates on T-DXd Exposure at Steady State (AUCss/D)



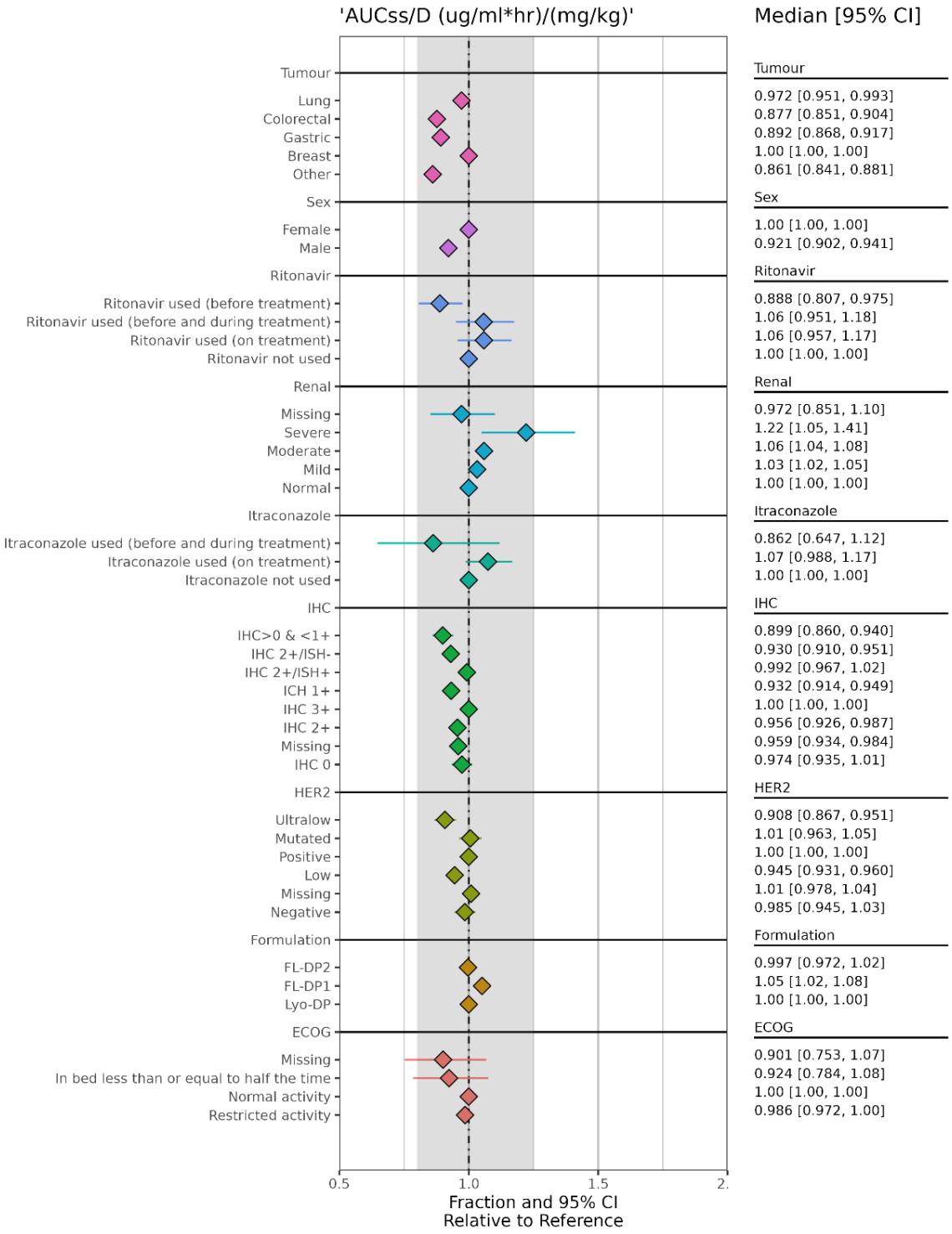
A typical patient is defined as a 58-year-old female with body weight 61 kg, bilirubin 8 µM, AST 28 U/L, albumin 40 g/L and tumour size at baseline of 56 mm.

Figure 6 Covariate Effects Plot of Ethnic Factors on T-DXd Exposure at Steady State (AUCss/D)



A typical patient is defined as having the most common category for each ethnicity covariate.

Figure 7 Covariate Effects Plot of Categorical Factors on T-DXd Exposure at Steady State (AUCss/D)



A typical patient is defined as female with HER2 positive breast cancer with IHC3+, without co-administration with ritonavir and/or itraconazole, with normal renal function and with ECOG normal activity who was administered a Lyo-DP formulation of T-DXd.

2.3.3. Pharmacodynamics

Mechanism of action

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

Primary and secondary pharmacology

There are no new studies related to QT intervals submitted with this application.

Exposure-Response analysis

Data from all evaluable patients with IHC 3+ tumours from Studies DP-02 (solid tumours), DC-02 (CRC), and DL-01 (NSCLC) who received T-DXd 5.4 mg/kg and 6.4 mg/kg Q3W were included in all E-R efficacy and safety analyses.

In total, 236 observations from 236 patients with IHC 3+ tumours who received IV doses of T-DXd, at doses of 5.4 mg/kg Q3W or 6.4 mg/kg Q3W, were included in each of the analysis sets; 27 (11.4%) with lung cancer, 98 (41.5%) with CRC and 111 (47.1%) with other solid tumours (bladder cancer [27], biliary tract cancer [22], rare tumours [16], endometrial cancer [16], ovarian cancer [15], cervical cancer [10], and pancreatic cancer [5]). A dose of 5.4 mg/kg Q3W was received by 192 (81.3%) patients, and a dose of 6.4 mg/kg (comprised of lung and CRC patients) was received by 44 (18.7%) patients.

Table 19 Probability of Achieving ORR, OS, or Experiencing Any-grade ILD or ≥ Grade 3 ILD Events in IHC 3+ Patients by Dose and Study

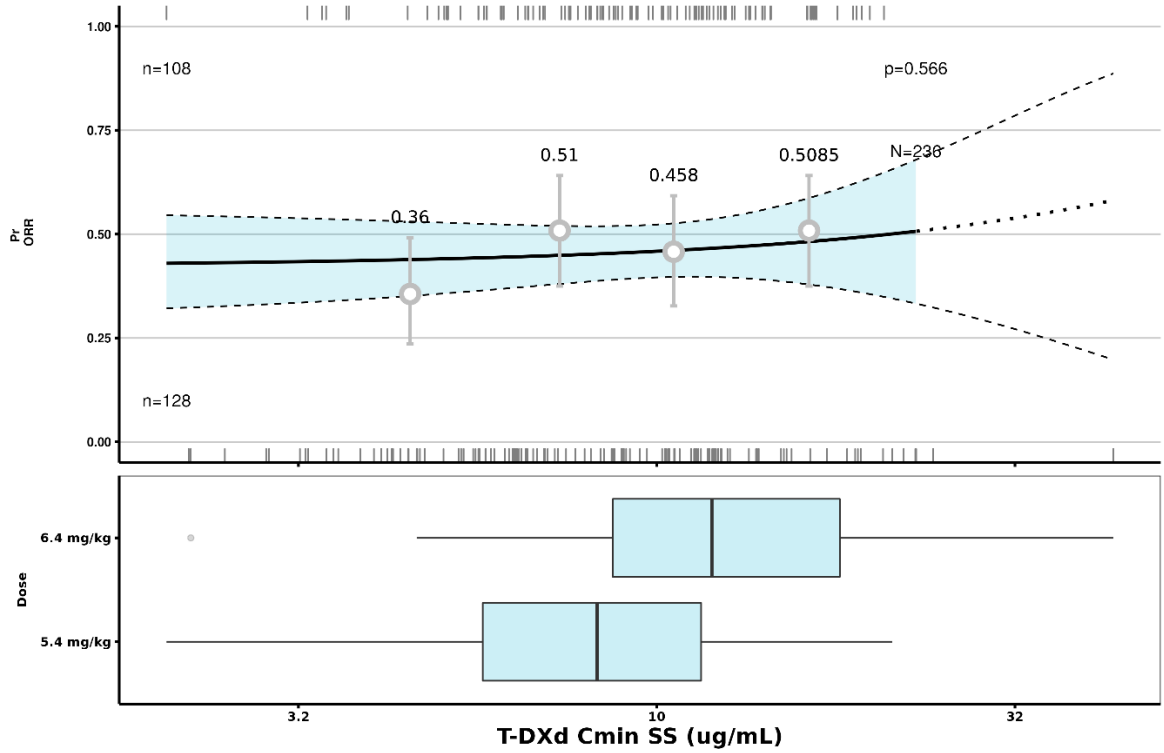
Endpoint	Level	DC-02 5.4 mg/kg (N = 64)	DC-02 6.4 mg/kg (N = 34)	DL-01 5.4 mg/kg (N = 17)	DL-01 6.4 mg/kg (N = 10)	DP-02 5.4 mg/kg (N = 111)	Total (N = 236)
ORR	No-response	34 (53.1)	24 (70.6)	8 (47.1)	8 (80.0)	54 (48.6)	128 (54.2)
ORR	Response	30 (46.9)	10 (29.4)	9 (52.9)	2 (20.0)	57 (51.4)	108 (45.8)
OS	Censored	48 (75.0)	25 (73.5)	7 (41.2)	0 (0.0)	27 (24.3)	107 (45.3)
OS	Death	16 (25.0)	9 (26.5)	10 (58.8)	10 (100.0)	84 (75.7)	129 (54.7)
ILD any grade	No event	57 (89.1)	29 (85.3)	15 (88.2)	8 (80.0)	90 (81.1)	199 (84.3)
ILD any grade	Event	7 (10.9)	5 (14.7)	2 (11.8)	2 (20.0)	21 (18.9)	37 (15.7)
ILD grade ≥ 3	No event	64 (100.0)	33 (97.1)	16 (94.1)	9 (90.0)	108 (97.3)	230 (97.5)
ILD grade ≥ 3	Event	0 (0.0)	1 (2.9)	1 (5.9)	1 (10.0)	3 (2.7)	6 (2.5)

Primary endpoint ORR by BICR

Correlations between ORR by BICR and a range of steady-state exposure metrics for both T-DXd and DXd (AUC, Cmax, and Ctrough) were explored graphically using logistic regression (glm) fits in

R, none of the metrics reached significance ($p \leq 0.05$); therefore, no further exposure-response analysis for ORR were pursued.

Figure 8 T-DXd AUC at Steady-State vs ORR in Patients with IHC3+ Tumours



There was no notable relationship between any exposure metric for T-DXd or DXd and ORR at doses of 5.4 or 6.4 mg/kg Q3W.

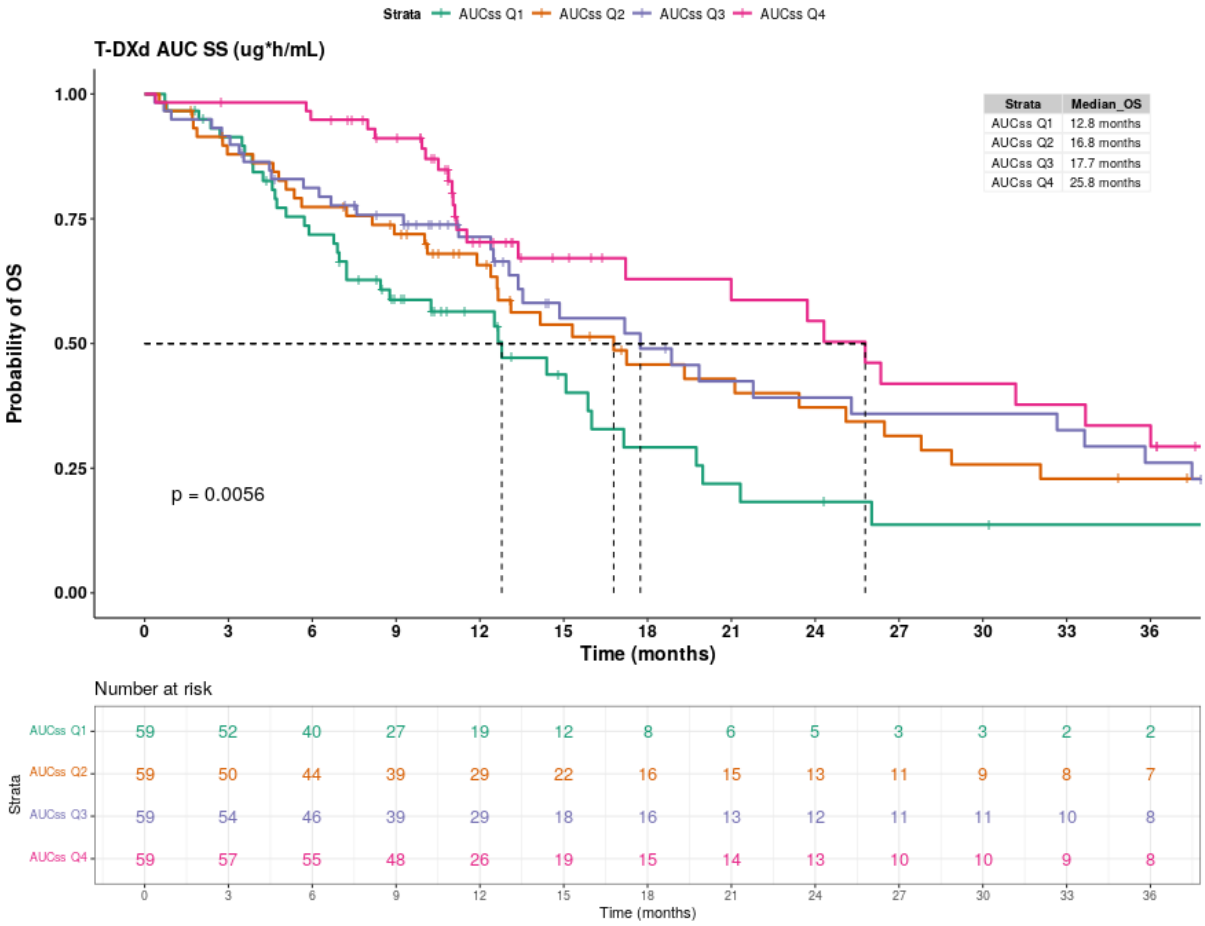
Secondary endpoint Overall survival

The log-rank test for the Kaplan-Meier curves showed a statistically significant difference in OS across quartiles of T-DXd AUC ($p = 0.0056$), as well as across quartiles of T-DXd Cmax ($p = 0.00046$) and T-DXd Cmin ($p = 0.0013$). The log-rank test for the Kaplan-Meier curves showed no statistically significant difference in OS across quartiles of DXd AUC ($p = 0.56$), as well as across quartiles of DXd Cmax ($p = 0.14$) and DXd Cmin ($p = 0.034$). Any relationship between exposure metrics for T-DXd or DXd and OS was confounded by markers of disease condition e.g., baseline albumin level.

When a relationship between steady-state T-DXd exposure and OS was considered, there was a trend towards an increase in OS with increasing exposure, with OS being 12.8 months in the lowest exposure quartile, and 25.8 months in the highest quartile ($p = 0.0056$).

Steady-state DXd AUC did not appear to be linked with OS, since median OS was in the range of 13 to 17 months for all 4 quartiles of DXd exposure, and the p-value was 0.569, suggesting no difference between the groups.

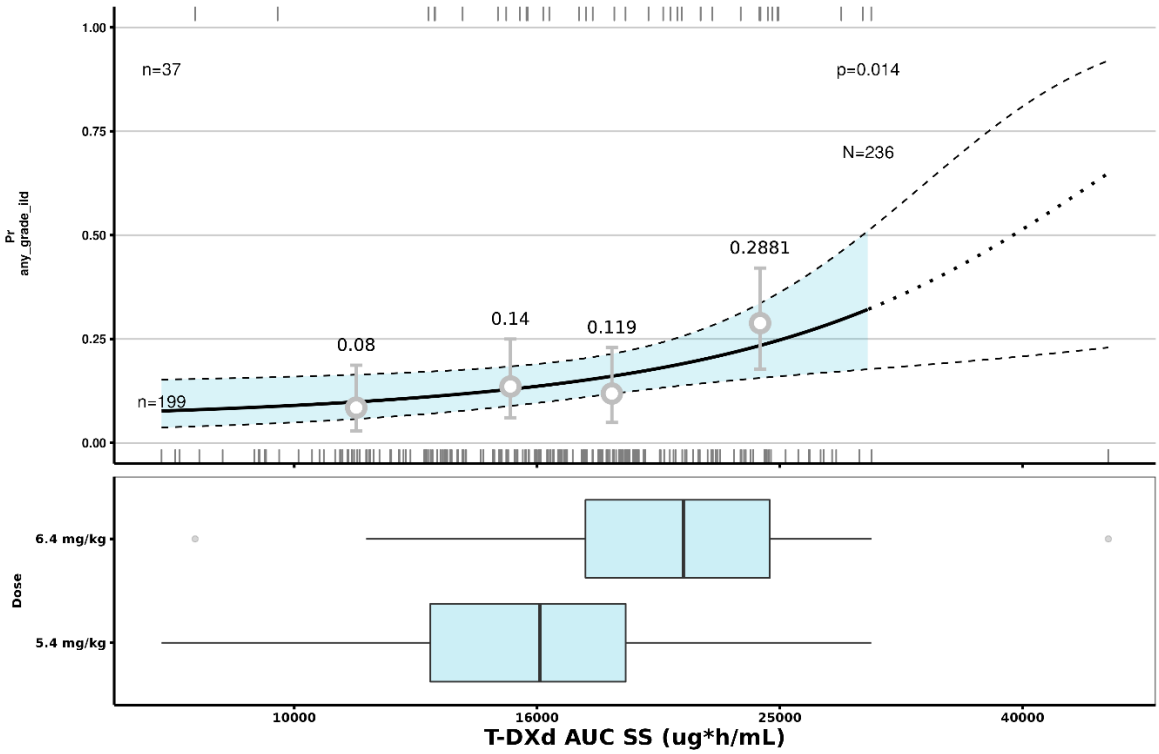
Figure 9 T-DXd Exposure (AUCss) vs OS in Patients with IHC3+ Tumours



Exposure-Safety analysis

Exposure-safety analysis was carried out on data from Studies DL-01, DC-02, and DP-02. The safety endpoints were ILD events irrespective of grade and ≥ Grade 3 ILD events versus selected exposure metrics for both T-DXd and DXd.

Figure 10 T-DXd AUC at Steady-State vs Incidence of ILD (Any Grade) in Patients with IHC3+ Tumours



Immunogenicity

Eighteen studies are included in the following 4 pools for reporting immunogenicity summaries, including immunogenicity PK correlation, immunogenicity efficacy correlation, and immunogenicity safety correlation:

- IHC 3+ Pool T-DXd 5.4 mg/kg, which includes patients with HER2 positive (IHC 3+) tumours, who received T-DXd 5.4 mg/kg every 3 weeks. Central test results will be used for patients in DB-01, DC-02, and DL-01. For Study DP-02 results could be obtained via local or central test.
- IHC 3+ Pool T-DXd 6.4 mg/kg, which includes patients with HER2 positive (IHC 3+) tumours, who received T-DXd 6.4 mg/kg every 3 weeks.
- All Tumour Types Pool T-DXd 5.4 mg/kg, which includes all patients receiving T-DXd 5.4 mg/kg every 3 weeks.
- All Tumour Types Pool T-DXd 6.4 mg/kg, which includes all patients receiving T-DXd 6.4 mg/kg every 3 weeks.

The prevalence and incidence of ADA to T-DXd across the 4 pooled immunogenicity datasets ranged from 6.6% to 9.0% and 0.6% to 3.0%, respectively. The majority of ADA+ patients were ADA+ at baseline only, and the majority of TE-ADA+ patients were transiently ADA+ and were nAb-negative. The medians of maximum T-DXd post-baseline ADA titer of patients with TE-ADA were low relative to the minimum required dilution of 45 (range: 45 to 405).

Table 20 Summary of ADA Responses to T-DXd by Pools (Immunogenicity Analysis Set)

ADA category	IHC 3+ pool T-DXd 5.4 mg/kg (N = 347)	IHC 3+ T-DXd 6.4 mg/kg (N = 67)	All tumour types pool T-DXd 5.4 mg/kg (N = 2540)	All tumour types pool T-DXd 6.4 mg/kg (N = 888)
ADA+ prevalence at baseline or post-baseline [a], n (%)	23 (6.6)	6 (9.0)	255 (8.9)	66 (7.4)
Median of maximum titer	720.0	67.5	45.0	45.0
TE-ADA+ (ADA incidence) [b], n (%)	2 (0.6)	2 (3.0)	58 (2.3)	23 (2.6)
Median of maximum titer	405.0	67.5	45.0	45.0
ADA+ post-baseline only (treatment-induced ADA+ [c]) n (%)	2 (0.6)	2 (3.0)	58 (2.3)	22 (2.5)
Median of maximum titer	405.0	67.5	45.0	45.0
Treatment-boosted ADA+ [d], n (%)	0	0	0	1 (0.1)
Median of maximum titer	NC	NC	NC	1440.0
ADA+ prevalence at both baseline and post-baseline [e], n (%)	3 (0.9)	0	29 (1.1)	7 (0.8)
Median of maximum titer	720.0	NC	45.0	90.0
ADA+ prevalence at baseline [f], n (%)	18 (5.2)	4 (6.0)	138 (5.4)	37 (4.2)
Median of maximum titer	180.0	112.5	67.5	45.0
TE-persistently ADA+ [g], n (%)	0	0	7 (0.3)	1 (0.1)
Median of maximum titer	NC	NC	180.0	1440.0
TE-transiently ADA+ [h], n (%)	2 (0.6)	2 (3.0)	51 (2.0)	22 (2.5)
Median of maximum titer	405.0	67.5	45.0	45.0
nAb+ prevalence at baseline or post-baseline [i], n (%)	0	0	12 (0.5)	0
Median of maximum titer	NC	NC	180.0	NC
TE-nAb+ (nAb incidence) [j], n (%)	0	0	3 (0.1)	0
Median of maximum titer	NC	NC	45.0	NC

[a] ADA+ prevalence at baseline or post-baseline: Patients with any positive ADA assessment at baseline or post-baseline. The percentage of these patients in a population is known as ADA prevalence.
[b] Treatment-Emergent ADA+: Patients who were either treatment-boosted ADA+ or treatment-induced ADA+. The percentage of these patients in a population is known as ADA incidence.
[c] Treatment-induced ADA+: Subjects who were ADA negative or missing at baseline and became ADA positive post-baseline.
[d] Treatment-boosted ADA+: Patients who were ADA+ at both baseline and post-baseline, but had a meaningful increase in ADA titer by at least 4-fold from baseline to post-baseline.
[e] ADA+ prevalence at both baseline and post-baseline: Patients with both a positive ADA assessment at baseline and any positive ADA assessment post-baseline.
[f] ADA+ prevalence at baseline: Patients with a positive ADA assessment at baseline and no positive ADA assessment at any post-baseline assessments.
[g] Treatment-emergent persistently ADA+: TE-ADA+ and having at least 2 post-baseline ADA+ measurements with ≥ 16 weeks between first and last positive.
[h] Treatment-emergent transiently ADA+: TE-ADA+ and having at least one post-baseline ADA+ measurement and not fulfilling the conditions for persistently positive.
[i] nAb+ prevalence at baseline or post-baseline: Patients with any positive nAb assessment at baseline or post-baseline. The percentage of these patients in a population is known as nAb prevalence.
[j] Treatment-Emergent nAb+: Treatment-emergent ADA+ patients with any positive nAb assessment post-baseline. The percentage of these patients in a population is known as nAb incidence. nAb test results not available for DP-01, DB-01, DB-07, and DL-03.

Impact of ADA on ORR

Table 21 Summary of Clinical Response Parameters by Pools and ADA Status (Immunogenicity Analysis Set)

	IHC 3+ pool				All tumour types pool			
	TE-ADA+	Non-TE-ADA+	ADA-	TE-nAb+[a]	TE-ADA+	Non-TE-ADA+	ADA-	TE-nAb+[a]
T-DXd 5.4 mg/kg	**N = 2**	**N =21**	**N = 324**	**N = 0**	**N =50**	**N = 154**	**N = 2235**	**N = 3**
Confirmed ORR, n (%)	0	12 (57.1)	181 (55.9)	0	31 (62.0)	89 (57.8)	1246 (55.7)	2 (66.7)
PFS (months), n [b]	2	21	324	0	50	154	2235	3
Median	3.5	8.5	12.7	NE	13.1	13.1	12.3	10.3
95% CI	2.8 to NE	4.2 to NE	9.7 to 16.8	NE	9.2 to 24.5	10.3 to 20.3	11.3 to 13.2	4.3 to NE
Duration of confirmed response (months), n [b]	0	12	181	0	31	89	1246	2
Median	NE	7.9	18.2	NE	15.4	19.1	15.6	NE
95% CI	NE	5.6 to NE	11.4 to 21.5	NE	7.4 to 24.9	11.0 to 27.6	13.9 to 16.9	2.8 to NE
T-Dxd 6.4 mg/kg	**N = 2**	**N = 4**	**N = 61**	**N = 0**	**N = 23**	**N = 43**	**N = 822**	**N = 0**
Confirmed ORR, n (%)	1 (50.0)	1 (25.0)	30 (49.2)	0	13 (56.5)	21 (48.8)	313 (38.1)	0
PFS (months), n [b]	2	4	61	0	23	43	810	0
Median	NE	6.7	7.3	NE	9.6	6.7	6.9	NE
95% CI	4.2 to NE	1.3 to NE	4.7 to 10.6	NE	5.4 to NE	4.2 to 16.9	5.8 to 7.3	NE
Duration of confirmed response (months), n [b]	1	1	30	0	13	21	313	0
Median	NE	5.5	8.3	NE	9.3	14.1	9.7	NE
95% CI	NE	NE	6.9 to NE	NE	4.5 to NE	5.5 to NE	8.3 to 12.5	NE

[a] nAb test results not available for DP-01, DB-01, DB-07, and DL-03. DL-03 did not have ICR performed, and so efficacy analysis uses investigator assessment. DB-07 is excluded, as only safety data are available.
[b] Calculated using the Kaplan-Meier technique. CI for median derived based on Brookmeyer-Crowley method. DP-02 reported clinical responses according to investigator as primary, but DP-02 results per ICR included for consistency with other studies.

2.3.4. PK/PD modelling

E-R modelling

This E-R analysis was conducted to support the assessment of T-DXd 5.4 mg/kg and 6.4 mg/kg Q3W as monotherapy for patients with HER2 IHC3+ tumours of various types. The objective was to investigate the relationship between T-DXd exposure and both efficacy, as measured by ORR (assessed by BICR) and OS, and safety, as measured by the incidence of ILD as an adverse event of special interest, in patients receiving this treatment. Exposure metrics for efficacy and safety analyses were derived from the established population PK (popPK) model of T-DXd, which included data from 21 clinical trials.

Exposure-Efficacy modelling

Multivariate Cox models and covariate search were conducted to evaluate the relationship of the covariates and OS. The analysis was conducted with a predefined total of 15 tests (15 initial

covariates), resulting in a Bonferroni-adjusted p-value threshold of 0.003 for the forward selection and 0.0006 for the backward elimination procedures. The results identify ECOG performance status and albumin as significant factors.

The correspondent hazard ratios with 95% CI and associated p-values are presented in Table 22.

Table 22 Summary of Hazard Ratio for the Multivariate OS Model

Code	Label	Hazard Ratio	Lower CI	Upper CI	Wald's P-value
ECOG Normal activity	ECOG	0.427	0.297	0.615	< 0.0006
BALB	Baseline albumin (g/L)	0.909	0.874	0.946	< 0.0006

Posterior simulations were used to predict the covariate effects.

Exposure-Safety modelling

The exposure-safety analysis aimed to assess the relationship between T-DXd and DXd exposure metrics and drug-related, adjudicated ILD of any grade, as well as Grade ≥3 ILD.

A univariate logistic regression analysis was conducted utilising each exposure metric as a continuous variable. T-DXd AUC at cycle 1 was found to be statistically significantly associated ($p<0.01$) with the probability of any grade ILD.

Multivariate logistic regression analysis on E-S was conducted to estimate the effect of T-DXd or DXd exposure adjusted for the stratification factors in the model and to evaluate their relative contribution. The impact of T-DXd or DXd exposure on safety endpoints was assessed as the initial step, preceding the evaluation of covariates. Non-relevant exposure metrics and/or prognostic factors were eliminated following the principle of parsimony. A covariate search with the logistic regression model was conducted for any grade ILD. The SCM analysis identified T-DXd AUC at cycle 1 (TDXD_AUC_C1) as the only statistically significant factor, see Table 23.

Table 23 Summary of Logistic Regression for any Grade ILD

Quantile	Estimate	StdError	z-value	p-value
(Intercept)	-1.83	0.199	-9.205	<0.001
TDXD_AUC_C1	0.139	0.049	2.822	0.005

Posterior simulations by dose level 5.4 mg/kg and 6.4 m/kg were employed to predict the effects of T-DXd AUC at cycle 1 in the any grade ILD model.

2.3.5. Discussion on clinical pharmacology

In the current variation, the MAH applies for an indication of T-DXd in the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumours who have received prior treatment and who have no satisfactory alternative treatment options. The recommended dosing regimen administered by IV infusion is 5.4 mg/kg Q3W, except for GC, where the recommended dosing regimen is 6.4 mg/kg IV Q3W.

No new data corresponding to mechanism of action, primary or secondary pharmacology were submitted.

Overall, the bioanalysis and immunogenicity analysis were conducted with previously validated methods in accordance with regulatory requirements. The software and methods used for PK data analysis are appropriate.

The current PopPK analysis dataset included 5 additional studies to the previously included 16 studies. The current T-DXd and DXd models was based on previous models. Covariates were re-evaluated and resulted in maintaining baseline albumin, Japanese, tumour size at baseline, body weight and tumour type (gastric cancer (GC) and CRC) on CLT-DXd, body weight, sex and tumour type (GC) on V1T-DXd, Japanese on V2T-DXd, ritonavir coadministration, itraconazole coadministration, AST, baseline bilirubin, body weight and tumour type (NSCLC, CRC and Others) on CLDXd, age, formulation, tumour type (NSCLC and CRC) and non-Asian on V3DXd. Outliers were removed after finalizing the covariate structure. The model parameters were re-estimated. For the T-DXd model, the Relative Standard Error (RSE) of parameter estimates were <20%, except for CRC on CL with RSE of 21.4%, with eta-shrinkage <20%, except for IIV on Q (51.5%) and V2 (31.4%). For the DXd model, RSE were all <20%, eta-shrinkage ranged from 20.6% to 36.8%. Epsilon-shrinkage were ≤10.6%. The presented GOF and pcVPC plots indicated that both T-DXd and DXd observations was reasonably described by the PopPK model. DXd exposure of body weights <47 kg and >83.05 kg fell outside the bioequivalence range of 0.8 to 1.25 of the AUCss/D forest plot.

In the pivotal study DP-02 (5.4 mg/kg Q3W), PK of T-DXd (+ total antibody and DXd) was investigated using sparse sampling. Sparse PK-data was reported for the whole PK-set of 267 patients. Observed mean plasma concentrations of T-DXd was consistent with PK-data using the same dosing regimen in already approved indications, BC and NSCLC. Post hoc. calculated AUC_{ss} and C_{max} values of T-Dxd and DXd from study DP-02, stratified according to solid tumour, shows that exposure of T-DXd and DXd were comparable across most solid tumour types, except for pancreatic cancer patients, and comparable with exposure in already approved cancer indications getting the same dosage regimen. In pancreatic cancer patients the exposure of T-DXd was lower, i.e. gmean AUCss of 10066 ng*hr/mL vs a gmean range of 14485-16827 ng*hr/mL in other cancer types. In the larger group of IHC2+ pancreatic cancer patients (n=20) in DP02 study, a gmean AUCss of 14,016 ng·h/mL was determined, comparable to other tumour types. Overall, these data indicates that the lower exposure in IHC3+ pancreatic cancer patients is not due to specific tumour type, but likely due to the small sample size and interindividual variability, in addition to other factors of this group of patients compared to IHC2+ patients, i.e. overall lower body weight and larger baseline tumour size.

In the supportive studies DL-01 and DC-02, PK parameters of relevant ICH3+ patient subgroup were estimated post hoc. with PopPK. Overall, the post hoc estimated AUC_{ss} and $C_{max,ss}$ of T-DXd and DXd in ICH3+ patients were comparable with the exposure in the total population of cancer patients (metastatic BC, NSCLC, or HER2-positive (IHC 3+) Solid Tumours). Overall, the suggested posology in HER2 IHC3+ solid tumour is supported by PK data. An updated pooled immunogenicity analysis shows that there is no apparent effect of immunogenicity on the PK parameters of T-DXd. The impact of range of different covariates on dose normalized AUC_{ss} was investigated using the updated Pop-PK model. A clinically meaningful effect of any covariates was not identified, consistent with previous analysis (see EPARs of Enhertu).

The SmPC was updated with the new estimates of PK-parameters for T-DXd and DXd by the updated population PK model and with exposure information (AUCss, Cmax,ss) of T-DXd and DXd in approved cancer indications.

Exposure-efficacy modelling utilized a Cox proportional hazard model with Bonferroni adjusted p-values in the covariate search. ECOG activity and baseline albumin were identified as significant covariates.

Exposure-safety modelling utilised univariate and multivariate logistic regression to examine the relationship between exposure and any grade ILD. Stepwise covariate search was performed for the multivariate logistic regression, identifying only T-DXd cycle 1 AUC as a significant covariate in the inclusion step. Backwards elimination was not performed.

Exposure-response and exposure-safety analyses were performed in patients with IHC 3+ tumours who received T-DXd at doses of 5.4 mg/kg and 6.4 mg/kg in studies DP-02, DL-01 and DC-02. Correlations between exposure to T-DXd and ORR by BICR and OS were explored. The relationship between T-DXd exposure and ORR in Studies DP-02, DC-02, and DL-01 was not statistically significant, suggesting a flat E-R relationship.

The analysis for OS reveals a trend towards an increase in OS with increasing exposure to T-DXd, with a significant difference in OS across quartiles of T-DXd AUC ($p = 0.0056$). The median OS ranges from 12.8 months in the lowest exposure quartile to 25.8 months in the highest quartile. This indicates a potential exposure-response relationship for T-DXd in terms of OS. However, the relationship between steady-state DXd exposure and OS does not appear to be significant, with median OS ranging from 13 to 17 months across all quartiles of DXd exposure. In the multivariate Cox analysis with 15 predefined covariates and Bonferroni-adjusted thresholds (0.003 for forward, 0.0006 for backward selection), exposure was excluded during backward elimination, leaving only ECOG and albumin as significant predictors.

The exposure-safety analysis was conducted to evaluate the relationship between selected exposure metrics for T-DXd and DXd and ILD events irrespective of grade and ≥ Grade 3 ILD events. The relationship between T-DXd AUC at steady-state and the incidence of ILD (any grade) in patients with IHC3+ tumours was positive with a p-value of 0.014. This suggests that higher T-DXd exposure is associated with an increased risk of ILD events. Higher T-DXd AUC C1 values were associated with an increased probability of any grade ILD, with a median probability of 0.158 (95% CI: 0.119–0.199) at the reference level. The probability was also higher at the 6.4 mg/kg dose compared to 5.4 mg/kg. The incidence of ≥ Grade 3 ILD events is low, with 6 events (2.5%) reported out of 236 patients. The highest incidence of ≥ Grade 3 ILD events was observed in the DL01 study at the 6.4 mg/kg dose level, with 1 event (10.0%) reported out of 10 patients. However, due to limited number of ILD events and small sample size, the results should be interpreted with caution. The interpretation of the E-R results becomes more difficult when results from three different studies including a number of different tumour types and doses are pooled.

Presented data indicates a low prevalence and incidence of ADA across the studied patient populations. The majority of ADA-positive patients had pre-existing antibodies, and the incidence of treatment-emergent ADA was low. Neutralizing antibodies were rare, suggesting a minimal impact on the drug's efficacy due to immunogenicity. However, the small number of ADA-positive patients limits the ability to conclusively determine the effects of ADA on pharmacokinetics, efficacy, and safety.

2.3.6. Conclusions on clinical pharmacology

The Pharmacokinetics of T-DXd in HER2 IHC3+ solid tumour patients were investigated in three clinical studies DP-01 (pivotal) and DL-01 and DC-02. The previous Pop-PK model was updated.

In conclusion, the conducted clinical pharmacology investigations are considered as adequate and supportive for approval of T-DXd for treatment of patients with IHC3+ solid tumour.

2.4. Clinical efficacy

2.4.1. Dose response study

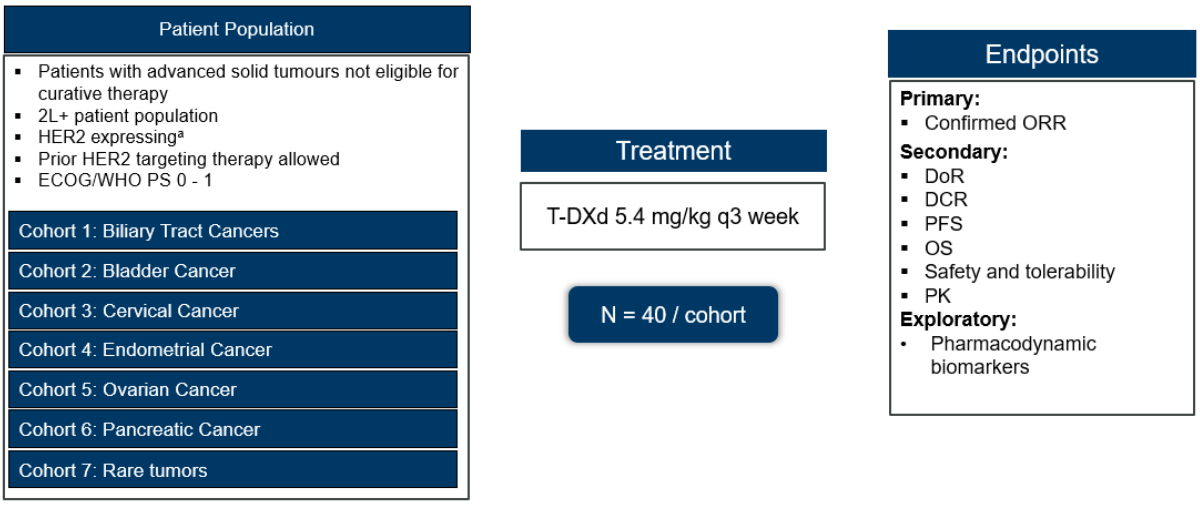
Doses including 5.4 mg/kg and 6.4 mg/kg T-DXd monotherapy have been tested in clinical studies. The maximum tolerated dose was not reached in the dose escalation phase of Study DS8201-A-J101. Both doses showed efficacy in different tumour types. A numerically higher incidence of AEs ≥ Grade 3 (overall and causally related), SAEs (including causally related), AEs leading to drug withdrawal (overall and causally related), and AEs leading to dose reduction (overall and causally related) were noted with 6.4 mg/kg compared to 5.4 mg/kg. For details on dose finding study please refer to the initial marketing authorization report of T-DXd.

2.4.2. Main study

DP-02 (Destiny PanTumor-02)

Study DP-02 is an ongoing, open-label, multicentre, multi-cohort, single-arm, Phase II study to evaluate the antitumor activity and safety of T-DXd for the treatment of selected HER2-expressing solid tumours.

Figure 11 DP-02 Study Design



The primary endpoint of confirmed ORR was assessed by investigator.

Methods

Study participants

Key inclusion criteria for this study were as follows:

1. Male and female patients were at least 18 years of age at the time of signing the ICF.
2. Locally advanced, unresectable, or metastatic solid tumours based on most recent imaging. Patients were to have tumours with histology specific to respective cohorts, progression following at least one prior systemic treatment for metastatic or advanced disease, or no satisfactory alternative treatment option. Prior HER2-targeting therapy was permitted. The respective cohorts included patients with the following metastatic or advanced cancer:
    - Cohort 1 (BTC): BTCs, including intra- or extrahepatic cholangiocarcinoma and tumours arising in the ampulla of Vater or gallbladder

- Cohort 2 (bladder cancer): Urothelial carcinoma, including transitional cell or predominantly transitional cell carcinoma of the renal pelvis, ureter, urinary bladder or urethra
- Cohort 3 (cervical cancer): Cervical carcinoma
- Cohort 4 (endometrial cancer): Endometrial carcinoma
- Cohort 5 (ovarian cancer): Epithelial ovarian carcinoma
- Cohort 6 (pancreatic cancer): Pancreatic cancer
- Cohort 7 (rare tumours): this cohort consisted of patients with tumours that express HER2-overexpression (IHC 3+ and IHC 2+), excluding the tumours mentioned above, and BC, NSCLC, GC, and CRC

3. Patients had HER2-overexpression (IHC 3+ or IHC 2+) as determined by local or central assessment scored using current ASCO/CAP guidelines for scoring HER2 for GC:
    - For each Cohort 1 to 6, up to 10 IHC 1+ patients could be included if ≥ 3 objective responses were observed in the first 15 patients with confirmed HER2-overexpression (IHC 3+ or IHC 2+) by central testing
    - The rare tumour cohort (Cohort 7) enrolled only patients with HER2-overexpression (IHC 3+ or IHC 2+)
4. Adequate tumour samples for assessment of HER2-expression and other correlatives
5. Measurable target disease assessed by the Investigator based on RECIST v1.1
6. ECOG performance status of 0 or 1
7. LVEF ≥ 50% by either ECHO or MUGA scan within 28 days before treatment assignment
8. Protocol-defined adequate organ function and treatment washout.

<u>Key exclusion criteria for this study were as follows:</u>

A. Known somatic DNA mutation of HER2 (ERBB2) without tumoral HER2-expression as defined in inclusion criteria.

B. Primary diagnosis of adenocarcinoma of the breast, adenocarcinoma of the colon or rectum, adenocarcinoma of the gastric body or gastro-oesophageal junction, or NSCLC.

C. Spinal cord compression or clinically active central nervous system metastases.

D. Medical history of myocardial infarction within 6 months before treatment assignment, or symptomatic congestive heart failure (New York Heart Association Class II to IV).

E. A corrected QTCF prolongation to > 470 msec (females) or > 450 msec (males) based on average of the screening triplicate 12-lead ECG.

F. History of (non-infectious) ILD/pneumonitis that required steroids, had current ILD/pneumonitis, or suspected ILD/pneumonitis could not be ruled out by imaging at screening.

G. Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disorder (i.e., pulmonary emboli within 3 months of the study assignment, severe asthma, severe COPD, restrictive lung disease, pleural effusion), and

any autoimmune, connective tissue or inflammatory disorders (e.g., rheumatoid arthritis, Sjogren's, sarcoidosis, etc), and/or prior pneumonectomy.

For detailed information on the diagnostic tests used for inclusion, refer to the section *In vitro* biomarkers test for patient selection for efficacy.

Treatments

Patients received Enhertu 5.4 mg/kg by intravenous infusion every three weeks. T-DXd was administered using an IV bag containing 5% (w/v) Dextrose Injection infusion solution and delivered through an IV administration set with a 0.2 or 0.22 µm filter. The standard infusion time for T-DXd was approximately at least 90 minutes for the first infusion. Prior to each dose of T-DXd, patients should be premedicated with a combination regimen of 2 or 3 medicinal products (e.g., dexamethasone with either a 5-hydroxytryptamine receptor antagonist and/or a Neurokinin-1 receptor antagonist, as well as other medicinal products as indicated) for prevention of chemotherapy-induced nausea and vomiting.

Table 24 Investigational Products

Name	Dosage Presentation	Unit Dose Strength(s)	Dosage Levels	Route of Administration	Use	Sourcing	Packaging and Labeling
T-DXd [a]	Vial	Powder for concentrate for solution for infusion 100 mg/vial	5.4 mg/kg	IV	Experimental	Provided centrally by the Sponsor	IP will be provided in a vial in carton. Each vial and carton will be labeled in accordance with GMP Annex 13 and per country requirements.

[a] Label text for trastuzumab deruxtecan (T-DXd, DS-8201a) will show "DS-8201a", depending on the agreed product name used in the respective approved study master label document. All naming conventions for these compounds are correct during this transitional period.
GMP, Good Manufacturing Practice; IP, investigational product; IV, intravenous; T-DXd, trastuzumab deruxtecan

Duration of treatment: The number of treatment cycles with T-DXd is not fixed. Patients continued to receive T-DXd until RECIST v1.1 disease progression, withdrawal of consent or any of the discontinuation criteria were met.

