14 September 2023
EMA/444980/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Enhertu

International non-proprietary name: trastuzumab deruxtecan

Procedure No. EMEA/H/C/005124/II/0027

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	Definition
ADA	anti-drug antibody
ADC	antibody-drug conjugate
ADR	adverse drug reaction
AE	adverse event
ALK	anaplastic lymphoma kinase
BC	breast cancer
BOR	best overall response
BRAF	v-raf murine sarcoma viral oncogene homolog B1 (B-Raf proto-oncogene)
BSC	best supportive care
Cavg,Cycle 2	average serum concentration over Cycle 1 and Cycle 2
CE	Conformitè Europëenne
CI	confidence interval
CLDXd	elimination clearance of DXd
CLIA	Clinical Laboratory Improvement Amendment
CLT-DXd	elimination clearance of T-DXd
CNS	central nervous system
CR	complete response
CSP	clinical study protocol
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DAR	drug-to-antibody ratio
DCO	data cut-off
DCR	disease control rate
DNA	deoxyribonucleic acid
DoR	duration of response
DXd	the released payload (MAAA-1181a)
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	epidermal growth factor receptor
E-R	exposure-response
ERBB2	Erb-B2 receptor tyrosine kinase 2; HER2

Abbreviation	Definition
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GC	gastric cancer
GEJ	gastroesophageal junction
GI	gastrointestinal
HER2	human epidermal growth factor receptor 2, ERBB2
HR	hazard ratio
IA	interim analysis
ICR	independent central review
IHC	immunohistochemistry
ILD	interstitial lung disease
IQR	interquartile range
IV	intravenous
LCMC	Lung Cancer Mutation Consortium
LV	left ventricular
LVEF	left ventricular ejection fraction
Lyo-DP	lyophilized drug product
mAb	monoclonal antibody
MRI	magnetic resonance imaging
NAb	neutralizing antibody
NE	not evaluable
NSCLC	non-small cell lung cancer
ODxTT	Oncomine™ Dx Target Test
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PK	pharmacokinetic(s)
PopPK	population pharmacokinetic

Abbreviation	Definition
pp	percentage points
PR	partial response
PT	preferred term
Q3W	every 3 weeks
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
ROS1	ROS proto-oncogene 1
RP2D	Recommended phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	stable disease
SNV	single nucleotide variant
SoC	standard of care
T-DM1	trastuzumab emtansine
T-DXd	trastuzumab deruxtecan (Enhertu®)
TEAE	treatment-emergent adverse event
TFS	Thermo Fisher Scientific
TPS	tumor proportion score
US	United States
V1,T-DXd	intact T-DXd central volume of distribution
V2,T-DXd	intact T-DXd peripheral volume of distribution
VDXd	DXd volume of distribution
vs.	versus

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Daiichi Sankyo Europe GmbH submitted to the European Medicines Agency on 30 November 2022 an application for a variation.

The following variation was requested:

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

Extension of indication to include the indication treatment of non-small cell lung cancer for Enhertu (trastuzumab deruxtecan), based on results from study DS8201-A-U204 (DESTINY-Lung01) and study DS8201-A-U206 (DESTINY-Lung02).
Study DESTINY-Lung01 is a phase 2, multicentre, open-label, 2-cohort study of trastuzumab deruxtecan (DS-8201a), an anti-HER2 antibody drug conjugate (ADC), for HER2-over-expressing or -mutated, unresectable and/or metastatic non-small cell lung cancer (NSCLC) conducted at sites in Japan, the United States and Europe.
Study DESTINY-Lung02 is an ongoing phase 2, multicentre, randomised study to evaluate the safety and efficacy of trastuzumab deruxtecan in subjects with HER2-mutated metastatic non-small cell lung cancer, conducted in North America, Europe and Asia-Pacific.
As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.
Version 2.2 of the RMP has also been submitted.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision P/0275/2021 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Aaron Sosa Mejia Co-Rapporteur: Peter Mol

Timetable	Actual dates
Submission date	30 November 2022
Start of procedure:	31 December 2022
CHMP Co-Rapporteur Assessment Report	10 March 2023
CHMP Rapporteur Assessment Report	28 February 2023
PRAC Rapporteur Assessment Report	3 March 2023
CHMP Co-Rapporteur Assessment	9 March 2023
PRAC Outcome	16 March 2023
CHMP members comments	20 March 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 March 2023
Request for supplementary information (RSI)	30 March 2023
CHMP Rapporteur Assessment Report	23 June 2023
PRAC Rapporteur Assessment Report	23 June 2023
PRAC members comments	28 June 2023
Updated PRAC Rapporteur Assessment Report	29 June 2023
PRAC Outcome	6 July 2023
CHMP members comments	10 July 2023
Updated CHMP Rapporteur Assessment Report	14 July 2023
Request for supplementary information (RSI)	20 July 2023
CHMP Rapporteur Assessment Report	25 August 2023
PRAC Rapporteur Assessment Report	25 August 2023
PRAC members comments	4 September 2023
CHMP members comments	4 September 2023
Updated CHMP Rapporteur Assessment Report	8 September 2023
Updated PRAC Rapporteur Assessment Report	8 September 2023
Opinion	14 September 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The MAH initially applied for the following indication:

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic NSCLC whose tumours have activating HER2 (ERBB2) mutations and who have received a prior systemic therapy.

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

Enhertu as monotherapy is indicated for the treatment of adult patients with advanced NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy.

Epidemiology and risk factors, screening tools/prevention

Lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer death in the world. In 2020, there were an estimated 2.21 million new cases of lung cancer globally (11.4% of all new cancers), with an estimated 1.8 million deaths due to the disease (18.0% of all cancer deaths). (Sung H et al., 2021). Despite progress in earlier detection, a majority of lung cancers (57% in the US for the 2009 to 2015 period) are still commonly diagnosed at the metastatic stage, when the disease is not curable, with a 5-year relative survival rate of 5.2%. (Howlader N et al., 2019)

The therapeutic approach to lung cancers is based on the specific histologic and genetic characteristics of the tumor. Lung cancers are classified into 2 major histologic types: the most common is NSCLC, found in ~85% of all lung cancers; small cell lung cancer occurs in ~15% of lung cancers. With the recent progress in targeted therapies for specific histologic subtypes in the last decade, NSCLC has been further categorized into 2 subtypes to determine eligibility for molecular testing and therapeutic strategies: non-squamous carcinoma accounts for ~60% of all lung cancers and includes adenocarcinoma (~50% of all lung cancers3), large cell carcinoma (~9% of all lung cancers), and other tumor subtypes; squamous cell carcinoma accounts for ~30% of all lung cancers. (Pikor LA et al., 2013; Berbescu EA et al., 2012; NCCN Clinical Practice Guidelines in Oncology, 2021).

The identification of specific genomic alterations in tumors or immune biomarkers (programmed cell death ligand 1 [PD L1]) that are indicative of therapeutic efficacy of targeted therapies or immunotherapy transformed the therapeutic approach to and prognosis of metastatic NSCLC. On the basis of current clinical practice guidelines in the US, Europe, and Japan, patients with metastatic NSCLC should undergo testing for PD L1 by immunohistochemistry (IHC) to determine whether they are candidates for immunotherapy. (NCCN Clinical Practice Guidelines in Oncology, 2021; Planchard D et al., 2018; Akamatsu H et al., 2019). In addition, patients should be tested for "predictive biomarkers" including, but not limited to, sensitizing epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) gene rearrangements, ROS proto-oncogene 1 (ROS1) rearrangements, B Raf proto-oncogene (BRAF) point mutations, neurotrophin tyrosine receptor kinase gene (NTRK) fusions, and c mesenchymal-epithelial transition factor exon 14 skipping mutations. Patients with metastatic lung

cancer who are eligible for targeted therapies or immunotherapies are now surviving longer, with 5-year survival rates ranging from 15% to 50% depending on the predictive biomarker. (NCCN Clinical Practice Guidelines in Oncology, 2021).

Despite these recent advances, most lung adenocarcinomas lack an actionable driver oncogene or eventually progress after treatment with targeted therapies or immunotherapies, and are still treated with conventional chemotherapy. (The Cancer Genome Atlas Research Network, Nature 2014).

HER2 (also known as ERBB2) is an emerging targetable oncogenic driver in NSCLC. Sequencing of HER2 in lung tumors revealed the presence of somatic mutations within the kinase domain of HER2 in ~3% of all lung tumors (all of which were adenocarcinomas), suggesting a potential role for HER2-targeted therapies in patients whose tumors contain HER2 mutations. The majority of these mutations occur in exon 20. HER2 mutations and other driver oncogene genomic alterations are usually mutually exclusive. Patients with tumors that have HER2 mutations tend to be female, never smoker, and younger (median age ~60 years). (The Cancer Genome Atlas Research Network, Nature 2014; Pillai RN et al., 2017; Stephens P et al., 2004; Pao W et al., 2011; Mazières J et al., 2013).

Clinical presentation, diagnosis and stage/prognosis

In several studies, the survival outcome for patients with metastatic HER2-mutant lung adenocarcinoma was found to be shorter than that for patients with tumors harboring other driver mutations. In a US Lung Cancer Mutation Consortium (LCMC) study (Pillai RN et al., 2017) conducted in 1007 patients with advanced lung adenocarcinoma, the median overall survival (OS) was lower in patients with HER2 mutations independent of treatment received (1.37 years [~16.4 months] for those who received HER2-directed therapy and 2.09 years [~25.1 months] for those who received systemic chemotherapy). In comparison, in the overall LCMC study population, patients who had received targeted therapy for a driver mutation achieved a median OS of 3.5 years (~42.0 months) and those not treated with targeted therapy achieved a median OS of 2.4 years (~28.8 months) (Pillai RN et al., 2017). The survival outcome in patients with HER2-mutant NSCLC in the LCMC study were similar to those reported in patients with HER2-mutant adenocarcinoma in the retrospective EUHER2 cohort (N = 101; median OS, 24 months) and the nationwide genome screening project in Japan (LC-SCRUM) (N = 73; median OS, 18.8 months). (Mazières J et al., 2013; Udagawa H et al., 2019)

Management

Outside of the US, there is no approved targeted therapy currently available for metastatic HER2 mutant NSCLC.

Currently approved treatment options in the second-line setting without actionable oncogenic driver mutations show ORRs ranging from 5.5% to 22.9%, median DoR from 6.3 to 8.4 months, median PFS from 2.8 to 4.5 months, and median OS from 6.0 to 13.8 months. (Planchard D et al., 2019)

The data obtained for the HER2-mutant population is limited and consists of real-world data and data from small retrospective cohorts (n=12-52 patients). The latter reported ORRs varying between 5-18% with median PFS 2.9-4.9 months , and median OS after first-line therapy 9.9-24 months. (Mazières J et al., 2013; Auliac, JB et al., 2019)

Only one study provided data for the second line population for the HER2-NSCLC population. In the second line, the EUHER2 cohort (Mazières J et al., 2013) showed an ORR of 10% and a median PFS of 4.3 months (95% CI: 3.1, 5.5). The reported median OS was 19.4 months (95% CI: 9.6, 24.7). This appears to be prolonged, but the reported mOS in HER2 NSCLC show a large variability.

Patients may receive targeted therapy off-label by means of irreversible pan-HER TKIs or during trials. Limited evidence (n=24) with HER-2 targeted therapy shows that the OS might improve if HER 2 targeted therapy is given (median OS 1.4-year [~16 months] vs 2.1 years [~258 months]. (Pillai RN et al., 2017).

A Phase 2 basket study of the HER2-targeting ADC trastuzumab emtansine (T-DM1) in a small (N = 18) (Li, BT et al., 2018) cohort of patients with metastatic or recurrent HER2 mutant lung cancer who had received a median of 2 prior lines of systemic therapy (range: 0 to 4) suggested a potential role for HER2-targeting ADCs in this patient population. In this study, confirmed ORR was 44% (95% CI: 22, 69) and median duration of response (DoR) was 4 months (range: 2 to 9). Responders were seen across HER2 mutation subtypes, including exon 20 insertions and transmembrane and extracellular domain point mutations.

The limited efficacy of available therapies highlights the high unmet medical need for efficacious HER2 targeted therapy for patients with metastatic HER2-mutant NSCLC who have received at least 1 prior therapy, which might be addressed by new targeted agents. There are currently no approved HER2-targeted therapies for metastatic HER2-mutant NSCLC in Europe.

2.1.2. About the product

Enhertu (trastuzumab deruxtecan, T-DXd) is a HER2-directed antibody-drug conjugate (ADC) composed of a humanized anti-HER2 immunoglobulin G1 monoclonal antibody with the same amino acid sequence as trastuzumab, covalently linked to the membrane-permeable topoisomerase I inhibitor deruxtecan (DXd) via a stable tetrapeptide based linker.

In Europe, Enhertu is approved as monotherapy for advanced HER2+ breast cancer in second or ulterior line of treatment (5.4 mg/kg Q3W), advanced HER2-low breast cancer after chemotherapy (5.4 mg/kg Q3W), and advanced HER2+ gastric or gastroesophageal adenocarcinoma after a trastuzumab-based regimen (6.4 mg/kg Q3W).