Dose modifications (i.e., interruptions or reductions) of T-DXd were allowed during the study. The starting dose of T-DXd was 5.4 mg/kg Q3W, with dose reduction to 4.4 mg/kg or 3.2 mg/kg permitted due to the occurrence of clinically important and/or unacceptable toxicity per protocol-specified guidelines. A dose could be delayed for up to 28 days from the planned date of administration. If a patient required a dose delay longer than 28 days, treatment was to be discontinued.

Study assessments: Imaging for radiological assessment of tumour burden at baseline included CT or MRI scans of the chest, abdomen, and pelvis. Tumour assessments by Investigator were performed according to the RECIST v1.1. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients; e.g., patients with suspected brain metastases at screening should have an IV contrast-enhanced MRI of the brain prior to study entry. Brain metastases were not recorded as RECIST Target Lesions at baseline. All on-study assessments should utilize the same modality of scanning (e.g., CT or MRI) as was used at baseline for accurate comparisons.

Radiologic efficacy for all patients was assessed on images collected q6w (± 1 week) for the first 48 weeks after the date of first dose of IP and then q12w (± 1 week) thereafter, until disease

progression or withdrawal consent by patient. Scanning will continue if patients discontinue IP due to toxicity without progression until PD is detected.

Objectives / endpoints

Table 25 Objectives and Endpoints

Primary objective	**Outcome measure**
To assess the efficacy of T-DXd in patients with metastatic or unresectable tumours in selected HER2-expressing tumour types	Confirmed ORR according to RECIST v1.1, as assessed by Investigator
Secondary objective	**Outcome measures**
To further evaluate the efficacy of T-DXd in patients with metastatic or unresectable tumours in selected HER2-expressing tumour types	Investigator assessments, based on RECIST v1.1, to allow the calculation of: • DoR • DCR • PFS Proportion of patients alive and progression-free at 6 months and 12 months
To further investigate the efficacy of T-DXd in patients with metastatic or unresectable tumours in selected HER2-expressing tumour types as measured by OS	OS Proportion of patients alive at 6 and 12 months
To assess the safety and tolerability of T-DXd	Assessed by the occurrence of AEs, SAEs, and changes from baseline in laboratory parameters, vital signs, electrocardiogram, and ECHO or MUGA results
To assess the PK of T-DXd, total anti-HER2 antibody and MAAA-1181 in serum	Serum concentration of T-DXd, total anti-HER2 antibody and MAAA-1181
To investigate the immunogenicity of T-DXd	Presence of ADAs for T-DXd

Table 26 Pre-planned Statistical Analyses

Endpoints analysed	**Notes [All endpoints derived from RECIST use Investigator assessment]**
Objective response rate (ORR)	Number and percentage of patients that achieve confirmed OR as determined by the Investigator according to RECIST v1.1 (with the associated two-sided 95% exact CI).
Duration of response (DoR)	Kaplan-Meier median estimates and their corresponding two-sided 95% confidence intervals will be reported.
Disease control rate (DCR)	Number and percentage of patients that achieve disease control (with the associated two-sided 95% exact CI).

Progression-free survival (PFS)	Kaplan-Meier median estimates and their corresponding two-sided 95% confidence intervals will be reported. The proportion of patients alive and progression-free at 6 and 12 months (Kaplan-Meier estimates) will be presented.
Overall survival (OS)	Kaplan-Meier median estimates and their corresponding two-sided 95% confidence intervals will be reported. The proportion of patients alive at 6 and 12 months (Kaplan-Meier estimates) will be presented.
Safety	Summary statistics for AEs, SAEs, laboratory findings, vital signs, and ECG, ECHO or MUGA results, ECOG/WHO performance status and deaths.

Sample size

A sample size of 40 patients per cohort was determined to provide sufficient precision for the estimation of the ORR in the respective populations. Table 27 provides the 95% exact CI for a range of possible ORRs out of 40 patients.

Part 1

Once 15 patients within a cohort had been centrally determined to have HER2 IHC 3+ or IHC 2+ and had the opportunity to complete at least 2 scheduled post-baseline scans per RECIST v1.1 Guidelines, the following applied:

For each tumour specific cohort (cohorts 1-6), the inclusion criteria were expanded to include up to 10 IHC 1+ patients if ≥ 3 responses had been observed in the first 15 patients. If 1 or 2 responses were observed in the first 15 patients, the cohort continued recruiting without change. If zero responses were observed in the first 15 patients, the cohort was closed to further recruitment.

For the rare tumour cohort (cohort 7), if ≥ 1 response had been observed in the first 15 patients, the cohort continued recruitment without change. If zero responses were observed in the first 15 patients, the cohort was closed to further recruitment.

Recruitment was not held while this evaluation is performed. Decisions on cohort recruitment were based on confirmed objective responses. If the true ORR was 35%, the probability of observing < 3/15 responses was 0.06, while the probability of observing zero responses was 0.0016. Recruitment within a given cohort, potentially including IHC 1+ patients, could have been expanded by protocol amendment to more precisely quantify estimates of efficacy and safety, based on the initial data observed from the N = 40 patients.

Table 27 Sample size estimate: 95% CI for a Range of ORRs

True ORR (%)	95% CI (%) N = 40/arm
30	(16.6, 46.5)
35	(20.6, 51.7)
40	(24.9, 56.7)
45	(29.3, 61.5)

Part 2

Cohort A and Cohort B also recruited approximately 40 patients per cohort, comprising any eligible tumour type. Recruitment of patients with ovarian, endometrial, and cervical cancer was capped at

a maximum of 20 patients in Cohort A. No specific criteria to close Cohorts A and B recruitment applied.

Within Part 2 Cohorts C, D, and E, a futility analysis was planned for the first 15 IHC 1+ subjects once all such subjects within a cohort were evaluable for RECIST response (i.e., subject had responded, progressed, withdrawn, or been on-study for at least 12 weeks with all scheduled scans conducted). If no responses were observed within a cohort (0 out of 15 subjects), further enrolment of IHC 1+ subjects was closed and the cohort continued to recruit IHC 2+ only. Recruitment was not paused while this evaluation was performed. Decisions on cohort recruitment were based on confirmed objective responses.

Analysis sets

Table 28 Populations for Analyses

Population/analysis set	Description
Full Analysis Set (FAS)	All patients who received at least 1 dose of study treatment. The FAS will be used for primary efficacy analyses.
Centrally-determined Efficacy Analysis Set (CEAS)	All patients who received at least 1 dose of study treatment, and who were confirmed HER2-eligible by central assessment. The CEAS will be used for 15-patient interim analyses, and for sensitivity analyses on efficacy endpoints.
Pharmacokinetics (PK) Analysis Set	All patients who received at least 1 dose of study treatment and had at least 1 post-dose evaluable PK data point. The population will be defined by the study pharmacokineticist, and the statistician prior to any PK analyses being performed.
Safety Analysis Set (SAF)	All patients who received at least 1 dose of study treatment.

Statistical methods

There were no formal statistical hypotheses for this study.

Objective response rate was defined as the proportion of patients who had a confirmed CR or PR, as determined by the Investigator per RECIST v1.1. A confirmed response of CR/PR meant that a response of CR/PR was recorded at a visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed, with no evidence of progression between the initial and CR/PR confirmation visit. Data obtained up until disease progression, or the last evaluable assessment in the absence of progression, were included in the assessment of ORR. Patients who went off treatment without progression, received a subsequent therapy, and then responded, were not included as responders in the ORR. The confirmed ORR was estimated and presented as the number (%) of patients along with the corresponding exact 95% Clopper-Pearson confidence interval. The exploratory analysis of ORR assessed by ICR was performed on both FAS and FAS excluding patients with no post-baseline tumour assessments.

Disease control rate was defined as the percentage of patients who had a confirmed CR or PR or who had SD (without subsequent cancer therapy) after the date of first dose of IP. Summaries of DCR were presented for each cohort. Progression-free survival was defined as time from the date of first dose of IP until progression per RECIST v1.1 as assessed by the Investigator, or death due to any cause. Patients who had not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST v1.1 assessment. A Kaplan-

Meier plot of PFS was presented. The median PFS with 95% CI was estimated based on the Kaplan-Meier curve.

Progression-free survival was defined as time from the date of first dose of IP until progression per RECIST v1.1 as assessed by the Investigator, or death due to any cause. Patients who had not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST v1.1 assessment. A Kaplan-Meier plot of PFS was presented. The median PFS with 95% CI was estimated based on the Kaplan-Meier curve. The proportion of patients alive and progression-free at 3 monthly intervals starting from 6 months was summarized (using the Kaplan-Meier curve).

Duration of response was defined as the time from the date of first documented response (CR or PR) until the date of documented progression, or death in the absence of disease progression. Only patients who had achieved OR (confirmed CR or confirmed PR) were evaluated for DoR. Duration of Response was summarized using the same methodology as for PFS.

Overall survival was defined from the date of first dose of IP until the date of death due to any cause. Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive. OS was summarized using the same methodology as for PFS.

See also Table 26 Pre-planned Statistical Analyses

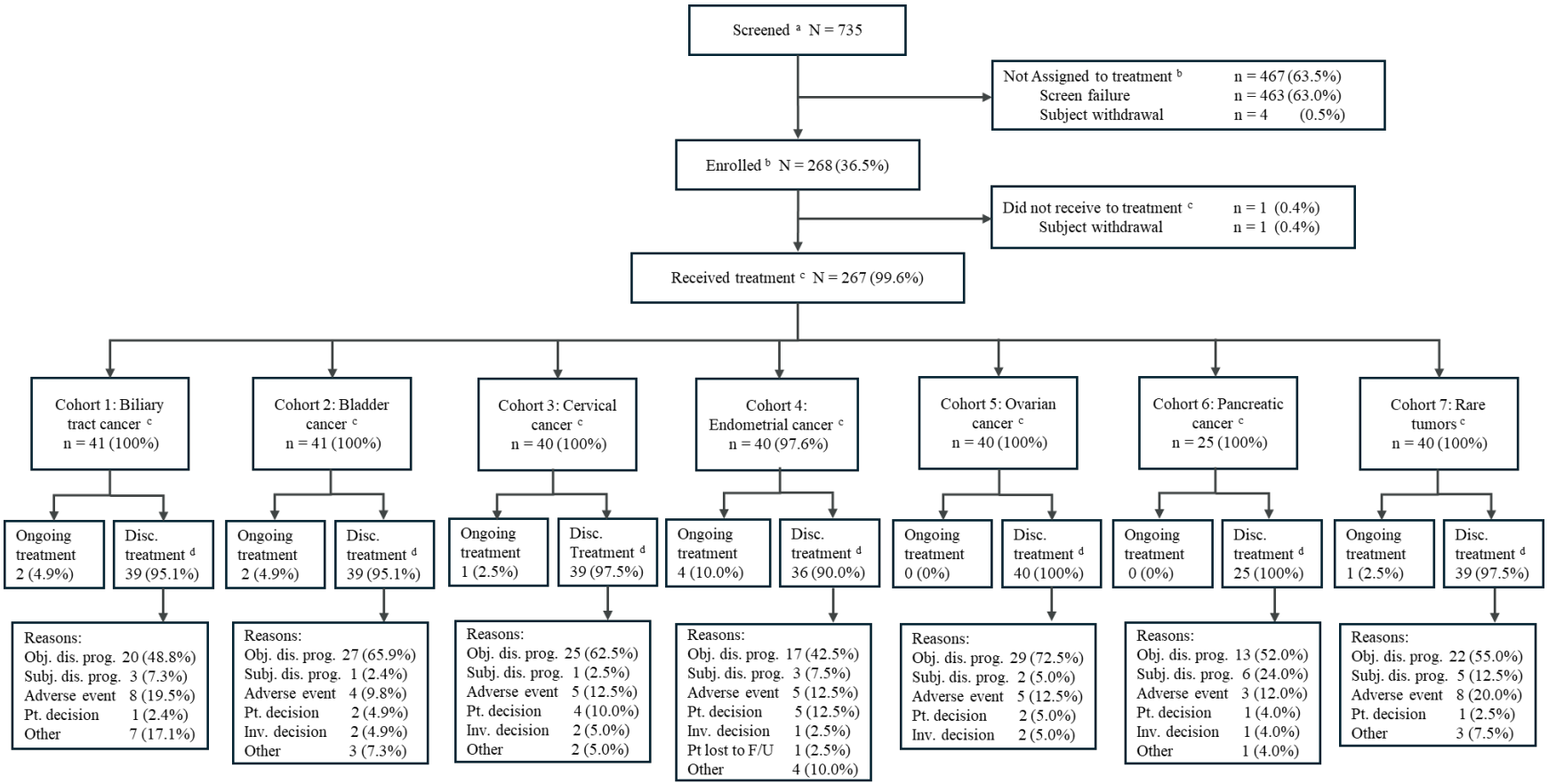
Interim analyses

For Part 1, interim efficacy analyses used the CEAS principle. For Part 2, interim analyses used the FAS principle. For cohorts 1 to 6 in Part 1 and cohorts C, D, and E in Part 2, interim analyses were performed after 15 centrally determined HER2-eligible patients, meeting cohort-specific criteria, within a cohort had the opportunity to complete 2 scheduled post-baseline scans per RECIST v1.1 Guideline. Safety data were reviewed alongside efficacy to support any decision to expand the inclusion criteria or size of a cohort. No adjustment for multiple testing was planned for this study.

Results

Participant flow

Figure 12 Study DP-02 Patient Disposition



[a] Informed consent received.

[b] Percentages are calculated from the total number of screened patients across cohorts.

[c] Percentages are calculated from the number of patients in the cohort who were assigned to treatment.

[d] Percentages are calculated from the number of patients in the cohort who received treatment.

DCO: 10 Oct 2024

Recruitment

Patients were enrolled in the study globally at 65 study centres in 15 countries across North America, Europe, and Asia-Pacific. First patient was enrolled on 18 August 2020, last one on 16 June 2022.

DCO1 for the primary analysis was 08 June 2023; median duration (range) of follow-up time in all patients was 12.75 (0.4, 31.6) months.

DCO2 for the final analysis was 10 October 2024 with the median (range) duration of follow-up in all patients of 12.98 (0.4, 47.7) months.

Conduct of the study

Table 29 Protocol Amendments Related to Changes in Study Conduct

Key details of amendment	**Main reason(s) for amendment**
Amendments made *after* the start of subject recruitment	
Amendment 1, Protocol v2.0 (02 Feb 2021)	
Addition of the option to pre-screen patients, up to 180 days prior to screening, for HER2 status.	A more patient-centric approach to lower the patient burden (procedures and time) for HER2 failures and to enable sites to identify HER2+ patients well in advance of the 28-day screening window starting.
Updated Figure 1 'Study Design' to define HER2 expression status per cohort.	
Rare tumour cohort only recruited patients who had a HER2 status of IHC 3+ or IHC 2+. For all other cohorts, inclusion of IHC 1+ was possible of up to 10 IHC 1+ patients, if ≥ 3 objective responses had been observed in the first 15 patients with confirmed HER2 overexpression (IHC 3+ or IHC 2+) by central testing.	Clarification around HER2 status guidelines.
Changes to study conduct implemented after the initial DCO	
Amendment 2, Protocol v3.0 (02 May 2023) [a]	
The end of the study was changed to approximately 30 months after the last patient was enrolled or when all patients have completed the study, if earlier.	To allow for further follow-up.
Revised the frequency of tumour assessments based on RECIST v1.1 and serum sample collection for assessment of tumour markers following the first 48 weeks after the date of first dose of IP from Q6W to Q12W until disease progression.	To reduce patient burden.

Amendment 3, Protocol v4.0 (05 October 2023) [b]	
Section 1.1 Synopsis, Section 4.1 Overall Design, Section 1.2 Schema, Section 7.1.2 Procedures for Discontinuation of IP - Added description of Part 2 of the study which included 5 new cohorts.	Clarified which cohorts were included in Part 1 of the study and added description of Part 2 cohorts.
Section 1.1 Synopsis, Section 4.1 Overall Design - Added capping of patients with gynaecological tumours.	To seek enrolment across diverse tumour types.
Section 1.1 Synopsis, Section 4.1 Overall Design, Section 9.2 Sample Size Determination - Added description of criteria which apply to Part 2 of the study for sample size estimation; and added description of futility analysis for Part 2.	Clarified which statistical criteria for sample size estimation applied to Part 1 and added criteria for Part 2 of the study; and addition of futility analysis for Part 2.
Section 1.1 Synopsis (Table 3), Section 9.3 Populations for Analyses (Table 16, Table 17) - Changed from "four analysis sets" to "five analysis sets."	Added ADA Analysis Set which includes all patients in the SAF who received 1 dose of IP with a non-missing ADA T-DXd result at any time. Table 17 was updated to clarify that ADA data will be assessed in the ADA Analysis Set population.
Section 1.3 Schedule of Activities (Table 5), Section 8.6.2 Collection of Optional Biomarker Samples - Addition of optional on-treatment tumour tissue sample.	To assess the efficacy of T-DXd, an optional tumour tissue sample was added for collection at Cycle 1 Day 15.
Section 3 Objectives and Endpoints (Table 8) - For PFS outcome measure, 'Proportion of patients alive and progression-free at 6 months and 12 months' was updated to 'Proportion of patients alive and progression-free at 3 monthly intervals starting from 6 months.' and for OS outcome measure, 'Proportion of patients alive at 6 months and 12 months' was updated to 'Proportion of patients alive at 3 monthly intervals starting from 6 months.'	To align with the planned long-term follow-up for PFS and OS past 12 months.
Section 3 Objectives and Endpoints (Table 8) – for the exploratory objective 'To explore prognostic and predictive biomarkers for response to T-DXd therapy.', the endpoint of: 'Subgroup analysis of IHC 3+ compared with IHC 2+, and where applicable, IHC 3+/2+ compared with IHC 1+ • Subgroup analysis of HER2 amplification (ISH+/ISH-)' Changed to: 'Subgroup analysis will be presented by IHC expression level and HER2 amplification status.'	To more accurately capture the scope of subgroup analyses by IHC expression level and HER2 amplification status.
Section 5.1 Inclusion Criteria - Added criteria for cohorts in Part 2.	Clarified which criteria are specific to Part 1 of the study and added criteria specific to the cohorts in Part 2 of the study.

Section 9.5 Interim Analysis - Clarified that Interim Analyses is applicable to both Part 1 and Part 2.	To align with overall amendment addition of Part 2.

[a] This CSP was internally approved but was not in effect in any countries at the time of DCO for the data included in the main CSR.
[b] In Europe, all data up to the DCO of 10 October 2024 were collected according CSP v3.0/1.0 EU, as CSP v4.0 was not in effect in any European countries at the time of DCO for the data included in this CSR addendum
CSP = clinical study protocol; CSR = clinical study report; DCO = data cut-off; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; IP = investigational product; Q6W = every 6 weeks; Q12W = every 12 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours, version 1.1; v = version.

Table 30 Important Protocol Deviations (FAS)

	Number (%) patients
Important protocol deviation a	Total (N = 267)
Number of patients with at least one important protocol deviation	47 (17.6)
INC 2: Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports the Genomic Initiative	5 (1.9)
INC 3: Provision of signed and dated written ICF prior to any mandatory study specific procedures, sampling, or analyses	1 (0.4)
INC 7: All patients must provide an existing FFPE tumour sample for tissue-based IHC staining to centrally determine HER2-expression and other correlatives	12 (4.5)
INC 9: Has an ECOG performance status of 0-1	1 (0.4)
Any deviation considered important that was not predicted or prespecified	8 (3.0)
Failure to perform mandatory safety assessment(s) in ≥ 2 consecutive visits	2 (0.7)
IP non-compliance. Defined as important protocol deviation if the interval between IP doses is < 19 days in two instances or if the interval between doses is > 49 days in one instance	2 (0.7)
Participant received concomitant medication defined as prohibited in the CSP	1 (0.4)
Participant received incorrect dose of IP	8 (3.0)
Patients experiencing any of the following AEs will not be permitted to restart IP: ILD or non-infectious pneumonitis Grade ≥ 2, any Grade 4 haematological toxicity with significant clinical symptoms	2 (0.7)
Progressive disease per criteria set forth in RECIST v1.1	10 (3.7)
RECIST scans performed outside the scheduled window relative to first dose date on more than 2 occasions, or not performed at all	11 (4.1)

[a] Important deviations before the start of treatment and during treatment.
The same patient may have had more than one important protocol deviation.
Important protocol deviations were identified based on the appropriate version of the protocol deviation plan at the time. By DCO, the latest protocol deviation plan is version 5 dated 17 April 2024, the history of all rule updates can be found in the protocol deviation

Important protocol deviations occurred in 47 patients (17.6%) of FAS with Cohort 7 (rare tumours) having the highest frequency (13 patients).

Baseline data

Table 31 Baseline HER2 Status and Amplification (FAS)

	Number (%) of patients							
	Cohort 1 biliary tract cancer (N = 41)	**Cohort 2 bladder cancer (N = 41)**	**Cohort 3 cervical cancer (N = 40)**	**Cohort 4 endometrial cancer (N = 40)**	**Cohort 5 ovarian cancer (N = 40)**	**Cohort 6 pancreatic cancer (N = 25)**	**Cohort 7 rare Tumours (N = 40)**	**Total (N = 267)**
HER2 status (eligibility) assessed by [a]								
Local laboratory	34 (82.9)	33 (80.5)	23 (57.5)	31 (77.5)	37 (92.5)	15 (60.0)	29 (72.5)	202 (75.7)
Central laboratory	7 (17.1)	8 (19.5)	17 (42.5)	9 (22.5)	3 (7.5)	10 (40.0)	11 (27.5)	65 (24.3)
HER2 expression (eligibility) [a]								
Low HER2 expression (IHC 1+)	0	0	5 (12.5)	0	0	0	0	5 (1.9)
HER2 overexpression (IHC 3+ or 2+)	41 (100)	41 (100)	35 (87.5)	40 (100)	40 (100)	25 (100)	40 (100)	262 (98.1)
HER2 status (eligibility) [a]								
IHC 1+	0	0	5 (12.5)	0	0	0	0	5 (1.9)
IHC 2+	19 (46.3)	14 (34.1)	25 (62.5)	24 (60.0)	25 (62.5)	20 (80.0)	24 (60.0)	151 (56.6)
IHC 3+	22 (53.7)	27 (65.9)	10 (25.0)	16 (40.0)	15 (37.5)	5 (20.0)	16 (40.0)	111 (41.6)
HER2 status (central laboratory)								
IHC 0	7 (17.1)	2 (4.9)	4 (10.0)	5 (12.5)	5 (12.5)	3 (12.0)	4 (10.0)	30 (11.2)
IHC 1+	3 (7.3)	2 (4.9)	8 (20.0)	4 (10.0)	5 (12.5)	1 (4.0)	2 (5.0)	25 (9.4)
IHC 2+	14 (34.1)	20 (48.8)	20 (50.0)	17 (42.5)	19 (47.5)	19 (76.0)	16 (40.0)	125 (46.8)
IHC 3+	16 (39.0)	16 (39.0)	8 (20.0)	13 (32.5)	11 (27.5)	2 (8.0)	9 (22.5)	75 (28.1)
Unknown [b]	1 (2.4)	1 (2.4)	0	1 (2.5)	0	0	9 (22.5)	12 (4.5)
HER2 amplification (central laboratory)								

ISH positive	19 (46.3)	9 (22.0)	10 (25.0)	13 (32.5)	10 (25.0)	3 (12.0)	14 (35.0)	78 (29.2)
ISH negative	15 (36.6)	26 (63.4)	26 (65.0)	20 (50.0)	25 (62.5)	19 (76.0)	14 (35.0)	145 (54.3)
ISH unknown	7 (17.1)	6 (14.6)	4 (10.0)	7 (17.5)	5 (12.5)	3 (12.0)	12 (20.0)	44 (16.5)

[a] HER2 expression for eligibility can be based on local assessment (where available) or central testing. HER2 status (eligibility) summarizes whichever result (local/central) was used to determine eligibility (as recorded in the eCRF).

[b] Unknown central IHC test results include patients whose samples were unevaluable (for various technical reasons) and may include patients who did not provide a sample for central testing.

eCRF= electronic case report form; FAS = full analysis set; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ISH = in situ hybridization.

Table 32 Demographic and Baseline Characteristics in the IHC 3+ Population (FAS)

Demographic characteristic	Biliary tract cancer (N = 22)	Bladder cancer (N = 27)	Cervical cancer (N = 10)	Endometrial cancer (N = 16)	Ovarian cancer (N = 15)	Pancreatic cancer (N = 5)	Rare (N = 16)	DP02 ICH3+ (N=111)
Age (years)								
N	22	27	10	16	15	5	16	111
Median	66.0	68.0	49.0	68.5	56.0	52.0	62.5	64.0
Min, Max	31, 80	43, 85	31, 78	56, 79	34, 70	23, 68	38, 75	23, 85
Age group (years) n (%)								
< 65	10 (45.5)	12 (44.4)	9 (90.0)	4 (25.0)	11 (73.3)	4 (80.0)	9 (56.3)	59 (53.2)
≥ 65	12 (54.5)	15 (55.6)	1 (10.0)	12 (75.0)	4 (26.7)	1 (20.0)	7 (43.8)	52 (46.8)
Sex n (%)								
Male	12 (54.5)	17 (63.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (60.0)	13 (81.3)	45 (40.5)
Female	10 (45.5)	10 (37.0)	10 (100)	16 (100)	15 (100)	2 (40.0)	3 (18.8)	66 (59.5)
Race n (%)								
White	12 (54.5)	16 (59.3)	7 (70.0)	10 (62.5)	6 (40.0)	3 (60.0)	10 (62.5)	64 (57.7)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)	2 (12.5)	1 (6.7)	1 (20.0)	0 (0.0)	4 (3.6)
Asian	10 (45.5)	11 (40.7)	1 (10.0)	3 (18.8)	8 (53.3)	1 (20.0)	4 (25.0)	38 (34.2)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	3 (2.7)
Not Reported	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (6.3)	2 (1.8)
Ethnicity n (%)								
Hispanic or Latino	1 (4.5)	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)
Not Hispanic or Latino	21 (95.5)	27 (100)	8 (80.0)	16 (100)	15 (100)	5 (100)	16 (100)	108 (97.3)
Region n (%)								
Asia	10 (45.5)	11 (40.7)	1 (10.0)	1 (6.3)	8 (53.3)	1 (20.0)	4 (25.0)	36 (32.4)
North America	3 (13.6)	6 (22.2)	2 (20.0)	8 (50.0)	2 (13.3)	0 (0.0)	(31.3)	26 (23.4)
Europe	(40.9)	10 (37.0)	7 (70.0)	7 (43.8)	5 (33.3)	4 (80.0)	5 (31.3)	47 (42.3)

Demographic characteristic	Biliary tract cancer (N = 22)	Bladder cancer (N = 27)	Cervical cancer (N = 10)	Endometrial cancer (N = 16)	Ovarian cancer (N = 15)	Pancreatic cancer (N = 5)	Rare (N = 16)	DP02 ICH3+ (N=111)
ROW	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (12.5)	2 (1.8)
ECOG								
0	8 (36.4)	13 (48.1)	6 (60.0)	8 (50.0)	12 (80.0)	1 (20.0)	6 (37.5)	54 (48.6)
1	14 (63.6)	14 (51.9)	4 (40.0)	8 (50.0)	3 (20.0)	4 (80.0)	10 (62.5)	57 (51.4)
Number of prior regimens								
Median	2.0	3.0	2.5	2.0	3.0	1.0	1.5	2.0
Min, Max	1, 4	0, 9	1, 6	0, 7	1, 8	1, 4	1, 3	0, 9

Rare tumour cohort includes 9 patients with salivary, 1 each with extramammary Paget's disease, vulvar, head and neck, lip and/or oral cavity cancer, non-squamous oesophageal, squamous oesophageal and oropharyngeal.

N: Number of patients in full analysis set.

In the rare tumour cohort, the salivary gland cancer was the most common type of cancer (n=19; 47.5%), followed by malignant neoplasm of unknown primary site (n=5; 12.5%). Extramammary Paget's disease was reported in 3 (7.55) patients, and melanoma and oropharyngeal neoplasm in two (5.0%) patients. Adenocarcinoid tumour of the appendix, adenoid cystic carcinoma, head and neck, intestinal adenocarcinoma, lip and/or oral cavity cancer, oesophageal adenocarcinoma, oesophageal squamous carcinoma, testis cancer, and vulva cancer, were reported in one (2.5%) patient each.

Prior anticancer therapy:

Prior treatment with topoisomerase I inhibitors was most common in the pancreatic cancer cohort, with 72.0% of patients having received such treatment. 38 (14.2%) patients received prior anti-HER2 treatment, which was most frequently used in the rare tumours cohort, with 14 patients, followed by endometrial cancer (9 patients) and BTC (7 patients) cohorts.

The use of PD-1/PD-L1 inhibitors varied significantly across cohorts, with the bladder cancer cohort showing the highest usage at 68.3% of patients. In contrast, there was no prior use of PD-1/PD-L1 inhibitors in the pancreatic cancer cohort. Platinum compounds, including carboplatin, cisplatin, and oxaliplatin, were widely used across all cohorts, with some cohorts, such as BTC, cervical cancer, and ovarian cancer, having all patients receive prior platinum compound treatment. The overall usage of platinum compounds was high, at 91.4% in the FAS.

Numbers analysed

Table 33 Analysis Sets (All Patients)

	Number of patients							
	Cohort 1 BTC	**Cohort 2 bladder cancer**	**Cohort 3 cervical cancer**	**Cohort 4 endometrial cancer**	**Cohort 5 ovarian cancer**	**Cohort 6 pancreatic cancer**	**Cohort 7 rare tumours**	**Total**
Patients included in FAS/SAF	41	41	40	40	40	25	40	267
Patients excluded from FAS/SAF	0	0	0	1	0	0	0	1
Did not receive treatment	0	0	0	1	0	0	0	1
Patients included in ADA analysis set	41	41	40	40	40	25	40	267
Patients excluded from ADA analysis set	0	0	0	1	0	0	0	1
Did not receive treatment	0	0	0	1	0	0	0	1

FAS/SAF = all patients who received at least 1 dose of study treatment. |
ADA analysis set = all patients in the SAF who received at least 1 dose of study treatment and with a non-missing ADA for T-DXd.

Outcomes and estimation

Primary endpoint: Confirmed ORR by INV

Primary analysis (DCO1 08 June 2023):

Table 34 Confirmed ORR According to RECIST v1.1 (FAS)

Cohort	N	Investigator Assessment [a]		ICR Assessment [b]	
		Number (%) of patients with confirmed response	95% CI for ORR (%)	Number (%) of patients with confirmed response	95% CI for response
All patients	267	99 (37.1)	31.3, 43.2	100 (37.5)	31.6, 43.6
Cohort 1 biliary tract cancer	41	9 (22.0)	10.6, 37.6	11 (26.8)	14.2, 42.9
Cohort 2 bladder cancer	41	16 (39.0)	24.2, 55.5	17 (41.5)	26.3, 57.9
Cohort 3 cervical cancer	40	20 (50.0)	33.8, 66.2	15 (37.5)	22.7, 54.2
Cohort 4 endometrial cancer	40	23 (57.5)	40.9, 73.0	23 (57.5)	40.9, 73.0
Cohort 5 ovarian cancer	40	18 (45.0)	29.3, 61.5	17 (42.5)	27.0, 59.1
Cohort 6 pancreatic cancer	25	1 (4.0)	0.1, 20.4	3 (12.0)	2.5, 31.2
Cohort 7 rare tumours [c]	40	12 (30.0)	16.6, 46.5	14 (35.0)	20.6, 51.7

[a] Response is determined by Investigator assessment according to RECIST v1.1.
[b] Response is determined by ICR assessment according to RECIST v1.1.
CI is calculated using the Clopper-Pearson method.
Response requires confirmation after at least 4 weeks.
CI = confidence interval; FAS = full analysis set; ICR = Independent Central Review; ORR = objective response rate; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours, version 1.1.

Final analysis (DCO2 10 October 2024):

Table 35 Confirmed ORR According to RECIST v1.1 (FAS)

Cohort	N	INV Assessment [a]		ICR Assessment [b]	
		Number (%) of patients with confirmed response	95% CI for ORR (%)	Number (%) of patients with confirmed response	95% CI for ORR (%)
All patients	267	100 (37.5)	31.6, 43.6	100 (37.5)	31.6, 43.6
Cohort 1 BTC	41	9 (22.0)	10.6, 37.6	11 (26.8)	14.2, 42.9
Cohort 2 bladder cancer	41	17 (41.5)	26.3, 57.9	17 (41.5)	26.3, 57.9
Cohort 3 cervical cancer	40	20 (50.0)	33.8, 66.2	15 (37.5)	22.7, 54.2
Cohort 4 endometrial cancer	40	23 (57.5)	40.9, 73.0	23 (57.5)	40.9, 73.0
Cohort 5 ovarian cancer	40	18 (45.0)	29.3, 61.5	17 (42.5)	27.0, 59.1
Cohort 6 pancreatic cancer	25	1 (4.0)	0.1, 20.4	3 (12.0)	2.5, 31.2
Cohort 7 rare tumours [c]	40	12 (30.0)	16.6, 46.5	14 (35.0)	20.6, 51.7

[a] Response was determined by INV assessment according to RECIST v1.1.
[b] Response was determined by ICR assessment according to RECIST v1.1.
CI was calculated using the Clopper-Pearson method.
Response required confirmation after at least 4 weeks

Exploratory analysis of primary endpoint based on HER2 status (final analysis, DCO2 10 October 2024):

Table 36 Confirmed ORR per INV by Eligibility Assessment of HER2 Status (FAS) DCO2 10 October 2024

Subgroup	Category	N	Number (%) of patients with confirmed response [a]	95% CI for response
All patients		267	100 (37.5)	31.6, 43.6
HER2 status	IHC 3+	111	58 (52.3)	42.6, 61.8
	IHC 2+	151	40 (26.5)	19.6, 34.3
	IHC 1+	5	2 (40.0)	5.3, 85.3

[a] Response was determined by INV assessment according to RECIST v1.1.
CI was calculated using the Clopper-Pearson method.
Responses exclude unconfirmed responses and require confirmation after at least 4 weeks.

Table 37 Confirmed ORR in the IHC 3+ Population (FAS) DCO2 10 October 2024

	Confirmed ORR per ICR n/N (% [95% CI])	Confirmed ORR per INV n/N (% [95% CI])
Biliary tract cancer	10/ 22 (45.5 [24.4, 67.8])	9/ 22 (40.9 [20.7, 63.6])
Bladder cancer	10/ 27 (37.0 [19.4, 57.6])	12/ 27 (44.4 [25.5, 64.7])
Cervical cancer	7/ 10 (70.0 [34.8, 93.3])	8/ 10 (80.0 [44.4, 97.5])
Endometrial cancer	9/ 16 (56.3 [29.9, 80.2])	10/ 16 (62.5 [35.4, 84.8])
Ovarian cancer	10/ 15 (66.7 [38.4, 88.2])	11/ 15 (73.3 [44.9, 92.2])
Pancreatic cancer	0/ 5 (0 [0, 52.2])	0/ 5 (0 [0, 52.2])
Rare tumour	11/ 16 (68.8 [41.3, 89.0])	8/ 16 (50.0 [24.7, 75.3])

Response requires confirmation after at least 4 weeks.

n: number of confirmed response including CR/PR in Full Analysis Set.

N: number of patients in Full Analysis Set

Exact (Clopper-Pearson) method is used for 95% CI.

Rare tumour cohort includes 9 patients with salivary, 1 each with extramammary Paget's disease, vulvar, head and neck, lip and/or oral cavity cancer, non-squamous oesophageal, squamous oesophageal, oropharyngeal.

Table 38 Confirmed Objective Response Rate and Duration of Response per Sub-Tumour Type of Rare Tumour Cohort of DP02 – IHC 3+ Population (Full Analysis Set)

	Confirmed Objective Response Rate (ORR) n/N (% [95% CI])		Duration of response from onset of response (months)[ab] Median (95% CI)	
	ICR	INV	ICR	INV
Salivary Gland Cancer	6/ 9 (66.7 [29.9, 92.5])	5/ 9 (55.6 [21.2, 86.3])	20.1 (5.6, NE)	10.9 (4.1, NE)
Adenocarcinoid Tumor Of The Appendix	NA	NA	NA	NA
Adenoid Cystic Carcinoma	NA	NA	NA	NA
Extramammary Paget's Disease	1/ 1 (100 [2.5, 100])	1/ 1 (100 [2.5, 100])	19.4 (NE, NE)	23.6 (NE, NE)
Head And Neck	1/ 1 (100 [2.5, 100])	1/ 1 (100 [2.5, 100])	NE	NE
Intestinal Adenocarcinoma	NA	NA	NA	NA
Lip And/Or Oral Cavity Cancer	0/ 1 (0 [0, 97.5])	0/ 1 (0 [0, 97.5])	NE	NE
Malignant Neoplasm Of Unknown Primary Site	NA	NA	NA	NA
Melanoma	NA	NA	NA	NA
Oesophageal Adenocarcinoma	1/ 1 (100 [2.5, 100])	0/ 1 (0 [0, 97.5])	2.8 (NE, NE)	NE
Oesophageal Squamous Cell Carcinoma	0/ 1 (0 [0, 97.5])	0/ 1 (0 [0, 97.5])	NE	NE
Oropharyngeal Neoplasm	1/ 1 (100 [2.5, 100])	1/ 1 (100 [2.5, 100])	21.1 (NE, NE)	21.1 (NE, NE)
Testis Cancer	NA	NA	NA	NA
Vulva Cancer	1/ 1 (100 [2.5, 100])	0/ 1 (0 [0, 97.5])	2.6 (NE, NE)	NE

[a] Duration of response is the time from the first documentation of CR/PR (which is subsequently confirmed) until the date of progression or death in the absence of disease progression for patients with objective response (CR/PR). Patients who have not progressed or died are censored at their PFS censoring date.
[b] Calculated using Kaplan-Meier technique.
n: Number of patients with objective response in full analysis set in corresponding tumour type.
N: Number of patients in full analysis set in corresponding tumour type.
ORR (%) is calculated as percent of number of responders among number of patients in corresponding tumour type.
ICR: Independent Central Review; INV: Investigator. NA=Not Applicable. NE=Not Evaluable.

Table 39 Confirmed ORR per INV by Central Assessment of HER2 Status (FAS) DCO2 10 October 2024

Subgroup	Category	N	Number (%) of patients with confirmed response [a]	95% CI for response
All patients		267	100 (37.5)	31.6, 43.6
HER2 status	IHC 3+	75	46 (61.3)	49.4, 72.4
	IHC 2+	125	35 (28.0)	20.3, 36.7
	IHC 1+	25	6 (24.0)	9.4, 45.1
	IHC 0	30	9 (30.0)	14.7, 49.4
	Unknown	12	4 (33.3)	9.9, 65.1

[a] Response was determined by INV assessment according to RECIST v1.1.
Unknown central IHC test results included patients whose samples were unevaluable (for various technical reasons) and may have included patients who did not provide a sample for central testing.
CI was calculated using the Clopper-Pearson method.
Responses exclude unconfirmed responses and require confirmation after at least 4 weeks.

Table 40 Confirmed ORR by INV in HER2 IHC 3+ by central testing (primary analysis) DCO2 10 October 2024

Cohort	N	Number (%) of patients with response	95%CI
Cohort 1: Biliary Tract Cancer	16	9 (56.3)	29.9, 80.2
Cohort 2: Bladder Cancer	16	9 (56.3)	29.9, 80.2

Cohort	N	Number (%) of patients with response	95%CI
Cohort 3: Cervical Cancer	8	6 (75.0)	34.9, 96.8
Cohort 4: Endometrial Cancer	13	11 (84.6)	54.6, 98.1
Cohort 5: Ovarian Cancer	11	7 (63.6)	30.8, 89.1
Cohort 6: Pancreatic Cancer	2	0	0.0, 84.2
Cohort 7: Rare Tumours	9	4 (44.4)	13.7, 78.8

Table 41 Confirmed ORR per Investigator by Local Assessment of HER2 Status (DCO1 08 June 2023)

Category	N	Number (%) of patients with confirmed response [a]	95% CI for response
IHC 3+	93	48 (51.6)	41.0, 62.1
IHC 2+ or 3+	200	74 (37.0)	30.3, 44.1

[a] Response is determined by Investigator assessment according to RECIST v1.1.
The 2 patients with IHC 1+ by local assessment are not presented in this table.
CI is calculated using the Clopper-Pearson method.
Responses exclude unconfirmed responses and require confirmation after at least 4 weeks.
CI = confidence interval; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ORR = objective response rate.