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

This application is based on efficacy and safety data in the target population of subjects with metastatic and/or unresectable HER2-mutant NSCLC who have received T-DXd monotherapy at a dose of 5.4 mg/kg or 6.4 mg/kg in the ongoing Study DS8201-A-U206 (DESTINY-Lung02, hereafter referred to as Study U206), and at a dose of 6.4 mg/kg in the completed studies DS8201 A U204 (DESTINY Lung01, hereafter referred to as Study U204) and DS8201 A J101 (hereafter referred to as Study J101):

- Study U206 is an ongoing, multicentre, open-label, randomised, Phase 2 study evaluating 2 doses of T DXd (5.4 mg/kg and 6.4 mg/kg) in subjects with metastatic HER2-mutant NSCLC who have received at least 1 prior platinum-containing anti-cancer regimen. Data are provided for a data cut-off (DCO) date of 24 Mar 2022.
- Study U204 is a Phase 2 study of T DXd in subjects with unresectable or metastatic NSCLC that includes 91 subjects with HER2-mutant NSCLC treated with T DXd 6.4 mg/kg. Data are provided for a DCO date of 03 Dec 2021.
- First-in-human Study J101 enrolled 11 subjects with metastatic HER2-mutant NSCLC treated with T DXd 6.4 mg/kg. Data from Study J101 are from the DCO date of 01 Aug 2019.
- Two additional studies, DESTINY-Lung 03 (Study D967YC0001) and DESTINY-Lung04 (Study D967SC00001) are ongoing. Both studies contributed safety data to the listing of serious adverse

events (SAEs), and SAEs reported cumulatively through 19 Jun 2022 are listed in the summary of clinical safety (SCS).

DESTINY-Lung 04 has been ongoing since 28 Oct 2021. As of 20 Apr 2023, 195 subjects (target sample size is N=264, (https://clinicaltrials.gov/ct2/show/NCT05048797) have been randomized. Enrolment is expected to be completed by Q3 2023.

No scientific advice from the SAWP/CHMP was requested concerning the design of these trials.

2.1.4. General comments on compliance with GCP

The clinical studies included in this application were conducted with the approval of Ethics Committees or Institutional Review Boards and in accordance with established regulatory guidance, including relevant International Council for Harmonisation guidelines. Informed consent was obtained from all subjects. The studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time they were conducted and with the principles of Good Clinical Practice.

2.2. Non-clinical aspects

2.2.1. Introduction

New non-clinical primary pharmacology studies in support of the new indication of mutant HER-2 positive NSCLC were submitted for assessment. Moreover, a secondary pharmacodynamics study has been submitted in support of this application and as a post-approval measure for the previous indications of breast-cancer. Finally, the environmental risk assessment was updated to include the new indication.

T-DXd exhibits antitumor activity in HER2-expressing cancer cells by topoisomerase I inhibition through DXd which is released from T-DXd. T-DXd also exhibits antibody dependent cellular cytotoxic (ADCC) activity and HER2-mediated Akt phosphorylation inhibition. In vitro studies indicated that T-DXd exhibits HER2-expression-dependent cell growth inhibitory activity, and that the impact of drug conjugation on HER2 binding activity and ADCC activity is minimal. In vivo studies using HER2-positive tumor mouse xenograft models indicated that T-DXd exhibits more potent HER2-targeting antitumor activity and tumor regression than its mAb alone.

Various mutations in HER2 have been reported across a variety of cancers including lung cancer, in various domains such as extracellular domain, transmembrane domain, juxtamembrane domain, and kinase domain. Many of these mutations are believed to induce HER2 activation and promote oncogenesis despite the variety of locations and types of mutations (point mutations or insertion-deletion mutations). Activated HER2 is believed to undergo efficient internalization and subsequent degradation. The activation of HER2 by mutation is therefore thought to facilitate HER2 internalization and degradation, which could be utilized by anti- HER2-ADCs and contribute to antitumor activity as a mechanism of action in HER2-mutated tumors.

Increased internalization is hypothesized to be one of the mechanisms of action in anti-HER2-ADCs for HER2-mutant tumors. Albeit with some variations, an increased tendency of internalization of T-DXd was observed in transgenic non-small cell lung cancer (NSCLC) cells expressing various mutated HER2 (15 mutations) compared to that in the cells expressing wild type (WT) HER2. In vivo studies suggested that T-DXd was effective in HER2-mutant lung cancer, see table below for overview of new primary pharmacology studies. T-DXd has shown potent antitumor activity superior to trastuzumab emtansine (T-

DM1) and the combination of T-DM1 and neratinib in a patient-derived xenograft model of HER2-mutant (A775_G776insYVMA) NSCLC.14 T-DXd showed potent antitumor activity in a xenograft model of HER2-mutant (G776delinsVC) NSCLC cells in which HER2 expression was low. T-DXd also showed antitumor activity in xenograft models of transgenic NSCLC cells expressing various mutated HER2 (15 mutations) relative to the WT HER2-expressing model.

Study	Test System	Test Article	Route of Administration	Report Number
In vitro				
Internalization activity	Human NSCLC NCI-H322-derived transgenic cells with WT HER2 or mutated HER2 (15 mutations) and HER2-mutant (G776delinsVC) NSCLC NCI-H1781 cells	T-DXd	In vitro	CY20-H0009-R01
In vivo				
Antitumor activity in HER2-mutant NSCLC	NOD *Scid* Gamma mice; PDX model of HER2-mutant (A775_G776insYVMA) NSCLC	T-DXd, T-DM1, neratinib	Intravenous or oral	Li BT et al. 2020
Antitumor activity in HER2-mutant NSCLC and HER2 expression in tumors	Nude mice; xenograft model of human HER2-mutant (G776delinsVC) NSCLC NCI-H1781 cells and human NSCLC NCI-H322-derived transgenic cells with WT HER2 or mutated HER2 (15 mutations)	T-DXd	Intravenous	P200604 P200605

NSCLC, non-small cell lung cancer; PDX, patient-derived xenograft; T-DM1, trastuzumab emtansine; WT, wild type.

2.2.2. Pharmacology

Primary pharmacodynamic studies

In vitro

Internalization Activity of T-DXd in Non-Small Cell Lung Cancer Cells Expressing Wild Type or Mutated HER2 (Report Number CY20-H0009-R01)

The activation of HER2 by mutation is thought to facilitate the internalization and degradation of HER2, and increased internalization may contribute to the mechanism of action of anti-HER2- ADCs against HER2-mutant tumors. The internalization activity of T-DXd in NSCLC cells was evaluated for various forms of HER2 mutations that are potentially HER2- activating in comparison with WT HER2 using a transgenic cell approach similar to that reported.

Transgenic cells were established using an NSCLC NCI-H322 cell line. HER2 genes of WT or 15 mutations (extracellular domain mutation S310F; transmembrane domain mutations V659E and G660D; juxtamembrane domain mutations R678Q and V697L; kinase domain mutations L755S, L755P, D769Y,

A775_G776insYVMA, G776delinsVC, G776_V777insVGC, V777_G778insGSP, V777L, V842I, and T862A) were then introduced into the cells. Flow cytometry was used to quantify the amount of T-DXd bound to HER2 on the cell surface, before and after the 3-hour internalization. Internalization activity was determined as the ratio of internalized T-DXd after incubation for 3 hours in comparison to T-DXd on the cell surface prior to incubation. Internalization activity of T-DXd was also examined in the NSCLC cell line NCIH1781 harboring a HER2 mutation G776delinsVC.

The results are shown in the Table below. The internalization activity of T-DXd was 23.2% in the WT HER2-expressing cells and ranged from 26.9% to 71.3% in the mutated HER2-expressing cells. The internalization activity of T-DXd was significantly higher in some mutated HER2- expressing cells than in the WT HER2-expressing cells.

The internalization activity of T-DXd in the NCI-H1781 cell line was 60.1% ± 3.9% (mean ± standard error for 3 independent experiments).

These results suggested that T-DXd showed various levels of internalization activity in the tumor cells expressing mutated HER2 that were examined in this study. An increased tendency toward internalization of T-DXd was noted in mutated HER2 compared with WT HER2 in this experimental setting.

Table 1: In Vitro Internalization Activity of T-DXd in NCI-H322-Derived Transgenic Cells Expressing Wild Type or Mutated HER2

HER2 Type	Internalization Activity (%)	*P* value
WT	23.2 ± 1.8	Not applicable
S310F	31.8 ± 1.2	0.0157*
V659E	55.5 ± 0.9	0.0018**
G660D	33.6 ± 1.2	0.0145*
R678Q	28.8 ± 1.0	0.0370*
V697L	31.0 ± 1.8	0.1446
L755S	53.6 ± 1.9	0.0007***
L755P	71.3 ± 0.8	0.0020**
D769Y	37.6 ± 1.1	0.0077**
A775_G776insYVMA	69.2 ± 1.1	0.0013**
G776delinsVC	63.3 ± 0.7	0.0031**
G776_V777insVGC	45.1 ± 1.1	0.0061**
V777_G778insGSP	38.5 ± 1.8	0.0010**
V777L	26.9 ± 2.5	0.0730
V842I	30.8 ± 1.3	0.0186*
T862A	27.6 ± 2.1	0.3112

WT, wild type.
Data are shown as mean ± standard error for 3 independent experiments.
The paired t-test was used to compare internalization activity of T-DXd in each line of NCI-H322-derived transgenic cells expressing mutated HER2 and that in the NCI-H322-derived transgenic cells expressing WT HER2.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

In vivo

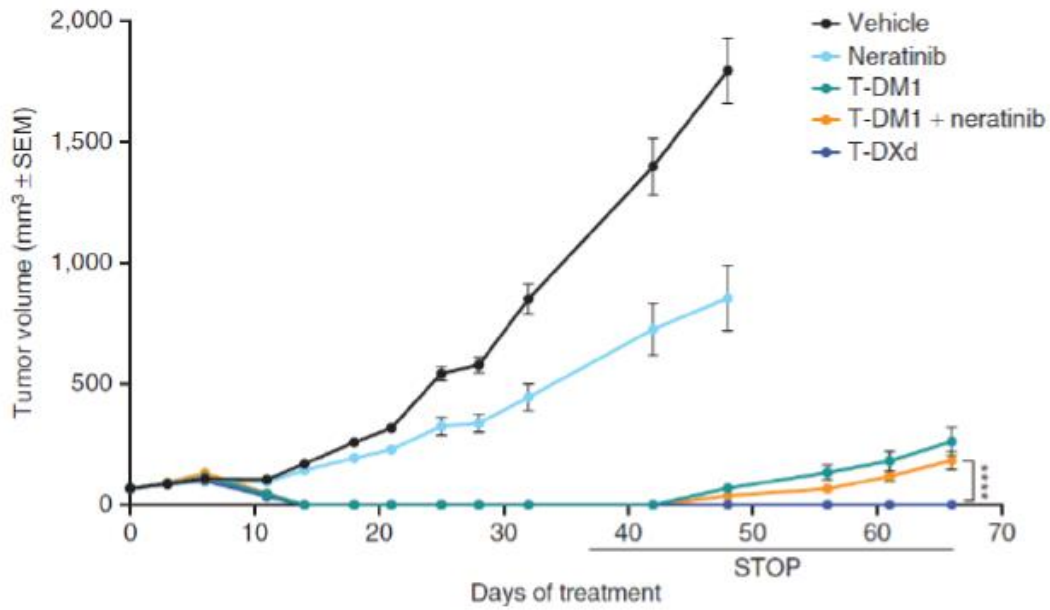
Antitumor Activity of T-DXd in a Patient-Derived Xenograft Model of HER2- Mutant (A775_G776insYVMA) Non-Small Cell Lung Cancer in NOD Scid Gamma Mice (Report Number Li BT et al. 2020)

Antitumor activity of T-DXd was evaluated in a PDX model of HER2-mutant (A775_G776insYVMA) NSCLC in female NOD scid gamma mice, originally generated at Memorial Sloan Kettering. T-DXd was administered intravenously at 10 mg/kg once every 3 weeks to the mice (n = 6/group, initial dosing on Day 0). Antitumor activity was also evaluated for T-DM1 administered intravenously at 15 mg/kg weekly, neratinib administered orally at 20 mg/kg for 5 days a week, and a combination of T-DM1 and neratinib. Tumor dimensions and body weight for each mouse were measured twice a week.

The results are shown in the figure below. Although the model was initially sensitive to both the T-DXd and the T-DM1 regimens, mice receiving T-DM1 or the combination of T-DM1 and neratinib showed tumor relapse shortly after treatment was discontinued. In contrast, mice receiving T-DXd showed no signs of tumor regrowth up to 1 month after treatment discontinuation. Antitumor activity of T-DXd was significantly superior to the combination of T-DM1 and neratinib ($P < 0.0001$, two-way ANOVA test).

The results suggested that T-DXd was effective and superior to T-DM1 in NSCLC harbouring HER2 mutation A775_G776insYVMA.

Figure 1: **Antitumor Activity of T-DXd in a Patient-Derived Xenograft Model of HER2-Mutant (A775_G776insYVMA) Non-Small Cell Lung Cancer in NOD Scid Gamma Mice**



The data are expressed as the mean ± standard error (n = 6).
Estimated tumor volume for each mouse was calculated using the following equation:
Estimated tumor volume (mm^3) = 0.52 × length × $width^2$
****$P \leq 0.0001$

Antitumor Activity of T-DXd in Mouse Xenograft Models of Non-Small Cell Lung Cancer NCI-H322-Derived Transgenic Cells Expressing Wild Type or Mutated HER2 in Nude Mice (Report Number P200604, P200605)

In order to examine antitumor activity of T-DXd for mutated HER2 in comparison with WT HER2, antitumor activity of T-DXd was evaluated in mouse xenograft models of NSCLC NCIH322- derived transgenic cells expressing WT or mutated HER2 (extracellular domain mutation S310F; transmembrane

domain mutations V659E and G660D; juxtamembrane domain mutations R678Q, V697L; kinase domain mutations L755S, L755P, D769Y, A775_G776insYVMA, G776delinsVC, G776_V777insVGC, V777_G778insGSP, V777L, V842I, and T862A) in female CAnN.Cg-Foxn1nu/CrlCrlj mice (nude mice). T-DXd was administered intravenously at a single dose of 1, 3, or 10 mg/kg to the mice (n = 6/group, Day 0). Tumor dimensions and body weight for each mouse were measured twice a week until Day 21. Antitumor activity was evaluated on Day 21. For any mice that were euthanized before Day 21, this evaluation was performed on the last measurement day when data from all mice were obtained. To compare the in vivo effectiveness of T-DXd in each mutated HER2 model against the WT HER2 model, the effectiveness ratio of T-DXd to WT HER2 model was calculated for each model by parallel line test.

The results are shown in the table below. T-DXd at 10 mg/kg significantly inhibited tumor growth in all models tested. T-DXd also showed significant antitumor activity at the lower doses of 1 mg/kg and 3 mg/kg, depending on the model. The ED50 value of T-DXd for the WT HER2 model was estimated to be 4.3531 mg/kg, and for the 15 mutated HER2 models were estimated to range from 1.1167 mg/kg to 6.2382 mg/kg (Table below). Effectiveness ratios of T-DXd in each mutated HER2 model, compared with the WT HER2 model, ranged from 0.7991 to 4.0257. Higher effectiveness ratios represent equivalent activity at lower doses than in the WT HER2 model, suggesting that T-DXd provides greater in vivo effectiveness in some mutated HER2 models than in the WT HER2 model. HER2 expressions in the xenografted tumors were determined as IHC scores ranging from 1+ to 3+.

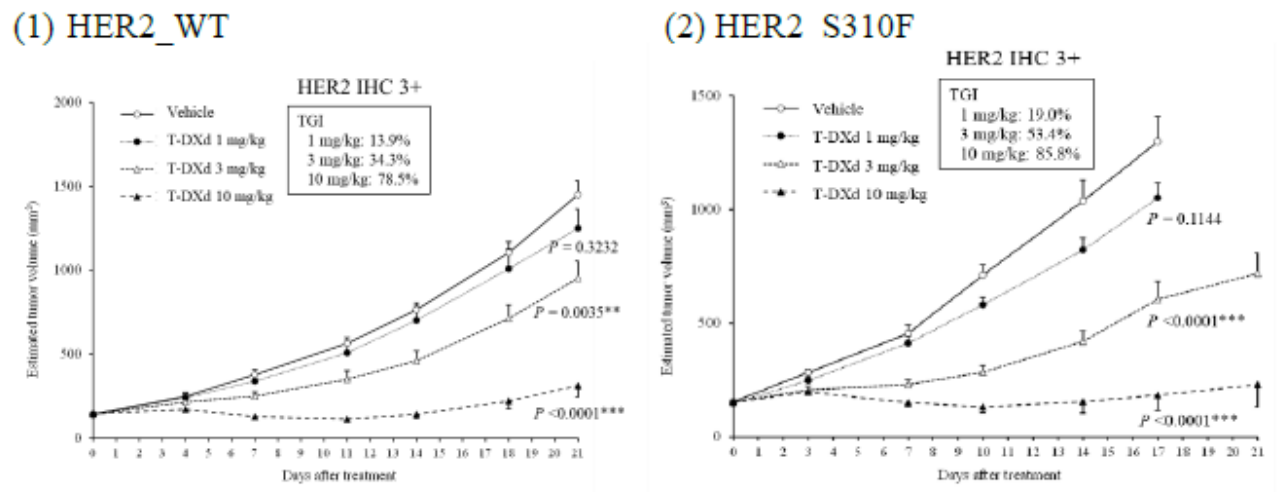
These results suggested that T-DXd showed antitumor activity in the tumor models expressing mutated HER2 that were examined in this study. The in vivo effectiveness of T-DXd in the mutated models relative to the WT HER2 model varied depending on the mutation. T-DXd showed higher effectiveness in some mutated HER2 models than in the WT HER2 model in this experimental setting.

Table 2: 50% Effective Doses of T-DXd in Mouse Xenograft Models with Non-Small Cell Lung Cancer NCI-H322-Derived Transgenic Cells Expressing Wild Type or Mutated HER2 in Nude Mice

Model	HER2 IHC	ED_{50} (mg/kg)	95% Confidence Interval
HER2_WT	3+	4.3531	3.1796 to 5.9598
HER2_S310F	3+	2.7491	2.1360 to 3.5381
HER2_V659E	1+	4.1373	3.3146 to 5.1643
HER2_G660D	3+	2.0750	1.7320 to 2.4861
HER2_R678Q	3+	2.7717	1.8384 to 4.1787
HER2_V697L	3+	2.1429	1.6262 to 2.8238
HER2_L755S	3+	3.2132	2.5830 to 3.9971
HER2_L755P	2+	5.5354	4.0496 to 7.5665
HER2_D769Y	3+	6.2382	4.0894 to 9.5162
HER2_A775_G776insYVMA	2+	1.9455	1.4565 to 2.5986
HER2_G776delinsVC	3+	1.2212	1.0069 to 1.4812
HER2_G776_V777insVGC	3+	4.4788	2.9123 to 6.8881
HER2_V777_G778insGSP	3+	1.1167	0.9243 to 1.3490
HER2_V777L	3+	3.7772	2.8801 to 4.9537
HER2_V842I	3+	1.3699	0.9671 to 1.9404
HER2_T862A	3+	5.4550	3.8943 to 7.6412

ED_{50}, 50 % effective dose which was defined as the estimated dose resulting in 50% tumor growth inhibition compared with the vehicle control; IHC, immunohistochemistry; WT, wild type.
HER2 IHC staining was conducted using Hercep Test II (Agilent Technologies, Inc.) and IHC scores were assessed according to package insert of Hercep Test II and guidelines for HER2 pathological diagnostics in gastric cancer.[16]

Figure 2: **Examples of antitumour activity**



Antitumor Activity of T-DXd in a Mouse Xenograft Model of HER2-Mutant (G776delinsVC) Non-Small Cell Lung Cancer in Nude Mice (Report Number P200604, P200605)

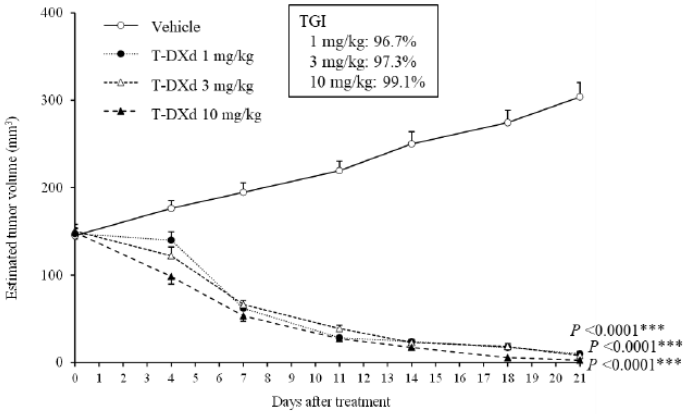
Antitumor activity of T-DXd was evaluated in a mouse xenograft model of HER2-mutant (G776delinsVC) NSCLC NCI-H1781 cells in female CAnN.Cg-Foxn1nu/CrlCrlj mice (nude mice). T-DXd was administered

intravenously at a single dose of 1, 3, or 10 mg/kg to the mice (n = 6/group, Day 0). Tumor dimensions and body weight for each mouse were measured twice a week until Day 21.

The results are shown in the figure below. T-DXd at 1, 3, and 10 mg/kg significantly inhibited tumor growth by 96.7%, 97.3%, and 99.1%, respectively, compared with the vehicle control on Day 21 (P < 0.0001 for all comparisons, Dunnett's test). The 50% effective dose (ED50), which was defined as the estimated dose resulting in 50% tumor growth inhibition compared with the vehicle control, was <1 mg/kg. HER2 expressed at a low level (immunohistochemistry [IHC] 1+) in this model.

The results suggested that T-DXd was effective in NSCLC harboring HER2 mutation G776delinsVC, even at low levels of HER2 expression (IHC 1+).

Figure 3: **Antitumor Activity of T-DXd in a Mouse Xenograft Model of HER2-mutant (G776delinsVC) Non-Small Cell Lung Cancer NCI-H1781 in Nude Mice**



TGI, tumor growth inhibition.
Each point and bar represents mean and standard error, respectively (n = 6).
Mice were subcutaneously inoculated with NCI-H1781 cells.
Estimated tumor volume for each mouse was calculated using the following equation:
Estimated tumor volume (mm^3) = 0.5 × length × $width^2$
Tumor volumes of treated groups were compared that of vehicle control at the evaluation point using Dunnett's test.
***$P < 0.0001$

Secondary pharmacodynamic studies

In vitro pharmacological actions of DXd were evaluated on a total of 86 receptors, channels, transporters, and enzymes by radioligand binding and enzyme assays at Eurofins Panlabs, Taiwan. The assays were performed in duplicate at concentrations of 10 µmol/L. Results showed that DXd had no significant response (within 50% inhibition of baseline) to those 86 receptors, channels, transporters, or enzymes (Report Number TW04-0008917), see Table below.

In conclusion, DXd showed no significant affinity for any of the 86 targets at 10 µmol/L (approximately 5000 ng/mL).

Assay#	Assay Name	Batch	Conc. (µmol/L)	Inhibition (%)
104010	Cholinesterase, Acetyl, ACES	468406	10	19
107300	Peptidase, Angiotensin Converting Enzyme	468520	10	2
107710	ATPase, Na^+/K^+, Heart, Pig	468496	10	3
112510	Peptidase, CTSG (Cathepsin G)	468385	10	-24
116030	Cyclooxygenase COX-1	468482	10	4
118030	Cyclooxygenase COX-2	468485	10	24
140010	Monoamine Oxidase MAO-A	468499	10	0
140120	Monoamine Oxidase MAO-B	468502	10	3
152300	Phosphodiesterase PDE3A	468559	10	6
154420	Phosphodiesterase PDE4D2	468562	10	1
174990	Protein Tyrosine Kinase, Insulin Receptor	468391	10	11
176020	Protein Tyrosine Kinase, LCK	468394	10	8
180010	Protein Serine/Threonine Kinase, PRKCA (PKCα)	468388	10	10
200510	Adenosine A_1	468442	10	-4
200610	Adenosine A_{2A}	468444	10	4
202000	Transporter, Adenosine	469323	10	-33
203110	Adrenergic α_{1A}	468414	10	-10
203210	Adrenergic α_{1B}	468416	10	-5
203400	Adrenergic α_{1D}	468339	10	1
203630	Adrenergic α_{2A}	468428	10	-8
203710	Adrenergic α_{2B}	468699	10	2
204010	Adrenergic $ß_1$	468419	10	-8
204110	Adrenergic $ß_2$	468430	10	-1
204410	Transporter, Norepinephrine (NET)	468567	10	8
206000	Androgen (Testosterone)	468565	10	8
210030	Angiotensin AT_1	468748	10	-6
214510	Calcium Channel L-Type, Benzothiazepine	468571	10	12
214600	Calcium Channel L-Type, Dihydropyridine	468573	10	-7

Assay#	Assay Name	Batch	Conc. (µmol/L)	Inhibition (%)
215000	Calcium Channel L-Type, Phenylalkylamine	468344	10	18
216000	Calcium Channel N-Type	468577	10	-13
217050	Cannabinoid CB_1	468436	10	-22
217100	Cannabinoid CB_2	468439	10	-4
217510	Chemokine CCR1	468733	10	1
218030	Cholecystokinin CCK_1 (CCK_A)	468705	10	-23
218130	Cholecystokinin CCK_2 (CCK_B)	468708	10	2
219500	Dopamine D_1	468461	10	4
219600	Dopamine D_{2L}	468347	10	7
219700	Dopamine D_{2S}	468350	10	-11
220320	Transporter, Dopamine (DAT)	468569	10	7
224010	Endothelin ET_A	469324	10	0
226010	Estrogen ERα	468354	10	-11
226400	Transporter, GABA	468575	10	10
226600	$GABA_A$, Flunitrazepam, Central	468433	10	3
226630	$GABA_A$, Ro-15-1788, Hippocampus	468742	10	-3
226810	$GABA_A$, Chloride Channel, TBOB	468357	10	1
228610	$GABA_{BIA}$	468745	10	-1
232030	Glucocorticoid	468526	10	9
232600	Glutamate, AMPA	468579	10	35
232710	Glutamate, Kainate	468696	10	2
232810	Glutamate, NMDA, Agonism	468450	10	11
232910	Glutamate, NMDA, Glycine	468453	10	14
233000	Glutamate, NMDA, Phencyclidine	468714	10	-4
234000	Glutamate, NMDA, Polyamine	468360	10	-5
237000	Glutamate, Metabotropic, $mGlu_5$	468583	10	-10
239000	Glycine, Strychnine-Sensitive	468363	10	13
239610	Histamine H_1	468366	10	3
239710	Histamine H_2	468421	10	-8