Key secondary endpoints (final analysis)

DoR by INV

Table 42 Duration of Response by INV Assessment (FAS, Patients with Objective Response)

	Cohort 1 BTC (N = 9)	Cohort 2 bladder cancer (N = 17)	Cohort 3 cervical cancer (N = 20)	Cohort 4 endometrial cancer (N = 23)	Cohort 5 ovarian cancer (N = 18)	Cohort 6 pancreatic cancer (N = 1)	Cohort 7 rare tumours (N = 12)	Total (N = 100)
Number of responders who subsequently progressed or died, n (%)	6 (66.7)	14 (82.4)	12 (60.0)	15 (65.2)	13 (72.2)	1 (100)	8 (66.7)	69 (69.0)
Duration of response from onset of response (months) [a,b], median (95% CI)	8.6 (2.1, NE)	9.5 (4.3, 11.8)	13.1 (4.1, NE)	27.7 (9.9, NE)	11.3 (4.1, 25.0)	5.7 (NE, NE)	21.1 (4.1, 23.6)	11.3 (9.8, 17.8)
Percentage remaining in response [b]								
3 months	88.9	94.1	90.0	95.7	82.4	100.0	91.7	90.9
6 months	77.8	76.5	75.0	86.5	64.7	0	75.0	75.5
9 months	44.4	51.8	64.3	82.0	58.8	0	75.0	64.0
12 months	33.3	22.6	53.6	68.3	47.1	0	56.3	48.9
15 months	33.3	15.1	40.8	63.8	35.3	0	56.3	41.9

18 months	33.3	7.5	34.0	63.8	35.3	0	56.3	39.5
21 months	33.3	7.5	34.0	59.2	35.3	0	56.3	38.3
24 months	33.3	7.5	34.0	54.7	28.2	0	14.1	31.9
27 months	33.3	7.5	34.0	50.1	21.2	0	14.1	29.3
30 months	33.3	7.5	34.0	36.4	21.2	0	0	25.0
33 months	33.3	7.5	34.0	36.4	21.2	0	0	25.0
36 months	33.3	0	34.0	31.2	21.2	0	0	23.1
39 months	0	0	34.0	31.2	0	0	0	23.1
42 months	0	0	0	31.2	0	0	0	23.1
45 months	0	0	0	31.2	0	0	0	23.1

Duration of response is the time from the first documentation of CR/PR (which was subsequently confirmed) until the date of progression or death in the absence of disease progression. Patients who had not progressed or died were censored at their PFS censoring date.
Calculated using Kaplan-Meier technique.
DCO2 10 October 2024

Table 43 INV-assessed DoR by Eligibility Assessment of HER2 Status (FAS, Patients with Objective Response)

Subgroup	**Category**	**N (patients with confirmed objective response)**	**Number of responders who subsequently progressed or died, n (%)**	**Duration of response from onset of response (months) [a,b]**	
				Median	**95% CI**
All patients		100	69 (69.0)	11.3	9.8, 17.8
HER2 status	IHC 3+	58	37 (63.8)	21.1	10.6, 25.0
	IHC 2+	40	30 (75.0)	9.8	4.5, 12.6
	IHC 1+	2	2 (100)	10.7	8.3, NE

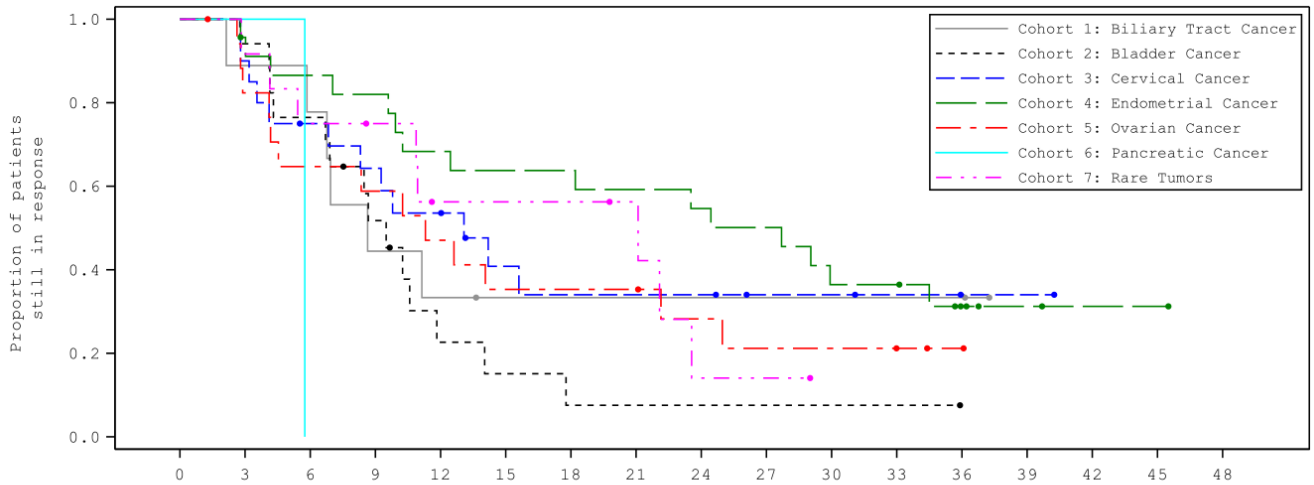
[a] Duration of response is the time from the first documentation of CR/PR (which was subsequently confirmed) until the date of progression or death in the absence of disease progression. Patients who had not progressed or died are censored at their PFS censoring date.
[b] Calculated using Kaplan-Meier technique.
Response is determined by INV assessment according to RECIST v1.1.
DCO2 10 October 2024

Table 44 Duration of Objective Response and Time to Response by INV – IHC 3+ Population (Full Analysis Set, patients with objective response)

	BTC (N= 9)	BLC (N= 12)	CC (N= 8)	EC (N= 10)	OC (N= 11)	PC (N= 0)	Rare (N= 8)
Number of responders who subsequently progressed or died, n (%)	6 (66.7)	10 (83.3)	2 (25.0)	7 (70.0)	6 (54.5)	0	6 (75.0)
Duration of response from onset of response (months) [ab]							
25th percentile	6.8	5.6	14.2	23.5	10.3	NE	10.9
Median	8.6	8.7	NE	28.8	22.1	NE	21.1
75th percentile	NE	10.6	NE	NE	NE	NE	22.1
95% CI for median duration of response	2.1, NE	4.1, 10.6	9.3, NE	4.2, NE	2.8, NE	NE	4.1, NE

N: number of patients with objective response per INV in full analysis set of IHC 3+ population.
[a] Duration of response is the time from the first documentation of CR/PR (which is subsequently confirmed) until the date of progression or death in the absence of disease progression. Patients who have not progressed or died are censored at their PFS censoring date.
[b] Calculated using Kaplan-Meier technique.
DCO 10 Oct 2024

Table 45 Duration of objective response by Investigator assessment, Kaplan-Meier plot (Full analysis set, patients with objective response)



n at months

Cohort 1	9	8	7	4	3	2	2	2	2	2	2	2	2	0	0	0	0
Cohort 2	17	16	13	8	3	2	1	1	1	1	1	1	0	0	0	0	0
Cohort 3	20	18	14	12	10	6	5	5	5	3	3	2	1	1	0	0	0
Cohort 4	23	21	19	18	15	14	14	13	12	11	8	8	4	2	1	1	0
Cohort 5	18	14	11	10	8	6	6	6	4	3	3	2	1	0	0	0	0
Cohort 6	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cohort 7	12	11	9	8	5	5	5	4	1	1	0	0	0	0	0	0	0

Circle indicates a censored observation.
Response is determined by Investigator assessment according to RECIST 1.1.
Data Cut-off 10OCT2024

Table 46 Duration of Objective Response by ICR in IHC 3+ Population (FAS, Patients With Objective Response)

	Biliary tract cancer (N = 10)	**Bladder cancer (N = 10)**	**Cervical cancer (N = 7)**	**Endometrial cancer (N = 9)**	**Ovarian cancer (N = 10)**	**Pancreatic cancer (N = 0)**	**Rare (N = 11)**
Number of responders who subsequently progressed or died, n (%)	5 (50.0)	8 (80.0)	2 (28.6)	4 (44.4)	4 (40.0)	0	7 (63.6)
Duration of response from onset of response (months) a, b							
25th percentile	5.8	5.5	15.6	24.4	5.9	NE	5.6
Median	10.9	5.7	NE	29.9	19.6	NE	19.4
75th percentile	NE	10.0	NE	NE	NE	NE	21.1
95% CI for median duration of response	2.1, NE	4.1, 10.0	9.3, NE	5.8, NE	5.1, NE	NE	2.8, NE
Percentage remaining in response [b]							
3 Months	90.0	100.0	100.0	100.0	100.0	NE	81.8
6 Months	67.5	44.4	100.0	88.9	71.4	NE	72.7
9 Months	54.0	44.4	100.0	88.9	71.4	NE	72.7
12 Months	40.5	14.8	85.7	77.8	57.1	NE	62.3
15 Months	40.5	14.8	85.7	77.8	57.1	NE	62.3
18 Months	40.5	0.0	64.3	77.8	57.1	NE	62.3
21 Months	40.5	0.0	64.3	77.8	42.9	NE	33.2
24 Months	40.5	0.0	64.3	77.8	42.9	NE	16.6
27 Months	40.5	0.0	64.3	62.2	42.9	NE	16.6
30 Months	40.5	0.0	64.3	46.7	42.9	NE	16.6

a Duration of response is the time from the first documentation of CR/PR (which is subsequently confirmed) until the date of progression or death in the absence of disease progression. Patients who have not progressed or died are censored at their PFS censoring date.

b Calculated using Kaplan-Meier technique.

Response is determined by ICR.
DCO 10 Oct 2024

Best objective Response by INV

Table 47 Best Objective Response by INV Assessment According to RECIST v1.1 (FAS)

Response status Best objective response	Number (%) of patients							
	Cohort 1 BTC (N = 41)	Cohort 2 bladder cancer (N = 41)	Cohort 3 cervical cancer (N = 40)	Cohort 4 endometrial cancer (N = 40)	Cohort 5 ovarian cancer (N = 40)	Cohort 6 pancreatic cancer (N = 25)	Cohort 7 rare tumours (N = 40)	Total (N = 267)
Response total	9 (22.0)	17 (41.5)	20 (50.0)	23 (57.5)	18 (45.0)	1 (4.0)	12 (30.0)	100 (37.5)
Complete response [a]	1 (2.4)	1 (2.4)	3 (7.5)	8 (20.0)	4 (10.0)	0	0	17 (6.4)
Partial response [a]	8 (19.5)	16 (39.0)	17 (42.5)	15 (37.5)	14 (35.0)	1 (4.0)	12 (30.0)	83 (31.1)
Non-response total	32 (78.0)	24 (58.5)	20 (50.0)	17 (42.5)	22 (55.0)	24 (96.0)	28 (70.0)	167 (62.5)
Stable disease ≥ 5 weeks [b]	25 (61.0)	17 (41.5)	12 (30.0)	13 (32.5)	14 (35.0)	17 (68.0)	24 (60.0)	122 (45.7)
Unconfirmed complete or partial response [c]	2 (4.9)	2 (4.9)	1 (2.5)	1 (2.5)	0	1 (4.0)	4 (10.0)	11 (4.1)
Stable disease	23 (56.1)	15 (36.6)	11 (27.5)	12 (30.0)	14 (35.0)	16 (64.0)	20 (50.0)	111 (41.6)
Progression	7 (17.1)	7 (17.1)	7 (17.5)	4 (10.0)	7 (17.5)	7 (28.0)	3 (7.5)	42 (15.7)
RECIST progression	7 (17.1)	5 (12.2)	6 (15.0)	3 (7.5)	5 (12.5)	5 (20.0)	2 (5.0)	33 (12.4)
Death	0	2 (4.9)	1 (2.5)	1 (2.5)	2 (5.0)	2 (8.0)	1 (2.5)	9 (3.4)
Not evaluable	0	0	1 (2.5)	0	1 (2.5)	0	1 (2.5)	3 (1.1)
Stable disease < 5 weeks [b]	0	0	0	0	0	0	0	0
Incomplete post-baseline assessments	0	0	1 (2.5)	0	1 (2.5)	0	1 (2.5)	3 (1.1)

[a] Response required confirmation after at least 4 weeks.
[b] Calculated as 6 weeks minus one week, to allow for an early RECIST assessment within the assessment window.
[c] PR or CR achieved but either no confirmation assessment performed, or a confirmation assessment performed but response not confirmed. Response was determined by INV assessment according to RECIST v1.1
Data Cut-off 10 OCT 2024

Table 48 Confirmed Best Overall Response and Disease Control Rate per INV – IHC 3+ Population (Full Analysis Set)

	Number (%) of Patients						
	BTC (N=22)	BLC (N=27)	CC (N=10)	EC (N=16)	OC (N=15)	PC (N=5)	Rare (N=16)
Best Overall Response n (%)							
Complete response[a]	1 (4.5)	1 (3.7)	3 (30.0)	4 (25.0)	3 (20.0)	0	0
Partial response[a]	8 (36.4)	11 (40.7)	5 (50.0)	6 (37.5)	8 (53.3)	0	8 (50.0)
Stable disease (SD)[b]	10 (45.5)	10 (37.0)	2 (20.0)	5 (31.3)	3 (20.0)	4 (80.0)	7 (43.8)
Progression	3 (13.6)	5 (18.5)	0	1 (6.3)	1 (6.7)	1 (20.0)	1 (6.3)
Not evaluable (NE)	0	0	0	0	0	0	0
Disease Control Rate (DCR)[c]							
n (% [95% CI])	19 (86.4 [65.1, 97.1])	22 (81.5 [61.9, 93.7])	10 (100 [69.2, 100])	15 (93.8 [69.8, 99.8])	14 (93.3 [68.1, 99.8])	4 (80.0 [28.4, 99.5])	15 (93.8 [69.8, 99.8])

CR Complete response. PR Partial response.
[a] Response requires confirmation after at least 4 weeks.
[b] Calculated as 6 weeks minus 1 week, to allow for an early RECIST assessment within the assessment window.
[c] Disease control = confirmed complete response + confirmed partial response + stable disease at or after 5 weeks.
DCO 10 Oct 2024

Table 49 Confirmed BOR per ICR in the IHC 3+ Population (FAS)

	Number (%) of Patients						
	Biliary tract cancer (N = 22)	**Bladder cancer (N = 27)**	**Cervical cancer (N = 10)**	**Endometrial cancer (N = 16)**	**Ovarian cancer (N = 15)**	**Pancreatic cancer (N = 5)**	**Rare (N = 16)**
Complete response[a]	1 (4.5)	0	1 (10.0)	2 (12.5)	0	0	0
Partial response[a]	9 (40.9)	10 (37.0)	6 (60.0)	7 (43.8)	10 (66.7)	0	11 (68.8)
Stable disease[b]	9 (40.9)	11 (40.7)	3 (30.0)	6 (37.5)	3 (20.0)	4 (80.0)	4 (25.0)
Progression	3 (13.6)	6 (22.2)	0	1 (6.3)	1 (6.7)	1 (20.0)	1 (6.3)
Not evaluable	0	0	0	0	0	0	0
No evidence of disease	0	0	0	0	1 (6.7)	0	0

a Response requires confirmation after at least 4 weeks.

b Calculated as 6 weeks minus 1 week, to allow for an early RECIST assessment within the assessment window.

Rare tumour cohort includes 9 patients with salivary, 1 each with extramammary Paget's disease, vulvar, head and neck, lip and/or oral cavity cancer, non-squamous oesophageal, squamous oesophageal and oropharyngeal.

Note: Patients with NED are included as disease control if they have NED at or after 5 weeks or 11 weeks (as appropriate).
DCO 10 Oct 2024

PFS and OS

Table 50 INV-assessed PFS by Eligibility Assessment of HER2 Status (FAS)

Subgroup	**Category**	**N**	**Number of patients with events [a]**	**PFS (months) [b]**	
				Median	**95% CI**
All patients		267	213 (79.8)	6.9	5.6, 8.0
HER2 status	IHC 3+	111	82 (73.9)	9.7	7.0, 12.5
	IHC 2+	151	126 (83.4)	5.1	4.1, 6.0
	IHC 1+	5	5 (100)	7.0	2.6, NE

[a] Patients who had not progressed or died, or who progressed or died after 2 or more missed visits, were censored at the latest evaluable RECIST assessment, or at Day 1 (first dose) if there were no evaluable visits or no baseline assessment (unless the patient died within 13 weeks of baseline).
[b] Calculated using the Kaplan-Meier technique. CI for median PFS was derived based on Brookmeyer-Crowley method.
DCO 10 Oct 2024

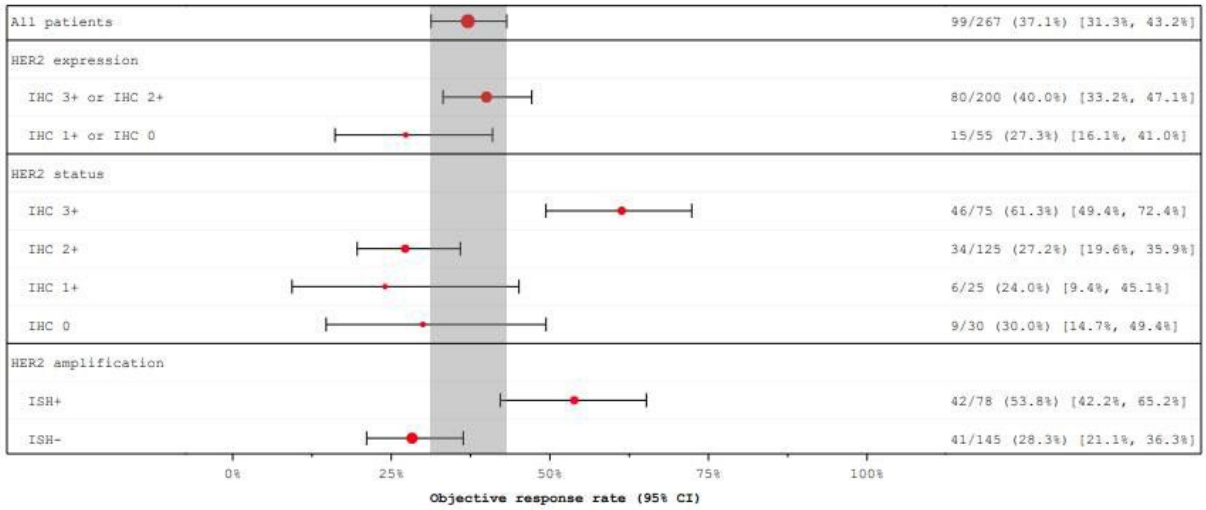
Table 51 OS by Eligibility Assessment of HER2 Status (FAS)

Subgroup	Category	N	Number of deaths	OS (months) [a]	
				Median	95% CI
All patients		267	216 (80.9)	13.4	11.9, 15.3
HER2 status	IHC 3+	111	84 (75.7)	17.7	12.8, 23.4
	IHC 2+	151	128 (84.8)	12.0	9.6, 13.5
	IHC 1+	5	4 (80.0)	17.3	6.1, NE

[a] Calculated using the Kaplan-Meier technique. CI for median OS was derived based on Brookmeyer-Crowley method.
DCO 10 Oct 2024

Ancillary analyses

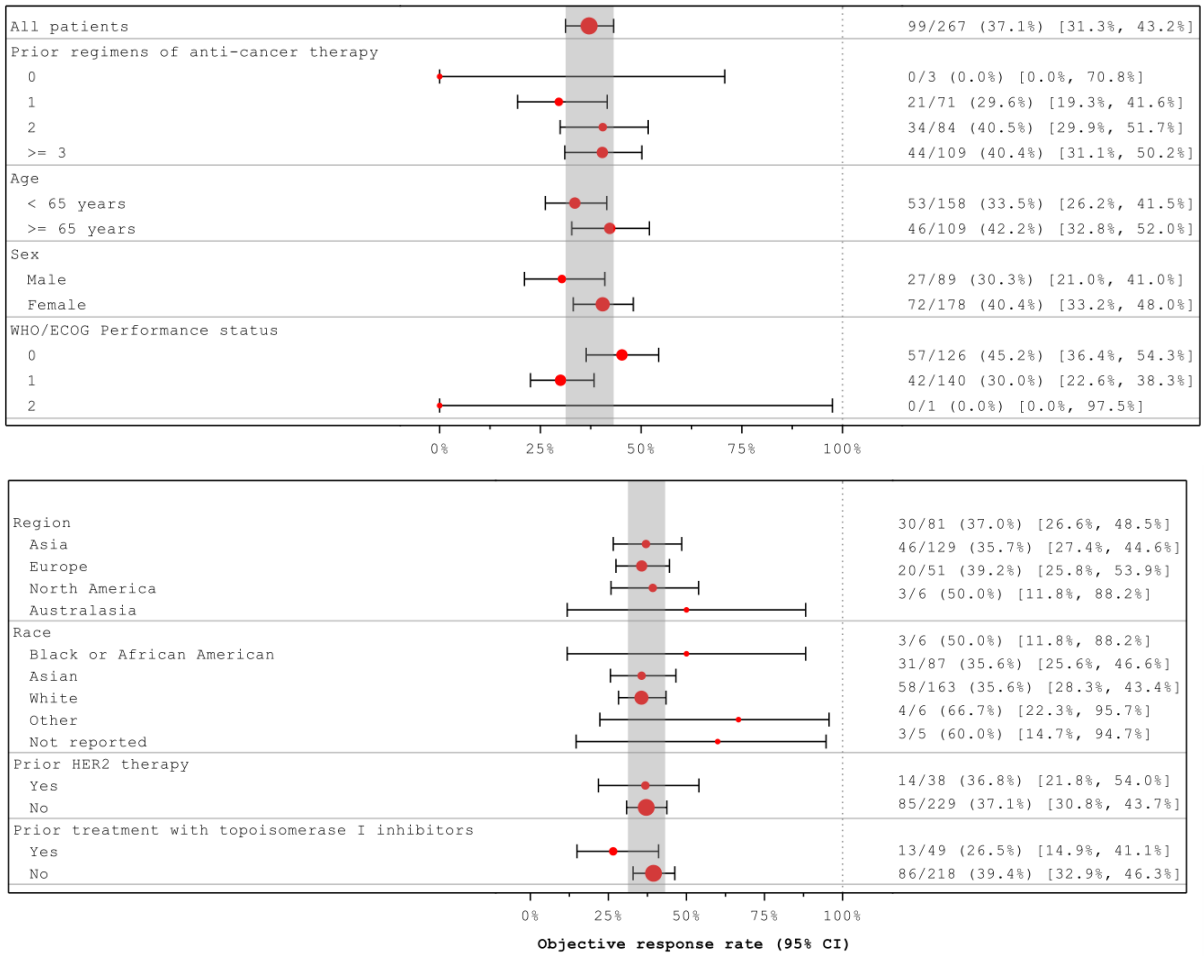
Figure 13 Forest Plot of Confirmed ORR per Investigator by Central Assessment of HER2 Status, HER2 Expression, and HER2 Amplification Subgroups in the Overall Population (FAS)



Size of circle is proportional to the number of patients within a subgroup.
Gray band represents the 95% confidence interval for the ORR.
Response is determined by Investigator assessment according to RECIST v1.1.
Unknown values in subgroups are not plotted in the Forest plot.
Statistics presented are n/N where n is the number of patients with response and N is the number of patients in the specific subgroup/population, the corresponding 95% confidence interval is calculated using the Clopper-Pearson method.
DCO1 08 June 2023

Subgroup analysis of confirmed ORR:

Figure 14 Forest Plot of Confirmed ORR per Investigator by Subgroup for All Patients (FAS)



Size of circle is proportional to the number of patients within a subgroup.
Gray band represents the 95% confidence interval for the ORR.
Response is determined by Investigator assessment according to RECIST v1.1.
Unknown values in subgroups are not plotted in the Forest plot.
Three subjects have no prior anti-cancer therapies noted but prior regimen is reported as 0.
Statistics presented are n/N where n is the number of patients with response and N is the number of patients in the specific subgroup/population, the corresponding 95% confidence interval is calculated using the Clopper-Pearson method.
ORR = objective response rate; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours, version 1.1.
DCO1 08 June 2023

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 52 Summary of Efficacy for trial DESTINY-PanTumor02 (DP-02)

Title: A Phase II, Multicenter, Open-label Study to Evaluate the Efficacy and Safety of Trastuzumab Deruxtecan (T-DXd, DS-8201a) for the Treatment of Selected HER2-expressing Tumours (DESTINY-PanTumor02)	
Study identifier	Study Code: D967VC00001

	EudraCT number: 2020-001574-29 NCT Number: NCT04482309	
Design	DESTINY-PanTumor02 (DP-02) is an open-label, multicenter, Phase II study to evaluate the efficacy and safety of trastuzumab deruxtecan (T-DXd) for the treatment of selected human epidermal growth factor receptor 2 (HER2)-expressing solid tumours. Eligible patients had locally advanced unresectable or metastatic disease that had progressed following prior treatment or had no satisfactory alternative treatment options. Prior HER2-targeting therapy was permitted. The study consisted of 7 cohorts: biliary tract cancer (BTC), bladder cancer, cervical cancer, endometrial cancer, ovarian cancer, pancreatic cancer, and a rare tumour cohort that consisted of patients with other HER2-expressing tumours, excluding the tumour types mentioned in the previous 6 cohorts, and excluding breast cancer (BC), non-small cell lung cancer, gastric cancer, and colorectal cancer.	
Duration of main phase:	Treatment until progressive disease, unacceptable toxicity, or withdrawal of consent	
Hypothesis	Meaningful clinical activity and a favourable risk benefit profile in selected HER2-expressing solid tumours.	
Treatment	T-DXd (N=267 dosed)	T-DXd: 5.4 mg/kg IV infusion Q3W
Endpoints and definitions		
Primary	Outcome measure	
To assess the efficacy of T-DXd in patients with metastatic or unresectable tumours in selected HER2-expressing tumour types	Confirmed ORR according to RECIST v1.1, as assessed by Investigator	
Secondary	Outcome measure	
To further evaluate the efficacy of T-DXd in patients with metastatic or unresectable tumours in selected HER2-expressing tumour types	Investigator assessments, based on RECIST v1.1, to allow the calculation of: DoR DCR PFS OS	
Data Base lock:	5 November 2024 (DCO: 10 October 2024)	

Results and Analysis								
Analysis description				Final Analysis for Part 1				
Endpoint Parameter	Cohort 1 biliary tract cancer	Cohort 2 bladder cancer	Cohort 3 cervical cancer	Cohort 4 endometrial cancer	Cohort 5 ovarian cancer	Cohort 6 pancreatic cancer	Cohort 7 rare tumours	Total
Confirmed ORR by INV (IHC 3+ by eligibility result) [a,g]								
N	22	27	10	16	15	5	16	111
Number (%) of patients with confirmed response	9 (40.9)	12 (44.4)	8 (80.0)	10 (62.5)	11 (73.3)	0	8 (50.0)	58 (52.3)
95% CI for ORR (%)	20.7, 63.6	25.5, 64.7	44.4, 97.5	35.4, 84.8	44.9, 92.2	0.0, 52.2	24.7, 75.3	42.6, 61.8
Duration of response by INV (IHC 3+ by eligibility result) [a,d,f,g]								
N	9	12	8	10	11	0	8	58
Median (months)	8.6	8.7	NE	28.8	22.1	NA	21.1	21.1
95% CI	2.1, NE	4.1, 10.6	9.3, NE	4.2, NE	2.8, NE	NA	4.1, NE	10.6, 25.0

a Response was determined by INV assessment according to RECIST v1.1.
b Response required confirmation after at least 4 weeks.
c Response was determined by ICR assessment according to RECIST v1.1.
d Duration of response is the time from the first documentation of complete response/partial response (which was subsequently confirmed) until the date of progression or death in the absence of disease progression. Patients who have not progressed or died are censored at their PFS censoring date. Calculated using Kaplan-Meier technique.
e Confirmed complete response + confirmed partial response + stable disease at or after 11 weeks.
f Calculated using the Kaplan-Meier technique.
g HER2 expression for eligibility can be based on local assessment (where available) or central testing. HER2 status (eligibility) summarizes whichever result (local/central) was used to determine eligibility (as recorded in the eCRF). CIs are calculated using the Clopper-Pearson method. CI for median PFS and median OS is derived based on Brookmeyer-Crowley method.

Clinical studies in special populations

Table 53 Exposure of Special Populations Included or Not in Clinical Trial Development Programme by Pool (Safety Analysis Set)

Type of Special Population	Number of Subjects	
	All Tumour Types 5.4 mg/kg Pool (N = 3057)	Patients added to the All Tumour Types 5.4 mg/kg Pool in the context of this variation (N = 722)
Older patients		
≥65 years	**828 (27.1)**	**154 (21.3)**
≥75 years	177 (5.8)	30 (4.16)
≥85 years	14 (0.5)	4 (0.55)
Subjects with relevant comorbidities (baseline)		
Subjects with renal impairment (all grades)	1534 (50.2)	310 (42.9)

≥65 years	828 (27.1)	154 (21.3)
Severe impairment (creatinine clearance ≥15, <30 mL/min)	5 (0.2)	0
Moderate impairment (creatinine clearance ≥30, <60 mL/min)	372 (12.2)	55 (40.0)
Mild impairment (creatinine clearance ≥60, <90 mL/min)	1157 (37.8)	289 ()
Subjects with hepatic impairment (all grades)[a]	1191 (39.0)	235 (32.5)
Severe impairment	1 (0.0)	0
Moderate impairment	23 (0.8)	5 (0.7)
Mild impairment	1167 (38.2)	230 (31.9)
Subjects with cardiovascular impairment	Subjects with LVEF <50% or recent symptomatic CHF were excluded from the clinical development programme	

Hepatic impairment: Severe impairment = TBL >3.0 × ULN and any AST regardless of Gilbert Syndrome; Moderate impairment = (TBL >1.5 × ULN and ≤3.0 × ULN) and any AST regardless of Gilbert Syndrome; Mild impairment = (TBL >ULN and ≤1.5 × ULN) and any AST except for participants with Gilbert Syndrome; (TBL >ULN and ≤3.0 × ULN) and AST >ULN for participants with Gilbert Syndrome; or (TBL ≤ULN and AST >ULN) regardless of Gilbert Syndrome.

In vitro biomarkers test for patient selection for efficacy

Companion diagnostic:

Patients with a HER2 IHC result of IHC 3+, IHC 2+ or, where the cohort permitted, IHC 1+, either from a local test or from prospective central testing were eligible to participate in screening. If patients met all inclusion/exclusion criteria and consented to join the study, they were enrolled into DP-02.
In the DP-02 study, HER2 IHC status was determined using the gastric interpretation algorithm, with the following modifications being applied:

- Samples with an IHC 2+ status were not reflexed to ISH testing

ISH testing was not required for eligibility into DP-02 but was performed retrospectively and reported in the clinical study report (CSR).

Table 54 Interpretation and Scoring of HER2 IHC Staining for Gastric Cancer

Score	Surgical Specimen – Staining Pattern	Biopsy Specimen – Staining Pattern	HER2 Overexpression Assessment	ISH Testing Required?
0	No reactivity or no membranous reactivity in < 10% of tumour cells	No reactivity or no membranous reactivity in any (or < 5 clustered) tumour cell	Negative	No
1+	Faint/barely perceptible membranous reactivity in ≥ 10% of tumour cells; cells are reactive only in part of their membrane	Tumour cell cluster (> 5 cells) with a faint/barely perceptible membranous reactivity irrespective of percentage of tumour cells stained	Negative	No

2+	Weak to moderate complete, basolateral or lateral membranous reactivity in ≥ 10% of tumour cells	Tumour cell cluster (> 5 cells) with a weak to moderate complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained	Equivocal	Yes
3+	Strong complete, basolateral or lateral membranous reactivity in ≥ 10% of tumour cells	Tumour cell cluster (> 5 cells) with a strong complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained	Positive	No

Table 55 ISH Interpretation Guidelines for Gastric Cancer

HER2 ISH Status	Interpretation Guideline
ISH-positive	HER2/CEP17 ratio ≥ 2.0 HER2/CEP17 ratio < 2.0 and average HER2 copy number ≥ 6.0
ISH-equivocal	HER2/CEP17 ratio < 2.0 with average HER2 copy number ≥ 4.0 and < 6.0
ISH-negative	HER2/CEP17 ratio < 2.0 with average HER2 copy number < 4.0

Source Bartley et al 2017[2]
CEP17 = chromosome enumeration probe17

Most common used local tests in DP-02 were:

- PATHWAY anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody
- HercepTest (Agilent/Dako)
- Bond Oracle HER2 IHC System (Leica)

Central HER2 IHC testing:

Formalin-fixed paraffin-embedded (FFPE) tumour samples from patients who prospectively tested for eligibility or were determined to be eligible based on a local test result and had samples retrospectively tested post enrolment, were tested using the HercepTest CTA (CE marked for breast and gastric cancers). The MAH has made a partnership to develop a test as an all-solid-tumour HER2 IHC CDx. The diagnostic development is anticipated to require approximately 18 months. The device manufacturer intends to include clinical validation data from studies in HER2-expressing NSCLC (DL-01) and colorectal cancer (DC-02), in addition to clinical validation data from Study DP-02 to support CE-marking. Testing was performed in a CAP/CLIA certified laboratory at LabCorp Central Laboratory Services, Geneva, Switzerland.

[2] Angela N. Bartley et al.
HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma: Guideline From the College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology. *J Clin Oncol* **35**, 446-464(2017).DOI:10.1200/JCO.2016.69.4836

Retrospective Central HER2 ISH testing:

FFPE tumour samples from patients enrolled into DP-02 were retrospectively tested using the INFORM ISH RUO. Testing was performed in a CAP/CLIA laboratory at CellCarta, Antwerp, Belgium. No modifications to the ISH interpretation guidelines in Table 55 were made for retrospective ISH.

HER2 IHC testing used for the enrolment in DP-02

In total, 65 sites enrolled patients into the DP-02 study. Of these, 35 sites enrolled patients based solely on local HER2 IHC test results, 19 sites enrolled patients using prospective central HER2 IHC test results, and 11 sites used a combination of local testing and/or prospective central testing results to determine patient eligibility.

Table 56 Summary of HER2 IHC Tests used for Enrolment in DP-02 via a Local Test Result in DP-02

Tests used for local HER2 IHC assessment	Number of Sites	Number of Patients Enrolled
PATHWAY anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody	27	161
HercepTest (Agilent/Dako)	9	24
Bond Oracle HER2 IHC System (Leica)	3	5
Laboratory Developed Test	2	3
Test Name Not Reported	5	9
Total	46	202

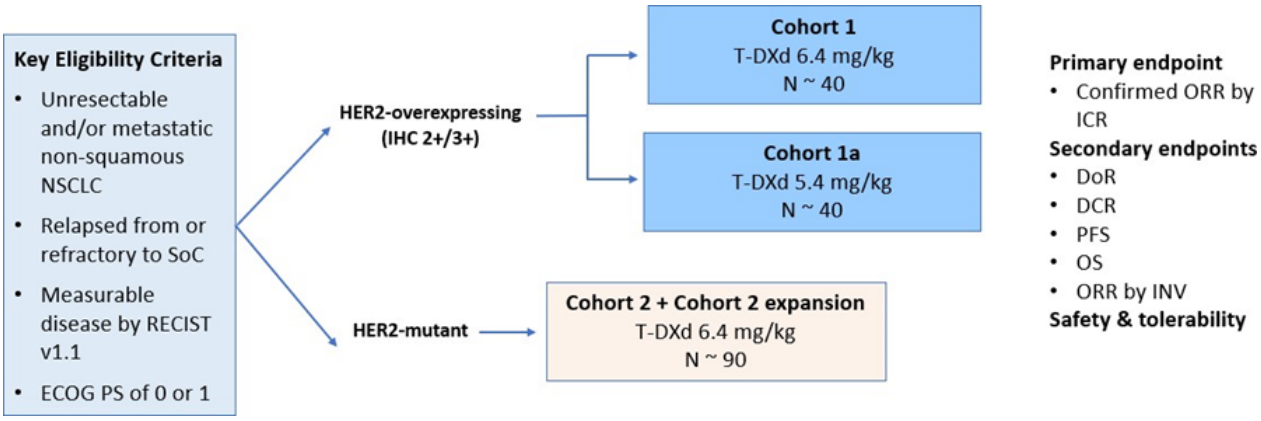
Table 57 HER2 IHC Status Distribution for DP-02 Based on Eligibility IHC Test

HER2 IHC status	Number of patients enrolled based on local test n=202	Number patients enrolled based on prospective central test n=65	Total number of patients n=267
IHC 3+	93 (46.0%)	18 (27.7%)	111 (41.6%)
IHC 2+	107 (53.0%)	43 (66.2%)	151 (56.6%)
IHC 1 +	2 (10%)	4 (6.2%)	5 (1.9%)

2.4.3. Supportive study(ies)

2.4.3.1. DL-01 (DESTINY LUNG-01)

Figure 15 DL-01 Study Design



The enrolment in Cohort 1a started after enrolment in Cohort 1.

Methods

Study participants

Key inclusion criteria:

1. Pathologically documented unresectable and/or metastatic non-squamous NSCLC.
2. Had relapsed from or was refractory to standard treatment or for which no standard treatment was available.
3. For Cohort 1 and Cohort 1a only: HER2-overexpressing status had to be assessed and confirmed by Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory or equivalent, from an archival tumour tissue sample.
4. Presence of at least one measurable lesion assessed by the investigator based on Response Evaluation Criteria in Solid Tumours (RECIST) v1.1.
5. Was willing and able to provide an adequate archival tumour tissue sample. Fine needle aspirates were not acceptable.
6. Was willing to undergo a tissue biopsy, taken after the completion of the most recent treatment regimen.
7. Had Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1.
8. Had adequate organ function within 14 days before enrolment.

Key exclusion criteria:

A. Had been previously treated with HER2-targeted therapies, except for pan-HER class
B. TKIs.
C. For Cohort 1 and Cohort 1a only: had known HER2 mutation.
D. Had uncontrolled or significant cardiovascular disease

E. Had a history of (non-infectious) ILD/pneumonitis that required steroids, had current ILD, or where suspected ILD/pneumonitis could not be ruled out by imaging at Screening.

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

G. Had unresolved toxicities from previous anti-cancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤1 or baseline.

Treatments

T-DXd was administered at 6.4 mg/kg Q3W or 5.4 mg/kg Q3W. T-DXd was administered as an IV infusion over 30 minutes to 90 minutes Q3W ± 2 days. The initial dose of T-DXd was infused for 90 minutes ± 10 minutes. The number of treatment cycles was not fixed. Treatment could continue until occurrence of one of the protocol specified events (PD, AE, physician decision etc.). Treatment beyond progression was not allowed.

Two dose reductions were permitted, as per following table:

Table 58 Dose reduction schedule

Recommended starting dose	5.4 mg/kg	6.4 mg/kg
First dose reduction	4.4 mg/kg	5.4 mg/kg
Second dose reduction	3.2 mg/kg	4.4 mg/kg

A dose could be delayed for up to 28 days (49 days from the last infusion date) from the planned date of administration. If a patient was assessed as requiring a dose delay of longer than 28 days, the patient was withdrawn from the study, but was followed for survival.

Study assessments: Tumour assessments were performed every 6 wk (±7 d) until PD or starting new anti-cancer treatment regardless of post-treatment follow-up period. Baseline and follow-up scans were assessed by BICR and RECIST 1.1 were employed.

Biomarker analyses: HER2 IHC status for DL-01 was determined through central tumour tissue testing performed by Ventana Medical Systems, Inc. using the HER2 (4B5) IHC RPA, in 88/90 (97.8%) enrolled patients. For 2 patients, a locally assessed HER2 IHC status was used for enrolment. In the DL-01 study, IHC interpretation guidelines for gastric cancer were applied, with the exception that samples with an IHC 2+ status were not reflexed to ISH testing. ISH testing was not required for patient enrolment into DL-01 and was not generated for retrospective reporting in the CSR.

FFPE tumour samples from patients prospectively screened for eligibility for DL-01 were tested using the HER2 (4B5) IHC RPA, modified so that the primary antibody incubation time was increased from 24 to 32 minutes. The HER2 (4B5) IHC RPA was approved under an investigational device exemption (IDE) for use in DL-01 by the FDA on 20th April 2018. The test was performed using FFPE tumour tissue in a CAP/CLIA certified laboratory.

HER2 IHC status was assessed by a local ISO15189-certified laboratory for two patients and this result was used to determine eligibility for enrolment. Details of the IHC test used locally are not available. Samples for these two patients were retrospectively assessed using the HER2 (4B5) IHC RPA in Ventana Medical Systems, Inc. CAP/CLIA laboratory.

Objectives

The primary objective was to evaluate the ORR of T-DXd in HER2-overexpressing and/or HER2-mutant advanced NSCLC subjects.

The secondary objectives were:

• To evaluate duration of response (DoR), DCR, PFS, and OS

• To further evaluate the safety of T-DXd

• To determine the PK of T-DXd

Outcomes/endpoints

The primary efficacy endpoint is ORR, defined as the proportion of subjects who achieved best overall response of complete response (CR) or PR as assessed by ICR based on RECIST v1.1. Confirmation of CR/PR by ICR was required for this study.

Secondary efficacy endpoints were:

• DoR, defined as the time from initial response (CR or PR) that was subsequently confirmed, until documented tumour progression or death from any cause. DoR was only defined for subjects who achieved confirmed CR or PR. DoR was calculated based on ICR assessments, and as a separate variable of DoR based on investigator assessment (INV).

• DCR, defined as the proportion of subjects who achieved a best overall response of CR, PR, or SD during study treatment. DCR was calculated based on ICR assessments, and as a separate variable of DCR based on INV.

• PFS, defined as the time from date of enrolment until first objective radiographic tumour progression or death due to any cause. The disease progression was determined based on RECIST v1.1. PFS was calculated based on ICR assessments, and as a separate variable of PFS based on INV.

• OS, defined as the time interval between the date of enrolment and the date of death due to any cause. If death was not reported for a subject before the data cut-off (DCO) for the OS analysis, OS was censored at the last contact date at which the subject was known to be alive.

• ORR, based on INV.

Sample size

The sample size was based on the assumption that at the time of the primary statistical analysis, approximately 40 subjects would have been enrolled in each of Cohorts 1 and 1a (subjects in Cohort 1a enrolled after Protocol v6.0), and approximately 90 subjects in Cohort 2 (50 enrolled following Protocol v5.0).

Table 59 Operating Characteristics for Single-arm Expansion Design with 90 Subjects

True ORR	Observed ORR	95% Confidence Interval	Probability of Lower Confidence Limit Exceeding 30% Under the True ORR
30%	30% (27 out of 90)	(20.79% to 40.57%)	2.50%
40%	40% (36 out of 90)	(29.81% to 50.87%)	49.06%

True ORR	Observed ORR	95% Confidence Interval	Probability of Lower Confidence Limit Exceeding 30% Under the True ORR
50%	50% (45 out of 90)	(39.27% to 60.73%)	96.67%
60%	60% (54 out of 90)	(49.13% to 70.19%)	99.99%
70%	70% (63 out of 90)	(59.43% to 79.21%)	100.00%

The upper 95% confidence limit of the ORR for the current standard of care docetaxel was observed to be under 0.2 or 20%.30 The threshold of 0.3 or 30% was decided by benchmarking against this estimate of the upper limit of 20% and allowing a further increment of 10% to account for the sparseness of the available data.

Randomisation & Blinding (masking)

This is a multicenter, open-label, nonrandomized, 2-cohort, Phase 2 study to investigate the safety and efficacy of T-DXd in HER2-overexpressing (IHC 3+ or IHC 2+) or -mutant NSCLC subjects.

Analysis sets

Full Analysis Set

The Full Analysis Set (FAS) included all subjects who signed the main ICF and enrolled in the study. A subject was considered enrolled in the study upon the investigator or designee obtaining a signed main ICF from the subject at the time of Screening and upon determination that all inclusion and exclusion criteria had been satisfied. Following the intent-to-treat principle, subjects were analysed according to the cohort they were assigned to at enrolment.

Response Evaluable Set

The RES included all enrolled subjects who received at least 1 dose of study drug and had measurable disease at baseline per ICR. Following the intent-to-treat principle, subjects were analysed according to the cohort they were assigned to at enrolment.

Safety Analysis Set

The Safety Analysis Set included all enrolled subjects who received at least 1 dose of study drug. Subjects were analysed according to the treatment (dose level) received. Treatment (dose level) received was the planned treatment (dose level) for the cohort which the subject was assigned to at enrolment unless the planned treatment (dose level) for another cohort, for which the subject would also have been eligible for enrolment, was received throughout the study.

Statistical methods

No adjustments for covariates were planned. In general, missing or dropout data were not imputed for the purpose of data analysis, unless otherwise specified.

Primary Efficacy Analyses

The primary efficacy endpoint was ORR based on ICR. Confirmation of CR/PR was required for this study. The primary analysis of ORR was summarized for the FAS. The point estimate of ORR and its 2-sided exact 95% CI using Clopper-Pearson method was reported. A sensitivity analysis of the primary efficacy endpoint was performed in the RES using the same analyses as described from the primary efficacy endpoint.

Secondary Efficacy Analyses

The same analyses as described for the primary endpoint were performed in the FAS for ORR assessed by investigator. Concordance of confirmed overall response by ICR vs. INV was presented. Other secondary endpoints included DoR, DCR, and PFS assessed by ICR and investigator, and OS. All analyses were performed in the FAS.

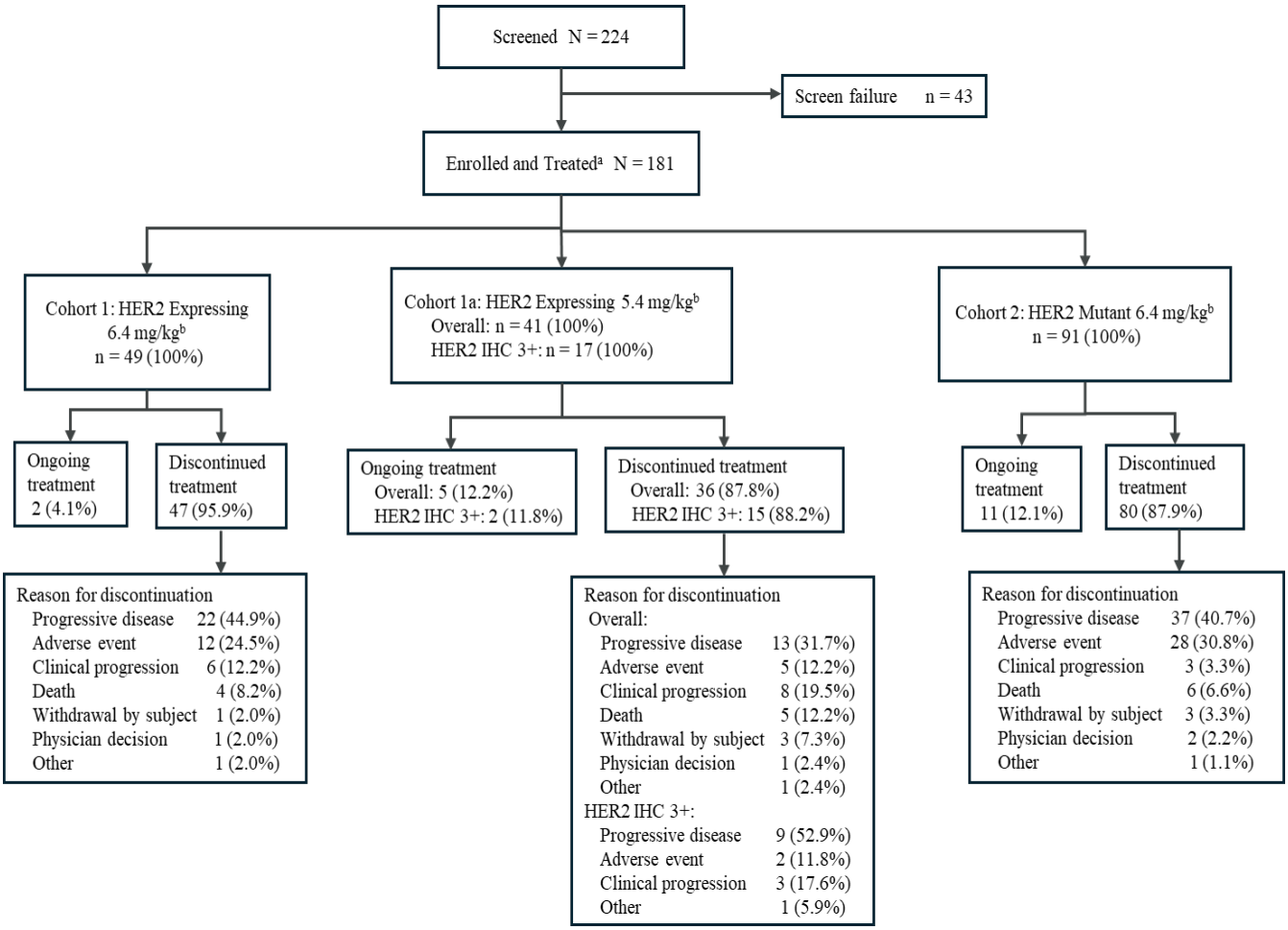
Interim analysis

No interim analysis was planned in the original protocol. With Amendment 3, the first efficacy and safety interim analysis was introduced. This interim analysis was performed on Cohorts 1 and 2 when approximately 20 subjects in Cohort 2 had at least 18 weeks of follow-up after initiation of therapy (usually 3 CT scans post-baseline) or had discontinued treatment. A second interim analysis was introduced with Amendment 4. The second interim analysis, focused primarily on safety, was conducted when at least 60 subjects in Cohort 2 had at least 12 weeks of follow-up after initiation of therapy or discontinued treatment. This interim analysis was performed on Cohorts 1 and 2. A third interim analysis was introduced to allow analysis of Cohort 1a data (this cohort was added to the study with Amendment 5). It was planned to have been performed when at least 20 subjects in Cohort 1a had completed at least 18 weeks of follow-up after initiation of therapy (usually 3 CT scans post-baseline).