Assay#	Assay Name	Batch	Conc. (µmol/L)	Inhibition (%)
244500	Chemokine CXCR2 (IL-8R_B)	468585	10	16
250460	Leukotriene, Cysteinyl $CysLT_1$	468532	10	-14
251100	Melanocortin MC_1	468640	10	4
251350	Melanocortin MC_4	468642	10	4
252610	Muscarinic M_1	468720	10	-11
252710	Muscarinic M_2	468722	10	4
252810	Muscarinic M_3	468725	10	-7
252910	Muscarinic M_4	468727	10	-10
255520	Tachykinin NK_1	468587	10	-1
257010	Neuropeptide Y Y_1	468456	10	-2
258700	Nicotinic Acetylcholine α1, Bungarotoxin	468372	10	5
258730	Nicotinic Acetylcholine α3ß4	468589	10	7
260130	Opiate δ_1 (OP1, DOP)	468591	10	7
260210	Opiate κ (OP2, KOP)	468593	10	-8
260410	Opiate µ (OP3, MOP)	468595	10	-1
265600	Potassium Channel [K_{ATP}]	468597	10	8
265900	Potassium Channel hERG	468599	10	-4
267500	PPARγ	468693	10	4
271110	Serotonin (5-Hydroxytryptamine) 5-HT_{1A}	468375	10	5
271230	Serotonin (5-Hydroxytryptamine) 5-HT_{1B}	468378	10	4
271650	Serotonin (5-Hydroxytryptamine) 5-HT_{2A}	469325	10	1
271700	Serotonin (5-Hydroxytryptamine) 5-HT_{2B}	468535	10	1
271800	Serotonin (5-Hydroxytryptamine) 5-HT_{2C}	468717	10	-21
271910	Serotonin (5-Hydroxytryptamine) 5-HT_3	468603	10	5
274030	Transporter, Serotonin (5-Hydroxytryptamine) (SERT)	468730	10	5
279510	Sodium Channel, Site 2	468381	10	6
287530	Vasopressin V_{1A}	468605	10	6
299005	Progesterone PR-B	468607	10	3
299037	Platelet Activating Factor (PAF)	468447	10	-8

Safety pharmacology programme

No new safety pharmacology study was submitted to support this application.

Pharmacodynamic drug interactions

No new pharmacodynamic drug interactions study was submitted to support this application.

2.2.3. Ecotoxicity/environmental risk assessment

An updated ERA was submitted by the MAH.

Appendix 1 : Tabulated Summary

Substance (INN/Invented Name): Trastuzumab derutxtecan (tested as MAAA-1181a)					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	**OECD107** (1075.00204)	pH 5 = 1.92 pH 7 = 1.80 pH 9 = 1.28			< 4.5: **not B** < 4.5: **not PBT**
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default	If Fpen=0.01 0.0565 (default)	µg/L			Refined PEC < 0.01 µg/L **No Phase II assessment required**
Breast cancer refined PEC$_{surfacewater}$	If Fpen=0.000288 1.40 ×10^{-3} (refined)	µg/L			
Gastric cancer refined PEC$_{surfacewater}$	If Fpen=0.000190 1.07 ×10^{-3} (refined)	µg/L			
Non-Small Cell Lung cancer (NSCLC) refined PEC$_{surfacewater}$	If Fpen=0.000533 2.55 ×10^{-3} (refined)	µg/L			
Combined (total) PEC$_{surfacewater}$	**0.00820**	**µg/L**			
Other concerns (e.g. chemical class)					None
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Water Solubility	**OECD 105** (1075.00203)	7.52 mg/L			
Dissociation Constant (pKa)	**OECD 112** (1075.00201)	N/A			*Study not possible due to low water solubility and other physical chemical properties*
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Activated Sludge Respiration Inhibition	**OECD 209** (1075.00211)	NOEC	1000	mg/L	*LOEC >1000 mg/L*
Algae Growth Inhibition Test – *Pseudokirchneriella subcapitata*	**OECD 201** (1075.00208)	NOE_rC E_rC_{10}	23 80.7	µg/L µg/L	*LOE_rC = 75.3 µg/L* *E_rC_{50} = 561 µg/L*
Algae Growth Inhibition Test – *Anabaena flos-aquae*	**OECD 201** (1075.00209)	NOE_rC	2580	µg/L	*LOE_rC >2580 µg/L*
Daphnia reproduction assay – *Daphnia magna*	**OECD 211** (1075.00210)	NOEC EC_{10}	34.2 60.7	µg/L µg/L	*LOEC = 107 µg/L (reproduction)* *EC_{20} = 87.2 µg/L*

2.2.4. Discussion on non-clinical aspects

A comprehensive effort has been presented to show that T-DXd promote internalisation and cell killing in both wild type and mutated HER2 tumour cells. This was shown for 15 different mutations compared to

wild type HER2 and both in vitro and in vivo. The efficacy of a single dose in a mouse tumour model determined as ED_{50} was 4.4 mg/kg for wild type HER2 and in the range of 1.1 and 6.2 mg/kg for mutated HER2. Hence, the non-clinical proof of concept can be accepted.

A safety pharmacology screen did not raise concern for off-target effects.

Based on the updated data submitted in this application, the new indication does not trigger a Phase II environmental risk assessment.

2.2.5. Conclusion on the non-clinical aspects

New primary pharmacology studies provide non-clinical proof of concept in support of the new indication of HER2 mutant NSCLC. A safety pharmacology screen did not raise concern for off-target effects.

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 is not expected to pose a risk 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 3: Overview of studies used in population pharmacokinetic analysis

Study Number Module	Dev. Phase	Study Objectives	N	Dose	Sampling Time Points
J101[6] Module 5.3.3.2	1	Determination of the MTD or the RP2D of trastuzumab deruxtecan, assessment of the PK profiles of trastuzumab deruxtecan, DXd, and total anti-HER2 antibody, evaluation of efficacy, and assessment of safety and tolerability	292	0.8, 1.6, 3.2, 5.4, 6.4, and 8.0 mg/kg	Cycle 1: Predose, EOI, 2, 4, and 7 hours, and 1, 3, 7, 14, and 21[a] days after SOA. Cycle 3: Predose, EOI, 4 hours, and 7 and 14 days after SOA. Cycles 2, 4, 6 and 8: Predose and EOI
J202[7]	2	Comparison of the efficacy and safety of trastuzumab deruxtecan and TPC in HER2-overexpressing advanced gastric or gastroesophageal junction adenocarcinoma subjects who have progressed on 2 prior regimens including fluoropyrimidine agent, platinum agent and trastuzumab (brand, approved biosimilar)	231	6.4 mg/kg	Cycle 1, 3: Predose, EOI, 4 and 7 hours, and 7, 14 and 21[a] days after SOA. Cycles 2, 4, 6, and 8: Predose and EOI
J102[8]	1	Assessment of the PK of trastuzumab deruxtecan after multiple dosing, assessment of the effect of T-DXd on the QTc interval, and evaluation of efficacy and safety	51	6.4 mg/kg	Cycles 1 and 3: Predose, EOI, 2, 4, and 7 hours, and 1, 3, 7, 14, and 21[a] days after SOA. Cycles 2, 4, 6, and 8: Predose and EOI
A103[9]	1	Assessment of the PK profiles of trastuzumab deruxtecan, DXd, and total anti-HER2 antibody, assessment of safety and tolerability of T-DXd, and investigation of antitumor activity	12	6.4 mg/kg	Cycles 1 and 3: Predose, EOI, 2, 4, and 7 hours, and 1, 3, 7, 14, and 21[a] days after SOA. Cycles 2, 4, 6 and 8: Predose and EOI
A104[10]	1	Evaluation of the effects of ritonavir and itraconazole on the PK of trastuzumab deruxtecan and DXd, assessment of safety, and evaluation of efficacy	40	5.4 mg/kg	Cycles 1, 4, 6 and 8: Predose and EOI. Cycles 2 and 3: Predose, EOI, 2, 4, and 7 hours, and 1, 3, 7, 11, and 16 days after SOA
U201[11]	2	Determination of the PK and RP2D of trastuzumab deruxtecan, evaluation of E-R relationships for efficacy and safety, and evaluation of efficacy and safety	253	5.4, 6.4, and 7.4 mg/kg	Part 1 PK: Cycle 1: Predose, EOI, 2, 4, and 7 hours, and 1, 3, 7, 14 and 21[a] days after SOA Cycle 2, 4, 6, and 8: Predose and EOI. Cycle 3: Predose, EOI, and 4 and 7 hours after SOA. Dose-finding/RP2D Evaluation: Cycle 1: Predose, EOI, 4 and 7 hours, and 7, 14, and 21[a] days after SOA. Cycles 2, 4, 6, and 8: Predose and EOI. Cycle 3: Predose, EOI, and 4 and 7 hours after SOA

Study Number Module	Dev. Phase	Study Objectives	N	Dose	Sampling Time Points
U205	2	Investigation of the efficacy of trastuzumab deruxtecan based on confirmed ORR, as assessed by an independent central imaging facility review using RECIST v1.1, in subjects with HER2-positive unresectable or metastatic gastric or GEJ adenocarcinoma that has progressed on or after a trastuzumab-containing regimen	79	6.4 mg/kg	Cycle 1: Predose, EOI, 5 ± 2 hours and 8, 15, and 21[a] days after SOA Cycles 2, 3, 4, 6, and 8: Predose and EOI
U204 Module 5.3.5.1	2	Evaluation of the ORR of trastuzumab deruxtecan in HER2-overexpressing and/or HER2-mutated advanced NSCLC subjects	181	5.4 and 6.4 mg/kg	Cycle 1: Predose, EOI, 5 hours and 8, 15, and 22[a] days after SOA Cycles 2, 3, 4, and subsequent: Predose and EOI
U302	3	Evaluation of the ORR of trastuzumab deruxtecan in HER2 positive, unresectable and/or metastatic BC subjects previously treated with trastuzumab and taxane	257 [b]	5.4 mg/kg	Cycle 1: Predose, EOI, 5 hours after SOA Cycles 2, 3, 4, 6, and 8: Predose and EOI
U303	3	Evaluation of the ORR of trastuzumab deruxtecan in HER2-low, unresectable and/or metastatic BC subjects	371 [b]	5.4 mg/kg	Cycle 1: Predose, and EOI. Cycles 2, 3, 4, and subsequent: Predose and EOI
U206 Module 5.3.5.1	2	Evaluation of the confirmed ORR of trastuzumab deruxtecan in HER2-mutated metastatic NSCLC subjects	152 (as of IA)	6.4 mg/kg	Cycle 1 Day 1: Predose, EOI, 5 hours and 8, 15, and 22[a] days after SOA Cycles 2, and 3: Predose and EOI Cycles 4 and subsequent: Predose

DXd = the released payload; EOI = end of infusion; E-R = exposure-response; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; IA – interim analysis; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; ORR = objective response rate; PFS = progression-free survival; PK = pharmacokinetics; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; RP2D = recommended Phase 2 dose; SOA = start of administration; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

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

[b] N refers to subjects treated with T-DXd only.

The clinical studies supporting this application are: the ongoing Study DS8201-A-U206 (DESTINY-Lung02, hereafter referred to as Study U206), the completed studies DS8201-A-U204 (DESTINY Lung01, hereafter referred to as Study U204) and DS8201 A J101 (hereafter referred to as Study J101).

The proposed dose of T-DXd in patients with unresectable or metastatic NSCLC with activating HER2 mutations is 5.4 mg/kg administered as an intravenous (IV) infusion Q3W.

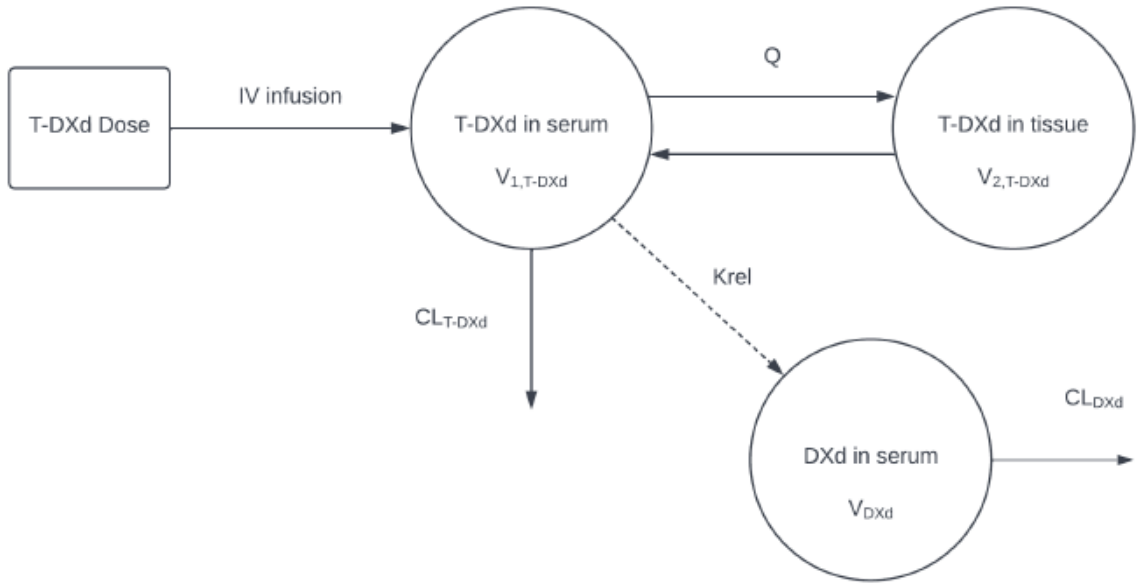
2.3.2. Pharmacokinetics

Serum concentrations of the intact ADC T-DXd, total anti-HER2 antibody, and the topoisomerase I inhibitor DXd were measured to evaluate the PK of T-DXd by noncompartmental analysis (NCA). An integrated PK analysis across studies was done using data from NCA analysis as well as by PopPK analysis. Total anti-HER2 antibody concentrations refer to the concentrations of the mAb against HER2. No new bioanalytical methods were employed.

Pop PK analyses

The PK of T-DXd was describe by a two-compartment model with linear elimination and IV infusion. The PK of the DXd was described using a one-compartment model with two-component, time-varying release rate from the T-DXd (Equation 1) and a linear elimination. The first component of this T-DXd release rate was a constant reduction after Cycle 1, and the second component was a gradual decline per cycle (See Figure 4).

Figure 4: T-DXd PK model structure



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

The T-DXd population PK model was updated with data from Study U206 (interim analysis with data cut-off date 24 Mar 2022) which was appended to the existing PK dataset. Study U206 enrolled patients with HER2-mutant metastatic NSCLC who received T-DXd 5.4 mg/kg (n=100) or 6.4 mg/kg (n=50). Study U204 also contributed data from patients with HER2 overexpressing and/or HER2 mutated NSCLC, where 49 patients with HER2 exp NSCLC received 6.4 mg/kg, 41 patients with HER2 exp NSCLC received 5.4 mg/kg and 91 patients with HER2 mutant NSCLC received 6.4 mg/kg.

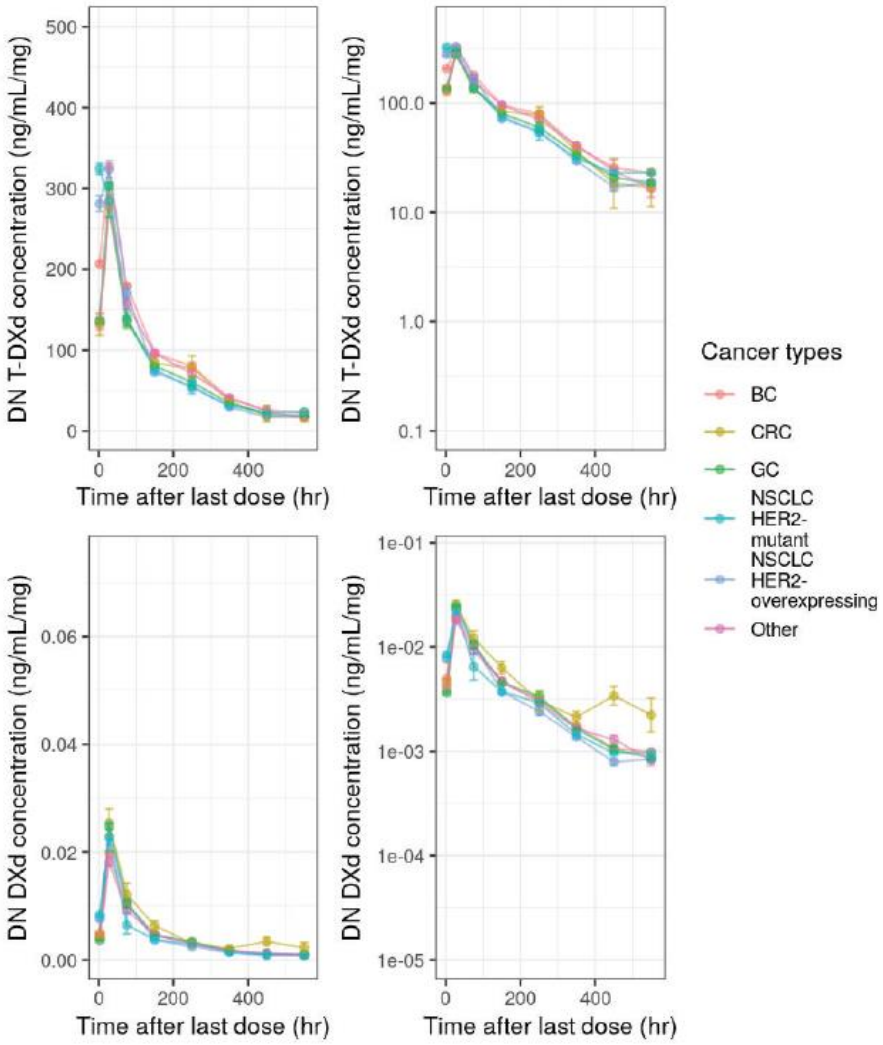
The full merged dataset was comprised of 24,558 T-DXd samples from 1821 subjects and 24,507 DXd samples from Studies J101, U204, U206, J102, A103, A104, U201, J202, U205, U302, and U303. A total of 1128, 293, 21, 346 and 34 subjects had breast cancer (BC), gastric or gastro-esophageal junction adenocarcinoma (GC), colorectal cancer (CRC), NSCLC and other cancers, respectively. A total of 65, 919, 246, 100, 468 and 24 subjects had negative, positive, mutant, overexpressing, low and missing HER2 status, respectively.

Model parameters were re-estimated after inclusion of data from Study U206 using a sequential modeling approach. First, the T-DXd model was re-estimated using T-DXd PK data only. Second, the T-DXd PK parameters were fixed, and the remaining model parameters were re-estimated using both the T-DXd and the DXd PK data. A covariate modeling approach emphasizing parameter estimation rather than stepwise hypothesis testing was implemented. The full covariate model was constructed with care to avoid correlation or collinearity in predictors. For the population PK analysis, covariate effect sizes between 80% and 125% from the typical reference subject were used as a limit for clinically meaningful changes.

Dose normalized concentration versus TAD profiles of T-DXd and DXd stratified by study and cancer type are shown in Figure 5.

Figure 5: T-DXd and DXd geometric mean dose normalised concentration versus time after dose plot by cancer type

Dots represent observations. Lines connect concentrations collected from the same subject. Colors represent cancer types. left and right panels show plots in linear and log scales, respectively. Error bars are ±1 standard error in the logarithmic domain. DN = dose normalized.



The re-estimated model parameters for T-DXd and DXd are shown in the below tables.

Table 4: T-DXd fixed effect parameter estimates

			Estimate	95% CI
Structural model parameters				
CL (L/day)	θ_1	T-DXd clearance	0.409	0.402, 0.417
V1 (L)	θ_2	T-DXd central volume	2.69	2.66, 2.72
Q (L/day)	θ_3	T-DXd inter-compartmental clearance	0.195	0.190, 0.199
V2 (L)	θ_4	T-DXd peripheral volume	6.46	6.08, 6.84
Covariate effect parameters				
CL ~ ALB (g/L)	θ_7	Baseline serum albumin effect on CL	-0.472	-0.565, -0.380
CL ~ JPGR1	θ_8	If Asian from Japan effect on CL	-0.0855	-0.111, -0.0604
CL ~ TTSUMB (mm)	θ_{10}	Baseline target tumor size effect on CL	0.0506	0.0341, 0.0670
CL ~ WGTB (kg)	θ_{11}	Baseline body weight effect on CL	0.399	0.338, 0.461
CL ~ GC	θ_{15}	If GC effect on CL	0.168	0.124, 0.213
CL ~ NSCLC HER2 mutant	θ_{16}	If NSCLC with HER2 mutant effect on CL	0.0155	-0.0222, 0.0532
CL ~ NSCLC HER2 overexpressing	θ_{17}	If NSCLC with HER2 overexpressing effect on CL	0.140	0.0750, 0.204
CL ~ CRC or others	θ_{18}	If cancer types other than BC, GC or NSCLC effect on CL	0.0708	-0.00916, 0.151
V1 ~ SEX	θ_{12}	Sex (male) effect on V1	0.131	0.102, 0.161
V1 ~ WGTB (kg)	θ_{13}	Baseline body weight effect on V1	0.443	0.402, 0.484
V1 ~ GC	θ_{19}	If GC effect on V1	0.100	0.0672, 0.133
V1 ~ NSCLC HER2 mutant	θ_{20}	If NSCLC with HER2 mutant effect on V1	-0.0689	-0.0914, -0.0463
V1 ~ NSCLC HER2 overexpressing	θ_{21}	If NSCLC with HER2 overexpressing effect on V1	-0.0185	-0.0636, 0.0265
V2 ~ JPGR1	θ_{14}	If Asian from Japan effect on V2	-0.238	-0.308, -0.168

Abbreviations: CI = confidence intervals; SE = standard error; BC = breast cancer; GC = gastric cancer; NSCLC = non-small cell lung cancer; CRC = colorectal cancer; HER2 = epidermal growth factor receptor 2
Confidence intervals = estimate ± 1.96 · SE
Source code: TDXd-pk-final-model-table.R
Source file: TDXd-pk-param-final-fixed.tex

Continuous covariate effects were expressed as the exponents of power functions. Categorical covariate effects were expressed as the fraction changes relative to reference groups.

Table 5: T-DXd random effect parameter estimates

		Estimate	95% CI	Shrinkage (%)
Interindividual variance parameters				
IIV-CL	$\Omega_{(1,1)}$	0.0589 [CV%=24.6]	0.0550, 0.0628	10.7
IIV-V1	$\Omega_{(2,2)}$	0.0251 [CV%=15.9]	0.0240, 0.0262	8.40
IIV-Q	$\Omega_{(3,3)}$	0.0815 [CV%=29.1]	0.0682, 0.0948	40.1
IIV-V2	$\Omega_{(4,4)}$	0.503 [CV%=80.9]	0.444, 0.563	24.3
Interindividual covariance parameters				
CL-V1	$\Omega_{(2,1)}$	0.0209 [Corr=0.543]	0.0191, 0.0227	-
Residual variance				
T-DXd proportional	θ_5	0.169	0.169, 0.170	-
T-DXd additive	θ_6	1040	1000, 1070	-

Abbreviations: CI = confidence intervals; Corr = correlation coefficient; CV = coefficient of variation; SD = standard deviation; SE = standard error
CV% of log-normal omegas = sqrt(exp(estimate) - 1) · 100
Source code: TDXd-pk-final-model-table.R
Source file: TDXd-pk-param-final-random.tex

The proportional error is expressed as CV% and the additive error is expressed as SD. The unit for additive error is ng/mL.

Table 6: DXd fixed effect parameter estimates

			Estimate	95% CI
Structural model parameters				
CLPAY (L/h)	θ_{23}	DXd clearance	19.6	18.8, 20.4
KREL (/h)	θ_{24}	DXd release rate constant	0.0197	0.0189, 0.0206
FPC1	θ_{27}	DXd deconjugation fraction at CYCLE>1	0.732	0.718, 0.745
FPC2	θ_{28}	DXd deconjugation fraction power cycle effect	-0.155	-0.163, -0.146
V3 (L)	NA	DXd volume	17*BSA	FIXED
Covariate effect parameters				
CLPAY ~ RITONVR	θ_{29}	Ritonavir effect on CLPAY	-0.122	-0.156, -0.0871
CLPAY ~ ITRACNZL	θ_{30}	Itraconazole effect on CLPAY	-0.109	-0.152, -0.0661
CLPAY ~ SGOTB (U/L)	θ_{31}	Baseline aspartate aminotransferase effect on CLPAY	-0.195	-0.233, -0.157
CLPAY ~ BILITLB (umol/L)	θ_{32}	Baseline total bilirubin effect on CLPAY	-0.139	-0.178, -0.0997
CLPAY ~ WGTB (kg)	θ_{33}	Baseline body weight effect on CLPAY	0.341	0.246, 0.437
V3 ~ AGE (years)	θ_{34}	Age effect on V3	0.590	0.471, 0.709
V3 ~ FORM1	θ_{35}	If FL-DP2 effect on V3	0.579	0.443, 0.714
V3 ~ NSCLC	θ_{38}	If NSCLC effect on V3	-0.247	-0.309, -0.185
V3 ~ JPGR3	θ_{44}	If non-Asian effect on V3	-0.236	-0.277, -0.195

Abbreviations: CI = confidence intervals; SE = standard error; BC = breast cancer; GC = gastric cancer; NSCLC = non-small cell lung cancer; FL-DP2 = frozen liquid drug product 2 BSA = body surface area (m^2)
Confidence intervals = estimate ± 1.96 · SE
Source code: DXd-pk-final-model-table.R
Source file: DXd-pk-param-final-fixed.tex

Continuous covariate effects were expressed as the exponents of power functions. Categorical covariate effects were expressed as the fraction changes relative to reference groups.