Results

Participant flow

Figure 16 Study DL-01 Patient Disposition Including IHC 3+ in Cohort 1a



[a] The number of patients who signed an informed consent form and enrolled (i.e., Full Analysis Set) and the number of enrolled patients who received at least one dose of study drug (i.e., Safety Analysis Set) is the same.

[b] Percentages are calculated based on the number of subjects in the Safety Analysis Set.

DCO: 03 Dec 2021

Recruitment

The study was conducted globally in 20 sites in Japan, USA, France, Netherlands and Spain.

First patient enrolled: 30 May 2018

Last patient enrolled: 09 Dec 2020

Data cut-off (DCO) date: 03 Dec 2021

Median (range) duration of follow-up was 12.0 (0.4 to 29.9) months in Cohort 1 and 6.3 (0.6 to 10) months in Cohort 1a.

Conduct of the study

D-01 was amended six time. Key changes of amendments implemented (2 amendments were implemented before enrolment of patients) during the course of study were as follows:

Amendment 3 (Protocol v4.0) - 02 May 2019, During the Course of the Study

- Enrolment period was increased to 18 months and study duration to 24 months. The number of global study sites increased to 20.
- Updated general statistical consideration by clarifying which efficacy analyses will be performed in the FAS/RES and added text/section on interim analysis.
- Updated definition of the FAS to align it with the intent to treat principle (include all enrolled subjects into the primary efficacy assessment) and the primary efficacy analysis to be performed for the FAS instead of the RES.

Amendment 4 (Protocol v5.0) - 12 Aug 2019, During the Course of the Study

- Increased Cohort 2 enrolment from 40 to 90 subjects, provided rationale for Cohort 2 expansion and updated planned sample size calculations.
- Increased enrolment period to 23 months and study duration to 29 months.
- Added text on second interim analysis and on final analysis and provided a plan for the second interim analysis.

Amendment 5 (Protocol v6.0) - 21 Feb 2020, During the Course of the Study

- Added Cohort 1a to the study and updated all relevant sections to accommodate the change.
- Added a third interim analysis to allow the analysis of Cohort 1a data.

Amendment 6 (Protocol v7.0) - 14 Jul 2020, During the Course of the Study

- Second dose reduction level was changed from 3.4 mg/kg to 3.2 mg/kg.
- Management guidelines for COVID-19 were added.

Major protocol deviations:

Table 60 DL-01 Major Protocol Deviations in Patients with HER2 IHC 3+ (Full Analysis Set)

Category **Deviation**	**Cohort 1a** **HER2 IHC 3+ 5.4 mg/kg** **(N = 17)** **n (%)**
Patients with any major protocol deviation	10 (58.8)
Dosing	3 (17.6)
Enrolment criteria	2 (11.8)
Informed consent	2 (11.8)
Laboratory	0
Non-compliance	1 (5.9)
Visit/procedure required	1 (5.9)
Other	1 (5.9)

Notes: Percentage is calculated using the number of subjects in the column heading as the denominator. For each category and deviation, subjects are counted only once if they experienced multiple events in that category or deviation.

DCO: 03 Dec 2021

Baseline data

Table 61 Study DL-01 Baseline Disease Characteristics and Prior Anticancer Therapy in Patients with HER2 IHC 3+ (Full Analysis Set)

	Cohort 1a HER2 IHC 3+ 5.4 mg/kg (N = 17)
Age (years)	
N	17
Median	59.0
Min, max	31, 74
Age group (years) (n [%])	
< 65	13 (76.5)
≥ 65	4 (23.5)
Sex (n [%])	
Male	10 (58.8)
Female	7 (41.2)
Race (n [%])	
White	11 (64.7)
Black or African American	2 (11.8)
Asian	3 (17.6)
American Indian or Alaska Native	0 (0.0)
Native Hawaiian or other Pacific Islander	0 (0.0)
Other	1 (5.9)
Region (n [%])	
Asia	2 (11.8)
North America	6 (35.2)
Europe	9 (52.9)
ECOG (n [%])	
0	2 (11.8)
1	15 (88.2)
Other	0 (0.0)
Any prior systemic anti-cancer therapy (n [%])	
Yes	17 (100.0)
No	0 (0.0)
Number of regimens	
Mean (Std Dev)	2.8 (1.13)
Median (min, max)	3.0 (1, 5)

	Cohort 1a HER2 IHC 3+ 5.4 mg/kg (N = 17)
Prior anti-cancer therapy intended for[b] (n [%])	
Neo-adjuvant	1 (5.9)
Adjuvant	0
Locally advanced/metastatic	15 (88.2)
Maintenance	7 (41.2)
Other	1 (5.9)
Best response to most recent prior therapy[c] (n [%])	
Complete response	0 (0.0)
Partial response	3 (17.6)
Stable disease	7 (41.2)
Progressive disease	4 (23.5)
Unknown	3 (17.6)
Note applicable	0 (0.0)
Prior cancer surgery (n [%])	
Yes	15 (88.2)
No	2 (11.8)

Numbers analysed

Table 62 Data Sets Analysed

	Cohort 1 HER2Exp 6.4 mg/kg (N = 49)	Cohort 1a HER2Exp 5.4 mg/kg (N = 41)	Cohort 2 HER2Mut 6.4 mg/kg (N = 91)	Total (N = 181)
Full Analysis Set	49 (100.0)	41 (100.0)	91 (100.0)	181 (100.0)
Safety Analysis Set	49 (100.0)	41 (100.0)	91 (100.0)	181 (100.0)
Response Evaluable Set	47 (95.9)	39 (95.1)	89 (97.8)	175 (96.7)
Pharmacokinetic Analysis Set	49 (100.0)	41 (100.0)	91 (100.0)	181 (100.0)

HER2Exp = human epidermal growth factor receptor 2-overexpressing; HER2Mut = human epidermal growth factor receptor 2-mutant Data cut-off: 03 May 2021

Outcomes and estimation

Primary endpoint: confirmed ORR by ICR

Table 63 Objective Response Rate by Independent Central Review (Full Analysis Set)

Parameter	Cohort 1 HER2Exp 6.4 mg/kg (N = 49)	Cohort 1a HER2Exp 5.4 mg/kg (N = 41)	Cohort 2 HER2Mut 6.4 mg/kg (N = 91)
Confirmed objective response rate			
n (%)	13 (26.5)	12 (29.3)	50 (54.9)
95% CI[a]	(15.0, 41.1)	(16.1, 45.5)	(44.2, 65.4)
Confirmed best overall response (n [%])			
CR	0	2 (4.9)	1 (1.1)
PR	13 (26.5)	10 (24.4)	49 (53.8)
SD	21 (42.9)	20 (48.8)	34 (37.4)
PD	11 (22.4)	4 (9.8)	3 (3.3)
Non-evaluable	4 (8.2)	5 (12.2)	4 (4.4)

Overall response was determined by independent central review based on RECIST v1.1. To derive best overall response, time-point response of non-CR/non-PD was considered as SD. For objective response rate, confirmation was required for CR/PR.
Percentage was calculated using the number of subjects in the column heading as the denominator.
[a] The 2-sided 95% CIs are based on the exact (Clopper-Pearson) method for binomial distribution.
Data cut-off: 03 May 2021

Key Secondary endpoint: DoR

Table 64 Duration of Response Based on Independent Central Review (Full Analysis Set)

Parameter	Cohort 1 HER2Exp 6.4 mg/kg (N = 49)	Cohort 1a HER2Exp 5.4 mg/kg (N = 41)	Cohort 2 HER2Mut 6.4 mg/kg (N = 91)
Subjects with confirmed CR/PR, n	13	12	50
Subject with events (n [%])	8 (61.5)	4 (33.3)	27 (54.0)
PD	5 (38.5)	4 (33.3)	19 (38.0)
Death	3 (23.1)	0	8 (16.0)
Subjects without events (censored) (n [%])	5 (38.5)	8 (66.7)	23 (46.0)
New anti-cancer therapy	3 (23.1)	0	9 (18.0)
Event after missing 2 consecutive assessments	1 (7.7)	0	0
Lost to follow-up	0	0	0

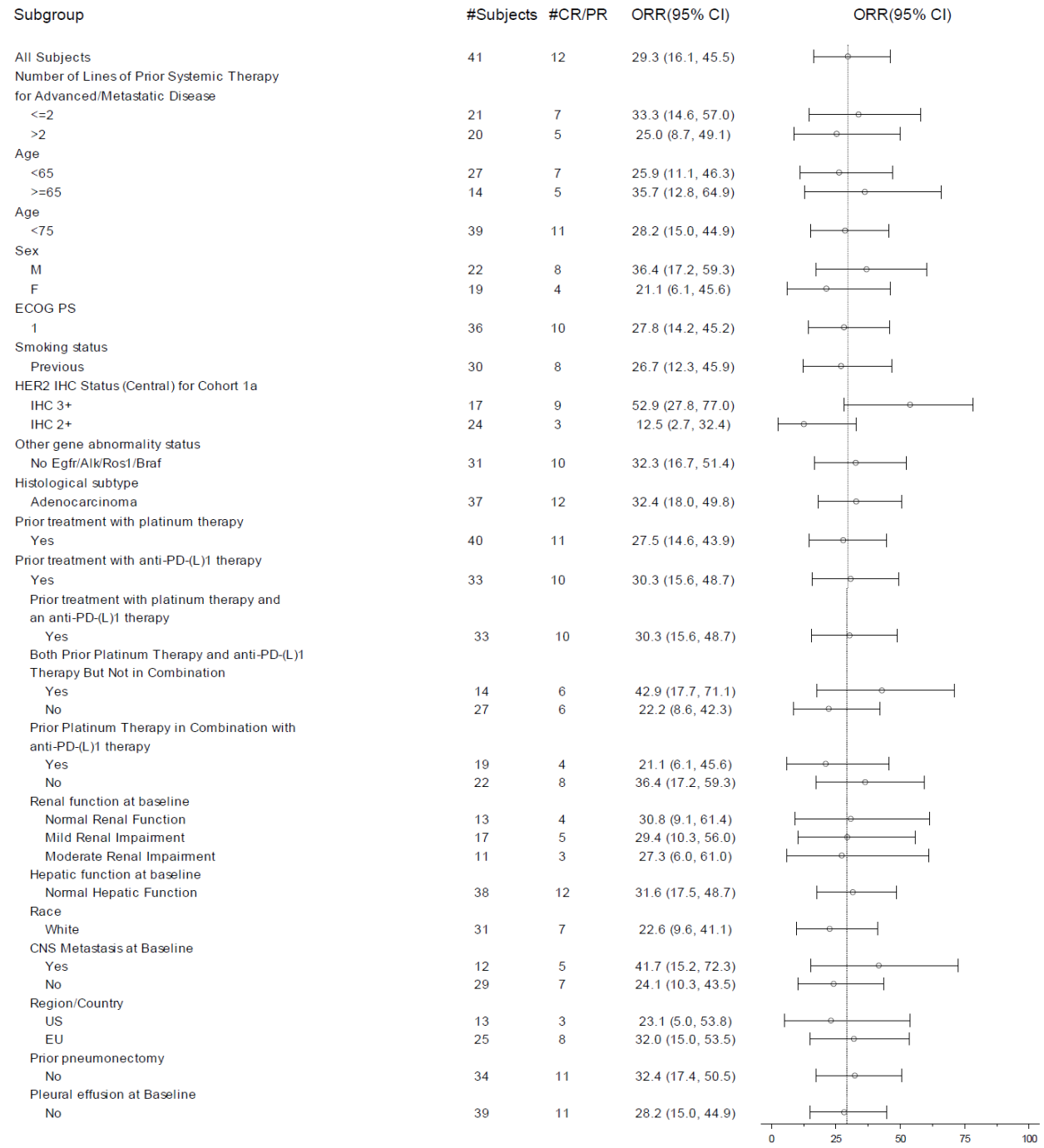
Parameter	Cohort 1 HER2Exp 6.4 mg/kg (N = 49)	Cohort 1a HER2Exp 5.4 mg/kg (N = 41)	Cohort 2 HER2Mut 6.4 mg/kg (N = 91)
Withdrew consent	0	0	0
Ongoing without event	0	7 (58.3)	9 (18.0)
Adequate tumour assessment no longer available	1 (7.7)	1 (8.3)	5 (10.0)
DoR of confirmed CR or PR (months)			
Median DoR estimate (95% CI)[a]	5.8 (4.3, NE)	4.7 (4.0, NE)	9.3 (5.7, 14.7)
Estimated percentage of responders maintaining response at[b]			
6 months (95% CI)	49.4 (19.7, 73.6)	NE (NE, NE)	60.7 (44.9, 73.2)
12 months (95% CI)	39.5 (12.9, 65.6)	NE (NE, NE)	45.4 (29.2, 60.2)
18 months (95% CI)	NE (NE, NE)	NE (NE, NE)	31.4 (15.4, 48.8)
24 months (95% CI)	NE (NE, NE)	NE (NE, NE)	15.7 (1.6, 43.8)
Number of subjects with DoR >6 months (n [%])[c]	5 (38.5)	0	24 (48.0)
Number of subjects with DoR >12 months (n [%])[c]	2 (15.4)	0	13 (26.0)

Percentage was calculated using number of subjects with CR or PR as denominator. Best overall response of CR/PR was assessed by independent central review using RECIST v1.1.
[a] 95% CI for median is from Kaplan-Meier analysis and computed using the Brookmeyer-Crowley method.
[b] 95% CI is from Kaplan-Meier analysis.
[c] For the rows of number of subjects with DoR >6 (alternatively >12) months, only those with observed DoR >6 (or >12) months are counted.
Data cut-off: 03 May 2021

Ancillary analyses

Figure 17 Forest Plot of Objective Response Rate on Independent Central Review in Cohort 1a by Subgroup (Full Analysis Set)

Cohort 1a HER2Exp 5.4 mg/kg (N=41)



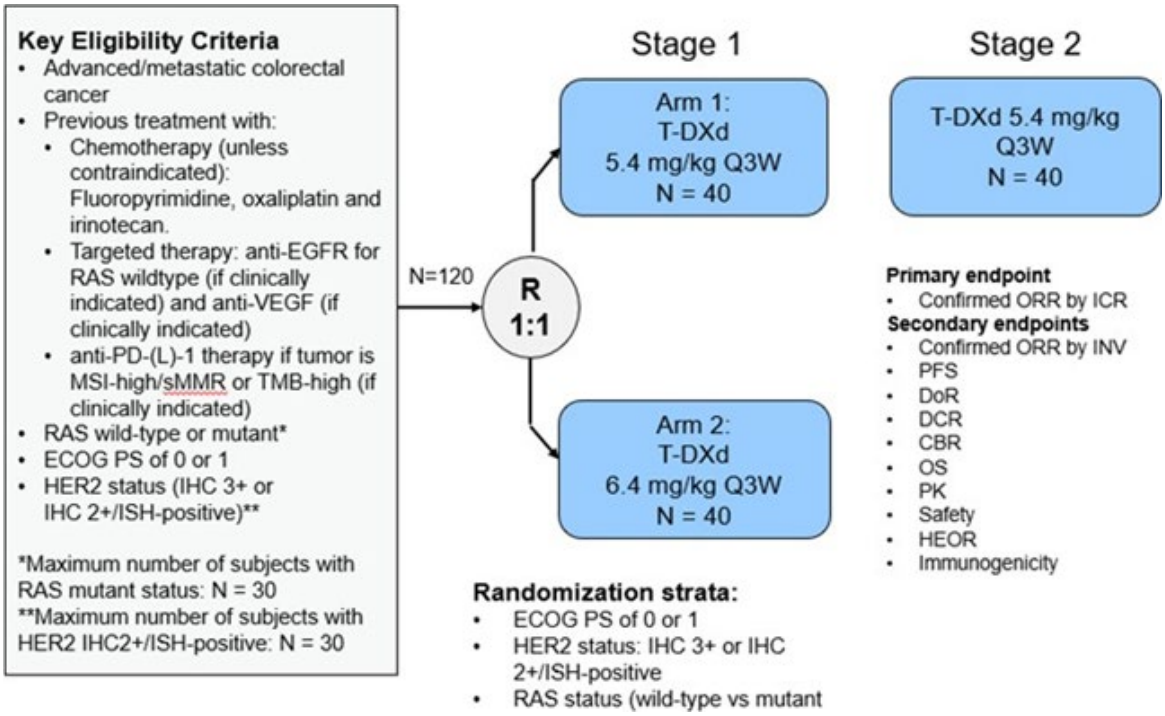
CI = confidence interval; CNS = central nervous system; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; EU = European Union;F = female; HER2 = human epidermal growth factor receptor 2; HER2Exp = human epidermal growth factor receptor 2-overexpressing; IHC = immunohistochemistry; M = male,ORR = objective response rate; PD-(L)-1 = programmed cell death protein 1 or programmed cell death ligand 1; PR = partial response; US = United States
The 2-sided 95% CIs were based on the exact (Clopper-Pearson) method for binomial distribution.

Table 65 DoR in IHC 3+ subgroup from cohort 1a

	NSCLC (N = 9)
Number of responders who subsequently progressed or died, n (%)	7 (77.8)
Duration of response from onset of response (months) a, b	
25th percentile	4.3
Median	6.9
75th percentile	9.8
95% CI for median duration of response	4.0, 9.8
Percentage remaining in response b	
3 Months	100.0
6 Months	55.6
9 Months	27.8
12 Months	NE
15 Months	NE
18 Months	NE
21 Months	NE
24 Months	NE
27 Months	NE
30 Months	NE

2.4.3.2. DC-02 (DESTINY-CRC02)

Figure 18 DC-02 Study Design



Methods

Study participants

Main Inclusion Criteria:

1. Pathologically documented, unresectable, recurrent, or metastatic colorectal adenocarcinoma. Patient must have had BRAF wild-type cancer and RAS status identified in primary or metastatic site, tested by a Clinical Laboratory Improvement Act, ISO15189, or equivalent-certified laboratory.
2. The following therapies were included in prior lines of therapy:

   Fluoropyrimidine, oxaliplatin, and irinotecan, unless contraindicated

   Anti-EGFR treatment, if RAS wild-type and if clinically indicated

   Anti-VEGF treatment, if clinically indicated

   Anti-programmed death-ligand 1 therapy, if tumour is microsatellite instable-high/deficient mismatch repair, or tumour mutational burden-high, if clinically indicated
3. Was willing and able to provide an adequate tumour sample for tissue pre-screening to confirm HER2 status by central laboratory (most recent tumour tissue was preferred).
4. Confirmed HER2-overexpressing status assessed by central laboratory and defined as IHC 3+ or IHC 2+/ISH+.
5. Presence of at least 1 measurable lesion assessed by the investigator per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.
6. ECOG PS of 0 or 1.
7. Had left ventricular ejection fraction ≥50% within 28 days before randomization/registration.
8. Had adequate organ function within 14 days before randomization/registration.

Main Exclusion criteria:

A. Medical history of myocardial infarction (MI) within 6 months before randomization/registration, symptomatic congestive heart failure (New York Heart Association Class II to IV).
B. Had a corrected QT interval (QT interval corrected with Fridericia's formula) prolongation to >470 ms (female subjects) or >450 ms (male subjects) based on the average of the Screening triplicate 12-lead electrocardiograms.
C. Had a history of (non-infectious) interstitial lung disease (ILD)/pneumonitis that required steroids, had current ILD/pneumonitis, or where suspected ILD/pneumonitis could not be ruled out by imaging at Screening.
D. Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disorder (e.g., pulmonary emboli within 3 months of the randomization/registration, severe asthma, severe chronic obstructive pulmonary disease,
E. Had spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic, or required therapy with corticosteroids or anticonvulsants to control associated symptoms.

F. Subjects with leptomeningeal carcinomatosis.

G. Unresolved toxicities from previous anticancer therapy.

Treatments

Patients continued to receive the assigned dose of T-DXd (5.4 mg/kg Q3W or 6.4 mg/kg Q3W) if they experienced clinical benefit or until unacceptable toxicity/symptomatic deterioration attributed to progressive disease (i.e., pain secondary to disease or unmanageable ascites, etc), after an integrated assessment of both radiographic data and clinical status by the investigator.

Dose modifications were allowed according to the principles described in Table 58r

Study assessments:

Computed tomography and/or MRI (spiral CT or MRI with ≤5 mm cuts) of chest, abdomen, and pelvis should be used for tumour assessment unless another modality of disease assessment is necessary for the lesions. Baseline tumour assessment should be performed within 28 days of randomization/registration. Subsequently, antitumor activity will be assessed every 6 weeks (±7 days) from Cycle 1 Day 1 in the first 12 months. After 12 months (365 days [±7] days), subjects who remain on treatment will have imaging performed every 12 weeks (±14 days) until disease progression or start of new anticancer treatment.

Biomarker analyses:

HER2 IHC and ISH status was determined during screening of DC-02 through central tumour tissue testing performed by Ventana Medical Systems. HER2 status in tissue samples was determined by IHC and ISH methodology in parallel. If patients with a HER2 status of IHC 3+ or IHC 2+/ISH+ met all inclusion/exclusion and consented to join the study, they were enrolled into DC-02.

FFPE tumour samples from patients prospectively screened for eligibility for DC-02 were tested using the VENTANA 4B5 CTA. The HER2 (4B5) IHC CTA was approved under an IDE for the use in DC-02 by the FDA on 08 December 2020. Testing was performed in a CAP/CLIA laboratory at Ventana Medical Systems, Inc., Tucson, AZ, USA. Testing and IHC scoring was per guidelines for gastric cancer with the exception that samples had IHC and ISH testing performed in parallel.

FFPE tumour samples from patients prospectively screened for eligibility for DC-02 were tested using the INFORM ISH CTA. The INFORM ISH CTA was approved under an IDE for the use in DC-02 by the FDA on 08 December 2020. Testing was performed in a CAP/CLIA laboratory at Ventana Medical Systems, Inc., Tucson, AZ, USA. Result interpretation was as per gastric cancer guidelines.

Objectives

The primary objective was to assess the efficacy of T-DXd, as measured by the confirmed ORR by BICR in HER2-overexpressing (defined as IHC 3+ or IHC 2+/ISH+) mCRC subjects treated at the 5.4 and 6.4 mg/kg doses Q3W.

Secondary objectives were as follows:

• To evaluate the clinical efficacy of T-DXd by confirmed ORR by investigator assessment

• To evaluate the clinical efficacy of T-DXd at 5.4 and 6.4 mg/kg doses by DoR by BICR and investigator assessment

• To further evaluate the clinical efficacy of T-DXd by disease control rate (DCR), clinical benefit rate (CBR), and PFS by BICR and investigator assessment and OS.

Outcomes/endpoints

The primary efficacy endpoint was confirmed ORR, defined as the proportion of subjects with a best overall response (BOR) of confirmed CR or confirmed PR, assessed by BICR based on RECIST version 1.1.

Secondary efficacy endpoints included the following:

• Confirmed ORR assessed by the investigator based on RECIST version 1.1

• DoR, defined as the time from the initial response (CR or PR) until document tumour progression based on RECIST version 1.1 or death from any cause by BICR and by investigator assessment

• DCR, defined as the proportion of subjects with BOR of CR, PR, or stable disease (SD) by BICR and by investigator assessment

• CBR, defined as the proportion of subjects who achieved CR, PR, or SD for at least 6 months by BICR and by investigator assessment

• PFS, defined as the time from the date of randomization/registration until the first objective radiographic tumour progression or death from any cause by BICR and by investigator assessment

• OS, defined as the time from date of randomization/registration until death from any cause (based on records in clinical database and public records where it is allowed by law)

Sample size

The sample size in this study was determined based on the probability evaluation that the 95% Clopper-Pearson CI exceeds and excludes the ORR benchmark of 20.0%. This benchmark was the lower bound of the 95% CI (ORR 32.0; 95% CI = 20.0 to 45.0) in pertuzumab plus trastuzumab arm in the Phase 2a open-label MyPathway study, which was investigated for subjects with HER2-amplified mCRC. 23 Approximately 120 subjects were enrolled in this study. In Stage 1, the first 80 subjects were randomized in a 1:1 ratio to receive T-DXd at either the 5.4 mg/kg or 6.4 mg/kg dose level. In Stage 2, an additional 40 subjects were registered at the 5.4 mg/kg dose level to further inform on the efficacy and safety of this dose in mCRC. In Stage 1, with 40 subjects in each treatment group, the probability to exclude the ORR benchmark of 20.0% was at least 80% when the true ORR is 41%. At the end of Stage 2, assuming 80 total subjects in the 5.4 mg/kg, the probability to of excluding the ORR benchmark of 20.0% was at least 80% when the true ORR was 34%.

Randomisation

This was a global, multicenter, randomized, 2-arm, parallel, Phase 2 study to evaluate 2 doses of T-DXd (5.4 mg/kg Q3W or 6.4 mg/kg Q3W) in subjects with locally advanced, unresectable, or metastatic HER2-overexpressing CRC (IHC 3+ or IHC 2+/ISH+) in 2 stages.

Stage 1

Randomization to either 5.4 mg/kg Q3W or 6.4 mg/kg Q3W occurred in Stage 1 of the study. Subjects were randomized into 1 of the 2 treatment groups (T-DXd at 5.4 mg/kg Q3W or 6.4 mg/kg Q3W) in a 1:1 ratio. The randomization was stratified by the following 3 stratification factors:

- ECOG PS (0 or 1)
- HER2 status (IHC 3+ or IHC 2+/ISH+)
- RAS status (wild-type or mutant)

Stage 2

For Stage 2, all subjects were registered onto the 5.4 mg/kg treatment group only. Combining both stages of the study, a maximum of 30 subjects per subgroup were registered onto each of the HER2 IHC 2+/ISH+ and RAS-mutant subgroups.

Blinding (masking)

The treatment assignment remained unknown to the study subjects, investigators, study site personnel (except the unblinded pharmacist and other staff members who were assigned as unblinded staff for site operations to maintain the blind), central imaging readers, and the ILD AC. The Sponsor was not blinded to the treatment assignment of the subjects, nor the CRO except for the central imaging vendor. The randomization schedule was kept securely.

Analysis sets

Full Analysis Set

The Full Analysis Set (FAS) included all subjects randomized/registered in Stage 1 and/or Stage 2. The FAS was the primary analysis set for all efficacy analyses. Following the intent-to-treat principle, subjects were analysed according to the treatments and strata they were assigned at randomization/registration.

Safety Analysis Set

The Safety Analysis Set (SAF) included all randomized/registered subjects in Stage 1 and/or Stage 2 who received at least 1 dose of study treatment. Subjects were summarized according to treatment received.

Response Evaluable Analysis Set

The Response Evaluable Analysis Set (RES) included all subjects in FAS in Stage 1 and/or Stage 2 who received at least 1 dose of study treatment and had measurable target lesions as assessed by BICR at baseline. Following the intent-to-treat principle, subjects were analysed according to the treatment and strata they were assigned to at randomization/registration.

Statistical methods

In general, missing or dropout data were not imputed for the purpose of data analysis, unless otherwise specified.

Primary analysis

The primary analysis of ORR was performed for FAS in Stage 1 and Stage 2. The ORR for each stage/treatment group and 5.4 mg/kg total was estimated along with the 2-sided Clopper-Pearson 95% CI. Confirmed ORR based on BOR within a fixed duration (3, 6, 9, and 12 months) along with their 2-sided exact 95% CIs using Clopper-Pearson method was also computed for each stage/treatment group and 5.4 mg/kg total. A swimmer's plot for response over time for the FAS was also provided.

The ORR difference between dose levels for Stage 1 was estimated and provided with 95% CI using a stratified analysis and a summary score estimate of the common risk difference24 for the stratification factors listed above

Interim analysis

An IA of efficacy and safety for both the 5.4 and 6.4 mg/kg doses of T-DXd was performed when all subjects in Stage 1 (i.e., the randomized portion of the study) were randomized and had at least 12 weeks of follow-up after initiation of therapy or have discontinued treatment. No formal direct comparison was made between both treatment groups. The purpose of this IA was to look at preliminary efficacy and safety signals. As specified in the protocol, no modification to the study design was made following the IA.

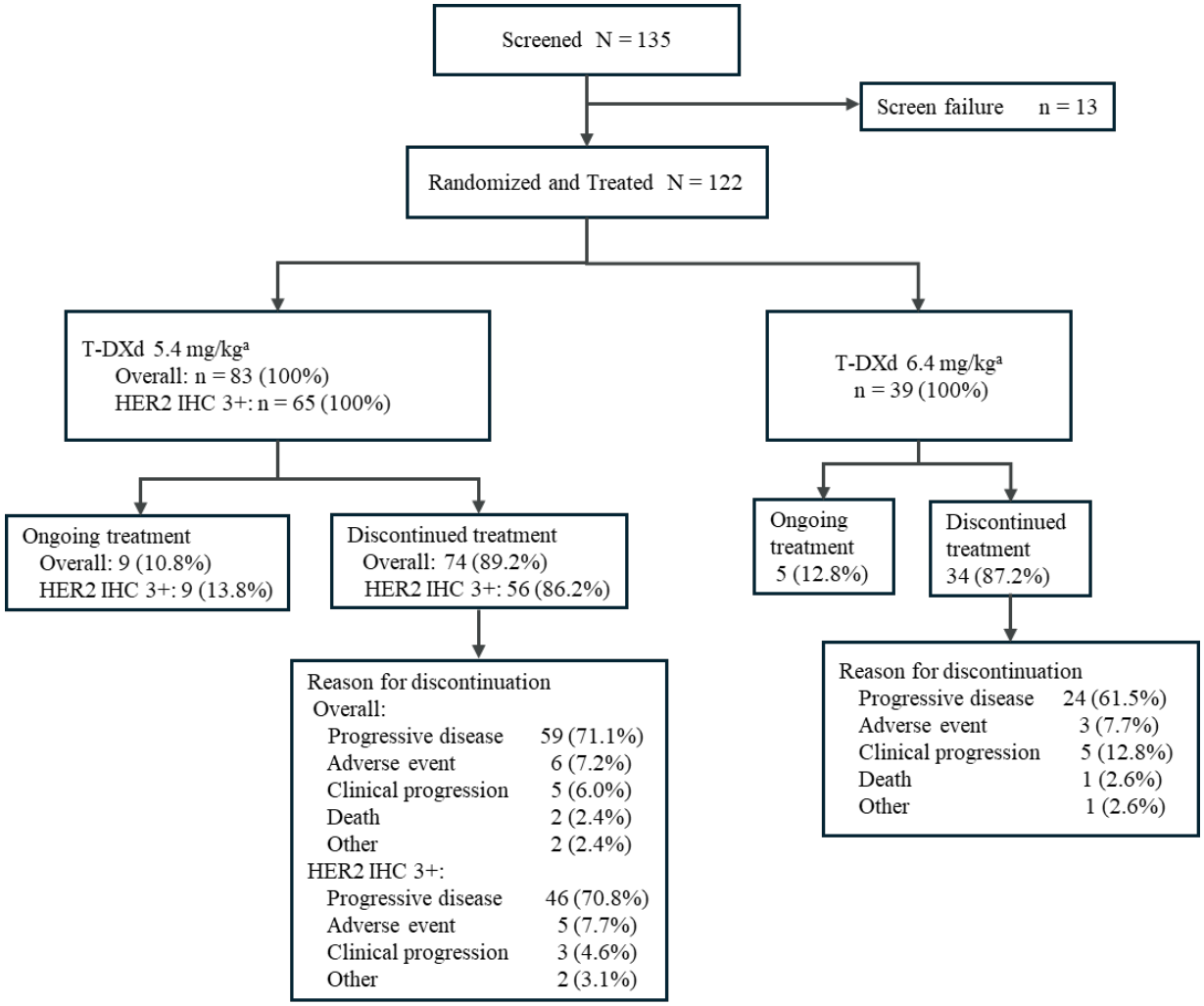
Multiplicity

The evaluation of the study results at DCOs for both the IA and primary analysis was performed on each dose level separately as a single arm. There was no futility analysis planned in this study. The multiplicity adjustment was not applicable.

Results

Participant flow

Figure 19 Study DC-02 Patient Disposition Including IHC 3+ Arm 1



[c] Number of patients in the Safety Analysis Set. Percentages are calculated based on the number of subjects in the Safety Analysis Set based on the actual treatment received.

DCO: 01 Nov 2022

Recruitment

First patient first visit date: 29 Mar 2021

The last patient enrolment date: 29 March 2022.

Last patient last follow-up date: Ongoing

Data cut-off (DCO) Date: 01 Nov 2022

Patients were randomized and treated at study centres in the United States (4), Belgium (3), France (4), Spain (2), Italy (3), Australia (5), Japan (10), South Korea (6), and Taiwan (3).

Conduct of the study

There were no changes in the conduct of the study; there were no protocol amendments.
This study was conducted during the COVID-19 pandemic; therefore, contingency measures related to the conduct of the study were included as a result of the COVID-19 pandemic. However, no changes to study procedures were necessary. During the COVID-19 pandemic, based on site and/or country policy, onsite monitoring visits were not conducted if sites could not accept visitors. During this time, onsite monitoring visits were replaced with remote visits/more frequent remote monitoring, and telephone contacts were made, where permissible, by local regulations.
Major protocol deviations:
A total of 35/122 (28.7%) patients were found to meet 1 or more of the criteria for major protocol deviations. Of these, 25/82 (30.5%) patients were in the 5.4 mg/kg treatment group and 10/40 (25%) patients were in the 6.4 mg/kg treatment group. Overall, the most frequent categories (≥5%) of major protocol deviation were "study procedures" with 16/82 (19.5%) patients in the 5.4 mg/kg treatment group and 4/40 (10.0%) patients in the 6.4 mg/kg treatment group, "informed consent" with 6/82 (7.3%) patients in the 5.4 mg/kg treatment group and 3/40 (7.5%) patients in the 6.4 mg/kg treatment group, "serious adverse event (SAE) reporting" with 5/82 (6.1%) patients in the 5.4 mg/kg treatment group and 2/40 (5.0%) patients in the 6.4 mg/kg treatment group, and "investigational product" with 3/40 (7.5%) patients in the 6.4 mg/kg treatment group.

No major protocol deviations were considered COVID-19 related.

Table 66 DC-02 Major Protocol Deviations in Patients with HER2 IHC 3+ (Full Analysis Set)

Category **Deviation**	**T-DXd 5.4 mg/kg** **(N = 64)** **n (%)**
Patients with any major protocol deviation	19 (29.7)
Eligibility criteria	0
Informed consent	5 (7.8)
Investigational product	2 (3.1)
Serious adverse event reporting	4 (6.3)
Study procedures	11 (17.2)

Percentage is calculated using the number of subjects in the column heading as the denominator. For each category and deviation, subjects are counted only once if they experienced multiple events in that category or deviation.
DCO: 01 Nov 2022

Baseline data

Table 67 Demographic and baseline disease characteristic in the IHC 3+ subgroup

Demographic characteristic	**Colorectal cancer (N = 64)**
Age (years)	
N	64
Median	58.0
Min, Max	25, 78

Demographic characteristic	Colorectal cancer (N = 64)
Age group (years) n (%)	
< 65	45 (70.3)
≥ 65	19 (29.7)
Sex n (%)	
Male	34 (53.1)
Female	30 (46.9)
Race n (%)	
White	26 (40.6)
Black or African American	0 (0.0)
Asian	35 (54.7)
American Indian or Alaska Native	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)
Other	3 (4.7)
Not Reported	0 (0.0)
Ethnicity n (%)	
Hispanic or Latino	1 (1.6)
Not Hispanic or Latino	60 (93.8)
Unknown	3 (4.7)
Not Applicable	0 (0.0)
Not Reported	0 (0.0)
Missing	0 (0.0)
Region n (%)	
Asia	32(50.0)
North America	6 (9.4)
Europe	19 (29.7)
ROW	7 (10.9)
ECOG	
0	38 (59.4)
1	26 (40.6)
Other	0 (0.0)
Number of prior regimens	
N	64
Median	4.0
Min, Max	1, 14

Numbers analysed

Table 68 Data Sets Analysed (All Screened Subjects)

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W	
Analysis Set	Stage 1 (N = 40)	Stage 2 (N = 42)	Total (N = 82)	Stage 1 (N = 40)	Total (N = 122)
Full Analysis Set	40	42	82	40	122
Safety Analysis Set [a]	41	42	83	39	122
Response Evaluable Analysis Set	40	42	82	39	121
PK Analysis Set [a]	41	42	83	39	122
Immunogenicity (ADA and NAb) Analysis Set [a]	41	41	82	39	121

a Safety Analysis Set, Pharmacokinetic Analysis Set, and Immunogenicity Analysis Set counts are based on the actual treatment received.
Notes: Percentages are based on the number of subjects who were randomized/registered.
Data cut-off: 01 Nov 2022

Outcomes and estimation

ORR by BICR

Table 69 Best Overall Response and Objective Response Rate by Blinded Independent Central Review (Full Analysis Set)

	T-DXd 5.4 mg/kg Q3W			**T-DXd 6.4 mg/kg Q3W**
Parameter	**Stage 1 (N = 40)**	**Stage 2 (N = 42)**	**Total (N = 82)**	**Stage 1 (N = 40)**
Best overall response (confirmed), n (%)				
PR	18 (45.0)	13 (31.0)	31 (37.8)	11 (27.5)
SD	20 (50.0)	20 (47.6)	40 (48.8)	23 (57.5)
PD	2 (5.0)	6 (14.3)	8 (9.8)	4 (10.0)
NE	0	3 (7.1)	3 (3.7)	2 (5.0)
Confirmed ORR (CR + PR)				
n (%)	18 (45.0)	13 (31.0)	31 (37.8)	11 (27.5)
95% CI[a]	(29.3, 61.5)	(17.6, 47.1)	(27.3, 49.2)	(14.6, 43.9)
Best overall response (unconfirmed), n (%)				
PR	20 (50.0)	16 (38.1)	36 (43.9)	14 (35.0)
SD	18 (45.0)	17 (40.5)	35 (42.7)	20 (50.0)
PD	2 (5.0)	6 (14.3)	8 (9.8)	4 (10.0)
NE	0	3 (7.1)	3 (3.7)	2 (5.0)
Unconfirmed ORR (CR + PR)				
n (%)	20 (50.0)	16 (38.1)	36 (43.9)	14 (35.0)
95% CI[a]	(33.8, 66.2)	23.6, 54.4)	(33.0, 55.3)	(20.6, 51.7)

CI = confidence interval; CR = complete response; NE = not evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria in Solid

Tumours; SD = stable disease; T-DXd = trastuzumab deruxtecan a Based on Clopper-Pearson method for single proportion.
Note: Overall response was determined by Blinded Independent Central Review based on RECIST, version 1.1. To derive best overall response, time point response of non-CR/non-PD was considered as SD. "Unconfirmed" means confirmation is not required.
Data cut-off: 01 Nov 2022

Duration of response

Table 70 Duration of Response and Time to Response for Confirmed Responders by Blinded Independent Central Review (Full Analysis Set)

	T-DXd 5.4 mg/kg Q3W			**T-DXd 6.4 mg/kg Q3W**
Parameter	Stage 1 (N = 40)	Stage 2 (N = 42)	Total (N = 82)	Stage 1 (N = 40)
Subjects with confirmed CR/PR (n)	18	13	31	11
Subjects with events (%)[a]	8 (44.4)	8 (61.5)	16 (51.6)	6 (54.5)
PD	7 (38.9)	8 (61.5)	15 (48.4)	6 (54.5)
Death	1 (5.6)	0	1 (3.2)	0
Subjects without events (censored) (%)[a]	10 (55.6)	5 (38.5)	15 (48.4)	5 (45.5)
DoR estimates and 95% CI (months)				
25th percentile	4.4	4.2	4.2	4.2
95% CI[b]	(2.5, 8.1)	(2.8, 4.6)	(2.8, 5.3)	(3.7, 5.6)
Median	8.1	4.6	5.5	5.5
95% CI[b]	(4.2, NE)	(4.1, 7.0)	(4.2, 8.1)	(3.7, NE)
75th percentile	NE	7.0	8.1	NE
95% CI[b]	(8.1, NE)	(4.2, NE)	(7.0, NE)	(5.3, NE)
Number of subjects with DoR >6 months[c], n (%)	5 (27.8)	2 (15.4)	7 (22.6)	3 (27.3)
Time to initial response (subjects with confirmed CR or PR) (months)[b]				
n	18	13	31	11
Mean	2.7	2.6	2.6	2.3
Standard deviation	1.70	1.46	1.58	1.16
25th percentile	1.5	1.4	1.5	1.4
Median	1.6	2.8	1.6	1.6
75th percentile	3.0	3.1	3.1	2.9
Min, max	1.4, 7.0	1.3, 6.1	1.3, 7.0	1.4, 4.4

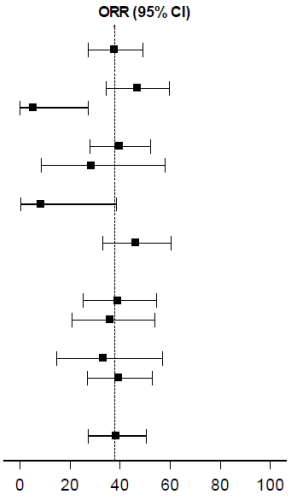
CI = confidence interval; CR = complete response; DoR = duration of response; max = maximum; min = minimum; NE = not evaluable; PD = progressive disease; PR = partial response; Q3W = every 3 weeks; T-DXd = trastuzumab deruxtecan [a] Percentage is calculated using number of subjects with CR/PR. [b] Percentiles are from Kaplan-Meier estimate. CIs are computed using the Brookmeyer-Crowley method. [c] Based on observed value.
Notes: Duration of response is defined as the time from date of initial response (CR or PR) to the date of disease progression or death due to any cause for subjects with a confirmed CR or PR.
Data cut-off: 01 Nov 2022

Ancillary analyses

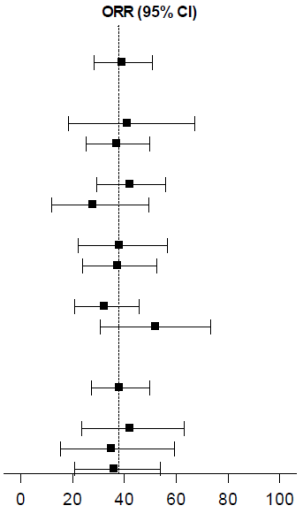
Figure 20 Forest Plot of Objective Response Rate by Blinded Independent Central Review (Full Analysis Set)

Treatment Group: T-DXd 5.4 mg/kg Q3W Total

Subgroup	# Subjects	# CR/PR	ORR (95% CI)
All Subjects	82	31	37.8 (27.3, 49.2)
HER2 status			
IHC 3+	64	30	46.9 (34.3, 59.8)
IHC 2+/ISH+	18	1	5.6 (0.1, 27.3)
RAS status			
Wild-Type	68	27	39.7 (28.0, 52.3)
Mutant	14	4	28.6 (8.4, 58.1)
Interaction: HER2/RAS Status			
IHC 2+/ISH+/Wild-Type	12	1	8.3 (0.2, 38.5)
IHC 2+/ISH+/Mutant	6	0	
IHC 3+/Wild-Type	56	26	46.4 (33.0, 60.3)
IHC 3+/Mutant	8	4	
ECOG PS			
0	46	18	39.1 (25.1, 54.6)
1	36	13	36.1 (20.8, 53.8)
Primary tumor site			
Right	21	7	33.3 (14.6, 57.0)
Left	61	24	39.3 (27.1, 52.7)
Number of metastatic sites			
< 2	9	3	
≥2	73	28	38.4 (27.2, 50.5)



Subgroup	# Subjects	# CR/PR	ORR (95% CI)
Prior treatment with irinotecan or other topoisomerase I inhibitors			
Yes	79	31	39.2 (28.4, 50.9)
No	3	0	
Prior treatment with HER2 targeted regimen			
Yes	17	7	41.2 (18.4, 67.1)
No	65	24	36.9 (25.3, 49.8)
Prior treatment with any anti EGFR antibody			
Yes	57	24	42.1 (29.1, 55.9)
No	25	7	28.0 (12.1, 49.4)
Prior treatment with regorafenib or TAS-102			
Yes	34	13	38.2 (22.2, 56.4)
No	48	18	37.5 (24.0, 52.6)
Presence of liver metastases at baseline			
Yes	59	19	32.2 (20.6, 45.6)
No	23	12	52.2 (30.6, 73.2)
Presence of central nervous system (CNS) metastases at baseline			
Yes	3	1	
No	79	30	38.0 (27.3, 49.6)
Lines of prior systemic therapy for advanced disease			
≤2	26	11	42.3 (23.4, 63.1)
3	20	7	35.0 (15.4, 59.2)
≥4	36	13	36.1 (20.8, 53.8)



Subgroup	# Subjects	# CR/PR	ORR (95% CI)
Age (years)			
< 65	54	22	40.7 (27.6, 55.0)
≥65	28	9	32.1 (15.9, 52.4)
Region			
Asia-Pacific	47	20	42.6 (28.3, 57.8)
US	6	2	
Europe	29	9	31.0 (15.3, 50.8)
Sex			
Female	37	14	37.8 (22.5, 55.2)
Male	45	17	37.8 (23.8, 53.5)

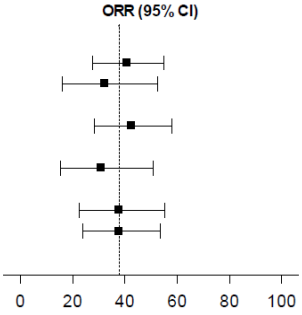


Table 71 DoR in IHC3+ subgroup

	Colorectal cancer (N = 30)
Number of responders who subsequently progressed or died, n (%)	16 (53.3)
Duration of response from onset of response (months) a, b	
25th percentile	4.2
Median	5.5
75th percentile	8.1
95% CI for median duration of response	4.2, 8.1
Percentage remaining in response b	
3 Months	88.4
6 Months	46.1
9 Months	19.8
12 Months	NE
15 Months	NE
18 Months	NE
21 Months	NE
24 Months	NE
27 Months	NE
30 Months	NE

a Duration of response is the time from the first documentation of CR/PR (which is subsequently confirmed) until the date of progression or death in the absence of disease progression. Patients who have not progressed or died are censored at their PFS censoring date.

b Calculated using Kaplan-Meier technique.