The typical volume of distribution of DXd is 28.05 L for a typical subject with an average BSA of 1.65 m2.

Table 7: DXd random effect parameter estimates

		Estimate	95% CI	Shrinkage (%)
Interindividual variance parameters				
IIV-CLPAY	$\Omega_{(5,5)}$	0.0852 [CV%=29.8]	0.0734, 0.0969	33.5
IIV-V3	$\Omega_{(6,6)}$	0.193 [CV%=46.1]	0.173, 0.212	22.4
IIV-KREL	$\Omega_{(7,7)}$	0.103 [CV%=33.0]	0.0896, 0.117	25.1
IIV-FPC1	$\Omega_{(8,8)}$	0.666 [SD=0.164]	0.569, 0.762	26.8
Residual variance				
DXd proportional	θ_{25}	0.309	0.307, 0.311	-

Abbreviations: CI = confidence intervals; Corr = correlation coefficient; CV = coefficient of variation; SD = standard deviation; SE = standard error
CV% of log-normal omegas = sqrt(exp(estimate) - 1) · 100
Source code: DXd-pk-final-model-table.R
Source file: DXd-pk-param-final-random.tex

The proportional error is expressed as CV%.

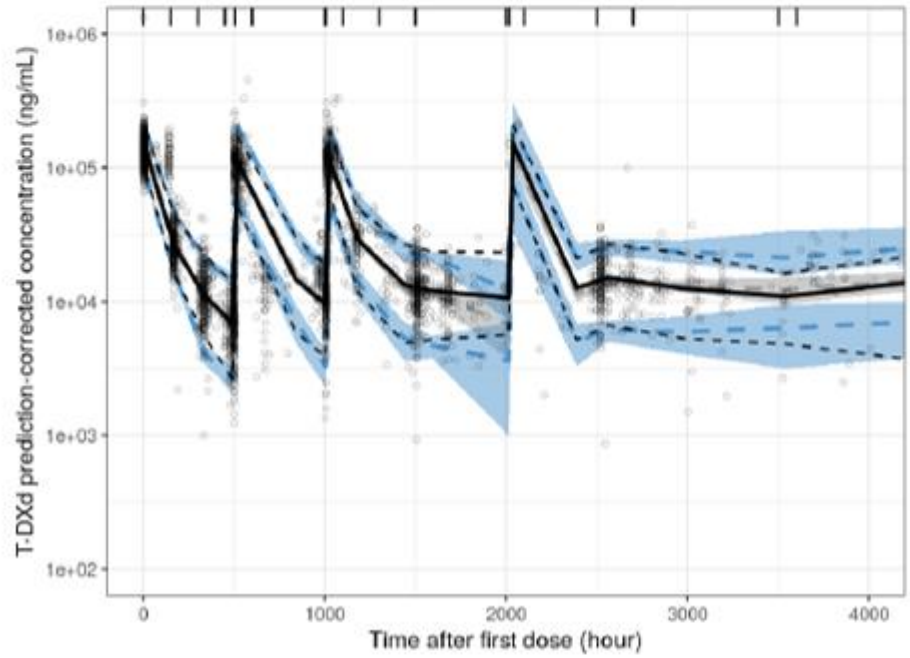
The T-DXd model and the DXd model parameter estimates were evaluated by GoF plots and by VPCs.

Precision corrected VPCs were presented as time after last dose and as time after first dose for the whole data set stratified for study, cancer type, HER2 expression or dose for T-DXd and for DXd. Figure 6 show the pc-VPCs for T-DXd and DXd concentrations vs time after first dose stratified by subjects with NSCLC.

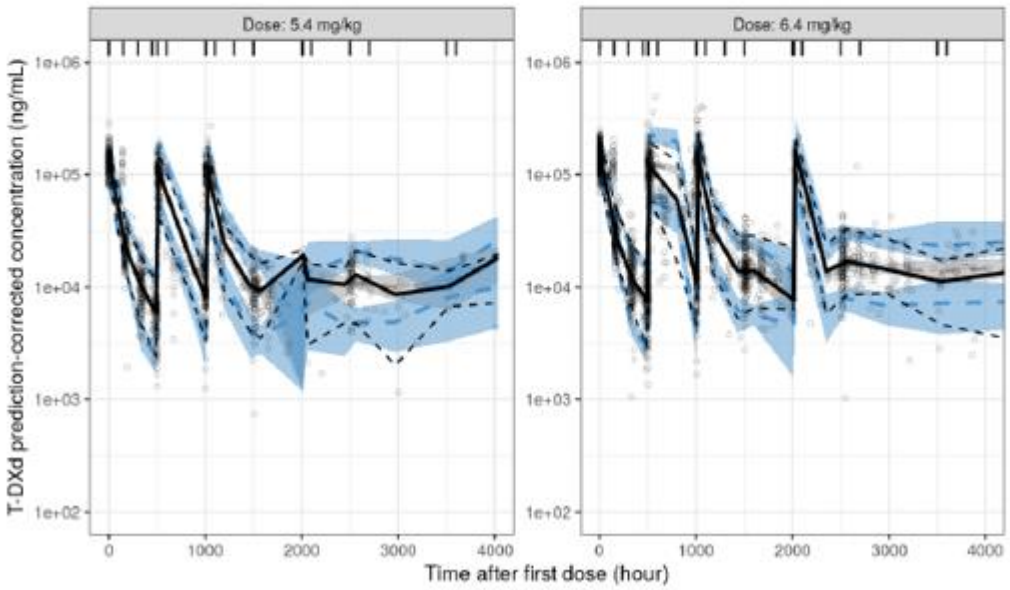
Figure 6: pcVPC of T-DXd using time after first dose in subjects with NSCLC

The black lines represent the median (solid) or 5th/95th (dashed) percentiles of the observed data. The gray and blue dashed lines represent the median of the medians or 5th/95th percentiles, respectively, for simulated data under the model. The shaded areas represent 95% prediction intervals for median (gray) or 5th/95th percentiles (blue) for simulated data under the model.

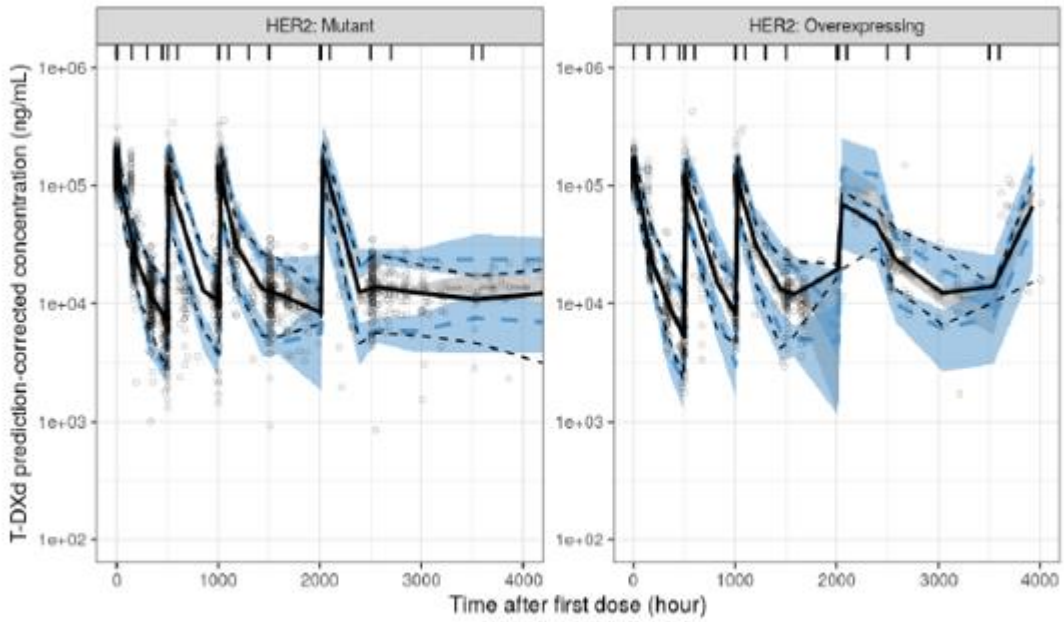
a) NSCLC subjects across 5.4 and 6.4 mg/kg and HER2 status combined



b) NSCLC subjects by dose (5.4 and 6.4 mg/kg)



c) NSCLC subjects by HER2 status (HER2 mutant and HER2 overexpressing)



HER2 = human epidermal growth factor receptor 2; NSCLC = non-small cell lung cancer; T-DXd = trastuzumab deruxtecan

Absorption

ADME characteristics

No new assessment for the absorption, distribution, metabolism, and excretion characteristics of T-DXd were conducted for this submission. After inclusion of data from Study U206, clearance values obtained from the updated Pop PK model were used.

PK data were collected in NSCLC subjects from Studies J101, U204 and U206. The Cycle 1 PK data (calculated using NCA methods) for T-DXd in subjects with NSCLC (HER2-mutant and HER2-overexpressing) were integrated across Studies J101, U204, and U206. Study J101 contributed with PK data from 18 NSCLC subjects.

Study U204

Overview of Study U204 cohorts are shown in Table 8. PK parameters for T-DXd and DXd determined by NCA for patients with HER2 overexpressing and/or HER2 mutated NSCLC from Study U204 are summarised in Table 9 and Table 10

Table 8: Data Sets Analysed

Analysis Set	Number (%) of Subjects			
	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

Table 9: Pharmacokinetic Parameters of T-DXd for all Cohorts (Pharmacokinetic Analysis Set)

	Cmax (µg/mL)	Tmax (h)[a]	AUClast (µg × d/mL)	AUC21d (µg × d/mL)	CL (mL/d/kg)	Vss (mL/kg)	t1/2 (d)
Cohort 1 (HER2Exp, 6.4 mg/kg) (N = 49)							
n	49	49	46	46	45	45	45
Mean (Std Dev)	152.78 (37.985)	3.50 (1.5, 14.2)	748.19 (202.311)	747.31 (198.718)	8.47 (2.278)	57.78 (13.579)	5.93 (1.574)
Cohort 1a (HER2Exp, 5.4 mg/kg) (N = 41)							
n	40	40	39	37	34	34	34
Mean (Std Dev)	135.21 (40.371)	1.75 (1.4, 456.0)	564.14 (146.399)	573.43 (140.350)	9.56 (2.689)	56.79 (11.800)	5.41 (1.248)
Cohort 2 (HER2Mut, 6.4 mg/kg) (N = 91)							
n	89	89	85	82	74	74	74
Mean (Std Dev)	146.50 (40.376)	1.97 (1.0, 211.4)	720.62 (203.102)	720.23 (202.312)	9.22 (3.682)	60.21 (13.435)	5.68 (1.284)
Cohort 1 and 2 (HER2Exp and HER2Mut, 6.4 mg/kg) (N = 140)							
n	138	138	131	128	119	119	119
Mean (Std Dev)	148.73 (39.519)	2.58 (1.0, 211.4)	730.30 (202.476)	729.96 (200.667)	8.94 (3.234)	59.29 (13.484)	5.78 (1.400)

AUC21d = area under the serum concentration-time curve up to 21 days; AUClast = area under the serum concentration-time curve up to the last quantifiable concentration in Cycle 1; CL = total body clearance; Cmax = maximum serum concentration; HER2Exp = human epidermal growth factor receptor 2-overexpressing; HER2Mut = human epidermal growth factor receptor 2-mutant; max = maximum; min = minimum; No. = number; t1/2 = terminal elimination half-life; T-DXd = trastuzumab deruxtecan; Tmax = time to reach maximum serum concentration; Std Dev = standard deviation; Vss =volume of distribution at steady state
Two subjects (Subject No. 31010030 of Cohort 1a and Subject No. 10020005 of Cohort 2) who received incorrect dosage of T-DXd were excluded.
[a] Median (min, max) is shown for Tmax.
Data cut-off: 03 May 2021

Table 10 Pharmacokinetic Parameters of T-DXd for all Cohorts (Pharmacokinetic Analysis Set)

	Cmax (ng/mL)	Tmax (h)[a]	AUClast (ng × d/mL)	AUC21d (ng × d/mL)	CL (mL/d/kg)	Vss (mL/kg)	t1/2 (d)
Cohort 1 (HER2Exp, 6.4 mg/kg) (N = 49)							
n	49	49	46	43	-	-	40
Mean (Std Dev)	14.46 (6.250)	4.00 (3.5, 16.2)	49.27 (16.102)	47.99 (15.229)	-	-	6.64 (3.316)
Cohort 1a (HER2Exp, 5.4 mg/kg) (N = 41)							
n	40	40	39	36	-	-	31
Mean (Std Dev)	13.16 (5.215)	3.15 (1.8, 5.3)	45.24 (13.460)	44.02 (13.192)	-	-	5.80 (1.356)
Cohort 2 (HER2Mut, 6.4 mg/kg) (N = 91)							
n	89	89	85	80	-	-	66
Mean (Std Dev)	13.02 (6.414)	4.02 (1.0, 211.4)	46.38 (17.505)	46.93 (17.805)	-	-	6.19 (1.345)
Cohort 1 and 2 (HER2Exp and HER2Mut, 6.4 mg/kg) (N = 140)							
n	138	138	131	123	-	-	106
Mean (Std Dev)	13.53 (6.371)	4.01 (1.0, 211.4)	47.40 (17.019)	47.30 (16.893)	-	-	6.36 (2.292)

AUC21d = area under the serum concentration-time curve up to 21 days; AUClast = area under the serum concentration-time curve up to the last quantifiable concentration in Cycle 1; CL = total body clearance; Cmax = maximum serum concentration; DXd = the released drug; HER2Exp = human epidermal growth factor receptor 2-overexpressing; HER2Mut = human epidermal growth factor receptor 2-mutant; max = maximum; min = minimum; No. = number; t1/2 = terminal elimination half-life; T-DXd = trastuzumab deruxtecan; Tmax = time to reach maximum serum concentration; Std Dev = standard deviation; Vss = volume of distribution at steady state

[a] Median (min, max) is shown for Tmax.

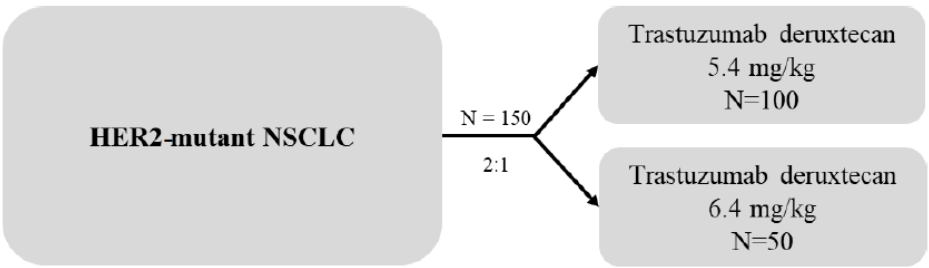
Two subjects (Subject No. 31010030 of Cohort 1a and Subject No. 10020005 of Cohort 2) who received incorrect dosage of T-DXd were excluded.

Data cut-off: 03 May 2021

Study U206

Study design and PK parameters determined by NCA for patients with HER2 mutated NSCLC from Study U206 are summarised in Tables 6.1 and 9.1.

Figure 6.1: Study Level Flow Diagram



HER2 = human epidermal growth factor receptor 2; NSCLC = non-small cell lung cancer

Table 9.1: Descriptive Statistics of Pharmacokinetic Parameters of T-DXd, Total Anti-HER2 Antibody, and DXd at Cycle 1 (PK Analysis Set)

	T-DXd		Total Anti-HER2 Antibody		DXd	
PK Parameter (Unit)	T-DXd 5.4 mg/kg	T-DXd 6.4 mg/kg	T-DXd 5.4 mg/kg	T-DXd 6.4 mg/kg	T-DXd 5.4 mg/kg	T-DXd 6.4 mg/kg
PK Analysis Set						
Cmax (µg/mL; ng/mL)[a]						
n	96	46	96	46	94	46
Mean	143	198	135	180	15.0	17.8
Std. Dev.	39.4	188	43.0	199	7.34	6.89
t1/2 (d)						
n	82	40	83	44	80	37
Mean	5.39	5.70	5.37	5.67	6.16	6.38
Std. Dev.	1.08	1.37	1.43	1.44	1.13	1.87
Tmax (h)						
n	96	46	96	46	94	46
Median	3.03	3.05	1.80	2.99	3.12	3.11
Range	(1.43 - 4.87)	(1.50 - 5.07)	(1.43 - 4.82)	(1.50 - 5.83)	(1.75 - 5.52)	(1.63 - 5.83)
AUC21d (µg × d/mL)[b]						
n	82	38	81	38	53	21
Mean	637	790	688	824	47.5	56.2
Std. Dev.	159	194	195	250	20.1	15.7

Integrated Analyses

Mean concentration-time profiles for HER2 mutant NSCLC subjects by dose are shown in Figure 7 for T-DXd, in Figure 8 for Total Anti-HER2 antibody and in Figure 9 for DXd. The data are pooled across Studies J101, U202 and U206.

Figure 7: Concentration-Time profile : All studies combined, by dose and HER2 status-DS-8201a PK Analysis Set-NSCLC Subjects

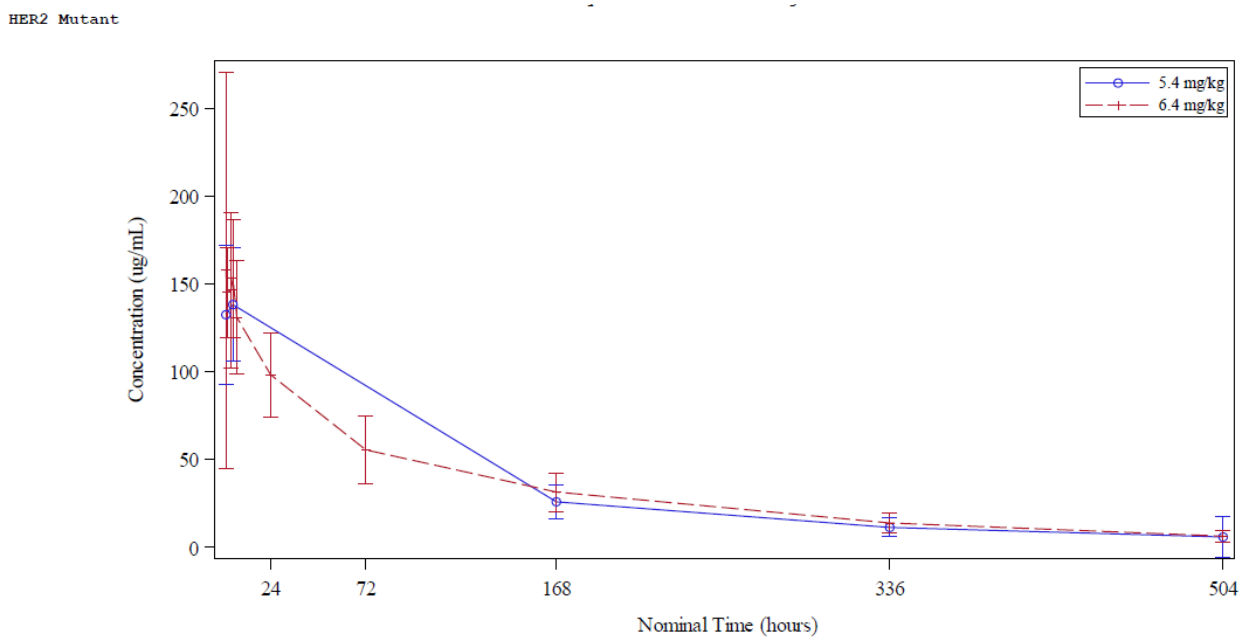


Figure 8 : Concentration-Time profile : All studies combined, by dose and HER2 status-Total Anti-Her2 Antibody PK Analysis Set-NSCLC Subjects

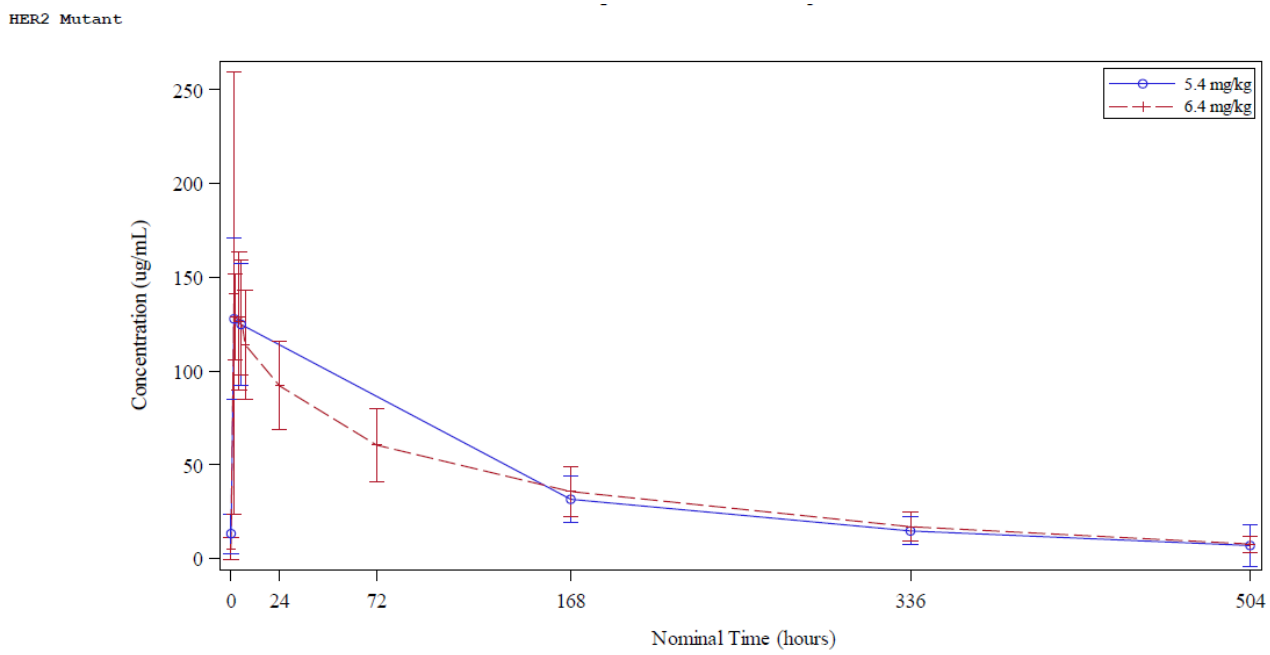
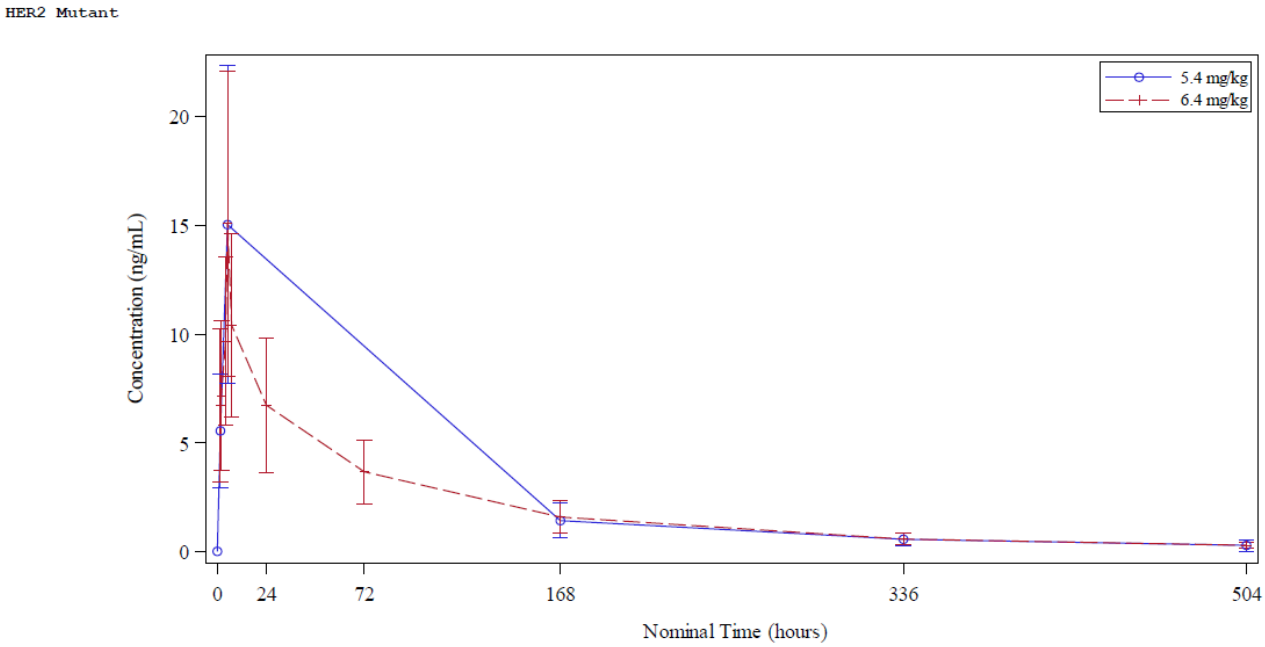


Figure 9 Concentration-Time profile : All studies combined, by dose and HER2 status-Dxd PK Analysis Set-NSCLC Subjects



Model derived Cmax, Cmin and AUC, at Cycle 1 and steady-state (Cycle 9) for subjects in the analysis dataset including Study U206 (Data cutoff 24 March 2022) were also generated using the post hoc individual parameter estimates.

Table 11 and **Table 12** show the model predicted exposure of T-DXd and DXd in NSCLC subjects by HER2 status and for BC subjects.