Response is determined by ICR.

2.4.4. Discussion on clinical efficacy

Enhertu is a HER2-directed ADC composed of a humanised anti-HER2 IgG1 monoclonal antibody with the same amino acid sequence as trastuzumab. It includes a plasma-stable, selectively cleavable linker and potent topoisomerase I inhibitor payload, (a derivative of exatecan). Enhertu is authorised in the EU for use in HER2 overexpressing breast cancer and gastric cancer.

Design and conduct of clinical studies

The most relevant SA pertaining to the current submission was given in November 2022 (EMA/SA/0000102946), where it was pointed out that the study had several limitations, including a limited sample size, a questionable case for a histology-independent indication, and a lack of convincing non-clinical evidence to support a consistent benefit across tumour types.

The MAH applied for an extension of indication under the CMA framework in a 2L+ setting for patients with solid tumours with HER2 3+ overexpression, as confirmed by immunohistochemistry (IHC). The sought indication is not limited to a specific tumour type or origin, i.e. histology independent, or histology independent. The MAH proposed to pool data from 5 clinical studies (DESTINY-PanTumor02

[DP-02], DESTINY-Lung01 [DL-01], DESTINY-Colorectal02 [DC-02], DESTINY-Breast01 [DB-01], DESTINY-Gastric02 [DG-02]). However, this pooling strategy was not supported as:

- Pooling of ORR across heterogeneous phase 2 datasets is not appropriate due to differences in design, populations, endpoint assessments, doses, and assays, which limits exchangeability and risks overstating precision if between-study variability is ignored.
- The primary endpoint in the DP-02 study was ORR by INV in contrast to ORR by ICR in the other 4 studies, DP-02 included patients in 2L+ treatment setting while other 2 studies included patients who had received lines of therapy (except BC and GC);
- Different companion diagnostic tests were used across all 5 studies, where in DP-02 inclusion was based on the local testing vs. central testing in other studies; pooling across different doses (including GC study with 6.4 mg/kg), no type I error control in DP-02.
- Furthermore, the selection of HER-2 IHC 3+ as a target population was solely based on exploratory analysis from DP-02 and this strategy was then applied to the other 4 clinical studies leading to selective data reporting of patients from other studies.
- Additionally, studies DB-01 and DG-02 were previously reviewed and led to breast and gastric cancer indications approvals (see Enhertu initial authorisation EPAR and variation II-12 EPAR, respectively). Of note, the role of HER-2 overexpression and targeted therapies in breast and gastric cancer are well-described and higher responses to T-Dxd could be expected in those two diseases, leading to an overestimation of the observed ORR for the proposed histology independent indication.

Therefore, DP-02 is considered to be the pivotal study for B/R assessment with DL-01 and DC-02 serving as supportive studies.

DESTINY-PanTumor02 is an open label, multiple cohorts, ongoing, global phase 2 study evaluating efficacy and safety of T-DXd in specific solid tumours expressing HER2 (IHC 2+ or 3+). The study consists of two parts and the already completed part 1, forms the basis for this application. Patients who received at least one prior line of treatment or had no satisfactory treatment options could be enrolled into one of 7 cohorts: BTC, bladder cancer, cervical cancer, endometrial cancer, ovarian cancer, pancreatic cancer, and a rare tumour cohort (excluded BC, GC, NSCLC, CRC), a total of 40 patients were enrolled in each cohort . All patients received 5.4 mg/kg of T-DXd every three weeks until PD, withdrawal of consent or any of the discontinuation criteria were met. To be enrolled in DP-02, patients should have HER2 IHC 2+ or 3+ expression either by local test or prospectively central tested using HerceptTest. Patients who had local testing should also have had tissue sample available for retrospective central testing with HerceptTest. The most common local test used was PATHWAY anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody, which is CE marked and clinically validated in breast and gastric cancers. A clinical validation of an all-solid-tumour HER2 IHC CDx is anticipated. The gastric algorithm was used for scoring and interpretation of IHC, however no ISH was performed with IHC 2+ results. Testing strategy/evaluation of HER2 and use of CE marked tests (even if not clinically validated for the proposed histology independent indication) is considered acceptable. The in- and exclusion criteria from DP-02 study are considered adequate and reflect the target population with HER2 overexpressing tumours. The primary endpoint was confirmed ORR by INV according to RECIST 1.1.

Statistical methods: The ORR by investigator as the primary endpoint was analysed on the full analysis set using intent to treat with non-evaluable counted as non-responders and exact 95% confidence intervals, and with an exploratory independent central review conducted on the same denominator. Time to event endpoints including DoR, PFS, and OS were summarized by Kaplan–Meier with medians

and fixed time rates, and censoring was most pronounced for DoR and also notable for PFS and OS, most often due to patients being ongoing without an event at the data cut or starting new anticancer therapy or lacking an adequate assessment near cut off. No hypothesis testing, alpha allocation, or multiplicity control was prespecified across the seven cohorts or interim looks, and the protocol allowed midstream IHC 1+ enrichment after early responses in IHC 2+ or 3+ which altered the case mix over time and introduced selection and calendar-time effects, so all efficacy results were interpreted descriptively and cohort specific.

Recruitment and participant flow: The enrolment of the part 1 DP-02 study is complete with the first patient enrolled on 18 August 2020 and last one on 16 June 2022. The median follow-up for patients in DP-02 study was 12.75 months across all cohorts at the primary analysis and 12.98 months at the final analysis. The median duration of FU is considered sufficient for the B/R assessment of T-DXd in the HER2 IHC 3+ population. Of 735 screened patients, 268 (35.5%) patients were enrolled. The most common reasons for not being included in DP-02 were screening failures (63%). At the DCO1 (primary analysis) 257 (96.3%) patients discontinued study treatment. The most common reasons were: objective PD (57.3%), adverse events (14.2%) and clinical PD (7.9%). At the time of final analysis 37 patients (13.9%) were still on study. Majority of patients (80.9%) had succumbed at the time of final analysis.

Conduct of the study: DP-02 was amended three times, all amendments occurred during recruiting phase of the pivotal study and two of the amendments were implemented after DCO for the primary analysis. The timing of the final analysis was updated to 1 year after the last patient enrolled, instead of 2 years after the last patient enrolled. The interim analysis, which was planned in FAS after all patients in a full cohort have had 2 scheduled post-baseline scans, was removed. Overall, amendments concerning part 1 study are accepted and not expected to affect reliability of the study results. Part 2 of the study, including its sample size and statistical plan, was introduced in Amendment 3 (dated 05 Oct 2023), after the results of Part 1 were already known. However, part 2 analyses will be performed separately without pooling of results with part 1. Results of part 2 will be provided as estimates with confidence intervals and interpreted descriptively, without hypothesis testing. This is acceptable.

Important protocol deviations occurred in 47 patients (17.6%) of FAS and are not expected to have an impact on overall study integrity.

Baseline characteristics

The range of previous anti-cancer therapies was very high (0-12) and included two patients without any prior therapy for whom the investigators did not consider alternative treatment options to be suitable for these patients. Anti-HER2 therapies were received by 14.2% of patients overall, most frequently in the rare tumours cohort (14 patients), followed by endometrial (9) and BTC (7) cohorts. Use of PD-1/PD-L1 inhibitors varied widely, with the highest use in the bladder cancer cohort (68.3%) and none in the pancreatic cancer cohort. Platinum-based therapies (carboplatin, cisplatin, or oxaliplatin) were widely administered across all cohorts, with 100% exposure in BTC, cervical, and ovarian cancer cohorts, and an overall usage of 91.4% in the FAS. In the subgroup of patients with HER2 IHC3+ tumours (N=111), ages ranged from 23 to 85 years, with a median age of 64. Most patients were female (59.5%), and the majority identified as White (57.7%) or Asian (34.2%). At screening, over half of the patients had a performance status of 1 (51.4%), and 46.8% presented with AJCC stage IV disease. Patients had received between 0 and 9 prior treatment regimens, with a median of 2. Most therapies were administered in the metastatic setting (91%). The most frequently used prior agents included cisplatin (50.5%), paclitaxel (47.7%), and carboplatin (42.3%). Immunotherapy had been given to 32 patients (28%). A total of 26 patients had previously received HER2-targeted therapy, including 2 patients treated with zanidatamab.

Overall, the demographics and disease characteristics are in line with the expected population with cohort specific tumours in 2+ line without satisfactory treatment options.

Efficacy data and additional analyses

Outcomes

Primary analysis at DCO1 with a median follow-up of 12.75 months across all cohorts resulted in confirmed ORR by INV of 37.1% (95%CI: 31.6, 43.2). ORR ranges from 4% in cohort 6 (pancreatic cancer) to 57.5% in cohort 4 (endometrial cancer). Overall, sensitivity analysis of the primary endpoint by ICR assessment of ORR yields similar results in the FAS, but some discrepancies across individual cohorts are observed, i.e. in cohort 6, ORR by ICR is three-fold higher compared to the INV assessment. Since ICR assessment was performed retrospectively, when results were already known, this analysis cannot be considered robust. The results of final analysis are in line with the primary analysis, with confirmed ORR by INV across all cohorts of 37.5%. Similarly, there is a quite large difference in response rates between individual cohorts, with only one response observed in pancreatic cancer.

Results from a predefined exploratory analysis of the primary endpoint by HER2 status (IHC) form the basis for the proposed tumour-agnostic indication in the subgroup of patients with HER2 IHC 3+ overexpression. Confirmed ORR by INV in IHC 3+ patients (both central and locally tested) was 52.3% (95% CI: 42.6, 61.8) while it was 26.5% (95% CI: 19.6, 34.3) in IHC 2+ group. Response rates were variable according to tumour type but, nonetheless, were observed in most of the tumour types represented except for pancreatic cancer. The response rate appears promising for previously treated gynaecological tumours with ORRs of 62.5% for endometrial cancer, 73.3% for ovarian cancer, and 80.0% for cervical cancer. Response rates are less compelling for BTC and bladder cancer (about 40-45%, lower limit CI around 20-25%) in the context of a SAT. The ORR in the rare tumour cohort was 50.0% (95% CI: 24.7, 75.3); among whom 9/16 (56%) of the patients had a salivary gland cancer and in which ORR was 55.6% (95% CI: 21.2, 86.3). For the other tumours with one patient each (extramammary Paget's disease, vulvar, head and neck, lip and/or oral cavity cancer, non-squamous oesophageal, squamous oesophageal and oropharyngeal), 3/7 (43%) showed a response. The number of patients with IHC 3+ per individual cohorts was low, notably with cohort 6 including 5 patients only. The final analysis of ORR by INV in this subgroup shows wide range from 0% in pancreatic cancer to 80 % in endometrial cancer. The observed response rates can be viewed as clinically relevant in patients with various HER2 IHC 3+ solid tumours who received median two lines of prior therapy and have no other satisfactory treatment options. This is based on a limited sample size, heterogeneous responses across different tumour types with no responses observed in pancreatic cancer. The main methodological issues concerning the DP-02 study were its exploratory character without predefined success criteria or type 1 error control. However, given that the mechanism of action of Enhertu is well characterized and supported by multiple randomized controlled trials across different tumour types, the methodological limitations and uncertainties in this context can be considered acceptable. Additionally, the proposed indication is based on results of exploratory subgroup with HER2 IHC 3+. Based on the principles outlined in the Guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013) and on the fact that the IHC3+ subgroup was part of the pre-specified exploratory analyses, that the differential effect is directionally consistent with prior expectations, and that differential effect per IHC expression was observed across several supportive trials (see below), the finding was considered credible and a claimed indication in a restricted subgroup acceptable.

The median duration of response by INV in FAS was 11.3 months (95% CI: 9.8, 17.8). The longest DoR in FAS was observed in cohort 4 (endometrial cancer, mDoR 27.7 months) and the shortest in cohort 6 (pancreatic cancer, 5.7 months). DoR in patients with HER2 IHC 3+ tumours (locally and centrally tested) was 21.1 months (95% CI: 10.6, 25) compared to 9.8 months with IHC 2+ tumours

(95% CI: 4.5, 12.6). mDoR by cohorts in IHC 3+ subgroup revealed the longest response in endometrial cancer (29.9 months) and shortest in bladder cancer (5.7 months). The observed duration of response in the intended population (HER2 IHC 3+) is encouraging, particularly considering the second-line or later setting and the patient population, where most had WHO PS 1, and durable responses are uncommon. The majority of responses in the FAS (regardless of HER2 expression or cohorts) were partial responses, observed in 83 (31.1%) responders. There were 17 (6.4%) complete responses recorded, with 8 CR seen in cohort 4 (endometrial cancer). However, only 4 patients with IHC 3+ status had a complete response per ICR indicating that the chance of CR is very low in this late line setting.

Subgroup analysis in FAS indicates higher response rates among patients aged ≥65 years (42.2%), females (40.4%), those with ECOG performance status 0 (45.2%), and individuals from North America (50.0%). Patients with two prior anti-cancer regimens showed the highest ORR (40.5%), while those with no prior regimens had an ORR of 0%. Prior treatment with topoisomerase I inhibitors was associated with a lower ORR (26.5%) compared to those without (39.4%). ORR was nearly identical in subgroup with prior anti- HER2 therapy. However, due to limited sample size of subgroups, no conclusions can be drawn based on observed results of specific subgroups.

A warning about quantitative differences of treatment effect depending on tumour type was added in section 4.4 of the SmPC and a table describing the observed response rates per tumour types was added in section 5.1 of the SmPC to inform treatment decision.

Supportive studies:

DL-01 was an open-label, phase 2 study examining the efficacy and safety of T-DXd in HER-2+ NSCLC. The study consisted of 2 cohorts: cohort 1, which enrolled patients with HER2 IHC 2+ or 3+ and cohort 2, which included patients with known HER-2 mutation. The additional cohort 1a was added when all patients were enrolled to cohort 1. Cohort 1 and 2 were treated with 6.4 mg/kg of T-DXd and cohort 1a was dosed 5.4 mg/kg. Patients in good condition (ECOG PS 0 or 1) with locally advanced or metastatic NSCLC who have exhausted all standard of care and had tumour tissue for central HER2 testing (cohorts 1 and 1a) or had documented HER2 mutation could be included in DL-01. The primary endpoint of study was confirmed ORR by ICR. Results from patients with HER2 IHC 3+ (n=17) from cohort 1a are supportive for the applied histology independent indication.

No formal hypothesis testing or multiplicity control was prespecified, so cohort results were interpreted separately and any cross-cohort differences were exploratory, with precision further limited by small cohort sizes and substantial censoring in time to event endpoints.

Of the 224 patients screened for cohorts 1 and 2, there were 43 screening failures. Cohort 1a included 41 patients, of whom 2 lacked measurable disease at baseline. At the data cut-off of 03 Dec 2021, 14 patients in cohort 1a remained on treatment. The most common reasons for discontinuation of T-DXd in this cohort were disease progression (15 patients) and adverse events (5 patients). The median follow-up for all patients in cohort 1a was 6.3 months. DL-01 was amended six time and were mostly related to aligning the in- and exclusion criteria, study procedures, definitions of efficacy population. The addition of the cohort 1a and a third interim analysis was implemented with the protocol amendment 5 (21 Feb 2020). The multiple amendments to the DL-01 protocol, particularly the addition of cohort 1a and the third interim analysis, could have been of concerns about the potential impact on study integrity and the reliability of the results. However, although the preliminary data from Cohort 1 were available at the time Cohort 1a was introduced, the decision to add a lower-dose cohort was primarily intended to support dose-optimization efforts for T-DXd in NSCLC and across the broader development program. The dose-optimization, including consideration of a 5.4 mg/kg dose, had been

discussed with the other regulators before the Cohort 1a was added, thus the issue is not further pursued.

Demographics and disease characteristics of Cohort 1a align with the expected profile of patients with advanced NSCLC receiving late-line treatment. With a median follow-up of 6 months, the confirmed ORR in all patients enrolled in cohort 1a was 29.3% (95%CI: 16.1, 45.5). Most patients achieved PR, only two complete response were observed. However, this is to be expected in heavily pre-treated patients. The median DoR was short with only 4 months and none of the patients had response over 6 months. A subgroup analysis of the primary endpoint was conducted to assess potential differences in response rates across patient subpopulations. A notable finding was the difference in confirmed ORR between HER2 IHC 3+ and IHC 2+ tumours. Patients with HER2 IHC 3+ tumours demonstrated a higher ORR (52.9%) compared to those with IHC 2+ tumours (12.5%). In a subgroup of patients with IHC 3+ tumours mDoR was 6.9 months and two patients had response at 9 months. This is encouraging in the last line setting, where durable responses are rarely achievable. Another interesting finding was that ORR was higher in patients with baseline CNS metastases (42% vs. 24%) and in those previously treated with both platinum-based chemotherapy and checkpoint inhibitors (42.9% vs. 22.2%), administered sequentially. Interpretation of these results should be cautious due to the small sample size of Cohort 1a and its subgroups, which may affect the precision and reliability of estimates.

DC-02 was a Phase 2, multicentre, randomized dose-finding study evaluating trastuzumab deruxtecan (T-DXd) in patients with HER2-overexpressing metastatic colorectal cancer (mCRC), defined as IHC 3+ or IHC 2+/ISH+. HER2 status was assessed via IHC and ISH in parallel. Testing was conducted centrally by Ventana Medical Systems using validated tests. The primary endpoint was confirmed ORR by BICR. Treatment allocation was blinded to participants, investigators, site staff (except essential unblinded personnel), imaging reviewers, and the ILD adjudication committee. The sponsor and CRO were unblinded. In Stage 1, 80 patients were randomized 1:1 to receive T-DXd at 5.4 mg/kg (Arm 1) or 6.4 mg/kg (Arm 2) every three weeks, stratified by ECOG performance status, HER2 status, and RAS mutation status. Stage 2 (single-arm expansion at 5.4 mg/kg) enrolled 40 additional patients to the 5.4 mg/kg arm. The inclusion and exclusion criteria are comprehensive and acceptable for selection of the most fit patients with HER2-overexpressing metastatic colorectal cancer. Results from patients with IHC 3+ from Arm 1 serve as supportive to DP-02.

No hypothesis tests, alpha allocation, or multiplicity control were prespecified, so all dose-wise and stage-wise results were interpreted descriptively with point estimates and 95% CIs, and any cross-dose or cross-stage comparisons were exploratory. Results from BICR and investigator assessments were generally consistent, but substantial censoring in the time-to-event endpoints and the small per-dose sample sizes reduced estimate precision and made interpretation less certain.

A total of 135 patients were screened for participation in DC-02 study, of these 122 were included across two arms. The median age of patients in subgroup with HER2 IHC 3+ CRC was 58 years, ranging from 25 to 78. Most patients (70.3%) were under 65 years old, while 29.7% were 65 or older. The sex distribution was fairly balanced, with 53.1% male and 46.9% female.

ECOG PS scores were 0 for 59.4% of patients and 1 for 40.6%. Patients had received a median of 4 prior treatment regimens, with a range from 1 to 14.

Overall demographics and disease characteristics align with a fit population with mCRC who have exhausted standard therapy and have limited treatment options. Median duration of follow-up at DCO of 01 Nov 2022 in Arm 1 was 8.9 months (range 0.5, 17.1)., the confirmed ORR by BICR was 37.8 % (95%CI: 27.3, 49.2); only PR were observed. Median duration of response was 1.6 months. Subgroup analyses of primary endpoint indicated a trend in higher ORR in patients without liver metastases (n=23, ORR of 52.2%), patients with HER2 IHC 3+ status (n=64, ORR of 46.9%), in patients who

receive max. two lines of prior therapy (n= 26, ORR of 42.3%), in those who received prior anti-EGFR treatment (n=57, ORR of 42.1%). Moreover, a trend in improvement response was also seen in patients who previously received anti-HER2 therapy (ORR of 41.2%, n=17). In the HER2 IHC 3+ subgroup, DoR was longer than in the full analysis set, with a median of 5.5 months. This can be considered clinically meaningful in the last-line setting, where durable responses are uncommon.

Although subgroup analyses should be interpreted cautiously due to small sample sizes, the IHC 3+ subgroup provides supportive evidence for the pivotal DP-02 study, as the observed ORR is reinforced by durable responses in this group.

Wording of the indication:

The indication initially applied for was:

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumours who have received prior treatment and who have no satisfactory alternative treatment options.

The proposed indication was revised to better reflect the targeted population as study DP-02 enrolled patients with median 2 lines of previous treatment and the landscape of treatment for many tumours has evolved.

The revised wording of indication states:

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumours who have received prior treatment and who have no satisfactory treatment options (see sections 4.4 and 5.1; for biomarker-based patient selection, see section 4.2).

Additional efficacy data needed in the context of a conditional marketing authorisation

The MAH will submit the final analysis from cohort A of Part 2 of study DP-02 as a specific obligation to fulfil the CMA criterion on providing comprehensive data. Part 2 of DP-02 is ongoing and will evaluate additional cohorts of patients with HER2-expressing tumours, as determined via central testing only, and includes 5 cohorts ((A to E), N=40 / cohort): A) any tumour type that is HER2 IHC 3+ (excluding breast, gastric cancer, and colorectal cancer), B) any tumour type that is HER2 IHC 2+/ISH+ (excluding breast, gastric cancer, and colorectal cancer), C) HER2 IHC 2+ or 1+ endometrial cancer, D) HER2 IHC 2+ or 1+ovarian cancer, and E) HER2 IHC 2+ or 1+ cervical cancer. The primary endpoint is ORR by INV with DoR as secondary endpoint. Cohort A will provide additional data from 44 patients with different tumour types with HER2 IHC 3+ leading to an increase of the sample size to 155 patients in study DP-02. The MAH argues that conducting a randomized clinical trial in a histology independent indication presents considerable challenges. The inclusion of multiple tumour types complicates the design of a randomized study with a single comparator or standardised control arm that is both ethically and clinically appropriate across a heterogeneous patient population. This complexity is further exacerbated by the rarity of HER2-positive tumours outside of breast and gastric cancers, which significantly limits patient recruitment. Given the small number of eligible patients and the need to maintain statistical power, randomization into control and experimental groups is not considered feasible according to the MAH. The argumentation regarding the challenges in designing a comparative study for a tumour-agnostic indication in this setting is accepted. Overall, the proposed SOB is considered acceptable. The results from cohort A of confirmatory part 2 of DP-02 study are included in Annex IIE with a defined timeframe for the fulfilment of the SOB.

2.4.5. Conclusions on the clinical efficacy

The observed response rates in DP-02 in patients with HER2 IHC 3+ solid tumours, who have exhausted standard treatments options, can be viewed as clinically relevant, and the benefit-risk assessment of Enhertu in the proposed indication is positive.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

In order to confirm the efficacy and safety of Enhertu in the treatment of adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumours who have received prior treatment and who have no satisfactory treatment options, the MAH should submit the results of Part 2, Cohort A of the study DESTINY-PanTumor02, Phase II, Multicenter Open-label Study to Evaluate the Efficacy and Safety of Trastuzumab Deruxtecan (T-DXd, DS-8201a) for the Treatment of Selected HER2-expressing Tumours by 2Q 2027.

2.5. Clinical safety

Introduction

Enhertu (Trastuzumab Deruxtecan), a HER2-directed ADC, was first approved in 2021 and has accumulated a well-established safety profile. The most common adverse events being gastrointestinal and hematologic in nature with known serious adverse events such as pneumonitis/ILD and decrease in LVEF. The drug's safety profile has been consistently demonstrated across different specific patient populations and tumour types.

This assessment of safety and tolerability in the intended population is based on data from 347 patients with IHC 3+ solid tumours who received T-DXd 5.4 mg/kg Q3W in 4 studies: Study DP-02, Study DL-01, Study DC-02, and Study DB-01. For the assessment procedure, DP-02 will be considered the pivotal safety trial with the DL-01 and DC-02 trials as supportive, furthermore patients receiving 6.4mg/kg dose in these trials will not be assessed as the suggested posology for the tissue agnostic indication specifies a 5.4mg/kg dose.

Table 72 Studies included in safety population for the proposed indication

Study Number / Phase	Objective(s) of Study	Study Population	Study Design	Data Cut-off Date	No. of Patients Treated with T-DXd 5.4 or 6.4 mg/kg
DESTINY-PanTumor02; DP-02) Phase 2	Efficacy and safety of T-DXd	HER2-expressing tumours and HER2-low tumours	Non-randomized, open-label No control arm	10 Oct 2024	267 T-DXd 5.4 mg/kg
DESTINY-Breast01; DB-01) Phase 2	Efficacy and safety of T-DXd	HER2-positive, unresectable and/or metastatic BC previously	Non-randomized, open-label No control arm	06 May 2024	184 T-DXd 5.4 mg/kg 48 T-DXd 6.4 mg/kg

Study Number / Phase	Objective(s) of Study	Study Population	Study Design	Data Cut-off Date	No. of Patients Treated with T-DXd 5.4 or 6.4 mg/kg
		treated with T-DM1			
DESTINY-Lung01; DL-01) Phase 2	Efficacy and safety of T-DXd	HER2-over-expressing and/or HER2-mutated advanced NSCLC	Non-randomized, open-label No control arm	03 Dec 2021	41 T-DXd 5.4 mg/kg 140 T-DXd 6.4 mg/kg
DESTINY-DC02; DC-02) Phase 2	Efficacy, safety, and PK of T-DXd	HER2-overexpressing locally advanced, unresectable, or metastatic CRC	Two-staged, randomized 1:1 with 2 doses of T-DXd. After Stage 1 enrolment is complete, all further eligible patients will be registered to T-DXd in Stage 2.	01 Nov 2022	83 T-DXd 5.4 mg/kg 39 T-DXd 6.4 mg/kg

Importantly, from these studies only the patients with IHC 3+ are presented in the IHC 3+ T-DXd 5.4 mg/kg Pool and the DP-02 IHC 3+ T-DXd 5.4 mg/kg Pool. Patients from these studies with IHC below 3+ are tallied with the All Tumour Types T-DXd 5.4 mg/kg Pool.

Table 73 Number of Patients in Safety Data Presentations

Group for Evaluation	Dose of T-DXd	Number of Patients Treated
HER2 IHC 3+		
IHC 3+ T-DXd 5.4 mg/kg Pool Multi-study pool of data from patients with IHC 3+ solid tumours who received the proposed registration dose of T-DXd 5.4 mg/kg	5.4 mg/kg	**Total: 347** DP-02: 111 DL-01: 17 DC-02: 65 DB-01: 154
Study DP-02 IHC 3+ T-DXd 5.4 mg/kg Data from the subgroup of patients with IHC 3+ solid tumours who received the proposed registration dose of T-DXd 5.4 mg/kg in Study DP-02	5.4 mg/kg	**DP-02: 111**
Study DG-02 IHC 3+ T-DXd 6.4 mg/kg Data from patients with IHC 3+ GC or GEJ cancer who received T-DXd 6.4 mg/kg in Study DG-02	6.4 mg/kg	**DG-02: 68**

Group for Evaluation	Dose of T-DXd	Number of Patients Treated
All Tumour Types		
All Tumour Types T-DXd 5.4 mg/kg Pool Multi-study pool of data from patients across various tumour types and IHC expression levels who received the proposed registration dose of T-DXd 5.4 mg/kg	5.4 mg/kg	**Total: 3057** DP-01: 102 DP-02: 267 DC-02: 83 DB-01: 184 DB-02: 404 DB-03: 257 DB-04: 371 DB-06: 434 DB-07: 110 DB-12: 504 J101: 91 DL-01: 41 DL-02: 101 DL-03: 36 DL-05: 72
All Tumour Types T-DXd 6.4 mg/kg Pool Multi-study pool of data from patients across various tumour types and IHC expression levels who received T-DXd 6.4 mg/kg	6.4 mg/kg	**Total: 889** DB-01: 48 DC-01:86 DC-02: 39 J101: 183 DL-01: 140 DL-02: 50 DG-01: 169 DG-02: 79 DG-06: 95

The safety profile of patients with IHC 3+ tumours treated with T-DXd 5.4 mg/kg in Study DP-02 was considered by the MAH to be similar to that of patients in the IHC 3+ T-DXd 5.4 mg/kg Pool. Differences between these 2 groups was only addressed if considered to be both notable (i.e., a difference of ≥ 10 pp) and clinically relevant.

Safety population characteristics

Table 74 Summary of Baseline Characteristics (Safety Analysis Set)

	Number (%) of Patients				
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	**Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)**	**Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)**	**All Tumour Types T-DXd 5.4 mg/kg Pool (N = 3057)**	**All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)**
Body weight (kg)					
Mean	65.24	68.54	74.99	64.68	62.39
Std Dev	14.542	16.147	14.982	14.664	14.684
Median	63.50	68.00	73.65	62.20	60.00

	Number (%) of Patients				
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	**Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)**	**Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)**	**All Tumour Types T-DXd 5.4 mg/kg Pool (N = 3057)**	**All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)**
Minimum, Maximum	35.6, 123.9	37, 123.9	42, 120.7	34, 137.8	27.3, 120.7
Body mass index (kg/m^2) [a]					
n	343	111	67	3042	875
Mean	24.42	25.19	25.37	24.78	22.78
Std Dev	4.886	5.779	3.971	5.130	4.350
Median	23.70	24.66	25.09	23.94	22.14
Minimum, Maximum	13.9, 42.7	13.9, 41.1	17.7, 35.4	12.8, 52.1	13.3, 45.7
ECOG performance status – n (%)					
0	179 (51.6)	54 (48.6)	26 (38.2)	1707 (55.8)	414 (46.6)
1	167 (48.1)	57 (51.4)	42 (61.8)	1340 (43.8)	474 (53.3)
2	1 (0.3)	0	0	5 (0.2)	1 (0.1)
Missing	0	0	0	5 (0.2)	0
Primary tumour location - n (%)					
Breast	154 (44.4)	0	0	2355 (77.0)	149 (16.8)
Colorectal	65 (18.7)	0	0	103 (3.4)	145 (16.3)
Bladder	27 (7.8)	27 (24.3)	0	48 (1.6)	0
Biliary tract	22 (6.3)	22 (19.8)	0	60 (2.0)	0
Lung - NSCLC	17 (4.9)	0	0	250 (8.2)	208 (23.4)
Endometrial	16 (4.6)	16 (14.4)	0	42 (1.4)	0
Rare Tumours	16 (4.6)	16 (14.4)	0	57 (1.9)	0
Ovarian	15 (4.3)	15 (13.5)	0	41 (1.3)	0
Cervical	10 (2.9)	10 (9.0)	0	43 (1.4)	0
Pancreatic	5 (1.4)	5 (4.5)	0	27 (0.9)	1 (0.1)
Gastric	0	0	68 (100)	12 (0.4)	250 (28.1)
Esophagogastric	0	0	0	11 (0.4)	95 (10.7)
Gastroesophageal junction	0	0	0	8 (0.3)	23 (2.6)
Other	0	0	0	0	18 (2.0)
Renal function - n (%) [b]					
Within normal range	157 (45.2)	40 (36.0)	27 (39.7)	1507 (49.3)	357 (40.2)
Mild impairment	138 (39.8)	45 (40.5)	21 (30.9)	1157 (37.8)	360 (40.5)
Moderate impairment	51 (14.7)	25 (22.5)	7 (10.3)	372 (12.2)	155 (17.4)

	Number (%) of Patients				
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)	Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)	All Tumour Types T-DXd 5.4 mg/kg Pool (N = 3057)	All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)
Severe impairment	1 (0.3)	1 (0.9)	0	5 (0.2)	2 (0.2)
Missing	0	0	13 (19.1)	16 (0.5)	15 (1.7)
Hepatic function - n (%) [c]					
Within normal range	218 (62.8)	85 (76.6)	55 (80.9)	1855 (60.7)	616 (69.3)
Mild impairment	121 (34.9)	22 (19.8)	12 (17.6)	1167 (38.2)	262 (29.5)
Moderate impairment	5 (1.4)	4 (3.6)	0	23 (0.8)	8 (0.9)
Severe impairment	1 (0.3)	0	0	1 (0.0)	0
Missing	2 (0.6)	0	1 (1.5)	11 (0.4)	3 (0.3)

[a] Body mass index = weight (kg) / height (m^2)

[b] Renal function: normal function = CrCl ≥ 90 mL/min; mild impairment = CrCl ≥ 60 to < 90 mL/min; moderate impairment = CrCl ≥ 30 to < 60 mL/min; severe impairment = CrCl ≥ 15 to < 30 mL/min. CrCl calculated as [(140 - age) × weight] / [(72 × creatinine (µmol/L) × 0.85 (if female)].

[c] Hepatic function:
Normal function = TBL ≤ ULN and (AST ≤ ULN) for patients without Gilbert syndrome, TBL ≤ 3.0 × ULN and (AST ≤ ULN) for patients with Gilbert syndrome.
Mild impairment = TBL > ULN, ≤ 1.5 × ULN and any AST for patients without Gilbert syndrome, TBL > ULN, ≤ 3.0 × ULN and (AST > ULN) for patients with Gilbert syndrome, TBL ≤ ULN and (AST >ULN) regardless of Gilbert syndrome.
Moderate impairment = TBL > 1.5 × ULN, ≤ 3.0 × ULN and any AST.
Severe impairment = TBL > 3.0 × ULN and any AST regardless of Gilbert syndrome.

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

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

Table 75 Summary of Demographics (Safety Analysis Set)

	Number (%) of Patients				
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)	Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)	All Tumour Types T-DXd 5.4 mg/kg Pool (N = 3057)	All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)
Age (years) [a]					
Mean	58.0	61.7	58.9	56.7	59.8
Std Dev	12.23	12.68	12.00	11.72	11.39
Median	59.6	64.0	60.2	57.0	61.0
Minimum, Maximum	23, 96	23, 85	20, 78	22, 96	20, 89
Age category (years) - n (%)					
< 65	236 (68.0)	59 (53.2)	41 (60.3)	2229 (72.9)	546 (61.4)
≥ 65 to <75	88 (25.4)	38 (34.2)	23 (33.8)	651 (21.3)	278 (31.3)
≥ 65	111 (32.0)	52 (46.8)	27 (39.7)	828 (27.1)	343 (38.6)

	Number (%) of Patients				
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	**Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)**	**Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)**	**All Tumour Types T-DXd 5.4 mg/kg Pool (N = 3057)**	**All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)**
< 75	324 (93.4)	97 (87.4)	64 (94.1)	2880 (94.2)	824 (92.7)
≥ 75	23 (6.6)	14 (12.6)	4 (5.9)	177 (5.8)	65 (7.3)
Sex - n (%)					
Female	258 (74.4)	66 (59.5)	21 (30.9)	2760 (90.3)	440 (49.5)
Male	89 (25.6)	45 (40.5)	47 (69.1)	297 (9.7)	449 (50.5)
Race - n (%)					
White	176 (50.7)	64 (57.7)	61 (89.7)	1689 (55.3)	280 (31.5)
Asian	144 (41.5)	38 (34.2)	2 (2.9)	1098 (35.9)	546 (61.4)
Black or African American	10 (2.9)	4 (3.6)	1 (1.5)	58 (1.9)	12 (1.3)
American Indian or Alaska Native	1 (0.3)	0	0	6 (0.2)	1 (0.1)
Native Hawaiian or Other Pacific Islander	1 (0.3)	0	1 (1.5)	3 (0.1)	2 (0.2)
Other	10 (2.9)	3 (2.7)	3 (4.4)	138 (4.5)	42 (4.7)
Not Reported	2 (0.6)	2 (1.8)	0	58 (1.9)	0
Missing	3 (0.9)	0	0	7 (0.2)	6 (0.7)
Country - n (%)					
Non-Japan	295 (85.0)	111 (100)	68 (100)	2715 (88.8)	522 (58.7)
Japan	52 (15.0)	0	0	342 (11.2)	367 (41.3)
Geographic region - n (%)					
Asia	132 (38.0)	36 (32.4)	0	1035 (33.9)	525 (59.1)
Europe	129 (37.2)	47 (42.3)	44 (64.7)	1374 (44.9)	185 (20.8)
North America	77 (22.2)	26 (23.4)	24 (35.3)	386 (12.6)	178 (20.0)
Rest of World	9 (2.6)	2 (1.8)	0	262 (8.6)	1 (0.1)
Ethnicity - n (%)					
Non-Hispanic/Non-Latino	302 (87.0)	108 (97.3)	60 (88.2)	2633 (86.1)	531 (59.7)
Hispanic/Latino	12 (3.5)	3 (2.7)	5 (7.4)	205 (6.7)	19 (2.1)
Not Applicable	27 (7.8)	0	0	109 (3.6)	6 (0.7)
Unknown	3 (0.9)	0	3 (4.4)	38 (1.2)	13 (1.5)
Not Reported	2 (0.6)	0	0	4 (0.1)	22 (2.5)
Missing	1 (0.3)	0	0	68 (2.2)	298 (33.5)

[a] Age in years is calculated using the informed consent date and the patient's birth date.

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

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

DCO dates are presented in Table 72, and the studies in each pool are presented in Table 73.

Data are presented in descending frequency within the IHC 3+ T-DXd 5.4 mg/kg Pool.

Patient exposure

The pivotal safety data for the evaluation of safety and tolerability in the proposed indication is pooled from 347 patients with HER2-positive (IHC 3+) solid tumours test who received T-DXd 5.4 mg/kg Q3W in 4 studies and compared to the IHC 3+ T-DXd 5.4 mg/kg and the All Tumour Types T-DXd 5.4 mg/kg. Data represents comprehensive exposure data across a large safety database and encompassing many different histologies such as breast cancer, colorectal cancer, non-small cell lung cancer, gastric cancer, esophagogastric junction cancer, biliary tract cancer, bladder cancer, endometrial cancer, ovarian cancer, cervical cancer, pancreatic cancer, but also more rare cancers were included via the DP-02 study (salivary, vulvar, head and neck, lip and/or oral cavity cancer).

Table 76 Summary of Exposure (Safety Analysis Set)

	Number (%) of Patients				
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	**Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)**	**Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)**	**All Tumour Types T-DXd 5.4 mg/kg Pool (N = 3057)**	**All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)**
Duration of treatment (months) [a]					
Mean	13.80	12.09	6.94	13.01	7.68
Std Dev	15.672	11.584	5.325	11.407	8.059
Median	8.28	7.23	5.62	9.89	5.03
Minimum, Maximum	0.7, 76.0	0.7, 42.5	0.7, 22.1	0.2, 76.0	0.4, 70.4
Duration of treatment category, n (%) [a]					
0 to ≤ 3 months	61 (17.6)	26 (23.4)	22 (32.4)	478 (15.6)	294 (33.1)
> 3 to ≤ 6 months	64 (18.4)	17 (15.3)	16 (23.5)	464 (15.2)	205 (23.1)
> 6 to ≤ 9 months	71 (20.5)	23 (20.7)	7 (10.3)	479 (15.7)	132 (14.8)
> 9 to ≤ 12 months	35 (10.1)	7 (6.3)	15 (22.1)	376 (12.3)	85 (9.6)
> 12 to ≤ 18 months	38 (11.0)	11 (9.9)	4 (5.9)	535 (17.5)	93 (10.5)
> 18 to ≤ 24 months	21 (6.1)	6 (5.4)	4 (5.9)	337 (11.0)	46 (5.2)
> 24 months	57 (16.4)	21 (18.9)	0	388 (12.7)	34 (3.8)
Number of cycles					
Mean	18.8	16.2	9.5	17.7	10.3
Std Dev	21.50	15.38	7.36	15.54	10.69
Median	11.0	10.0	7.5	13.0	7.0
Minimum, Maximum	1, 103	1, 59	1, 32	1, 103	1, 95
Number of cycles category, n (%)					
≤ 6 cycles	95 (27.4)	35 (31.5)	32 (47.1)	731 (23.9)	439 (49.4)
> 6 to ≤ 12 cycles	100 (28.8)	30 (27.0)	15 (22.1)	702 (23.0)	206 (23.2)
> 12 to ≤ 18 cycles	51 (14.7)	15 (13.5)	14 (20.6)	524 (17.1)	109 (12.3)
> 18 to ≤ 24 cycles	23 (6.6)	5 (4.5)	3 (4.4)	379 (12.4)	55 (6.2)
> 24 to ≤ 30 cycles	17 (4.9)	5 (4.5)	2 (2.9)	258 (8.4)	32 (3.6)
> 30 cycles	61 (17.6)	21 (18.9)	2 (2.9)	463 (15.1)	48 (5.4)
Total patient-years of exposure [b]	399.0	111.9	39.4	3313.5	569.1
Relative dose intensity (%) [c]					
Mean	90.62	89.84	92.91	96.18	90.20
Std Dev	13.866	16.949	9.183	9.060	11.583

	Number (%) of Patients				
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)	Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)	All Tumour Types T-DXd 5.4 mg/kg Pool (N = 3057)	All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)
Median	95.81	96.31	95.91	99.92	93.78
Minimum, Maximum	46.1, 199.6	55.2, 199.6	60.3, 104.0	30.8, 199.6	50.4, 109.3
Relative dose intensity (%) category, n (%)					
≥ 90%	225 (64.8)	62 (55.9)	51 (75.0)	2617 (85.6)	529 (59.5)
< 90% to ≥ 80%	54 (15.6)	22 (19.8)	7 (10.3)	217 (7.1)	195 (21.9)
< 80% to ≥ 60%	56 (16.1)	24 (21.6)	10 (14.7)	195 (6.4)	149 (16.8)
< 60%	12 (3.5)	3 (2.7)	0	28 (0.9)	16 (1.8)

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

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

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

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

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

Adverse events

General overview

Table 77 Overview of Treatment-emergent Adverse Events (Safety Analysis Set)

	Number (%) of Patients				
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)	Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)	All Tumour Types T-DXd 5.4 mg/kg Pool (N = 3057)	All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)
TEAE	342 (98.6)	108 (97.3)	68 (100)	3031 (99.1)	889 (100)
TEAE with CTCAE ≥ Grade 3 [a]	222 (64.0)	80 (72.1)	38 (55.9)	1685 (55.1)	635 (71.4)
Treatment-emergent SAE	124 (35.7)	57 (51.4)	27 (39.7)	863 (28.2)	350 (39.4)
TEAE associated with an outcome of death [b]	21 (6.1)	11 (9.9)	10 (14.7)	126 (4.1)	82 (9.2)
TEAE associated with study drug discontinuation	60 (17.3)	20 (18.0)	12 (17.6)	485 (15.9)	192 (21.6)
TEAE associated with study drug interruption	173 (49.9)	64 (57.7)	22 (32.4)	1466 (48.0)	426 (47.9)
TEAE associated with dose reduction	104 (30.0)	39 (35.1)	15 (22.1)	739 (24.2)	268 (30.1)
Drug-related TEAE [c]	327 (94.2)	96 (86.5)	65 (95.6)	2894 (94.7)	864 (97.2)
Drug-related TEAE with CTCAE ≥ Grade 3 [a]	176 (50.7)	52 (46.8)	23 (33.8)	1287 (42.1)	508 (57.1)
Drug-related treatment-emergent SAE	53 (15.3)	19 (17.1)	8 (11.8)	373 (12.2)	172 (19.3)

Drug-related TEAE associated with an outcome of death [b]	5 (1.4)	3 (2.7)	2 (2.9)	40 (1.3)	17 (1.9)
Drug-related TEAE associated with study drug discontinuation	54 (15.6)	17 (15.3)	8 (11.8)	407 (13.3)	140 (15.7)
Drug-related TEAE associated with study drug interruption	113 (32.6)	38 (34.2)	7 (10.3)	920 (30.1)	310 (34.9)
Drug-related TEAE associated with dose reduction	95 (27.4)	34 (30.6)	12 (17.6)	673 (22.0)	254 (28.6)

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

[b] For specific TEAEs associated with an outcome of death, refer to Table 87.

[c] Relationship to study drug was as determined by the investigator. If the relationship was missing, the TEAE was considered to be related to the drug.

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

Adverse events, general overview in the DP-02 trial

Table 78 Adverse Events in Any Category (Safety Analysis Set)

AE category	Number (%) of patients [a]							
	Cohort 1 biliary tract cancer (N = 41)	**Cohort 2 bladder cancer (N = 41)**	**Cohort 3 cervical cancer (N = 40)**	**Cohort 4 endometrial cancer (N = 40)**	**Cohort 5 ovarian cancer (N = 40)**	**Cohort 6 pancreatic cancer (N = 25)**	**Cohort 7 rare tumours (N = 40)**	**Total (N = 267)**
Any AE	41 (100)	41 (100)	40 (100)	39 (97.5)	38 (95.0)	24 (96.0)	38 (95.0)	261 (97.8)
Any AE possibly related to treatment [b]	33 (80.5)	38 (92.7)	36 (90.0)	36 (90.0)	34 (85.0)	15 (60.0)	34 (85.0)	226 (84.6)
Any AE CTCAE Grade 3 or higher	30 (73.2)	26 (63.4)	26 (65.0)	26 (65.0)	25 (62.5)	14 (56.0)	22 (55.0)	169 (63.3)
Any AE CTCAE Grade 3 or higher, possibly related to treatment [b]	16 (39.0)	17 (41.5)	19 (47.5)	14 (35.0)	21 (52.5)	7 (28.0)	15 (37.5)	109 (40.8)
Any AE with an outcome of death	6 (14.6)	3 (7.3)	1 (2.5)	3 (7.5)	1 (2.5)	2 (8.0)	3 (7.5)	19 (7.1)
Any AE with an outcome of death, possibly related to treatment [b]	0	1 (2.4)	0	2 (5.0)	0	0	1 (2.5)	4 (1.5)
Any SAE (including events with outcome of death)	23 (56.1)	17 (41.5)	15 (37.5)	15 (37.5)	16 (40.0)	9 (36.0)	19 (47.5)	114 (42.7)
Any SAE (including events with outcome of death), possibly related to treatment [b]	5 (12.2)	4 (9.8)	3 (7.5)	4 (10.0)	11 (27.5)	3 (12.0)	6 (15.0)	36 (13.5)
Any AE leading to discontinuation of T-DXd	8 (19.5)	4 (9.8)	4 (10.0)	3 (7.5)	3 (7.5)	3 (12.0)	7 (17.5)	32 (12.0)

Any AE leading to discontinuation of T-DXd, possibly related to treatment [b]	5 (12.2)	4 (9.8)	3 (7.5)	3 (7.5)	1 (2.5)	1 (4.0)	6 (15.0)	23 (8.6)
Any AE leading to dose reduction of T-DXd	10 (24.4)	7 (17.1)	9 (22.5)	12 (30.0)	17 (42.5)	0	6 (15.0)	61 (22.8)
Any AE leading to dose reduction of T-DXd, possibly related to treatment [b]	9 (22.0)	6 (14.6)	9 (22.5)	11 (27.5)	15 (37.5)	0	4 (10.0)	54 (20.2)
Any AE leading to dose interruption of T-DXd	13 (31.7)	24 (58.5)	17 (42.5)	14 (35.0)	19 (47.5)	3 (12.0)	21 (52.5)	111 (41.6)
Any AE leading to dose interruption of T-DXd, possibly related to treatment [b]	7 (17.1)	12 (29.3)	6 (15.0)	5 (12.5)	13 (32.5)	0	11 (27.5)	54 (20.2)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
[b] As assessed by the Investigator. Missing causalities are counted as possibly related.
Includes AEs with an onset date or worsening on or after the date of first dose and up to and including 47 days following the date of last dose of study medication or before the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment (whichever occurs first).
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Averse events by PT in across safety populations

Table 79 Treatment-emergent Adverse Events Reported in ≥ 10% of Patients in the IHC 3+ T DXd 5.4 mg/kg Pool, by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of Patients				
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)	Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)	All Tumour Types T-DXd 5.4 mg/kg Pool (N = 3057)	All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)
Patients with any TEAE	342 (98.6)	108 (97.3)	68 (100)	3031 (99.1)	889 (100)
Nausea	242 (69.7)	67 (60.4)	45 (66.2)	2149 (70.3)	599 (67.4)
Fatigue	143 (41.2)	39 (35.1)	28 (41.2)	979 (32.0)	270 (30.4)
Vomiting	124 (35.7)	32 (28.8)	31 (45.6)	1116 (36.5)	330 (37.1)
Anaemia	122 (35.2)	47 (42.3)	26 (38.2)	1070 (35.0)	419 (47.1)
Decreased appetite	121 (34.9)	35 (31.5)	22 (32.4)	895 (29.3)	432 (48.6)
Alopecia	117 (33.7)	22 (19.8)	18 (26.5)	1052 (34.4)	268 (30.1)
Diarrhoea	112 (32.3)	41 (36.9)	28 (41.2)	927 (30.3)	288 (32.4)
Constipation	100 (28.8)	23 (20.7)	19 (27.9)	1009 (33.0)	254 (28.6)
Neutrophil count decreased	80 (23.1)	24 (21.6)	12 (17.6)	628 (20.5)	363 (40.8)
Asthenia	66 (19.0)	29 (26.1)	12 (17.6)	688 (22.5)	106 (11.9)
Cough	63 (18.2)	9 (8.1)	9 (13.2)	466 (15.2)	101 (11.4)
Platelet count decreased	61 (17.6)	15 (13.5)	13 (19.1)	486 (15.9)	281 (31.6)
Neutropenia	57 (16.4)	24 (21.6)	8 (11.8)	513 (16.8)	46 (5.2)

MedDRA Preferred Term	Number (%) of Patients				
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)	Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)	All Tumour Types T-DXd 5.4 mg/kg Pool (N = 3057)	All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)
Headache	54 (15.6)	11 (9.9)	6 (8.8)	511 (16.7)	75 (8.4)
Aspartate aminotransferase increased	52 (15.0)	13 (11.7)	11 (16.2)	627 (20.5)	161 (18.1)
Stomatitis	50 (14.4)	13 (11.7)	1 (1.5)	374 (12.2)	115 (12.9)
Abdominal pain	49 (14.1)	20 (18.0)	11 (16.2)	323 (10.6)	87 (9.8)
White blood cell count decreased	49 (14.1)	9 (8.1)	8 (11.8)	470 (15.4)	275 (30.9)
Dyspepsia	45 (13.0)	13 (11.7)	2 (2.9)	323 (10.6)	45 (5.1)
Urinary tract infection	43 (12.4)	18 (16.2)	4 (5.9)	266 (8.7)	49 (5.5)
Pyrexia	43 (12.4)	14 (12.6)	7 (10.3)	412 (13.5)	155 (17.4)
Dyspnoea	43 (12.4)	5 (4.5)	7 (10.3)	272 (8.9)	79 (8.9)
COVID-19	42 (12.1)	17 (15.3)	5 (7.4)	486 (15.9)	43 (4.8)
Hypokalaemia	41 (11.8)	17 (15.3)	11 (16.2)	345 (11.3)	129 (14.5)
Arthralgia	38 (11.0)	14 (12.6)	3 (4.4)	321 (10.5)	58 (6.5)
Alanine aminotransferase increased	38 (11.0)	9 (8.1)	5 (7.4)	515 (16.8)	127 (14.3)
Weight decreased	36 (10.4)	14 (12.6)	25 (36.8)	375 (12.3)	167 (18.8)
Epistaxis	36 (10.4)	2 (1.8)	7 (10.3)	268 (8.8)	60 (6.7)

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

If a patient had multiple occurrences of the same PT, the patient was counted once for that PT. If a patient had multiple PTs, the patient was counted in each of the different PTs.

Preferred terms are sorted by descending frequency in the IHC 3+ T-DXd 5.4 mg/kg Pool.

Adverse events by PT in the DP-02 trial

Table 80 Adverse Events Reported in at Least 10% of Patients in the Total Column by PT (Safety Analysis Set)

Preferred term	Number (%) of patients							
	Cohort 1 biliary tract cancer (N = 41)	Cohort 2 bladder cancer (N = 41)	Cohort 3 cervical cancer (N = 40)	Cohort 4 endometrial cancer (N = 40)	Cohort 5 ovarian cancer (N = 40)	Cohort 6 pancreatic cancer (N = 25)	Cohort 7 rare tumours (N = 40)	Total (N = 267)
Patients with any AE	41 (100)	41 (100)	40 (100)	39 (97.5)	38 (95.0)	24 (96.0)	38 (95.0)	261 (97.8)
Nausea	23 (56.1)	23 (56.1)	30 (75.0)	32 (80.0)	25 (62.5)	12 (48.0)	28 (70.0)	173 (64.8)
Anaemia	16 (39.0)	19 (46.3)	21 (52.5)	14 (35.0)	25 (62.5)	8 (32.0)	17 (42.5)	120 (44.9)
Diarrhoea	10 (24.4)	18 (43.9)	16 (40.0)	19 (47.5)	13 (32.5)	4 (16.0)	10 (25.0)	90 (33.7)

Vomiting	12 (29.3)	7 (17.1)	13 (32.5)	19 (47.5)	9 (22.5)	7 (28.0)	16 (40.0)	83 (31.1)
Fatigue	10 (24.4)	12 (29.3)	10 (25.0)	12 (30.0)	14 (35.0)	6 (24.0)	17 (42.5)	81 (30.3)
Decreased appetite	11 (26.8)	15 (36.6)	8 (20.0)	12 (30.0)	13 (32.5)	5 (20.0)	9 (22.5)	73 (27.3)
Asthenia	11 (26.8)	5 (12.2)	11 (27.5)	14 (35.0)	10 (25.0)	5 (20.0)	8 (20.0)	64 (24.0)
Constipation	5 (12.2)	9 (22.0)	14 (35.0)	12 (30.0)	4 (10.0)	3 (12.0)	10 (25.0)	57 (21.3)
Neutropenia	9 (22.0)	11 (26.8)	8 (20.0)	5 (12.5)	6 (15.0)	6 (24.0)	9 (22.5)	54 (20.2)
Alopecia	11 (26.8)	5 (12.2)	9 (22.5)	12 (30.0)	5 (12.5)	2 (8.0)	7 (17.5)	51 (19.1)
Neutrophil count decreased	4 (9.8)	10 (24.4)	4 (10.0)	5 (12.5)	10 (25.0)	1 (4.0)	7 (17.5)	41 (15.4)
Abdominal pain	6 (14.6)	6 (14.6)	6 (15.0)	6 (15.0)	10 (25.0)	1 (4.0)	5 (12.5)	40 (15.0)
Hypokalaemia	6 (14.6)	5 (12.2)	9 (22.5)	8 (20.0)	8 (20.0)	1 (4.0)	2 (5.0)	39 (14.6)
Aspartate aminotransferase increased	4 (9.8)	3 (7.3)	4 (10.0)	7 (17.5)	9 (22.5)	4 (16.0)	5 (12.5)	36 (13.5)
COVID-19	2 (4.9)	7 (17.1)	6 (15.0)	5 (12.5)	7 (17.5)	1 (4.0)	7 (17.5)	35 (13.1)
Thrombocytopenia	6 (14.6)	7 (17.1)	3 (7.5)	3 (7.5)	5 (12.5)	3 (12.0)	8 (20.0)	35 (13.1)
Alanine aminotransferase increased	4 (9.8)	4 (9.8)	3 (7.5)	5 (12.5)	7 (17.5)	4 (16.0)	5 (12.5)	32 (12.0)
Urinary tract infection	2 (4.9)	6 (14.6)	7 (17.5)	6 (15.0)	8 (20.0)	0	2 (5.0)	31 (11.6)
Pyrexia	1 (2.4)	4 (9.8)	3 (7.5)	4 (10.0)	11 (27.5)	0	5 (12.5)	28 (10.5)
Hypoalbuminaemia	1 (2.4)	5 (12.2)	4 (10.0)	1 (2.5)	7 (17.5)	5 (20.0)	4 (10.0)	27 (10.1)
Platelet count decreased	3 (7.3)	6 (14.6)	2 (5.0)	2 (5.0)	9 (22.5)	0	5 (12.5)	27 (10.1)
Weight decreased	4 (9.8)	6 (14.6)	2 (5.0)	4 (10.0)	5 (12.5)	2 (8.0)	4 (10.0)	27 (10.1)

Sorted by decreasing frequency in the total column.

Patients with multiple events in the same PT are counted only once in that PT. Patients with events in more than one PT are counted once in each of those PTs.

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The most frequently reported TEAEs in the DP-02 trial was nausea (64.8%), anaemia (44.9%), diarrhoea (33.7%), vomiting (31.1%), fatigue (30.3%), decreased appetite (27.3%), asthenia (24.0%), constipation (21.3%), and neutropenia (20.2%).

TEAE of at least grade 3

Table 81 Treatment-emergent Adverse Events of at Least Grade 3 Reported in ≥ 5% of Patients in the IHC 3+ T DXd 5.4 mg/kg Pool, by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of Patients				
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)	Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)	All Tumour Types T-DXd 5.4 mg/kg Pool (N = 3057)	All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)
Patients with any TEAE of ≥ Grade 3	222 (64.0)	80 (72.1)	38 (55.9)	1685 (55.1)	635 (71.4)
Neutrophil count decreased	49 (14.1)	15 (13.5)	6 (8.8)	333 (10.9)	229 (25.8)
Anaemia	46 (13.3)	20 (18.0)	9 (13.2)	302 (9.9)	200 (22.5)
Neutropenia	32 (9.2)	13 (11.7)	4 (5.9)	246 (8.0)	29 (3.3)
Fatigue	30 (8.6)	11 (9.9)	3 (4.4)	148 (4.8)	48 (5.4)
Nausea	23 (6.6)	4 (3.6)	4 (5.9)	147 (4.8)	51 (5.7)
Platelet count decreased	20 (5.8)	8 (7.2)	2 (2.9)	128 (4.2)	91 (10.2)
White blood cell count decreased	19 (5.5)	3 (2.7)	5 (7.4)	138 (4.5)	117 (13.2)

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

If a patient had multiple occurrences of the same PT, the patient was counted once for that PT. If a patient had multiple PTs, the patient was counted in each of the different PTs.

TEAEs are sorted by descending frequency in the IHC 3+ T-DXd 5.4 mg/kg Pool.

For each PT, a patient was counted once at the maximum severity.

TEAEs of at least grade 3 in the DP-02 study

Table 82 Adverse Events of CTCAE ≥ Grade 3 Reported in at Least 5% of Patients in Any Cohort by PT (Safety Analysis Set)

Preferred term	Number (%) of patients							
	Cohort 1 biliary tract cancer (N = 41)	Cohort 2 bladder cancer (N = 41)	Cohort 3 cervical cancer (N = 40)	Cohort 4 endometrial cancer (N = 40)	Cohort 5 ovarian cancer (N = 40)	Cohort 6 pancreatic cancer (N = 25)	Cohort 7 rare tumours (N = 40)	Total (N = 267)
Patients with any AE of ≥ Grade 3	30 (73.2)	26 (63.4)	26 (65.0)	26 (65.0)	25 (62.5)	14 (56.0)	22 (55.0)	169 (63.3)
Anaemia	4 (9.8)	7 (17.1)	10 (25.0)	7 (17.5)	11 (27.5)	3 (12.0)	5 (12.5)	47 (17.6)
Neutropenia	4 (9.8)	6 (14.6)	5 (12.5)	3 (7.5)	4 (10.0)	2 (8.0)	6 (15.0)	30 (11.2)
Neutrophil count decreased	4 (9.8)	4 (9.8)	2 (5.0)	3 (7.5)	7 (17.5)	1 (4.0)	3 (7.5)	24 (9.0)
Fatigue	3 (7.3)	1 (2.4)	3 (7.5)	1 (2.5)	7 (17.5)	0	5 (12.5)	20 (7.5)
Diarrhoea	4 (9.8)	1 (2.4)	3 (7.5)	3 (7.5)	1 (2.5)	2 (8.0)	0	14 (5.2)
Platelet count decreased	2 (4.9)	3 (7.3)	0	1 (2.5)	7 (17.5)	0	1 (2.5)	14 (5.2)

Sorted by decreasing frequency for PT in the total column.
Patients with multiple events in the same PT are counted only once in that PT. Patients with events in more than

one PT are counted once in each of those PTs MedDRA version 26.0.
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events (version 5.0); MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term.

Adverse drug reactions

Table 83: All Adverse Drug Reactions in IHC 3+ Pool T-DXd 5.4 mg/kg and All Tumour Types Pool T-DXd 5.4 mg/kg, by MedDRA System Organ Class, Preferred Term/Grouped Term and Frequency (Safety Analysis Set)

MedDRA System Organ Class Preferred Term/Grouped Term	Number (%) of Patients				
	Supportive Safety Pools				
	All Tumour Types Pool T-DXd 5.4 mg/kg (N = 3057)				
	Frequency [1]	CTCAE Grade			SAE
		All Grades	Grade 3 or 4	Grade 5	
Patients with any ADR	--	3005 (98.3)	1386 (45.3)	35 (1.1)	421 (13.8)
Blood and lymphatic system disorders					
Neutropenia [2a]	Very Common	1098 (35.9)	567 (18.5)	0	11 (0.4)
Anaemia [2b]	Very Common	1083 (35.4)	303 (9.9)	0	43 (1.4)
Thrombocytopenia [2c]	Very Common	711 (23.3)	159 (5.2)	0	22 (0.7)
Leukopenia [2d]	Very Common	634 (20.7)	176 (5.8)	0	1 (0.0)
Lymphopenia [2e]	Common	289 (9.5)	128 (4.2)	0	0
Pancytopenia [2]	Common	154 (5.0)	4 (0.1)	0	0
Febrile neutropenia	Uncommon	28 (0.9)	26 (0.9)	1 (0.0)	20 (0.7)
Eye disorders					
Dry eye	Common	154 (5.0)	3 (0.1)	0	0
Vision blurred [2f]	Common	125 (4.1)	1 (0.0)	0	0
Gastrointestinal disorders					
Nausea	Very Common	2149 (70.3)	147 (4.8)	0	34 (1.1)
Vomiting	Very Common	1116 (36.5)	72 (2.4)	0	44 (1.4)
Diarrhoea	Very Common	927 (30.3)	76 (2.5)	0	17 (0.6)
Constipation	Very Common	1009 (33.0)	18 (0.6)	0	9 (0.3)
Abdominal pain [2g]	Very Common	593 (19.4)	25 (0.8)	0	14 (0.5)
Stomatitis [2h]	Very Common	427 (14.0)	16 (0.5)	0	3 (0.1)
Dyspepsia	Very Common	323 (10.6)	2 (0.1)	0	0
Abdominal distension	Common	114 (3.7)	3 (0.1)	0	2 (0.1)
Flatulence	Common	58 (1.9)	0	0	0
Gastritis	Common	52 (1.7)	5 (0.2)	0	3 (0.1)
General disorders and administration site conditions					
Fatigue [2i]	Very Common	1739 (56.9)	251 (8.2)	0	25 (0.8)
Pyrexia	Very Common	412 (13.5)	11 (0.4)	0	20 (0.7)
Oedema peripheral	Common	247 (8.1)	3 (0.1)	0	3 (0.1)

Hepatobiliary disorders					
Transaminases increased [2j]	Very Common	832 (27.2)	111 (3.6)	0	3 (0.1)
Infections and infestations					
Upper respiratory tract infection [2k]	Very Common	576 (18.8)	7 (0.2)	0	9 (0.3)
Pneumonia	Common	191 (6.2)	44 (1.4)	8 (0.3)	61 (2.0)
Injury, poisoning and procedural complications					
Infusion related reaction [2r]	Uncommon	29 (0.9)	1 (0.0)	0	1 (0.0)
Investigations					
Ejection fraction decreased [2t]	Very Common	452 (14.8)	31 (1.0)	0	5 (0.2)
Weight decreased	Very Common	375 (12.3)	19 (0.6)	0	1 (0.0)
Blood bilirubin increased [2l]	Common	238 (7.8)	23 (0.8)	0	6 (0.2)
Blood alkaline phosphatase increased	Common	241 (7.9)	13 (0.4)	0	0
Blood creatinine increased	Common	103 (3.4)	9 (0.3)	0	3 (0.1)
Metabolism and nutrition disorders					
Decreased appetite	Very Common	895 (29.3)	49 (1.6)	0	7 (0.2)
Hypokalaemia [2m]	Very Common	357 (11.7)	111 (3.6)	0	20 (0.7)
Dehydration	Common	62 (2.0)	8 (0.3)	0	5 (0.2)
Musculoskeletal and connective tissue disorders					
Musculoskeletal pain [2n]	Very Common	735 (24.0)	26 (0.9)	0	20 (0.7)
Nervous system disorders					
Headache [2o]	Very Common	524 (17.1)	10 (0.3)	0	6 (0.2)
Dizziness	Common	281 (9.2)	7 (0.2)	0	2 (0.1)
Dysgeusia	Common	232 (7.6)	1 (0.0)	0	0
Respiratory, thoracic and mediastinal disorders					
Cough	Very Common	466 (15.2)	2 (0.1)	0	1 (0.0)
Interstitial lung disease [2s]	Very Common	329 (12.9)	20 (0.8)	26 (1.0)	90 (3.5)
Dyspnoea	Common	272 (8.9)	23 (0.8)	1 (0.0)	21 (0.7)
Epistaxis	Common	268 (8.8)	2 (0.1)	0	1 (0.0)
Skin and subcutaneous tissue disorders					
Alopecia	Very Common	1052 (34.4)	7 (0.2)	0	0
Rash [2p]	Common	259 (8.5)	3 (0.1)	0	1 (0.0)
Pruritus	Common	142 (4.6)	1 (0.0)	0	0
Skin hyperpigmentation [2q]	Common	90 (2.9)	0	0	1 (0.0)

ADR = adverse drug reaction; CTCAE = Common Terminology Criteria for Adverse Events, version 5.0; MedDRA = Medical Dictionary for Regulatory Activities, version 27.1; N = total number of patients treated; NA = not applicable; PT = preferred term; SAE = serious adverse event; T-DXd = trastuzumab deruxtecan.

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

System Organ Class are presented by alphabetic order. PTs/grouped terms are presented by descending frequency in the All Grades column of IHC 3+ Pool T-DXd 5.4 mg/kg.

If a patient had multiple occurrences of the same ADR, the patient was counted once for that specific ADR.
[1] Within each pool, frequency was defined as follows: Very Common >=1/10 patients; Common >=1/100 to <1/10 patients; Uncommon >=1/1000 to <1/100 patients; Rare >=1/10000 to <1/1000 patients; Very rare <1/10000 patients.
[2] Pancytopenia was defined as all 3 criteria of Haemoglobin level < 100 g/L, Neutrophils < 1.5*10^9/L, and Platelets < 100*10^9/L met on the same lab sample collection date and/or PT of Pancytopenia.
[2a] Neutropenia (grouped term) includes PTs of Neutropenia, Neutrophil count decreased.
[2b] Anaemia (grouped term) includes PTs of Anaemia, Haematocrit decreased, Haemoglobin decreased, Red blood cell count decreased.
[2c] Thrombocytopenia (grouped term) includes PTs of Platelet count decreased, Thrombocytopenia.
[2d] Leukopenia (grouped term) includes PTs of Leukopenia, White blood cell count decreased.
[2e] Lymphopenia (grouped term) includes PTs of Lymphocyte count decreased, Lymphopenia.
[2f] Vision blurred (grouped term) includes PTs of Vision blurred, Visual impairment.
[2g] Abdominal pain (grouped term) includes PTs of Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Gastrointestinal pain.
[2h] Stomatitis (grouped term) includes PTs of Aphthous ulcer, Mouth ulceration, Oral mucosa erosion, Oral mucosal eruption, Stomatitis.
[2i] Fatigue (grouped term) includes PTs of Asthenia, Fatigue, Lethargy, Malaise.
[2j] Transaminases increased (grouped term) includes PTs of Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Hepatic function abnormal, Hypertransaminasaemia, Liver function test abnormal, Liver function test increased, Transaminases increased.
[2k] Upper respiratory tract infection (grouped term) includes PTs of Influenza, Influenza like illness, Laryngitis, Nasopharyngitis, Pharyngitis, Rhinitis, Sinusitis, Upper respiratory tract infection.
[2r] Infusion related reaction (grouped term) includes PTs of Hypersensitivity (n=3), Infusion related reaction (n=26).
[2t] Ejection fraction decreased (grouped term) includes Laboratory parameters of LVEF decrease (n=434) and PTs of Cardiac failure (n=5), Cardiac failure acute (n=1), Cardiac failure chronic (n=2), Cardiac failure congestive (n=1), Ejection fraction decreased (n=170), Left ventricular dysfunction (n=4).
[2l] Blood bilirubin increased (grouped term) includes PTs of Bilirubin conjugated increased, Blood bilirubin increased, Blood bilirubin unconjugated increased, Hyperbilirubinaemia.
[2m] Hypokalaemia (grouped term) includes PTs of Blood potassium decreased, Hypokalaemia.
[2n] Musculoskeletal pain (grouped term) includes PTs of Back pain, Bone pain, Limb discomfort, Muscle spasms, Musculoskeletal chest pain, Musculoskeletal pain, Myalgia, Neck pain, Pain in extremity.
[2o] Headache (grouped term) includes PTs of Headache, Migraine, Sinus headache.
[2s] Interstitial lung disease (grouped term) includes PTs of Acute respiratory failure (n=2), Alveolitis (n=2), Atypical pneumonia (n=1), Bronchiectasis (n=1), Bronchitis (n=1), Disease progression (n=1), Hypersensitivity pneumonitis (n=1), Idiopathic interstitial pneumonia (n=1), Interstitial lung disease (n=121), Lower respiratory tract infection (n=1), Lung disorder (n=1), Lung infiltration (n=1), Lung opacity (n=4), Lymphangitis (n=1), Organising pneumonia (n=13), Pneumonia (n=9), Pneumonia bacterial (n=2), Pneumonia fungal (n=1), Pneumonitis (n=160), Pulmonary fibrosis (n=2), Pulmonary mass (n=1), Pulmonary toxicity (n=4), Radiation pneumonitis (n=6), Respiratory failure (n=5). These events were adjudicated as ILD. Some studies did not have adjudication and were excluded for ILD grouped term. The number of patients in the All Tumour Types Pool T-DXd 5.4 mg/kg for ILD Grouped Term was 2553
[2p] Rash (grouped term) includes PTs of Rash, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash pustular.
[2q] Skin hyperpigmentation (grouped term) includes PTs of Pigmentation disorder, Skin discolouration, Skin hyperpigmentation.

Serious adverse event/deaths/other significant events

Serious adverse events

SAEs were collected from the time of informed consent, throughout the treatment period and including the safety follow-up period (defined as 47 days after study drug was discontinued for all studies).

Table 84 Serious Treatment-emergent Adverse Events Reported in ≥ 1% of Patients in the IHC 3+ T DXd 5.4 mg/kg Pool, by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of Patients				
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)	Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)	All Tumour Types T-DXd 5.4 mg/kg Pool (N = 3057)	All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)
Patients with any serious TEAE	124 (35.7)	57 (51.4)	27 (39.7)	863 (28.2)	350 (39.4)
Sepsis	11 (3.2)	8 (7.2)	0	28 (0.9)	10 (1.1)
Urinary tract infection	10 (2.9)	7 (6.3)	2 (2.9)	29 (0.9)	7 (0.8)
Pneumonia	9 (2.6)	5 (4.5)	2 (2.9)	61 (2.0)	28 (3.1)
Vomiting	9 (2.6)	3 (2.7)	2 (2.9)	44 (1.4)	14 (1.6)
Abdominal pain	7 (2.0)	5 (4.5)	1 (1.5)	14 (0.5)	7 (0.8)
COVID-19	7 (2.0)	4 (3.6)	1 (1.5)	48 (1.6)	7 (0.8)
Pneumonitis	7 (2.0)	3 (2.7)	2 (2.9)	61 (2.0)	31 (3.5)
Nausea	7 (2.0)	1 (0.9)	3 (4.4)	34 (1.1)	15 (1.7)
Pleural effusion	6 (1.7)	3 (2.7)	0	19 (0.6)	3 (0.3)
Fatigue	5 (1.4)	3 (2.7)	0	15 (0.5)	7 (0.8)
Cellulitis	5 (1.4)	1 (0.9)	0	16 (0.5)	2 (0.2)
Acute kidney injury	4 (1.2)	3 (2.7)	2 (2.9)	15 (0.5)	9 (1.0)
Dyspnoea	4 (1.2)	2 (1.8)	0	21 (0.7)	6 (0.7)
Anaemia	4 (1.2)	1 (0.9)	0	43 (1.4)	19 (2.1)
Hypoxia	4 (1.2)	0	0	5 (0.2)	1 (0.1)

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

SAEs with an onset or worsening 47 days (28 days for Study J101 and 90 days for Study DL-03) or more after the last dose of study drug, if considered related to the study treatment, were also considered to be TEAEs.

If a patient had multiple occurrences of the same serious PT, the patient was counted once for that serious PT. If a patient had multiple serious PTs, the patient was counted once for each of the different PTs.

TEAEs are sorted by descending frequency in the IHC 3+ T-DXd 5.4 mg/kg Pool.

SAEs in the DP-02 study

Table 85 Serious Adverse Events Reported in at Least 2% of Patients Total by PT (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of patients [a]							
	Cohort 1 biliary tract cancer (N = 41)	Cohort 2 bladder cancer (N = 41)	Cohort 3 cervical cancer (N = 40)	Cohort 4 endometrial cancer (N = 40)	Cohort 5 ovarian cancer (N = 40)	Cohort 6 pancreatic cancer (N = 25)	Cohort 7 rare tumours (N = 40)	Total (N = 267)
Patients with any SAE	23 (56.1)	17 (41.5)	15 (37.5)	15 (37.5)	16 (40.0)	9 (36.0)	19 (47.5)	114 (42.7)
Pneumonia	5 (12.2)	1 (2.4)	1 (2.5)	1 (2.5)	0	0	2 (5.0)	10 (3.7)
Sepsis	2 (4.9)	2 (4.9)	2 (5.0)	1 (2.5)	2 (5.0)	0	1 (2.5)	10 (3.7)
Abdominal pain	1 (2.4)	1 (2.4)	1 (2.5)	0	2 (5.0)	0	2 (5.0)	7 (2.6)
Anaemia	1 (2.4)	0	1 (2.5)	0	2 (5.0)	2 (8.0)	1 (2.5)	7 (2.6)
Urinary tract infection	0	3 (7.3)	1 (2.5)	2 (5.0)	1 (2.5)	0	0	7 (2.6)

Ileus	0	0	1 (2.5)	0	5 (12.5)	0	0	6 (2.2)
Vomiting	0	0	1 (2.5)	1 (2.5)	2 (5.0)	1 (4.0)	1 (2.5)	6 (2.2)

[a] Number (%) of patients with an SAE. Patients with multiple events in the same PT are counted only once in that PT. Patients with events in more than one PT are counted once in each of those PTs. Patients with events in more than one PT within the same SOC are counted only once in that SOC.
Includes AEs with an onset date or worsening on or after the date of first dose and up to and including 47 days following the date of last dose of study medication or before the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment (whichever occurs first). MedDRA version 26.0.
Sorted by decreasing frequency in the total column.

An 8.7% increased rate of SAEs is observed between the 111 patients of the DP-02 study with IHC 3+ and the whole cohort (n=267). The highest frequency of SAEs occurred in the biliary tract tumour cohort (56.1%), with 5/41 patients experiencing pneumonia (12.2%). This is higher than for all other cohorts in the DP-02 as well as the larger pools of IHC 3+ 5.4mg/kg patients and the All Tumour Types 5.4mg/kg where 2.6% and 2.0% experienced pneumonia. The rate of pneumonitis in the DP-02 study was 1.5% (4 patients, where two cases occurred in the biliary tract tumour cohort.

Deaths

Table 86 Primary Cause of Any Deaths and On-treatment Deaths (Safety Analysis Set)

	Number (%) of Patients				
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	**Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)**	**Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)**	**All Tumour Types T-DXd 5.4 mg/kg Pool (N = 3057)**	**All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)**
Any death	209 (60.2)	84 (75.7)	38 (55.9)	1396 (45.7)	529 (59.5)
Adverse event	13 (3.7)	8 (7.2)	7 (10.3)	93 (3.0)	52 (5.8)
Disease progression	91 (26.2)	0	25 (36.8)	643 (21.0)	353 (39.7)
Related to disease under investigation [a]	70 (20.2)	70 (63.1)	0	482 (15.8)	65 (7.3)
Unknown	23 (6.6)	6 (5.4)	4 (5.9)	109 (3.6)	43 (4.8)
Other	12 (3.5)	0	2 (2.9)	69 (2.3)	16 (1.8)
On-treatment death [b]	26 (7.5)	16 (14.4)	9 (13.2)	164 (5.4)	84 (9.4)
Adverse event	10 (2.9)	8 (7.2)	4 (5.9)	72 (2.4)	40 (4.5)
Disease progression	6 (1.7)	0	5 (7.4)	35 (1.1)	35 (3.9)
Related to disease under investigation	8 (2.3)	8 (7.2)	0	48 (1.6)	7 (0.8)
Unknown	0	0	0	4 (0.1)	2 (0.2)
Other	2 (0.6)	0	0	5 (0.2)	0

[a] Within the IHC 3+ T-DXd 5.4 mg/kg Pool, the eCRFs for Study DP-02 recorded "disease under investigation" as a primary cause of death, whereas the eCRFs for Study DB-01, Study DL-01, and DC-02, recorded the term of "disease progression."

[b] On-treatment death was defined as any death that occurred from the date of the first dose to 47 days (28 days for Study J101 and 90 days for Study DL-03) after the last dose of study drug.

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

Table 87 Treatment-emergent Adverse Events Associated with an Outcome of Death in at Least One Patient in the IHC 3+ T DXd 5.4 mg/kg Pool, by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of Patients				
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)	Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)	All Tumour Types T-DXd 5.4 mg/kg Pool (N = 3057)	All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)
Patients with any TEAE associated with an outcome of death	21 (6.1)	11 (9.9)	10 (14.7)	126 (4.1)	82 (9.2)
Death	3 (0.9)	3 (2.7)	0	10 (0.3)	2 (0.2)
Cardiac arrest	2 (0.6)	2 (1.8)	0	2 (0.1)	0
Pneumonitis	2 (0.6)	1 (0.9)	1 (1.5)	14 (0.5)	7 (0.8)
COVID-19	1 (0.3)	1 (0.9)	1 (1.5)	4 (0.1)	4 (0.4)
Cerebrovascular accident	1 (0.3)	1 (0.9)	1 (1.5)	3 (0.1)	1 (0.1)
COVID-19 pneumonia	1 (0.3)	1 (0.9)	0	4 (0.1)	3 (0.3)
Neutropenic sepsis	1 (0.3)	1 (0.9)	0	2 (0.1)	0
Pneumonia	1 (0.3)	1 (0.9)	0	8 (0.3)	2 (0.2)
Disease progression	1 (0.3)	0	2 (2.9)	16 (0.5)	25 (2.8)
Acute kidney injury	1 (0.3)	0	0	2 (0.1)	0
Acute respiratory failure	1 (0.3)	0	0	1 (0.0)	0
General physical health deterioration	1 (0.3)	0	0	3 (0.1)	2 (0.2)
Lymphangitis	1 (0.3)	0	0	1 (0.0)	0
Neoplasm malignant	1 (0.3)	0	0	1 (0.0)	0
Respiratory failure	1 (0.3)	0	0	6 (0.2)	3 (0.3)
Sepsis	1 (0.3)	0	0	6 (0.2)	1 (0.1)
Shock haemorrhagic	1 (0.3)	0	0	1 (0.0)	0

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

A death could be associated with multiple PTs.

If a patient had multiple occurrences of the same PT, the patient was counted once for the specific PT. If a patient had multiple PTs, the patient was counted in each of the different PTs.

TEAEs are sorted by descending frequency in the IHC 3+T-DXd 5.4 mg/kg Pool.

Grade 5 adverse reactions occurred in 1.1% of patients, including ILD/pneumonitis (1.0%) in the All Tumour Types 5.4mg/kg pool.

Deaths in the DP-02 study

Table 88 All Deaths (Full Analysis Set)

Category	Number (%) of patients							
	Cohort 1 biliary tract cancer (N = 41)	Cohort 2 bladder cancer (N = 41)	Cohort 3 cervical cancer (N = 40)	Cohort 4 endometrial cancer (N = 40)	Cohort 5 ovarian cancer (N = 40)	Cohort 6 pancreatic cancer (N = 25)	Cohort 7 rare tumours (N = 40)	Total (N = 267)
All deaths	30 (73.2)	33 (80.5)	20 (50.0)	20 (50.0)	29 (72.5)	21 (84.0)	23 (57.5)	176 (65.9)
Death related to disease under investigation only	23 (56.1)	28 (68.3)	19 (47.5)	16 (40.0)	26 (65.0)	18 (72.0)	18 (45.0)	148 (55.4)

AE with outcome of death only	5 (12.2)	2 (4.9)	0	4 (10.0)	0	1 (4.0)	2 (5.0)	14 (5.2)
Death related to disease under investigation and an AE with outcome of death	1 (2.4)	1 (2.4)	1 (2.5)	0	1 (2.5)	1 (4.0)	1 (2.5)	6 (2.2)
Other deaths [a]	1 (2.4)	2 (4.9)	0	0	2 (5.0)	1 (4.0)	2 (5.0)	8 (3.0)
On-treatment death or death within 47 days of last dose of study medication	8 (19.5)	6 (14.6)	2 (5.0)	6 (15.0)	4 (10.0)	3 (12.0)	5 (12.5)	34 (12.7)
Death related to disease under investigation only	2 (4.9)	3 (7.3)	1 (2.5)	2 (5.0)	3 (7.5)	1 (4.0)	2 (5.0)	14 (5.2)
AE with outcome of death only	5 (12.2)	2 (4.9)	0	4 (10.0)	0	1 (4.0)	2 (5.0)	14 (5.2)
Death related to disease under investigation and an AE with outcome of death	1 (2.4)	1 (2.4)	1 (2.5)	0	1 (2.5)	1 (4.0)	1 (2.5)	6 (2.2)

[a] Patients who died and are not captured in the earlier categories.
Death related to disease under investigation is determined by the Investigator.
Main categories are mutually exclusive; patients are only reported in one category.
AE = adverse event

Table 89 Adverse Events with an Outcome of Death by SOC and PT (Safety Analysis Set)

	Number (%) of patients [a]							
MedDRA system organ class Preferred Term	**Cohort 1 biliary tract cancer (N = 41)**	**Cohort 2 bladder cancer (N = 41)**	**Cohort 3 cervical cancer (N = 40)**	**Cohort 4 endometrial cancer (N = 40)**	**Cohort 5 ovarian cancer (N = 40)**	**Cohort 6 pancreatic cancer (N = 25)**	**Cohort 7 rare tumours (N = 40)**	**Total (N = 267)**
Patients with AE with outcome of death	6 (14.6)	3 (7.3)	1 (2.5)	3 (7.5)	1 (2.5)	2 (8.0)	3 (7.5)	19 (7.1)
Infections and infestations	4 (9.8)	1 (2.4)	1 (2.5)	1 (2.5)	0	0	0	7 (2.6)
COVID-19	1 (2.4)	0	0	0	0	0	0	1 (0.4)
COVID-19 pneumonia	1 (2.4)	0	0	0	0	0	0	1 (0.4)
Neutropenic sepsis	0	1 (2.4)	0	0	0	0	0	1 (0.4)
Pneumonia	2 (4.9)	0	0	1 (2.5)	0	0	0	3 (1.1)
Sepsis	0	0	1 (2.5)	0	0	0	0	1 (0.4)
Nervous system disorders	0	0	0	1 (2.5)	0	0	0	1 (0.4)
Cerebrovascular accident	0	0	0	1 (2.5)	0	0	0	1 (0.4)
Cardiac disorders	1 (2.4)	1 (2.4)	0	0	0	0	0	2 (0.7)
Cardiac arrest	1 (2.4)	1 (2.4)	0	0	0	0	0	2 (0.7)
Vascular disorders	0	0	0	0	1 (2.5)	0	0	1 (0.4)
Hypotension	0	0	0	0	1 (2.5)	0	0	1 (0.4)

Respiratory, thoracic and mediastinal disorders	0	0	0	1 (2.5)	0	1 (4.0)	1 (2.5)	3 (1.1)
Organising pneumonia	0	0	0	1 (2.5)	0	0	0	1 (0.4)
Pneumonitis	0	0	0	0	0	0	1 (2.5)	1 (0.4)
Pulmonary embolism	0	0	0	0	0	1 (4.0)	0	1 (0.4)
General disorders and administration site conditions	1 (2.4)	1 (2.4)	0	0	0	1 (4.0)	2 (5.0)	5 (1.9)
Death	1 (2.4)	1 (2.4)	0	0	0	1 (4.0)	2 (5.0)	5 (1.9)

[a] Number (%) of patients with AE with outcome of death, sorted by international order for SOC and alphabetically for PT. Patients with multiple events in the same PT are counted only once in that PT. Patients with events in more than one PT are counted once in each of those PTs. Patients with events in more than one PT within the same SOC are counted only once in that SOC.
Includes AEs with an onset date or worsening on or after the date of first dose and up to and including 47 days following the date of last dose of study medication or before the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment (whichever occurs first).
MedDRA version 26.0.

Deaths in the DP-02 was primarily related to the disease in question with an overall rate of 55.4% (148 deaths out of 267 patients) and 34 (12.7%) patients died in relation to an AEs on-treatment or within 47 days of last dose of study drug.

Adverse events of special interest

ILD/pneumonitis and LV dysfunction have been identified as AESIs for T-DXd. In the DP-02 "*all cases of potential ILD, based on the current MedDRA version for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure, were submitted to the ILD AC*."

ILD/pneumonitis

Table 90 Interstitial Lung Disease by Adjudicated Grade (Safety Analysis Set)

Adjudicated Outcome/ CTCAE Grade by Adjudication Committee	**Number (%) of Patients**				
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	**Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)**	**Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)**	**All Tumour Types T-DXd 5.4 mg/kg Pool (N = 2553)**	**All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)**
Total number of patients with events adjudicated by the ILD AC [a]	64 (18.4)	23 (20.7)	12 (17.6)	436 (17.1)	167 (18.8)
Adjudicated as ILD					
Any Grade	59 (17.0)	22 (19.8)	8 (11.8)	329 (12.9)	143 (16.1)
Grade 1	12 (3.5)	6 (5.4)	2 (2.9)	76 (3.0)	39 (4.4)
Grade 2	37 (10.7)	13 (11.7)	4 (5.9)	207 (8.1)	73 (8.2)
Grade 3	2 (0.6)	1 (0.9)	0	19 (0.7)	12 (1.3)
Grade 4	0	0	0	1 (0.0)	1 (0.1)
Grade 5	8 (2.3)	2 (1.8)	2 (2.9)	26 (1.0)	18 (2.0)
≥ Grade 3	10 (2.9)	3 (2.7)	2 (2.9)	46 (1.8)	31 (3.5)
Adjudicated as drug-related ILD					
Any Grade	57 (16.4)	21 (18.9)	7 (10.3)	317 (12.4)	139 (15.6)

Adjudicated Outcome/ CTCAE Grade by Adjudication Committee	Number (%) of Patients				
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)	Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)	All Tumour Types T-DXd 5.4 mg/kg Pool (N = 2553)	All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)
Grade 1	12 (3.5)	6 (5.4)	2 (2.9)	73 (2.9)	37 (4.2)
Grade 2	35 (10.1)	12 (10.8)	3 (4.4)	201 (7.9)	72 (8.1)
Grade 3	2 (0.6)	1 (0.9)	0	19 (0.7)	11 (1.2)
Grade 4	0	0	0	0	1 (0.1)
Grade 5	8 (2.3)	2 (1.8)	2 (2.9)	24 (0.9)	18 (2.0)
≥ Grade 3	10 (2.9)	3 (2.7)	2 (2.9)	43 (1.7)	30 (3.4)

[a] The ILD AC assigned grades to those events that were determined to be ILD.
Table includes all events that were submitted to the ILD AC for adjudication. Note that Study DB 12 is excluded from the All Tumour Types T DXd 5.4 mg/kg Pool, as ILD adjudication was not performed for this study.
If a patient had multiple ILD events, the CTCAE grade is shown for the event with the worst grade. If a patient has both missing and non-missing CTCAE grades for a TEAE, the worst grade is based on non-missing grade.
Percentages were calculated using the number of patients in the Safety Analysis Set as the denominator.

ILD/pneumonitis in the DP-02 Study

Table 91 Overview of Adjudicated Drug-related ILD Events (Safety Analysis Set)

Adjudicated drug-related ILD [a]	Cohort 1 biliary tract cancer (N = 41)	Cohort 2 bladder cancer (N = 41)	Cohort 3 cervical cancer (N = 40)	Cohort 4 endometrial cancer (N = 40)	Cohort 5 ovarian cancer (N = 40)	Cohort 6 pancreatic cancer (N = 25)	Cohort 7 rare tumours (N = 40)	Total (N = 267)
Total, n (%) [a, e]	7 (17.1)	4 (9.8)	5 (12.5)	4 (10.0)	4 (10.0)	1 (4.0)	3 (7.5)	8 (10.5)
Grade 1 [b, c]	0	1 (2.4)	0	1 (2.5)	3 (7.5)	1 (4.0)	1 (2.5)	7 (2.6)
Grade 2 [b, c]	5 (12.2)	3 (7.3)	5 (12.5)	2 (5.0)	1 (2.5)	0	1 (2.5)	17 (6.4)
Grade 3 [b, c]	1	0	0	0	0	0	0	1 (0.4)
Grade 5 [b, c]	1 (2.4)	0	0	1 (2.5)	0	0	1 (2.5)	3 (1.1)
Grade ≥ 3 [b, c]	2 (4.9)	0	0	1 (2.5)	0	0	1 (2.5)	4 (1.5)
Leading to treatment discontinuation, n (%) [a, e]	5 (12.2)	3 (7.3)	3 (7.5)	2 (5.0)	1 (2.5)	0	3 (7.5)	17 (6.4)
Duration of first adjudicated drug-related ILD [a, d]								
n	7	4	5	4	4	1	3	28
Median (days)	NE	89.0	60.5	NE	51.0	169.0	30.0	57.0

[a] Drug-related ILD cases adjudicated by the ILD Adjudication Committee. Causality and CTCAE grade is as determined by the ILD Adjudication Committee.

[b] Number (%) of patients with AESIs. Each patient is only represented with the maximum reported CTCAE grade for each AESI group term.

[c] Maximum reported CTCAE grade.

[d] Each patient is represented for the first occurrence of an AESI group term. Lower quartile, median and upper quartile are calculated using the Kaplan-Meier technique. Sorted by AESI group term.

[e] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

Unless specified otherwise, AESIs are identified based on PTs as reported by the Investigator.

Includes AEs with an onset date or worsening on or after the date of first dose and up to and including 47 days following the date of last dose of study medication or before the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment (whichever occurs first).
MedDRA version 26.0.

In the DP-02 study, a total of 38 (14.2%) patients had events of potential ILD, hereof 28 (10.5%) were adjudicated. Potential ILD events were most common among biliary tract cancer patients with 4.9% (2 events) ≥ grade 3 and 19.5% of any grade events compared to 10.5% for the entire DP-02 study.

In patients treated with Enhertu 5.4 mg/kg in clinical studies across multiple tumour types (n = 2553), ILD, pneumonitis, organising pneumonia and acute interstitial pneumonitis were reported by the investigator in 13.8% of patients. ILD/pneumonitis was confirmed by adjudication in 12.9% of patients, leading to drug discontinuation in 8.7% of patients and drug interruption in 3.0% of patients. Most ILD/pneumonitis cases were Grade 1 (3.0%) and Grade 2 (8.1%). Grade 3 cases occurred in 0.7% and one Grade 4 case occurred. Grade 5 (fatal) events occurred in 1.0% of patients. Median time to first onset was 5.5 months (range: -0.3 to 40.2), including two patients adjudicated as having pre-existing ILD. Recovery was not reported for 26.8% of patients with adjudicated ILD/pneumonitis at a median follow up of 279.5 days.

LVEF dysfunction

Since LVEF decrease and congestive heart failure have been reported for drugs in a similar class, LV dysfunction remains an important potential risk globally and as an important identified risk in the EU.

In the reference pools of IHC3+ 5.4mg/kg (n=347) and All Tumour Types (n=3057), the rate of 10-19% LVEF decrease from baseline was 13.0% and 12.5% respectively. An ≥20% decrease in LVEF was 0.3% and 0.7%, respectively. In the DP-02 study these rates were 2.2% and 0.4% respectively with the only case of a ≥20% decrease in LVEF observed among biliary tract cancer patients.

In patients treated with Enhertu 5.4 mg/kg in clinical studies across multiple tumour types (n = 3057), left ventricular dysfunction was reported in 181 patients (5.9%), of which 17 (0.6%) were Grade 1, 147 (4.8%) were Grade 2, 16 (0.5%) were Grade 3 and 1 (<0.1%) were Grade 4. The observed frequency of LVEF decreased based on laboratory parameters (echocardiogram or MUGA scanning) was 411/2740 (15.0%) for Grade 2 and 22/2740 (0.8%) for Grade 3. Treatment with Enhertu has not been studied in patients with LVEF less than 50% prior to initiation of treatment.

Left ventricular dysfunction led to treatment interruption in 31/3057 (1.0%) patients. The median time to worst grade LVEF was 6.9 months, and the median time to recovery (≥90% baseline) from worst grade LVEF was 2.8 months.

LVEF dysfunction in the DP-02 Study

Table 92 Number of patients with adverse events of special interest by group term, preferred term and maximum reported CTCAE grade

Group term / Sub-category / Preferred term	Maximum reported CTCAE grade	Number (%) of patients[a] Cohort 1: Biliary Tract Cancer (N=41)	Cohort 2: Bladder Cancer (N=41)	Cohort 3: Cervical Cancer (N=40)	Cohort 4: Endometrial Cancer (N=40)	Cohort 5: Ovarian Cancer (N=40)	Cohort 6: Pancreatic Cancer (N=25)	Cohort 7: Rare Tumors (N=40)	Total (N=267)
Cardiac failure chronic	Total	0	0	0	0	0	1 (4.0)	0	1 (0.4)
	Grade 3	0	0	0	0	0	1 (4.0)	0	1 (0.4)
	Grade >=3	0	0	0	0	0	1 (4.0)	0	1 (0.4)
Ejection fraction decreased	Total	2 (4.9)	1 (2.4)	2 (5.0)	3 (7.5)	0	0	0	8 (3.0)
	Grade 1	0	0	1 (2.5)	0	0	0	0	1 (0.4)
	Grade 2	1 (2.4)	1 (2.4)	1 (2.5)	3 (7.5)	0	0	0	6 (2.2)
	Grade 3	1 (2.4)	0	0	0	0	0	0	1 (0.4)
	Grade >=3	1 (2.4)	0	0	0	0	0	0	1 (0.4)

[a] Number (%) of patients with AESIs, sorted by AESI group term, AESI sub-category and alphabetically for preferred term and then maximum grade. Each patient is only represented with the maximum reported CTCAE grade for each AESI group term / sub-category / preferred term. Patients with events in more than 1 AESI group term / sub-category / preferred term are counted once in each of those AESI sub-categories / preferred terms.
[b] Drug-related ILD/pneumonitis cases adjudicated by the ILD Adjudication Committee. Causality is as determined by the ILD Adjudication Committee. Preferred terms are as reported by the investigator.
Unless specified otherwise, AESIs are identified based on preferred terms as reported by the investigator.
Includes AEs with an onset date or worsening on or after the date of first dose and up to and including 47 days following the date of last dose of study medication or before the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment (whichever occurs first).
MedDRA version 26.0.

Laboratory findings

Haematology

Table 93 Clinically Important Changes in Haematology Parameters Overall (Safety Analysis Set)

Parameter (unit)	Total n/N (%) of patients [a] (N = 267)	
	≥ 2 CTCAE Grade changes	CTCAE Grade changes to 3 or 4
B-haemoglobin (g/L) - low	53/266 (19.9)	50/266 (18.8)
B-leukocytes (10^9/L) - low	84/266 (31.6)	24/266 (9.0)
B-lymphocytes (10^9/L) – low	88/266 (33.1)	53/266 (19.9)
B-neutrophils (10^9/L) - low	115/266 (43.2)	56/266 (21.1)
B-platelets (10^9/L) - low	42/266 (15.8)	24/266 (9.0)
B-activated partial thromboplastin time (sec) - high	5/144 (3.5)	2/144 (1.4)

[a] N is the number of patients with a baseline value and at least one on-treatment value. Percentages are based on the number of patients with a baseline value and a post-baseline value.
Baseline is defined as the last result obtained prior to the start of study treatment.
Data collected from date of the first dose of study treatment up to 47 days following last dose of study treatment and before the initiation of the first subsequent anti-cancer therapy (whichever occurs first) are summarized.
Maximum CTCAE Grade on treatment is calculated over this period.

Haemoglobin

Table 94 Summary of Shifts from Baseline to Worst Post-baseline CTCAE Grade in Platelet Count Decreased (Safety Analysis Set)

	Baseline CTCAE Grade	Number (%) of Patients with Worst Post-baseline CTCAE Grade						
		Normal	1	2	3	4	Total	Missing
IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Normal	128 (37.4)	111 (32.5)	29 (8.5)	12 (3.5)	5 (1.5)	285 (83.3)	1
	1	2 (0.6)	30 (8.8)	16 (4.7)	7 (2.0)	1 (0.3)	56 (16.4)	0
	2	1 (0.3)	0	0	0	0	1 (0.3)	0
	3	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	Total	131 (38.3)	141 (41.2)	45 (13.2)	19 (5.6)	6 (1.8)	342 (100)	1
	Missing	1	3	0	0	0	4	0
Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)	Normal	35 (31.5)	42 (37.8)	9 (8.1)	7 (6.3)	4 (3.6)	97 (87.4)	0
	1	1 (0.9)	6 (5.4)	5 (4.5)	1 (0.9)	1 (0.9)	14 (12.6)	0
	2	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	Total	36 (32.4)	48 (43.2)	14 (12.6)	8 (7.2)	5 (4.5)	111 (100)	0
	Missing	0	0	0	0	0	0	0
Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)	Normal	31 (45.6)	27 (39.7)	3 (4.4)	1 (1.5)	0	62 (91.2)	0
	1	1 (1.5)	2 (2.9)	3 (4.4)	0	0	6 (8.8)	0
	2	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	Total	32 (47.1)	29 (42.6)	6 (8.8)	1 (1.5)	0	68 (100)	0
	Missing	0	0	0	0	0	0	0
All Tumour Types T-DXd 5.4 mg/kg Pool (N = 3057)	Normal	1437 (47.4)	974 (32.1)	191 (6.3)	91 (3.0)	29 (1.0)	2722 (89.8)	14
	1	8 (0.3)	172 (5.7)	87 (2.9)	31 (1.0)	8 (0.3)	306 (10.1)	2
	2	1 (0.0)	0	1 (0.0)	1 (0.0)	0	3 (0.1)	0
	3	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	Total	1446 (47.7)	1146 (37.8)	279 (9.2)	123 (4.1)	37 (1.2)	3031 (100)	16
	Missing	3	6	0	0	0	9	1

	Baseline CTCAE Grade	Number (%) of Patients with Worst Post-baseline CTCAE Grade						
		Normal	1	2	3	4	Total	Missing
All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)	Normal	282 (37.0)	285 (37.4)	50 (6.6)	24 (3.1)	17 (2.2)	658 (86.4)	46
	1	2 (0.3)	48 (6.3)	27 (3.5)	19 (2.5)	8 (1.0)	104 (13.6)	9
	2	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	Total	284 (37.3)	333 (43.7)	77 (10.1)	43 (5.6)	25 (3.3)	762 (100)	55
	Missing	0	26	9	3	1	39	33

For each group, percentages were based on the number of patients in the Safety Analysis Set who had a baseline and at least one post-baseline assessment.
Baseline value was defined as the last non-missing value prior to the first dose of study drug.

The overall rate of ≥ grade 3 low haemoglobin post-baseline in the DP-02 was 18.8%, which is higher compared to the IHC 3+ 5.4mg/kg pool (10.8%) and the All Tumour Types 5.4mg/kg pool (9.3%). Rates of anaemia by DP-02 cohorts showed that the highest rate of ≥ grade 3 low haemoglobin post-baseline was among patients with ovarian cancer (30%).

Platelets

The shifts from baseline to worst post-baseline CTCAE grade in platelet count decreased, for the safety populations IHC3+ 5.4mg/kg pool and All Tumour Types 5.4mg/kg pool, showed a rate of ≥ grade 3 platelet decrease of 7.4% and 6.3% respectively compared to 9.0% in the DP-02 study.

Within the specific cohorts of the DP-02 study, the rate of ≥ grade 3 platelet count decreased shifts from baseline was highest among ovarian cancer patients (20.0%) while this number was 9.0% for the entire DP-02 study.

Neutrophils

Table 95 Summary of Shifts from Baseline to Worst Post-baseline CTCAE Grade in Neutrophil Count Decreased (Safety Analysis Set)

	Baseline CTCAE Grade	Number (%) of Patients with Worst Post-baseline CTCAE Grade						
		Normal	1	2	3	4	Total	Missing
IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Normal	107 (31.4)	56 (16.4)	91 (26.7)	55 (16.1)	16 (4.7)	325 (95.3)	1
	1	0	0	8 (2.3)	4 (1.2)	1 (0.3)	13 (3.8)	0
	2	0	1 (0.3)	0	0	0	1 (0.3)	0
	3	0	2 (0.6)	0	0	0	2 (0.6)	0
	4	0	0	0	0	0	0	0
	Total	107 (31.4)	59 (17.3)	99 (29.0)	59 (17.3)	17 (5.0)	341 (100)	1
	Missing	1	0	1	1	0	3	2
	Normal	35 (31.5)	16 (14.4)	29 (26.1)	18 (16.2)	13 (11.7)	111 (100)	0

	Baseline CTCAE Grade	Number (%) of Patients with Worst Post-baseline CTCAE Grade						
		Normal	1	2	3	4	Total	Missing
Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)	1	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	Total	35 (31.5)	16 (14.4)	29 (26.1)	18 (16.2)	13 (11.7)	111 (100)	0
	Missing	0	0	0	0	0	0	0
Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)	Normal	28 (43.1)	12 (18.5)	17 (26.2)	5 (7.7)	3 (4.6)	65 (100)	3
	1	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	Total	28 (43.1)	12 (18.5)	17 (26.2)	5 (7.7)	3 (4.6)	65 (100)	3
	Missing	0	0	0	0	0	0	0
All Tumour Types T-DXd 5.4 mg/kg Pool (N = 3057)	Normal	1186 (39.3)	445 (14.7)	762 (25.2)	421 (13.9)	70 (2.3)	2884 (95.6)	20
	1	1 (0.0)	16 (0.5)	41 (1.4)	45 (1.5)	8 (0.3)	111 (3.7)	2
	2	1 (0.0)	3 (0.1)	5 (0.2)	11 (0.4)	1 (0.0)	21 (0.7)	0
	3	0	2 (0.1)	0	0	0	2 (0.1)	0
	4	0	0	0	0	0	0	0
	Total	1188 (39.4)	466 (15.4)	808 (26.8)	477 (15.8)	79 (2.6)	3018 (100)	22
	Missing	6	0	2	1	0	9	8
All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)	Normal	277 (40.0)	71 (10.2)	200 (28.9)	80 (11.5)	49 (7.1)	677 (97.7)	101
	1	0	1 (0.1)	3 (0.4)	6 (0.9)	0	10 (1.4)	4
	2	0	0	3 (0.4)	3 (0.4)	0	6 (0.9)	0
	3	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0
	Total	277 (40.0)	72 (10.4)	206 (29.7)	89 (12.8)	49 (7.1)	693 (100)	105
	Missing	1	0	1	0	1	3	88

For each group, percentages were based on the number of patients in the Safety Analysis Set who had a baseline and at least one post-baseline assessment.
Baseline value was defined as the last non-missing value prior to the first dose of study drug.

In the safety populations IHC3+ 5.4mg/kg pool and All Tumour Types 5.4mg/kg pool, here the rates of ≥ grade 3 shift from baseline neutrophils decreased was 22.3% and 18.4% respectively compared to 21.1% in the DP-02 study.

In patients treated with Enhertu 5.4 mg/kg in clinical studies (n = 3057) across multiple tumour types, neutropenia was reported in 35.9% of patients and 18.5% had Grade 3 or 4 events. Median time to onset was 43 days (range: 0 days to 51.5 months), and median duration of the first event was 22 days (range: 1 day to 30.9 months). Febrile neutropenia was reported in 0.9% of patients and <0.1% were Grade 5 (see section 4.2).

Within the specific cohorts of the DP-02 study, the rate of ≥ grade 3 neutrophils decreased shifts from baseline was highest among pancreatic cancer patients (44.0%) while this number was 37.2% for the entire DP-02 study.

Clinical Chemistry

Table 96 Clinically Important Changes in Clinical Chemistry Parameters Overall (Safety Analysis Set)

Parameter (unit)	Total n/N (%) of patients [a] (N = 267)	
	≥ 2 CTCAE Grade changes	CTCAE Grade Changes to 3 or 4
S/P-alanine aminotransferase (ukat/L) – high	16/266 (6.0)	9/266 (3.4)
S/P-aspartate aminotransferase (ukat/L) – high	15/266 (5.6)	6/266 (2.3)
S/P-alkaline phosphatase (ukat/L) - high	14/266 (5.3)	3/266 (1.1)
S/P-bilirubin (umol/L) - high	28/266 (10.5)	8/266 (3.0)
S/P-creatinine (umol/L) - high	29/266 (10.9)	7/266 (2.6)
S/P-albumin (g/L) - low	65/266 (24.4)	3/266 (1.1)

[a] N is the number of patients with a baseline value and at least one on-treatment value. Percentages are based on the number of patients with a baseline value and a post-baseline value.
Baseline is defined as the last result obtained prior to the start of study treatment.
Data collected from date of the first dose of study treatment up to 47 days following last dose of study treatment and before the initiation of the first subsequent anti-cancer therapy (whichever occurs first) are summarized.
Maximum CTCAE Grade on treatment is calculated over this period.

Serum Creatinine

A total of 15 (4.3%) patients in the IHC 3+ T-DXd 5.4 mg/kg Pool had blood creatinine increased reported as a TEAE, with 1 (0.3%) patient having a Grade 3 event and no patients having events > Grade 3. The overall rate of creatinine increased in the DP-02 study was 2.6%, which was similar to the IHC 3+ T-DXd 5.4 mg/kg Pool, were 18 (5.2%) patients had shifts of ≥2 grades.

Liver function

Table 97 Liver Function Test Abnormalities (Safety Analysis Set)

	Number (%) of Patients				
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)	Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)	All Tumour Types T-DXd 5.4 mg/kg Pool (N = 3057)	All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)
ALT					
Non-missing n [a]	343	111	68	3039	885
Baseline value ≥ ULN	63 (18.4)	21 (18.9)	7 (10.3)	735 (24.2)	138 (15.6)
Maximum post-baseline value					
≥ 3 × ULN	26 (7.6)	14 (12.6)	3 (4.4)	334 (11.0)	69 (7.8)

	Number (%) of Patients				
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	**Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)**	**Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)**	**All Tumour Types T-DXd 5.4 mg/kg Pool (N = 3057)**	**All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)**
≥ 5 × ULN	6 (1.7)	4 (3.6)	1 (1.5)	87 (2.9)	26 (2.9)
≥ 8 × ULN	6 (1.7)	4 (3.6)	1 (1.5)	29 (1.0)	8 (0.9)
≥ 10 × ULN	3 (0.9)	2 (1.8)	1 (1.5)	16 (0.5)	5 (0.6)
≥ 20 × ULN	1 (0.3)	1 (0.9)	1 (1.5)	2 (0.1)	4 (0.5)
AST					
Non-missing n [a]	343	111	68	3038	884
Baseline value ≥ULN	127 (37.0)	25 (22.5)	11 (16.2)	1204 (39.6)	272 (30.8)
Maximum post-baseline value					
≥ 3 × ULN	37 (10.8)	14 (12.6)	7 (10.3)	392 (12.9)	107 (12.1)
≥ 5 × ULN	9 (2.6)	4 (3.6)	2 (2.9)	100 (3.3)	34 (3.8)
≥ 8 × ULN	6 (1.7)	3 (2.7)	0	39 (1.3)	12 (1.4)
≥ 10 × ULN	2 (0.6)	1 (0.9)	0	23 (0.8)	9 (1.0)
≥ 20 × ULN	2 (0.6)	1 (0.9)	0	7 (0.2)	1 (0.1)
ALT or AST					
Non-missing n [a]	343	111	68	3039	885
Baseline ≥ ULN	139 (40.5)	32 (28.8)	13 (19.1)	1305 (42.9)	287 (32.4)
Maximum post-baseline value					
≥ 3 × ULN	52 (15.2)	22 (19.8)	9 (13.2)	526 (17.3)	131 (14.8)
≥ 5 × ULN	10 (2.9)	5 (4.5)	2 (2.9)	147 (4.8)	44 (5.0)
≥ 8 × ULN	7 (2.0)	4 (3.6)	1 (1.5)	52 (1.7)	15 (1.7)
≥ 10 × ULN	3 (0.9)	2 (1.8)	1 (1.5)	29 (1.0)	10 (1.1)
≥ 20 × ULN	3 (0.9)	2 (1.8)	1 (1.5)	9 (0.3)	4 (0.5)
ALP					
Non-missing n [a]	345	111	67	3029	885
Baseline value ≥ ULN	136 (39.4)	38 (34.2)	24 (35.8)	969 (32.0)	340 (38.4)
Maximum post-baseline value					
≥ 1.5 × ULN	149 (43.2)	48 (43.2)	21 (31.3)	1201 (39.7)	401 (45.3)
≥ 2 × ULN	99 (28.7)	32 (28.8)	14 (20.9)	742 (24.5)	267 (30.2)
Total bilirubin					
Non-missing n [a]	345	111	67	3039	884
Baseline value ≥ ULN	12 (3.5)	5 (4.5)	1 (1.5)	116 (3.8)	32 (3.6)
Maximum post-baseline value					
≥ 1.5 × ULN	31 (9.0)	17 (15.3)	3 (4.5)	259 (8.5)	77 (8.7)
≥ 2 × ULN	15 (4.3)	10 (9.0)	2 (3.0)	130 (4.3)	55 (6.2)
≥ 3 × ULN	4 (1.2)	3 (2.7)	1 (1.5)	52 (1.7)	24 (2.7)
TBL elevation concurrent with ALT or AST elevation [b]					
Non-missing n [a]	343	111	0	3037	806
(ALT or AST ≥ 3 × ULN) and TBL ≥ 2 × ULN	8 (2.3)	6 (5.4)	0	63 (2.1)	25 (3.1)

	Number (%) of Patients				
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)	Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)	All Tumour Types T-DXd 5.4 mg/kg Pool (N = 3057)	All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)
TBL elevation concurrent with ALT or AST elevation and ALP < 2 × ULN [b]					
Non-missing n [a]	343	111	0	3025	787
(ALT or AST ≥ 3 × ULN) and ALP < 2 × ULN and TBL ≥ 2 × ULN	4 (1.2)	3 (2.7)	0	36 (1.2)	7 (0.9)

[a] Non-missing n is the number of patients with both baseline and post-baseline data.
[b] Concurrent was defined as abnormalities that occurred within a 28-day window.
Percentages are calculated using the non-missing n as the denominator.
Each patient was counted for only the worst case observed post-baseline.

Table 98 Liver Test Abnormalities (Safety Analysis Set)

Parameter	Number (%) of patients							
	Cohort 1 biliary tract cancer (N = 41)	Cohort 2 bladder cancer (N = 41)	Cohort 3 cervical cancer (N = 40)	Cohort 4 endometrial cancer (N = 40)	Cohort 5 ovarian cancer (N = 40)	Cohort 6 pancreatic cancer (N = 25)	Cohort 7 rare tumours (N = 40)	Total (N = 267)
ALT								
≥3 × to ≤5 × ULN	4 (9.8)	5 (12.2)	2 (5.0)	0	3 (7.5)	4 (16.0)	2 (5.0)	20 (7.5)
>5 × to ≤8 × ULN	0	1 (2.4)	0	1 (2.5)	2 (5.0)	1 (4.0)	0	5 (1.9)
>8 × to ≤10 × ULN	1 (2.4)	0	2 (5.0)	0	0	1 (4.0)	0	4 (1.5)
>10 × to ≤20 × ULN	1 (2.4)	0	0	0	0	0	0	1 (0.4)
>20 × ULN	0	0	0	0	0	0	1 (2.5)	1 (0.4)
AST								
≥3 × to ≤5 × ULN	6 (14.6)	4 (9.8)	2 (5.0)	3 (7.5)	3 (7.5)	4 (16.0)	0	22 (8.2)
>5 × to ≤8 × ULN	1 (2.4)	1 (2.4)	0	0	1 (2.5)	0	0	3 (1.1)
>8 × to ≤10 × ULN	1 (2.4)	0	0	0	1 (2.5)	1 (4.0)	0	3 (1.1)
>10 × to ≤20 × ULN	0	0	1 (2.5)	0	0	0	0	1 (0.4)
>20 × ULN	1 (2.4)	0	0	0	0	0	0	1 (0.4)
Total bilirubin								
≥2 × to ≤3 × ULN	6 (14.6)	0	1 (2.5)	0	3 (7.5)	1 (4.0)	1 (2.5)	12 (4.5)
>3 × to ≤5 × ULN	1 (2.4)	0	1 (2.5)	1 (2.5)	0	0	0	3 (1.1)
>5 × ULN	1 (2.4)	2 (4.9)	1 (2.5)	0	0	1 (4.0)	1 (2.5)	6 (2.2)
ALT or AST								

≥3 × to ≤5 × ULN	9 (22.0)	6 (14.6)	3 (7.5)	3 (7.5)	5 (12.5)	5 (20.0)	2 (5.0)	33 (12.4)
>5 × to ≤8 × ULN	1 (2.4)	1 (2.4)	0	1 (2.5)	2 (5.0)	1 (4.0)	0	6 (2.2)
>8 × to ≤10 × ULN	1 (2.4)	0	2 (5.0)	0	1 (2.5)	1 (4.0)	0	5 (1.9)
>10 × to ≤20 × ULN	1 (2.4)	0	1 (2.5)	0	0	0	0	2 (0.7)
>20 × ULN	1 (2.4)	0	0	0	0	0	1 (2.5)	2 (0.7)
Potential Hy's law [a] ALT or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN	5 (12.2)	2 (4.9)	2 (5.0)	0	1 (2.5)	2 (8.0)	1 (2.5)	13 (4.9)

[a] The onset date of ALT or AST elevation should be prior to or on the onset date of total bilirubin elevation.
Data collected from date of the first dose of study treatment up to 47 days following last dose of study treatment and before the initiation of the first subsequent anti-cancer therapy (whichever occurs first) are summarized.
Patients with multiple abnormalities are included only into the worst category.

The overall rate of significant ALT increased (>5) was 1.9% in the DP-02 study, however the rate of potential Hy's Law was 4.9% (13 patients). Overall, 8 (2.3%) patients in the IHC 3+ T-DXd 5.4 mg/kg Pool had potential Hy's Law. This was similar to the 63 (2.1%) patients who met the criteria in the All Tumour Types T-DXd 5.4 mg/kg Pool.

Hypokalaemia

Overall rate of Hypokalaemia (any grade) in the DP-02 study was 14.6%, highest among cervical cancer patients (22.5%).

Safety in special populations

The CSR and extended safety data tables of DP-02 trial does not include data presentations on sex. The Summary of Clinical Safety includes a section of safety in special populations presented for the IHC3+ 5.4mg/kg pool and, Pooled Safety Outputs includes tables by age, sex and race, but only for the IHC+3 population in the DP-02 study (presented below)

Sex

In the DP-02 study 72.7% of female experienced a grade ≥3 TEAE compared to 71.1% of males. This was higher than for the reference pool IHC3+ 5.4mg/kg and the All Tumour Types 5.4mg/kg (53.9% and 54.2% for males respectively, and 67.4% vs 55.2% for females, respectively.

Age

Table 99 Overall Summary of Treatment-emergent Adverse Events by Age Group in All Tumour Types Pool T-DXd 5.4 mg/kg (Safety Analysis Set

Parameter	**Number (%) of patients**	
	All Tumour Types Pool T-DXd 5.4 mg/kg(N = 3057)	
	Age Group >=65 Years (N = 828)	**Age Group >=75 Years (N = 177)**

Duration of treatment (months)		
Median	8.51	7.62
Minimum, Maximum	0.4, 76.0	0.4, 64.3
Patients with any TEAE	820 (99.0)	175 (98.9)
TEAEs with worst CTCAE >=Grade 3 [a]	508 (61.4)	110 (62.1)
TEAEs with worst CTCAE Grade 3 or 4 [a]	452 (54.6)	94 (53.1)
Serious TEAEs	297 (35.9)	64 (36.2)
TEAEs associated with study drug discontinuation	159 (19.2)	42 (23.7)
TEAEs associated with dose reduction	209 (25.2)	38 (21.5)
TEAEs associated with study drug interruption	417 (50.4)	85 (48.0)
TEAEs associated with an outcome of death	57 (6.9)	17 (9.6)
Patients with any drug-related TEAE [b]	767 (92.6)	166 (93.8)
Drug-related TEAEs with worst CTCAE >=Grade 3 [a]	380 (45.9)	85 (48.0)
Drug-related TEAEs with worst CTCAE Grade 3 or 4 [a]	363 (43.8)	80 (45.2)
Drug-related serious TEAEs	130 (15.7)	28 (15.8)
Drug-related TEAEs associated with study drug discontinuation	131 (15.8)	35 (19.8)
Drug-related TEAEs associated with dose reduction	182 (22.0)	30 (16.9)
Drug-related TEAEs associated with study drug interruption	268 (32.4)	51 (28.8)

Percentages were calculated using the number of patients in the Safety Analysis Set as the denominator.
Age in years was calculated using the date of birth and the date of informed consent.
[a] A patient was counted once at the maximum severity.
[b] If relationship was missing, the TEAE was considered to be related to the drug.

Table 100 Subgroup Analysis of Treatment-Emergent Adverse Events with NCI CTCAE Grade >=3 by Preferred Term

Age: <65 years

	Number (%) of Patients				
MedDRA Preferred Term	IHC 3+ Pool T-DXd 5.4 mg/kg (N=236)	DP02 IHC 3+ subgroup T-DXd 5.4 mg/kg (N=59)	IHC 3+ DG02 T-DXd 6.4 mg/kg (N=41)	All Tumor Types Pool T-DXd 5.4 mg/kg (N=2229)	All Tumor Types Pool T-DXd 6.4 mg/kg (N=546)
Patients with any TEAE with NCI CTCAE grade >=3	142 (60.2)	42 (71.2)	27 (65.9)	1177 (52.8)	386 (70.7)
Anaemia	29 (12.3)	12 (20.3)	4 (9.8)	184 (8.3)	112 (20.5)
Neutrophil count decreased	26 (11.0)	9 (15.3)	3 (7.3)	226 (10.1)	128 (23.4)
Neutropenia	21 (8.9)	5 (8.5)	4 (9.8)	178 (8.0)	22 (4.0)
Fatigue	19 (8.1)	10 (16.9)	1 (2.4)	106 (4.8)	27 (4.9)
Nausea	16 (6.8)	3 (5.1)	4 (9.8)	111 (5.0)	34 (6.2)
Platelet count decreased	14 (5.9)	6 (10.2)	1 (2.4)	92 (4.1)	51 (9.3)
White blood cell count decreased	11 (4.7)	2 (3.4)	4 (9.8)	96 (4.3)	66 (12.1)
Hypokalaemia	9 (3.8)	5 (8.5)	1 (2.4)	70 (3.1)	30 (5.5)
Diarrhoea	9 (3.8)	4 (6.8)	0	52 (2.3)	7 (1.3)
Vomiting	9 (3.8)	1 (1.7)	1 (2.4)	52 (2.3)	13 (2.4)
Asthenia	7 (3.0)	2 (3.4)	0	56 (2.5)	12 (2.2)
Abdominal pain	6 (2.5)	4 (6.8)	2 (4.9)	17 (0.8)	8 (1.5)
Lymphocyte count decreased	6 (2.5)	2 (3.4)	1 (2.4)	61 (2.7)	27 (4.9)
Sepsis	5 (2.1)	3 (5.1)	0	19 (0.9)	5 (0.9)
Cellulitis	5 (2.1)	1 (1.7)	0	10 (0.4)	1 (0.2)
Urinary tract infection	4 (1.7)	4 (6.8)	0	18 (0.8)	3 (0.5)
Pleural effusion	4 (1.7)	3 (5.1)	1 (2.4)	14 (0.6)	2 (0.4)
Hypophosphataemia	4 (1.7)	1 (1.7)	1 (2.4)	8 (0.4)	2 (0.4)
Thrombocytopenia	4 (1.7)	1 (1.7)	1 (2.4)	21 (0.9)	7 (1.3)

Age: >=65 years

MedDRA Preferred Term	Number (%) of Patients IHC 3+ Pool T-DXd 5.4 mg/kg (N=111)	DP02 IHC 3+ subgroup T-DXd 5.4 mg/kg (N=52)	IHC 3+ DG02 T-DXd 6.4 mg/kg (N=27)	All Tumor Types Pool T-DXd 5.4 mg/kg (N=828)	All Tumor Types Pool T-DXd 6.4 mg/kg (N=343)
Patients with any TEAE with NCI CTCAE grade >=3	80 (72.1)	38 (73.1)	11 (40.7)	508 (61.4)	249 (72.6)
Neutrophil count decreased	23 (20.7)	6 (11.5)	3 (11.1)	107 (12.9)	101 (29.4)
Anaemia	17 (15.3)	8 (15.4)	5 (18.5)	118 (14.3)	88 (25.7)
Neutropenia	11 (9.9)	8 (15.4)	0	68 (8.2)	7 (2.0)
Fatigue	11 (9.9)	1 (1.9)	2 (7.4)	42 (5.1)	21 (6.1)
White blood cell count decreased	8 (7.2)	1 (1.9)	1 (3.7)	42 (5.1)	51 (14.9)
Pneumonia	7 (6.3)	5 (9.6)	1 (3.7)	28 (3.4)	15 (4.4)
Nausea	7 (6.3)	1 (1.9)	0	36 (4.3)	17 (5.0)
Sepsis	6 (5.4)	4 (7.7)	0	11 (1.3)	5 (1.5)
Diarrhoea	6 (5.4)	3 (5.8)	0	24 (2.9)	11 (3.2)
Decreased appetite	6 (5.4)	2 (3.8)	2 (7.4)	16 (1.9)	35 (10.2)
Platelet count decreased	6 (5.4)	2 (3.8)	1 (3.7)	36 (4.3)	40 (11.7)
Hypokalaemia	6 (5.4)	2 (3.8)	0	38 (4.6)	15 (4.4)
Febrile neutropenia	5 (4.5)	1 (1.9)	1 (3.7)	15 (1.8)	10 (2.9)
Dyspnoea	5 (4.5)	1 (1.9)	0	11 (1.3)	4 (1.2)
Pneumonitis	4 (3.6)	3 (5.8)	1 (3.7)	13 (1.6)	11 (3.2)
Urinary tract infection	3 (2.7)	3 (5.8)	2 (7.4)	10 (1.2)	7 (2.0)
Acute kidney injury	3 (2.7)	2 (3.8)	1 (3.7)	8 (1.0)	6 (1.7)
Ascites	3 (2.7)	2 (3.8)	1 (3.7)	7 (0.8)	6 (1.7)
Asthenia	3 (2.7)	1 (1.9)	1 (3.7)	36 (4.3)	15 (4.4)

Percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.
The pooled analysis group is based on first dose received for patients in each study.
A TEAE is defined as an AE that occurs, having been absent before the first dose of study drug, or worsens in severity or seriousness after initiating study drug up until 47 days (28 days for J101, 90 days for DL03) after last dose of the study drug. In DP01, DP02, DL03, DL05, DB06, DB07, DG06 and DB12, related SAEs after the last dose of study drug or any AEs after the first subsequent cancer therapy are not considered as TEAE. For other studies in the pooling, relates SAEs and AEs after the first subsequent cancer therapy are considered as TEAE. Please refer to individual SAPs for more details.
Adverse Events are coded using MedDRA Version 27.1 and graded per CTCAE 5.0.
Preferred Terms are sorted by descending frequency for IHC3+ Pool T-DXd 5.4 mg/kg.
If a patient has multiple occurrences of the same preferred term, the patient is counted once for the specific preferred term.
If a patient has multiple preferred terms, the patient is counted in each of the different preferred terms.
IHC3+ Pool T-DXd 5.4 mg/kg: DB01 (N=154), DC02 (N=65), DL01 (N=17) and DP02 (N=111)
All Tumour Types T-DXd 5.4 mg/kg Pooled Data: J101 (N=91), DB01 (N=184), DB02 (N=404), DB03 (N=257), DB04 (N=371), DB06 (N=434), DB07 (N=110), DB12 (N=504), DC02 (N=83), DL01 (N=41), DL02 (N=101), DL03 (N=36), DL05 (N=72), DP01 (N=102), and DP02 (N=267).
All Tumour Types T-DXd 6.4 mg/kg Pooled Data: J101 (N=183), DB01 (N=48), DC01 (N=86), DC02 (N=39), DG01 (N=169), DG02 (N=79), DG06 (N=95), DL01 (N=140), and DL02 (N=50).

In terms of age, patients above 65 had similar rates of grade 3 toxicity compared to patients below 65 (73.1% vs 71.2%). Differences in toxicity by age in reference pools was much larger with 60.2% vs 72.1% by age in the IHC+3 5.4mg/kg pool and 52.8% vs 72.6% in the All Tumour Types 5.4mg/kg pool.

In patients treated with Enhertu 5.4 mg/kg in clinical studies across multiple tumour types (n = 3057), 27.1% were 65 years or older and 5.8% were 75 years or older. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged 65 years or older (48.2%) as compared to patients younger than 65 years old (44.3%), leading to more discontinuations due to adverse reactions. The incidence of fatal adverse reactions was 2.2% in patients aged 65 years or older and 0.8% in patients younger than 65 years of age.

Race

The white patient population of the DP-02 study with IHC+3 experienced less grade ≥3 TEAE toxicity than the Asian patient population (62.5% vs 89.5%). This phenomenon was experienced across all reference pools with 61.9% vs 66.7% in the IHC3+ 5.4mg/kg pool and 51.8% vs 60.7% in the All Tumour Types 5.4mg/kg pool.

Discontinuation due to adverse events

The proportion of patients discontinued from study drug was markedly lower in the All Tumour Types T-DXd 5.4 mg/kg compared to the IHC 3+ T-DXd 5.4 mg/kg Pool and the patients in DP-02-study (81.7% vs 94.8% and 93.7%, respectively).

Discontinuation of therapy due to an adverse reaction occurred in 10.8% of patients in the All Tumour Types 5.4mg/kg pool. The most frequent adverse reaction associated with permanent discontinuation was ILD/pneumonitis (8.7%).

Table 101 Treatment-emergent Adverse Events Leading to Study Drug Discontinuation in at Least One Patient in the IHC 3+ T DXd 5.4 mg/kg Pool, by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of Patients				
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)	Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)	All Tumour Types T-DXd 5.4 mg/kg Pool (N = 3057)	All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)
Patients with any TEAE associated with any study drug discontinuation	60 (17.3)	20 (18.0)	12 (17.6)	485 (15.9)	192 (21.6)
Pneumonitis	28 (8.1)	12 (10.8)	5 (7.4)	164 (5.4)	63 (7.1)
Interstitial lung disease	8 (2.3)	2 (1.8)	2 (2.9)	110 (3.6)	39 (4.4)
Organising pneumonia	3 (0.9)	1 (0.9)	0	7 (0.2)	2 (0.2)
Platelet count decreased	3 (0.9)	1 (0.9)	0	11 (0.4)	3 (0.3)
Pneumonia	2 (0.6)	2 (1.8)	0	17 (0.6)	8 (0.9)
Dyspnoea	2 (0.6)	0	0	5 (0.2)	2 (0.2)
Back pain	1 (0.3)	1 (0.9)	0	1 (0.0)	0
Liver abscess	1 (0.3)	1 (0.9)	0	1 (0.0)	0
COVID-19 pneumonia	1 (0.3)	0	1 (1.5)	2 (0.1)	4 (0.4)
Acute hepatitis B	1 (0.3)	0	0	1 (0.0)	0
Alcoholic liver disease	1 (0.3)	0	0	1 (0.0)	0
Alveolitis	1 (0.3)	0	0	1 (0.0)	0
Cardiac failure congestive	1 (0.3)	0	0	1 (0.0)	0
Diarrhoea	1 (0.3)	0	0	2 (0.1)	1 (0.1)
Gamma-glutamyltransferase increased	1 (0.3)	0	0	5 (0.2)	0
Neuropathy peripheral	1 (0.3)	0	0	1 (0.0)	1 (0.1)
Neutrophil count decreased	1 (0.3)	0	0	4 (0.1)	0
Pancytopenia	1 (0.3)	0	0	2 (0.1)	0
Performance status decreased	1 (0.3)	0	0	1 (0.0)	0
Sepsis	1 (0.3)	0	0	4 (0.1)	2 (0.2)
Thrombocytopenia	1 (0.3)	0	0	6 (0.2)	2 (0.2)
Veno occlusive liver disease	1 (0.3)	0	0	1 (0.0)	0
White blood cell count decreased	1 (0.3)	0	0	1 (0.0)	1 (0.1)

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

If a patient had multiple occurrences of the same PT, the patient was counted once for that PT. If a patient had multiple PTs, the patient was counted in each of the different PTs.

Drug discontinuation in the DP-02 study

Table 102 Adverse Events Leading to Discontinuation of T-DXd Reported in at Least 2 Patients Total by PT (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of patients [a]							
	Cohort 1 biliary tract cancer (N = 41)	Cohort 2 bladder cancer (N = 41)	Cohort 3 cervical cancer (N = 40)	Cohort 4 endometrial cancer (N = 40)	Cohort 5 ovarian cancer (N = 40)	Cohort 6 pancreatic cancer (N = 25)	Cohort 7 rare tumours (N = 40)	Total (N = 267)
Patients with any AE leading to discontinuation of T-DXd [b]	8 (19.5)	4 (9.8)	4 (10.0)	3 (7.5)	3 (7.5)	3 (12.0)	7 (17.5)	32 (12.0)
Pneumonitis	5 (12.2)	3 (7.3)	2 (5.0)	2 (5.0)	0	0	2 (5.0)	14 (5.2)
Interstitial lung disease	0	1 (2.4)	1 (2.5)	0	1 (2.5)	0	2 (5.0)	5 (1.9)
Pneumonia	1 (2.4)	0	0	1 (2.5)	0	0	0	2 (0.7)
Sepsis	0	0	1 (2.5)	0	1 (2.5)	0	0	2 (0.7)
Anaemia	0	0	0	0	1 (2.5)	1 (4.0)	0	2 (0.7)
Blood bilirubin increased	1 (2.4)	0	0	0	0	0	1 (2.5)	2 (0.7)

[a] Number (%) of patients with an AE leading to discontinuation of IP. Patients with multiple events in the same PT are counted only once in that PT. Patients with events in more than one PT are counted once in each of those PTs. Patients with events in more than one PT within the same SOC are counted only once in that SOC.
[b] Action taken = drug permanently discontinued.
Includes AEs with an onset date or worsening on or after the date of first dose and up to and including 47 days following the date of last dose of study medication or before the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment (whichever occurs first).
MedDRA version 26.0.
Sorted by decreasing frequency in the total column

The highest treatment discontinuation rate was seen among biliary tract cancer patients (19.5%). For comparison the IHC3+ 5.4mg/kg pool had an overall discontinuation rate of 17.3% and the All Tumour Types pool had a rate of 15.9%. The main reason in 5/7 DP-02 cohort was pneumonitis with the highest observed rate among biliary tract cancer patients (12.2%). The rate among the larger pools were 8.1% and 5.4% for the IHC3+ 5.4mg/kg pool and All Tumour Types pool respectively.

Dose reductions

Table 103 Treatment-emergent Adverse Events Leading to Dose Reduction Reported in ≥ 1% of Patients in the IHC 3+ T DXd 5.4 mg/kg Pool, by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of Patients				
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)	Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)	All Tumour Types T-DXd 5.4 mg/kg Pool (N = 3057)	All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)
Patients with any TEAE associated with dose reduction	104 (30.0)	39 (35.1)	15 (22.1)	739 (24.2)	268 (30.1)
Fatigue	22 (6.3)	8 (7.2)	3 (4.4)	107 (3.5)	48 (5.4)
Nausea	18 (5.2)	7 (6.3)	5 (7.4)	149 (4.9)	50 (5.6)
Neutrophil count decreased	13 (3.7)	5 (4.5)	4 (5.9)	60 (2.0)	50 (5.6)
Diarrhoea	8 (2.3)	5 (4.5)	1 (1.5)	45 (1.5)	12 (1.3)
Platelet count decreased	7 (2.0)	4 (3.6)	0	55 (1.8)	30 (3.4)

MedDRA Preferred Term	Number (%) of Patients				
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DP-02 IHC 3+ T-DXd 5.4 mg/kg (N = 111)	Study DG-02 IHC 3+ T-DXd 6.4 mg/kg (N = 68)	All Tumour Types T-DXd 5.4 mg/kg Pool (N = 3057)	All Tumour Types T-DXd 6.4 mg/kg Pool (N = 889)
Neutropenia	7 (2.0)	3 (2.7)	0	41 (1.3)	3 (0.3)
Vomiting	7 (2.0)	2 (1.8)	0	46 (1.5)	5 (0.6)
Asthenia	6 (1.7)	4 (3.6)	0	59 (1.9)	14 (1.6)
Anaemia	6 (1.7)	3 (2.7)	0	34 (1.1)	14 (1.6)
Blood bilirubin increased	6 (1.7)	1 (0.9)	0	20 (0.7)	3 (0.3)
Pneumonitis	5 (1.4)	3 (2.7)	0	22 (0.7)	4 (0.4)
Febrile neutropenia	4 (1.2)	2 (1.8)	2 (2.9)	14 (0.5)	12 (1.3)
Interstitial lung disease	4 (1.2)	0	0	22 (0.7)	1 (0.1)

Percentages were calculated using the number of patients in the Safety Analysis Set as the denominator.
If a patient had multiple occurrences of the same PT, the patient was counted once for that PT. If a patient had multiple PTs, the patient was counted in each of the different PTs.
TEAEs are sorted by descending frequency in the IHC 3+ T-DXd 5.4 mg/kg Pool.

Dose reductions in the DP-02 study

Table 104 Adverse Events Leading to T-DXd Dose Reduction Reported in at Least 2% of Patients Total by PT (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of patients [a]							
	Cohort 1 biliary tract cancer (N = 41)	Cohort 2 bladder cancer (N = 41)	Cohort 3 cervical cancer (N = 40)	Cohort 4 endometrial cancer (N = 40)	Cohort 5 ovarian cancer (N = 40)	Cohort 6 pancreatic cancer (N = 25)	Cohort 7 rare tumours (N = 40)	Total (N = 267)
Patients with an AE leading to dose reduction of T-DXd [b]	10 (24.4)	7 (17.1)	9 (22.5)	12 (30.0)	17 (42.5)	0	6 (15.0)	61 (22.8)
Fatigue	3 (7.3)	0	3 (7.5)	0	5 (12.5)	0	2 (5.0)	13 (4.9)
Nausea	1 (2.4)	1 (2.4)	2 (5.0)	3 (7.5)	4 (10.0)	0	1 (2.5)	12 (4.5)
Diarrhoea	3 (7.3)	2 (4.9)	3 (7.5)	1 (2.5)	0	0	0	9 (3.4)
Neutropenia	1 (2.4)	3 (7.3)	1 (2.5)	1 (2.5)	1 (2.5)	0	0	7 (2.6)
Platelet count decreased	1 (2.4)	0	0	2 (5.0)	4 (10.0)	0	0	7 (2.6)
Neutrophil count decreased	2 (4.9)	1 (2.4)	0	1 (2.5)	1 (2.5)	0	1 (2.5)	6 (2.2)

[a] Number (%) of patients with AE leading to dose reduction. Patients with multiple events in the same PT are counted only once in that PT. Patients with events in more than 1 PT are counted once in each of those PTs. Patients with events in more than 1 PT within the same SOC are counted only once in that SOC.
[b] AE action taken = dose reduced.
Includes AEs with an onset date or worsening on or after the date of first dose and up to and including 47 days following the date of last dose of study medication or before the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment (whichever occurs first). MedDRA version 26.0.
Sorted by decreasing frequency in the total column.

Overall, 30% of patients in the IHC 3+ 5.4 mg/kg pool and All Tumour Types 5.4mg/kg had TEAEs leading to dose reduction, with fatigue, nausea, neutrophil count decreased most commonly reported

in ≥ 2% of patients. In the DP-02 study, rate of dose reduction was highest among ovarian cancer patients (42.5%) with an overall 22.8% rate of dose reduction for the total study. This was 35.1% for the patients in the DP-02 study with IHC3+. The most common reasons for dose reductions across studies were fatigue, nausea, diarrhoea and neutropenia.

Dose reductions occurred in 21.1% of patients in the All Tumour Types 5.4mg/kg pool. The most frequent adverse reactions associated with dose reduction were fatigue (5.9%), nausea (4.9%), neutropenia (3.3%) and thrombocytopenia (2.2%).

Dose interruption

Dose interruptions due to adverse reactions occurred in 34.2% of patients in the All Tumour Types 5.4mg/kg pool. The most frequent adverse reactions associated with dose interruption were neutropenia (12.7%), fatigue (4.4%), anaemia (4.3%), upper respiratory tract infection (3.8%), leukopenia (3.1%), ILD/pneumonitis (3.0%), thrombocytopenia (2.8%) and pneumonia (2.5%).

Post marketing experience

Cumulatively, since the first approval of T-DXd on 20 December 2019 through 19 December 2024 (the DCO of the latest PBRER), the estimated cumulative post-marketing patient exposure was 80,768.5 patient years. During the latest reporting period (20 June 2024 to 19 December 2024), no new data became available that would impact the benefit-risk assessment for T-DXd.

No new safety signals have been identified based on post-marketing safety reports.

2.5.1. Discussion on clinical safety

The pivotal safety data for the evaluation of safety and tolerability in the proposed indication is pooled from 347 patients with HER2-positive (IHC 3+) solid tumours who received T-DXd 5.4 mg/kg Q3W across 4 studies and compared to the IHC 3+ T-DXd 5.4 mg/kg and the DP-02 study patients with IHC3+ (n=111). For the assessment procedure, DP-02 will be considered the pivotal safety trial with the IHC 3+ T-DXd 5.4 mg/kg pool as supportive, furthermore patients receiving 6.4mg/kg dose in these trials will not be assessed as the posology suggested for the tissue agnostic indication specifies a 5.4mg/kg dose. The splitting of the DP-02 safety population by IHC 3+ is acceptable (into 111 patients with IHC 3+ and 156 below).

The All Tumour Types T-DXd 5.4 mg/kg is a reference pool of 3057 trial patients, is presented for safety comparison and used as reference for the safety information presented in the SmPC. Importantly, this also entails that patients from the DP-02 study with IHC below 3+ are tallied into the All Tumour Types pool and not in the IHC 3+ T-DXd 5.4 mg/kg and DP-02 IHC 3+ T-DXd 5.4 mg/kg Pools, making this pivotal study pool small (n=111) with limited precision based on a biomarker which is not expected (mechanistically nor statistically) to impact safety parameters. However, this is considered acceptable as the indication sought is based on IHC 3+ and the safety data is supplemented with the larger supportive IHC 3+ pool (n=347) in the context of an approved drug with a large background safety population (i.e. All Tumour Types T-DXd 5.4 mg/kg reference pool)

These **segmentations of the safety population** allow an assessment based on a large safety database encompassing differing and varied histologies including rare tumour types. Importantly for the context of this assessment, the All Tumour Types reference pool had a population of better ECOG performance score, younger patients with a higher proportion of females with better renal and hepatic function than the DP-02 IHC+3 study patients and the IHC3+ 5.4mg/kg supportive pool. For instance, the proportion of patients below the age of 65 in the All Tumour Types reference pool was 72.9% while

it was only 53.2% among patients with IHC+3 in DP-02 pivotal trial significantly impacting safety outcomes. Furthermore, the patients in the IHC 3+ T-DXd Pool were more heavily pre-treated than the All Tumour Types reference pool and the DP-02 study patients with 42.5% of patients having received more than 5 prior lines of therapy compared to 22.2% and 9.9% for the other pools respectively.

Exposure data indicates that the treatment duration, number of cycles, and RDI were generally similar across the different pools of patients.

Exposure across the cohorts of the DP-02 study showed high range from 2.07 months (pancreatic patients) to 8.97 months of median exposure with relative dose intensity (RDI) remaining relatively stable from 95.35% to 100%. Pancreatic patients showed lowest exposure, which align clinically with a low ORR of 4%.

The **overall safety profile of T-DXd** is deemed consistent across safety pools. Every patient treated with Enhertu also developed a TEAE (range: 98.6% – 100%). Incidences of TEAEs of ≥ Grade 3, SAE and deaths associated with an TEAE in the DP-02 pivotal trial was 63.3%, 42.7% and 7.1%, respectively. All three major safety parameters were worse when the DP-02 population was split into IHC3+ and lower expression, with 72.1% TEAEs of ≥ Grade 3, 51.4% SAEs and 9.9% deaths among patients with IHC3+. Compared to the All Tumour Types reference pool, the IHC 3+ supportive pool had a slightly higher percentage of patients with TEAEs of ≥ Grade 3 (64.0% vs 55.1%) and higher percentage of patients with treatment-emergent SAEs (35.7% vs 28.2%), and lastly, similar incidences of patients with TEAEs associated with an outcome of death (6.1% vs 4.1%) was observed between the two pools. However, the differences between the two pools are not concerning and it is most likely a result of differing population profiles.

The different safety pools were overall similar in terms of **common TEAEs,** as were the frequencies of TEAEs of the IHC 3+ DP-02 study population (n=111) compared to the whole study population of the DP-02 study (n=267). Compared to the large All Tumour Types reference pool, the IHC 3+ patients experienced similar rates of common TEAEs in line with the established safety profile of Enhertu when considering the differences in population size and characteristics. The most common TEAEs experienced among patients with IHC 3+ were nausea (69.7%), fatigue (41.2%), vomiting (35.7%), anaemia (35.2%), decreased appetite (34.9%), alopecia (33.7%), diarrhoea (32.3%), constipation (28.8%) and neutrophil count decreased (23.1%), which were also the most common TEAEs experienced among patients the ALL Tumour Types reference pool.

Consistent with the observed differences in population characteristics and expected higher burden of toxicity among older and more frail populations of the pivotal trial and the supportive IHC+3 population, there was a markedly higher rate of almost 10% more **TEAE of grade 3 or above** in the IHC 3+ supportive population (64%) and 16% more in the small DP-02 IHC 3+ population (72.1%) compared with the All Tumour Types reference pool (55.1%). TEAEs of grade 3 or above in the DP-02 study IHC3+ was consistent with prior safety populations with neutropenia (11.7%), anaemia (18%) and fatigue (9.9%) being the most common TEAEs. Differences in rates of toxicity between the DP-02 IHC3+ population and the IHC 2+/IHC 1+ are most likely a reflection of differences in demographic variables and longer exposure in the IHC3+ population (cumulative safety outcomes).

Overall rate of **SAEs** in the DP-02 study was 42.7% and an 8.7% increased rate of SAEs is observed between the 111 patients of the DP-02 study (51.4%) with IHC 3+ and the whole cohort (n=267), which is likely a reflection of differences in demographic variables and longer exposure in this group. SAEs among the patients with biliary tract cancer was uncharacteristically high (56.1%) compared to the whole cohort (42.7%) as well as the large safety reference pool of All Tumour Types (28.7%). This was driven mainly by a high rate of pneumonia (12.2%) albeit in numerically small numbers (5

patients) and it has been reported that rates of infections are higher among biliary cancer patients than other cancer diagnoses in the DP-02 trial.

The **cohorts of the DP-02 trial** are small with 25-40 patients in each cohort, which likely induce a high amount of uncertainty in estimates of safety parameters. Again, almost all patients on Enhertu developed a TEAE. TEAEs of grade 3 or above was highest in the biliary tract patients and lowest among rare tumours (73.2% vs 55%), which can be explained by the differing underlying patients profiles of these diseases and is also markedly observed in TEAEs with an outcome of death where the highest proportion was observed in the biliary tumour cohort (14.6%, 6/41 patients). Consistent with the safety profile of Enhertu, the most common TEAEs in the DP-02 study was nausea (64.8%), anaemia (44.9%), diarrhoea (33.7%), fatigue (30.3%) and neutropenia (20.2%). High variability was observed between cohorts, which is likely due to the small number of patients and underlying patient differences.

The pattern of deaths in the DP-02 study (IHC3+ and below groups) and the larger IHC 3+ T-DXd Pool are comparable with the All Tumour Types reference pool. Frequencies of Grade 5 TEAEs were 9.9% in study DP-02 IHC3+ T-DXd 5.4 mg/kg and 4.1% in the All Tumour Pool 5.4 mg/kg. TEAEs occurring in more than one patient in study DP-02 IHC3+ T-DXd 5.4 mg/kg were cardiac arrest (n=2) and death (n=3). Drug-related Grade 5 TEAE occurred in 3 patients (2.7%): pneumonitis, neutropenic sepsis, and pneumonia in one patient each. There were no signals for a new safety signal. The higher rate of SAE and deaths within the biliary tract cancer groups of the DP-02 study (14.6%), might be related to the specific patient and disease characteristics of this population compared to the other cohorts.

The common **ADRs** in the IHC 3+ supportive pool are consistent with the most common adverse events captured in the DP-02 pivotal trial. Some differences between IHC 3+ supportive pool and the DP-02 study was observed in rates of grade 3 or above ADRs are higher for anaemia (17.6% vs 13.3%) in the DP-02 study population compared the IHC 3+ reference pool, but lower for neutropenia (11.2% vs 22.8%) and fatigue (7.5% vs 11.2%) and most likely reflect variations owed to sample size differences. No new ADRs have been identified.

Overall **treatment discontinuation** from any AE in the DP-02 study was 12% (18% for patients with IHC 3+). The most common reason for discontinuation was pneumonitis (5.2% overall) with the highest observed rate among biliary tract cancer patients (12.2% / 5 patients). This is acceptable and in line with rates of discontinuations in the reference pools (IHC+3 and All tumour types), where the rates were 17.3% and 15.9%. Here pneumonitis was also the most common cause of discontinuation (8.1% and 5.4%, respectively). Dose reductions were common in the DP-02 study (22% for the entire study and 35.1% for the IHC3- patients). This was comparable to the reference studies where around 24.2% of patients experienced dose reductions. While rates of specific TEAEs leading to dose reduction varied between studies, the most common TEAEs were fatigue, nausea, diarrhoea and neutropenia and remained largely similar between studies.

Adverse events of special interest concern ILD pneumonitis and LVEF decreases in relation to Enhertu. The overall rate of adjudicated all-cause ILD/pneumonitis in the DP-02 study (10.5% any grade, 1.5% grade ≥ 3) was similar to that of reference trial safety populations i.e. the IHC3+ supportive pool (17.0% any grade, 2.9% grade ≥ 3) and the All Tumour Types reference pool (12.9% any grade, 1.8% grade ≥ 3). There were not more deaths from ILD/pneumonitis in the IHC3+ DP-02 than in the other safety pools (1.8% vs 2.3% and 1.0% respectively). Of the 57 patients who had events adjudicated as drug-related ILD in the IHC 3+ T-DXd 5.4 mg/kg Pool, 41/57 (71.9%) patients had events that had resolved, resolved with sequelae, or were resolving at the time of the DCO. LVEF decreases in the DP-02 study was not higher than the observed rates in reference pools, however LVEF dysfunction are considered too rare an event to manifest informatively in the small cohorts of the DP-

02 study (n~40). Of the 307 patients in the IHC 3+ T-DXd 5.4 mg/kg Pool who had a post-baseline LVEF value, 48 (15.6%) had values that met the laboratory criteria for a Grade 2 LVEF decrease, and 1 (0.3%) had values that met the criteria for a Grade 3 decrease, with no Grade 4 decrease. Results were comparable to the All Tumour Types T-DXd 5.4 mg/kg Pool. A warning in section 4.4 of the SmPC already mentions Cases of interstitial lung disease (ILD), and/or pneumonitis, have been reported with Enhertu (see section 4.8). Fatal outcomes have been observed. Patients should be advised to immediately report cough, dyspnoea, fever and/or any new or worsening respiratory symptoms as well as a warning on left ventricular ejection fraction (LVEF) function (LVD0), where standard cardiac function testing (echocardiogram or MUGA [multigated acquisition] scanning) should be performed to assess LVEF prior to initiation of Enhertu and at regular intervals during treatment as clinically indicated. LVD should be managed through treatment interruption. Enhertu should be permanently discontinued if LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed. Enhertu should be permanently discontinued in patients with symptomatic congestive heart failure (CHF) (please also see RMP).

The small samples of patients in each cohort of DP-02 study incur a high level of uncertainty about the true rate of haematological **laboratory findings** among these patients. With this in mind, it is accepted that the observed higher rate of haematological toxicity is not significantly worse among these patients than what can be expected from treating a frailer and more comorbid population (i.e. than breast cancer patients). In the safety populations IHC3+ reference pool and All Tumour Types supportive pool, the rates of ≥ grade 3 shift from baseline neutrophils decreased was 22.3% and 18.4% respectively compared to 21.1% in the DP-02 study. Among the specific cohorts this was highest among patients with bladder cancer (34.2%). As stated in section 4.4 of the SmPC: cases of neutropenia, including febrile neutropenia with a fatal outcome, were reported in clinical studies of Enhertu. Complete blood counts should be monitored prior to initiation of Enhertu and prior to each dose, and as clinically indicated. Based on the severity of neutropenia, Enhertu may require dose interruption or reduction (see section 4.2), please also see RMP.

The overall rate of significant ALT increased (ULN >5) was 1.9% in the DP-02 study and across the cohorts significant increases in AST and ALT were low (~1.5%). However, the rate of potential Hy's Law was 4.9% (13 patients). Overall, 8 (2.3%) patients in the IHC 3+ supportive pool had cases of potential Hy's Law. This was similar to the 63 (2.1%) patients who met the criteria in the All Tumour Types reference pool. At baseline, 40% had mild renal impairment, and 15% moderate impairment. As previously shown, the proportion with drug-related ILD increased with increasing severity of renal impairment. This is already reflected in section 4.2 and 4.4 of the SmPC.

Safety of special populations in the DP-02 study showed that 72.7% of female experienced a grade ≥3 TEAE compared to 71.1% of males. This was higher than for the reference pools IHC3+ supportive pool and the All Tumour Types reference pool, but acceptable given the differences in population variables (53.9% and 54.2% for males respectively, and 67.4% vs 55.2% for females, respectively. In terms of age, patients above 65 had similar rates of grade 3 toxicity compared to patients below 65 (73.1% vs 71.2%). Differences in toxicity by age in reference pools was much larger with 60.2% vs 72.1% by age in the IHC+3 supportive pool and 52.8% vs 72.6% in the All Tumour Types reference pool. Finally, the incidence of SAE pneumonitis plus ILD was higher in patients >65 years of age (5.8%) vs <65 years of age (1.7%), which was consistent finding across the reference pools following the higher overall incidence SAEs with higher age. As stated in section 4.4 of the SmPC: 'Enhertu can cause foetal harm when administered to a pregnant woman. In post-marketing reports, use of trastuzumab, a HER2 receptor antagonist, during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities and neonatal death.' Please also see RMP.

Quite markedly, Asian patients with IHC3+ in the DP-02 trial experienced significantly higher rates of grade ≥3 TEAEs than the white patient population (89.5% vs 62.5%), a difference which was also significantly higher than for Asian/white toxicity comparisons in reference populations (61.9% vs 66.7% in the IHC3+ 5.4mg/kg pool and 51.8% vs 60.7% in the All Tumour Types 5.4mg/kg pool). However, only 38 Asian patients were included with IHC3+ population, which adds uncertainty about whether this was due to chance.

ADA prevalence at baseline or postbaseline was 6.6% and TE-ADA incidence was 0.6% in the IHC 3+ T-DXd 5.4 mg/kg Pool. These results were comparable to the overall safety pool and confirm the low immunogenic potential of T-DXd. There was no impact on PK, efficacy or safety based on the totality of immunogenicity data for T-DXd.

Finally, no new safety signals have been identified based on post-marketing safety reports and no significant overall changes in safety happened between the primary CSR (05 October 2023) and the CSR Addendum 1 (15 April 2025). Frequency of SAEs were 42.7% in the primary CSR and reached 43.1% in the addendum 1. There were no added deaths in relation to an AE, deaths on treatment or within 47 days from last dose between the updates.

2.5.2. Conclusions on clinical safety

The safety profile of T-DXd in the DP-02 pivotal trial and among patients with IHC3+ diseases is consistent with prior safety populations including specific AEs (ILD/pneumonitis). No new adverse events or any AEs with a clearly higher frequency or severity were identified in the IHC3+ T-Dxd 5.4 mg/kg pool compared to the all tumours 5.4 mg/kg pool. Increased toxicity was observed in the DP-02 trial patients compared with the safety reference data. However the DP-02 study population was slightly older and had received more lines of therapy, which may explain the higher rates observed across major safety outcomes.

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 11 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 11 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 11 with the following content:

Safety concerns

Table 105 Summary of Safety Concerns

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

Pharmacovigilance plan

Table 106 Ongoing and Planned Additional Pharmacovigilance Activities

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

Risk minimisation measures

Table 107 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Recommendations for monitoring of left ventricular dysfunction are included in SmPC Section 4.4. Dose modification guidance for managing the risk of left ventricular dysfunction is included in SmPC Section 4.2. Additional risk minimisation activities: None	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 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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Missing Information		
Use in patients with severe hepatic impairment	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 5.2 Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Long-term safety	Routine risk minimisation measures: None Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

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

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4. 4.8, 5.1 and 5.2 of the SmPC have been updated. Particularly, a new warning with regard to efficacy across other unresectable or metastatic solid tumours has been added to the product information. 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:

- Enhertu is prescribed by a physician and administered intravenously under the supervision of a healthcare professional at a hospital/clinic setting. The posology, administration and method of reconstitution for the extension of indication is unchanged.
- The updates to the PL, including the safety sections, are not significant and utilise well recognised lay terms. Furthermore, the PL will be kept identical in format size, colours, layout/design as illustrated in the agreed mock-ups.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Enhertu (trastuzumab deruxtecan) is included in the additional monitoring list as it is approved under a conditional marketing authorisation [REG Art 14-a].

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The agreed indication is: 'Other unresectable or metastatic solid tumours.

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumours who have received prior treatment and who have no satisfactory treatment options (see sections 4.4 and 5.1; for biomarker-based patient selection, see section 4.2).'

3.1.1. Disease or condition

HER2 (IHC 3+) expression has been observed across diverse solid tumours[3]. Historically, HER2 expression has been defined in breast and GC as IHC 3+, or IHC 2+ with amplification, but HER2-expression, with or without ERBB2 amplification has been described more widely, including in biliary tract cancer, breast, bladder cancer, gastric, endometrial, NSCLC, colorectal cancer, oesophageal cancer, gallbladder cancer, cervical cancer, salivary gland and uterine cancer, but also in cancers of unknown primary, testicular, ovarian, head and neck, pancreatic, small intestinal cancers, and melanoma[4].

3.1.2. Available therapies and unmet medical need

Management of advanced/metastatic HER2 positive tumours depends on tumour type/site and previously used systemic therapy in neo-/adjuvant setting, as per ESMO guidelines for the specific tumour site. Upon progression following first-line therapy, patients may be considered for subsequent treatment options tailored to the clinical context—such as local interventions in cases of oligometastatic disease—as well as the patient's overall condition, individual preferences, and the presence of actionable genomic alterations, in alignment with current clinical guidelines. Overall, 5-

[3] Yan, M., Schwaederle, M., Arguello, D. *et al.* HER2 expression status in diverse cancers: review of results from 37,992 patients. *Cancer Metastasis Rev* **34**, 157–164 (2015). https://doi.org/10.1007/s10555-015-9552-6
[4] Quaquarini, Erica, Federica Grillo, Lorenzo Gervaso, Giovanni Arpa, Nicola Fazio, Alessandro Vanoli, and Paola Parente. 2024. "Prognostic and Predictive Roles of HER2 Status in Non-Breast and Non-Gastroesophageal Carcinomas" *Cancers* 16, no. 18: 3145. https://doi.org/10.3390/cancers16183145

year survival rates of ≤20 % in patients with distant metastatic disease across the range of tumour types further underlines the poor prognosis within this population.

The existing standard treatment options for most patients with HER-2 positive unresectable locally advanced or metastatic solid tumours, are not targeted toward biomarker identifiable vulnerabilities. and might provide modest clinical benefit. Therefore, there is a remaining unmet medical need for new targeted treatments options for patients who have been previously treated and have no other satisfactory treatment options.

3.1.3. Main clinical studies

DP-02 is an open label, multiple cohorts, ongoing, global phase 2 study evaluating efficacy and safety of T-DXd in specific solid tumours expressing HER2 (IHC 2+ or 3+). The study consists of two parts, part 1 which is completed and forms the basis for this application. Part 2 continues to enrol patients with HER2 IHC 3+ solid tumours and results of this cohort will be submitted as SOB. Patients who receive at least one prior line of treatment or had no satisfactory treatment options could be enrolled into one of 7 cohorts: BTC, bladder cancer, cervical cancer, endometrial cancer, ovarian cancer, pancreatic cancer, and a rare tumour cohort (excluded BC, GC, NSCLC, CRC). A total of 40 patients were enrolled in each cohort with IHC 2 or 3+, in cohorts 1-6 up to 10 IHC 1+ patients could be included if ≥ 3 objective responses were observed in the first 15 patients with confirmed HER2-overexpression by central testing). All patients received 5.4 mg/kg of T-DXd Q3W. HER2 testing was required and was performed either locally or centrally (if local test was not possible). Primary endpoint was a confirmed ORR by INV according to RECIST 1.1. Results are presented from primary and final analysis with DCO1 (08 June 2023) and DCO2 (10 October 2024), respectively.

As supportive evidence, the MAH submitted results in patients with HER2 IHC3+ NSCLC and CRC enrolled in 2 phase II, multicentre studies DESTINY-Lung01 (open-label; n=181) and DESTINY-CRC02 (double-blind, randomised; n=122), respectively. The primary efficacy outcome measure of both studies was confirmed ORR by independent central review (ICR) based on RECIST v1.1.

3.2. Favourable effects

With a median follow-up duration of 13 months, the confirmed ORR by investigator assessment in patients with HER2 IHC 3+ solid tumours was 52.3% (95% CI: 42.6–61.8). This was supported by a durable response, with a median duration of response of 21.1 months (95% CI: 10.6–25.0). The ORR ranged from 0-80% across tumour types.

Supportive data from studies DL-01 in NSCLC and DC-02 in CRC demonstrate objective response rates of a similar magnitude in patients with HER2 IHC 3+ status.

3.3. Uncertainties and limitations about favourable effects

The efficacy database is limited (111 patients) with limited number of patients in some tumour types; therefore, results cannot be considered comprehensive, see section 3.7.3. Additional considerations on the benefit-risk balance. The presented analyses are considered descriptive with limited prespecification and lack of type I error control. The data provided for this submission originate from a single non-randomized phase II study with two supportive phase II studies in NSCLC and CRC, thus hampering the assessment of time-dependent outcomes.
The observed objective response rates vary widely across tumour types. In the restricted IHC 3+ population, the confirmed ORRs per tumour type are based on a very limited sample size (e.g. only 5 patients in cohort 6), with heterogeneous responses across different tumour types, ranging from 40.9

to 80%, depending of the cohort, and with no responses observed in pancreatic cancer. A warning about quantitative differences of treatment effect depending on the tumour type is included in section 4.4 of the SmPC and a table describing the observed response rates per tumour types is reflected in section 5.1 of the SmPC to inform treatment decision.

Subgroup analyses are also limited by the small sample size considering the analysis by tumour type.

3.4. Unfavourable effects

Almost every patient treated with Enhertu developed a TEAE (97.8%). The incidences of TEAEs of ≥ Grade 3, SAE and deaths associated with an TEAE in the DP-02 pivotal trial was 63.3%, 42.7% and 7.1%, respectively. The three safety parameters were worsened among the ICH3+ subjects of the DP-02 study, with 72.1% TEAEs of ≥ Grade 3, 51.4% SAEs and 9.9% deaths. The rates were also higher than in the IHC 3+ supportive pool (TEAEs of ≥ Grade 3 = 55.1%, SAEs = 28.2%).

The most common TEAEs experienced among patients with HER2 IHC 3+ expression were nausea (69.7%), fatigue (41.2%), vomiting (35.7%), anaemia (35.2%), decreased appetite (34.9%), alopecia (33.7%), diarrhoea (32.3%), constipation (28.8%) and neutrophil count decreased (23.1%).

SAEs among the patients with biliary tract cancer in the DP02 study was high (56.1%) compared to the whole cohort (42.7%, n=267) as well as the large safety reference pool of All Tumour Types (28.7%). The most frequently reported SAEs were sepsis, urinary tract infection, and pneumonia. About 17% of patients in the IHC3+ Pool and in study DP-02 IHC3+ discontinued treatment due to AEs, which was primarily driven by events of ILD/pneumonitis.

Overall treatment discontinuation from any AE in the DP-02 study was 12% (18% for patients with IHC 3+). The most common reason for discontinuation was pneumonitis (5.2% overall) with the highest observed rate among biliary tract cancer patients (12.2% / 5 patients). The discontinuations rates in the reference pools (IHC3+ and All tumour types) were 17.3% and 15.9%. Dose reductions were common in the DP-02 study (22% for the entire study and 35.1% for the IHC3+ patients, ~30% for the IHC3+ 5.4 mg/kg pool). The most common TEAEs leading to dose reduction were fatigue, nausea, diarrhoea and neutropenia.

There were 59 (17.0%) patients with events of adjudicated ILD and 57 (16.4%) patients with events of adjudicated drug-related ILD in IHC 3+ T-DXd Pool. The overall rate of adjudicated all-cause grade ≥ 3 ILD/pneumonitis in the DP-02 study was 1.5%, and 2.9% in the IHC3+ supportive pool. Deaths from ILD/pneumonitis in the DP-02 study was 1.8% and 2.3% in the IHC+3 supportive pool. The incidence of SAE pneumonitis plus ILD was higher in patients >65 years of age (5.8%) vs <65 years of age (1.7%). Twelve patients (3.5%) in the IHC 3+ T-DXd Pool had an event of LV dysfunction: ejection fraction decreased in 10 (2.9%) patients, cardiac failure acute in 1 (0.3%) patient, and cardiac failure congestive in 1 (0.3%) patient. Of the 307 patients in the IHC 3+ T-DXd Pool who had a post-baseline LVEF value, 48 (15.6%) had values that met the laboratory criteria for a Grade 2 LVEF decrease, and 1 (0.3%) had values that met the criteria for a Grade 3 decrease.

The rate of ≥ grade 3 shift from baseline neutrophils decreased was 21.1% in the DP-02 study and highest among patients with bladder cancer (34.2%).

The rate of potential Hy's Law was 4.9% (13 patients). Overall, 8 (2.3%) patients in the IHC 3+ supportive pool had cases of potential Hy's Law.

3.5. Uncertainties and limitations about unfavourable effects

Safety parameters among patients with the specific tumour types in the DP-02 study are uncertain as the specific cohort populations are very small (~40 patients).

3.6. Effects Table

Table 108 Effects Table for Enhertu for solid tumours with HER2 IHC 3+

Effect	Short description	Unit	Treatment Enhertu 5.4 mg/m2	Uncertainties / Strength of evidence	References
Favourable effects					
DP-02 (Destiny PanTumor-02) N=111 DCO 10 October 2024					
ORR HER2 IHC 3+ by INV	Confirmed overall response rate per Investigator	N (%) (95%CI)	58 (52.3) (42.6, 61.8)	SAT, IHC3+ restriction of group was done post hoc but based on a pre-defined exploratory analysis Heterogenous results among cohorts (ORR range 40%-80%) and no response in pancreatic cohort (IHC3+)	CSR
DoR by INV	Duration of response per Investigator	Months (95%CI)	21.1 (10.6, 25)	Median follow-up (all patients): 12.98 months (range: 0.4, 47.7). Few patients on treatment	CSR
Unfavourable effects					

	Unit	DP-02 trial (n=267)	IHC3+ supportive pool (n=347)	All Tumour Types ref pool (n=3057)	Note
Grade≥3 AEs	%	63.3	64.0	55.9	
SAEs	%	42.7	35.7	28.2	
Deaths associated with TEAEs	%	7.1	6.1	4.1	
Discontinuations	%	12.0	17.3	15.9	
Neutropenia	%	20.2	23.1	16.8	
ILD/pneumonitis (any grade/≥3)	%	10.5 / 1.5	17.0 / 2.9	12.9 / 1.8	

	Unit	DP-02 trial (n=267)	IHC3+ supportive pool (n=347)	All Tumour Types ref pool (n=3057)	Note
Left ventricular dysfunction (any grade/≥3)	%	4.1 / 1.5	3.5 / 1.2	5.9 / 0.6	

Abbreviations: IHC: immunohistochemistry; HER2: human epidermal receptor 2; DCO: data cut off; FU: follow-up

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The activity of Enhertu in the applied tumour-agnostic indication has been evaluated in a single arm study, which included 111 patients with various HER2 IHC 3+ tumours without satisfactory treatment options. The observed response rates are considered clinically relevant in patients with HER2 IHC 3+ solid tumours who have received median two lines of prior therapy and have no other satisfactory treatment options. This is based on a limited sample size, heterogeneous responses across different tumour types and with no responses observed in pancreatic cancer. Although methodological and other uncertainties related to the pivotal study DP-02 are acknowledged, given the well described mechanism of action of Enhertu and results from the overall clinical development plan with multiple RCTs across different tumour types, these uncertainties can be considered acceptable in the applied indication.

Furthermore, there is an unmet need for patients with HER2 IHC 3+ tumours who have exhausted standard therapies, as they are left with limited treatment options. Such treatments exhibit overall low activity in this late treatment setting and cannot be considered satisfactory.

Considering the non-comprehensiveness of the data, the MAH is seeking a CMA and will submit the final analysis of Part 2, cohort A of study DP-02 as a specific obligation by 30 June 2027. Part 2 of DP-02 is ongoing and will evaluate additional cohorts of patients with HER2-expressing tumours, as determined via central testing, and includes 5 cohorts ((A to E), N=40 / cohort). Cohort A will provide additional data from 40 patients with different tumour types with HER2 IHC 3+ leading to an increase of the total sample size to 151 patients from study DP-02. Part 2 of DP-02 study is added to the Annex II as a SOB with a defined timeframe.

The safety profile of T-DXd in the DP-02 pivotal trial and among patients with IHC3+ diseases is consistent with the safety profile investigated in other populations including no significantly increased rate of specific AEs (ILD/pneumonitis). However, compared to previous trial settings, the DP-02 study population was slightly older and had received more lines of therapy, which may underlie the increased rates of all major safety outcomes observed. A 17.0% increase in ≥grade 3 toxicity, 23.3% more SAEs and 5.8% more TEAE-associated deaths were observed among the IHC+3 patients in the DP-02 in comparison with the All Tumour Types ref pool (n=3057).

Overall, the uncertainties and limitations of the single arm, uncontrolled pivotal study are acceptable considering the well described mechanism of action of Enhertu and results from the overall clinical development plan with multiple RCTs across different tumour types.

3.7.2. Balance of benefits and risks

Given the magnitude of observed response rates across different histologies and the characterised toxicities, Enhertu provides a treatment option in adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumours who have received prior treatment and who have no satisfactory treatment options. The benefit/risk balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

3.7.3.1. Conditional marketing authorisation

This extension of indication falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a seriously debilitating, life-threatening disease. See also Type of Application and aspects on development.

3.7.3.1.1. Discussion on the non-comprehensiveness of data in the context of a Conditional Marketing Authorisation

In regard to the request for conditional Marketing authorisation the CHMP consider that the following is to be accounted in terms of comprehensiveness of the dossier:

Due to the small sample size of the presented data, the data package is currently considered non-comprehensive. Uncertainties remain on the precise estimates of efficacy based on a larger sample size in terms of objective response rate and response duration, and time to event endpoints (OS, PFS); therefore, a conditional marketing authorisation is considered appropriate.

The main concerns of non-comprehensiveness for the present submission are:

Efficacy:

- The benefit in subgroups of patients based on histology. This may be studied in terms of ORR and DoR in prospective single-arm studies encompassing a broad variety of tumour types.

- The requirement for unbiased estimate of ORR and DoR. This may be studied in a prospective cohort study.

- The size of treatment effect on time-dependent outcome measures (OS, PFS). However, due to intended use of Enhertu in later lines in patients who have no satisfactory treatment options, it may not be feasible to conduct a randomised clinical trial with an acceptable comparator when targeting many different tumour histologies with a time-to-event based primary endpoint.

3.7.3.1.2. Conclusions and recommendation on Conditional Marketing Authorisation

The CHMP considers that the new indication for this product fulfils the requirements for a conditional marketing authorisation:

- **The benefit-risk balance is positive as discussed above.**
- **It is likely that the applicant will be able to provide comprehensive data:**

The MAH plans to provide final analysis of Part 2 of study DP-02 as specific obligation. The part 2 of DP-02 is ongoing and will evaluate additional cohorts of patients with HER2-expressing tumours, as determined via central testing only, and includes 5 cohorts ((A to E), N=40 / cohort): A) any tumour type that is HER2 IHC 3+ (excluding breast, gastric cancer, and colorectal cancer), B) any tumour type that is HER2 IHC 2+/ISH+ (excluding breast, gastric cancer, and colorectal cancer), C) HER2 IHC 2+

or 1+ endometrial cancer, D) HER2 IHC 2+ or 1+ovarian cancer, and E) HER2 IHC 2+ or 1+ cervical cancer. Thus, it will only be cohort A that will provide additional data in the histology independent setting. The primary endpoint is ORR by INV with DoR as secondary endpoint. The cohort A will provide additional data from 40 patients, expected to be submitted in Q2 2027, with different tumour types with HER2 IHC 3+ leading to increase of sample size to 151 patients from study DP-02. The actual number of patients enrolled in the cohort A is 44, with the first patient included in 30 May 2024 and the last one, in 16 September 2025 and planned DCO for cohort A will be in October 2026.

Acknowledging the challenges in conducting a randomized clinical trial in a tumour-agnostic indication (lack of suitable common comparator due to the heterogeneity of the population and the definition of a target population in later lines in patients who have no satisfactory treatment options, as well as the rarity of HER2-positive tumour), the MAH's proposal to expand the dataset by including additional patients from cohort A of Part 2 of the DP-02 study is considered acceptable.

- **Unmet medical needs will be addressed:**

Unmet medical needs will be addressed, as given the qualification of the indication for patients with solid tumours overexpressing HER2 who have received prior treatment and who have no satisfactory treatment options, it is ascertained that there is an unmet medical need which could be covered by Enhertu.

- **The benefits to public health of the immediate availability outweigh the risks** inherent in the fact that additional data are still required.

The confirmed ORR by investigator assessment in patients with HER2 IHC 3+ solid in 2L+ setting, supported by durable responses in DP-02, is considered clinically meaningful. This conclusion is based on limited data from a single phase 2 study, in which key time-to-event endpoints such as PFS and OS could not be evaluated. Although methodological and other uncertainties related to the pivotal study DP-02 are acknowledged, given the well described mechanism of action of Enhertu and extensive clinical development plan with multiple RCTs across different tumour types these can be considered acceptable. Moreover, the safety risks of Enhertu are well known. The benefits of immediate availability to public health of Enhertu outweighs the risk related to the absence of comprehensive data.

3.8. Conclusions

The overall B/R of Enhertu as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumours who have received prior treatment and who have no satisfactory treatment options is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends , by a majority of 28 out of 32 votes, 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 Addition of a new therapeutic indication or modification of an approved one	Variation type II	I, II, and IIIB

Extension of indication to include treatment of adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumours who have received prior treatment and who have no satisfactory treatment options for Enhertu, based on results from study D967VC00001 (DESTINY-PanTumor02); this is a Phase II, multicenter, open-label study to evaluate the efficacy and safety of trastuzumab deruxtecan for the treatment of selected HER2-expressing tumours; 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 11 of the RMP has also been agreed. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce editorial changes to the PI.

The variation leads to amendments to the annexes I, II, and IIIB and to the Risk Management Plan (RMP).

Divergent position(s) to the majority recommendation is appended to this report.

Amendments to the marketing authorisation

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

This recommendation is subject to the following new condition:

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

- **Risk management plan (RMP)**

The 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.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of Enhertu in the treatment of adult patients with unresectable or metastatic HER2-positive (IHC3+) solid	2Q 2027

Description	Due date
tumours who have received prior treatment and who have no satisfactory treatment options, the MAH should submit the results of Part 2, Cohort A of the study DESTINY-PanTumor02, Phase II, Multicenter Open-label Study to Evaluate the Efficacy and Safety of Trastuzumab Deruxtecan (T-DXd, DS-8201a) for the Treatment of Selected HER2-expressing Tumours.	

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Enhertu is not similar to Ayvakyt, Elahere, Ezmekly, Finlee, Hetronifly, Imdylltra, Kimmtrak, Koselugo, Lutathera, Ogsiveo, Ojemda, Onivyde pegylated liposomal, Pemazyre, Qarziba, Qinlock, Romvimza, Spexotras, Tibsovo, Voranigo, Vyloy, Zejula, Zepzelca, Ziihera, and Zynyz within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Appendices

1. Divergent position to the majority recommendation

APPENDIX

DIVERGENT POSITION DATED 21 May 2026

DIVERGENT POSITION DATED 21 May 2026

Enhertu EMA/VR/0000293327

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the approval of the following indication in the context of the conditional marketing authorisation of Enhertu (trastuzumab deruxtecan):

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumours who have received prior treatment and who have no satisfactory treatment options (see sections 4.4 and 5.1; for biomarker-based patient selection, see section 4.2).

The reasons for divergent opinion were inadequate methodological rigour of submitted study data and tumour agnostic activity has not sufficiently been established;

-Single arm trials which are submitted as pivotal evidence are expected to have an a priori definition of a clear success criterion which was not the case for study DESTINY-PanTumor02; The indication is based on exploratory subgroup (IHC3+) results.

-A tumour agnostic effect has not robustly been demonstrated. No responses in the pancreatic tumour IHC3+ cohort despite the presence of HER2+ expression (cohort stopped due to lack of response) were observed.

-It cannot be readily assumed that – in a target population for which overexpressed HER2 may be an oncogenic driver dependent on the type of tumour – HER2 as general marker for precise chemotherapy delivery would result in consistent benefit across tumours, assuming that the driving mechanism of action of T-DXd is delivery, internalization and release of deruxtecan, while the inhibition of HER2 signalling might not add much to the overall effect. This raises further uncertainty on the tumour agnostic approach assuming that results can be extrapolated to any HER2 IHC3+ tumour.

Finally, there is uncertainty on the representativeness of the study population for the proposed target population (who have no satisfactory alternative treatment options) as patients without prior therapies were enrolled.

CHMP Members expressing a divergent opinion:

Eva Skovlund - NO

Jan Müller-Berghaus

Janet Koenig - DE

Christian B. (Kit) Roes

Peter Mol – NL