Table 11: Summary of post hoc T-DXd exposures in NSCLC (by HER2 status) and BC subjects receiving 5.4 mg/kg and 6.4 mg/kg Q3W T-DXd

	Geometric Mean (CV%, N)			Geometric Mean Ratio	
Exposure Metric	BC	NSCLC HER2-mutant	NSCLC HER2-overexpressing	NSCLC HER2-mutant/BC	NSCLC HER2-overexpressing/BC
Dose: 5.4 mg/kg					
T-DXd Cycle 1 Cmin (μg/mL)	4.62 (56.4, 885)	4.36 (66.6, 99)	3.56 (52.9, 46)	0.944	0.770
T-DXd Cycle 1 Cmax (μg/mL)	120 (19.0, 885)	129 (19.4, 99)	122 (17.2, 46)	1.08	1.02
T-DXd Cycle 1 AUC (μg*day/mL)	591 (22.5, 885)	593 (28.8, 99)	535 (22.7, 46)	1.00	0.906
T-DXd Cycle 9 Cmin (μg/mL)	11.7 (48.2, 885)	11.1 (54.2, 99)	9.13 (50.0, 46)	0.950	0.783
T-DXd Cycle 9 Cmax (μg/mL)	132 (19.5, 885)	141 (21.1, 99)	131 (18.0, 46)	1.07	0.996
T-DXd Cycle 9 AUC (μg*day/mL)	781 (26.7, 885)	775 (32.5, 99)	687 (27.0, 46)	0.993	0.879
Dose: 6.4 mg/kg					
T-DXd Cycle 1 Cmin (μg/mL)	6.86 (47.3, 210)	5.95 (64.3, 147)	5.77 (51.2, 54)	0.868	0.842
T-DXd Cycle 1 Cmax (μg/mL)	136 (17.7, 210)	150 (22.1, 147)	143 (16.7, 54)	1.11	1.05
T-DXd Cycle 1 AUC (μg*day/mL)	705 (22.4, 210)	714 (26.3, 147)	689 (21.4, 54)	1.01	0.977
T-DXd Cycle 9 Cmin (μg/mL)	15.9 (40.9, 210)	14.9 (51.5, 147)	12.9 (43.0, 54)	0.934	0.809
T-DXd Cycle 9 Cmax (μg/mL)	152 (18.1, 210)	166 (22.7, 147)	156 (17.0, 54)	1.09	1.03
T-DXd Cycle 9 AUC (μg*day/mL)	957 (25.4, 210)	957 (30.2, 147)	892 (23.6, 54)	1.00	0.932

Source code: pk-ebe-simulate-table.R
Source file: TDXd-expo-table-2.tex

AUC = area under the concentration-time curve; NSCLC: non-small cell lung cancer; BC = breast cancer; Cmax = maximum concentration; Cmin = minimum concentration; CV = coefficient of variation; N = number of subjects; Q3W = every 3 weeks.

Table 12: Summary of post hoc DXd exposures in NSCLC (by HER2 status) and BC subjects receiving 5.4 mg/kg and 6.4 mg/kg Q3W T-DXd

Exposure Metric	Geometric Mean (CV%, N)			Geometric Mean Ratio	
	BC	NSCLC HER2-mutant	NSCLC HER2-overexpressing	NSCLC HER2-mutant/BC	NSCLC HER2-overexpressing/BC
Dose: 5.4 mg/kg					
DXd Cycle 1 Cmin (ng/mL)	0.356 (57.8, 885)	0.324 (55.6, 99)	0.284 (44.8, 46)	0.909	0.798
DXd Cycle 1 Cmax (ng/mL)	8.78 (45.6, 885)	9.23 (44.9, 99)	9.38 (31.7, 46)	1.05	1.07
DXd Cycle 1 AUC (ng*day/mL)	45.4 (43.9, 885)	43.9 (43.2, 99)	42.7 (31.5, 46)	0.967	0.941
DXd Cycle 9 Cmin (ng/mL)	0.638 (53.5, 885)	0.585 (51.8, 99)	0.519 (43.8, 46)	0.916	0.813
DXd Cycle 9 Cmax (ng/mL)	6.91 (44.5, 885)	7.20 (43.5, 99)	7.22 (30.9, 46)	1.04	1.05
DXd Cycle 9 AUC (ng*day/mL)	42.7 (44.1, 885)	40.9 (43.1, 99)	39.0 (31.8, 46)	0.957	0.913
Dose: 6.4 mg/kg					
DXd Cycle 1 Cmin (ng/mL)	0.459 (47.2, 210)	0.383 (58.3, 147)	0.396 (48.6, 54)	0.834	0.861
DXd Cycle 1 Cmax (ng/mL)	8.61 (43.2, 210)	9.33 (38.7, 147)	9.44 (37.5, 54)	1.08	1.10
DXd Cycle 1 AUC (ng*day/mL)	47.0 (41.0, 210)	45.8 (38.1, 147)	47.1 (34.8, 54)	0.975	1.00
DXd Cycle 9 Cmin (ng/mL)	0.758 (45.7, 210)	0.680 (49.0, 147)	0.627 (38.6, 54)	0.898	0.828
DXd Cycle 9 Cmax (ng/mL)	6.91 (41.9, 210)	7.35 (37.7, 147)	7.37 (35.9, 54)	1.06	1.07
DXd Cycle 9 AUC (ng*day/mL)	45.5 (40.8, 210)	43.8 (38.0, 147)	43.4 (32.6, 54)	0.963	0.955

Source code: pk-ebe-simulate-table.R
Source file: DXd-expo-table-2.tex

AUC = area under the concentration-time curve; NSCLC: non-small cell lung cancer; BC = breast cancer; Cmax = maximum concentration; Cmin = minimum concentration; CV = coefficient of variation; N = number of subjects; Q3W = every 3 weeks.

Distribution

Not applicable.

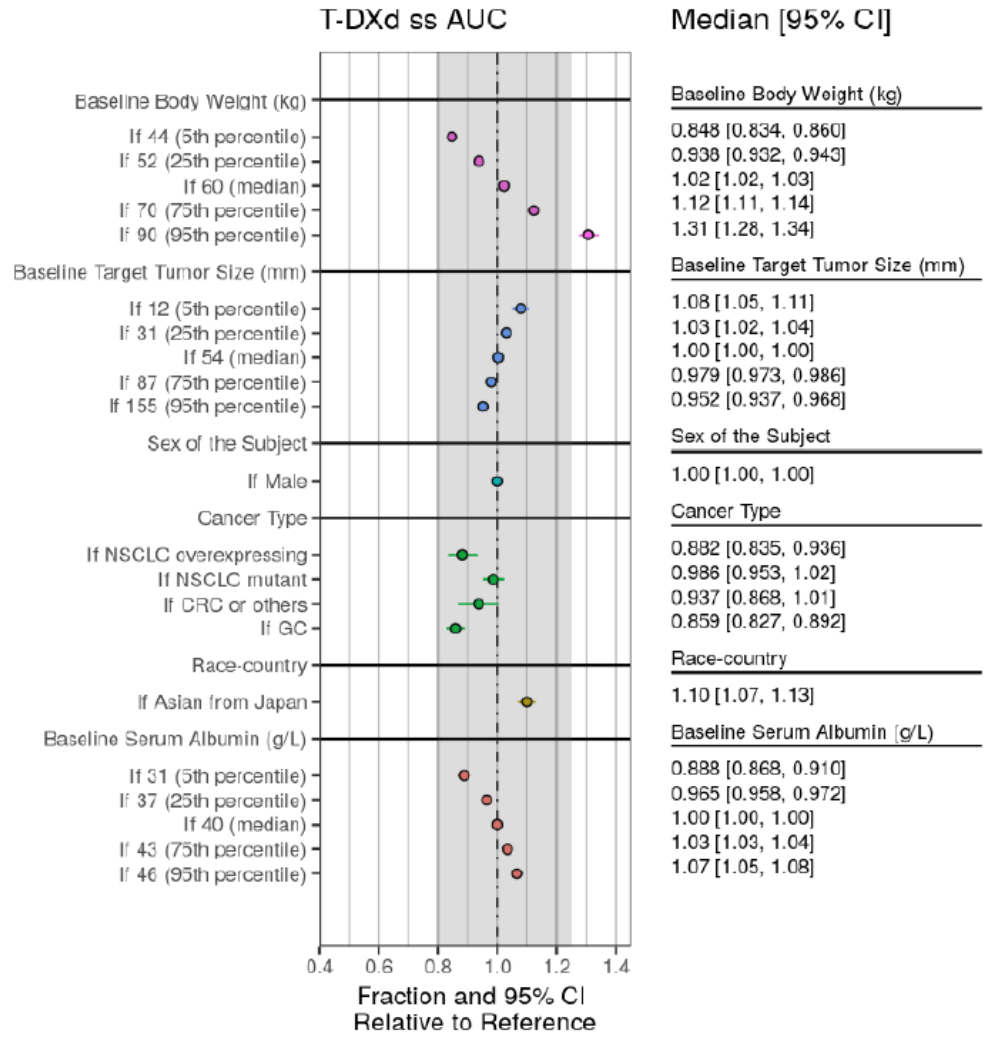
Elimination

Not applicable.

Special populations

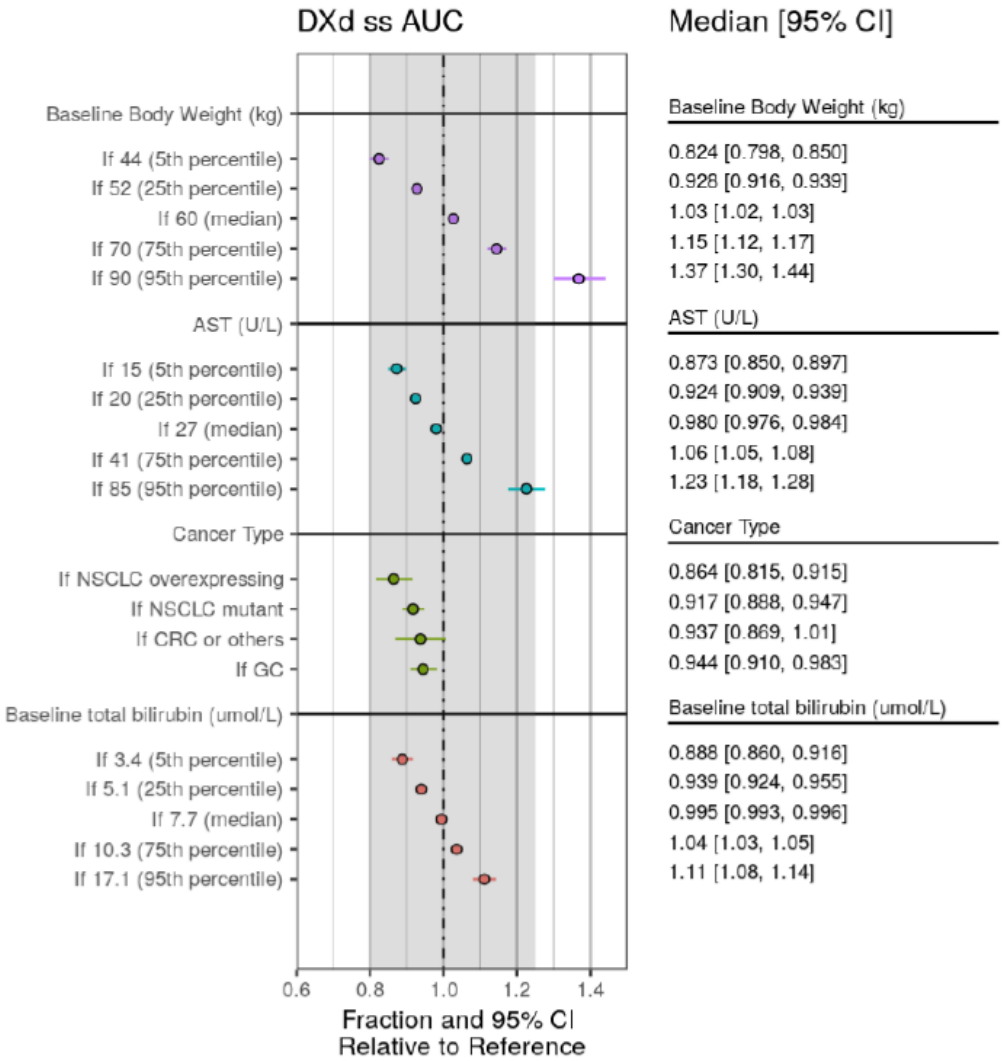
Forests plots showed the effects of different values of a covariate for a typical subject, defined as a female non-Japan subject with BC and 57.8 kg baseline body weight for T-DXd. For DXd the reference subject was restricted to Asia. (See Figure 10 and Figure 11).

Figure 10: Forest plot of covariate effects on the AUCss of T-DXd at steady state



AUC = area under the serum concentration-time curve; AUCss = area under the serum concentration-time curve at steady state; BC = breast cancer; CI = confidence interval; CRC = colorectal cancer; GC = gastric cancer; NSCLC = non-small cell lung cancer; ss = steady state; T-DXd = trastuzumab deruxtecan.
Note: The shaded area corresponds to the interval (0.8, 1.25). The reference group is female non-Japan (include Asian not from Japan and non-Asian as included for reference population in the popPK model for T-DXd) subject with BC with 57.8 kg baseline body weight, 57 mm baseline target tumor size, and 40 g/L baseline serum albumin.

Figure 11: Forest plot of covariate effect on the AUCss of DXd at steady state



AST = aspartate aminotransferase; AUC = area under the serum concentration-time curve; AUCss = area under the serum concentration-time curve at steady state; BC = breast cancer; CI = confidence interval; CRC = colorectal cancer; DXd = the released payload; GC = gastric cancer; NSCLC = non-small cell lung cancer; ss = steady state. Note: The shaded area corresponds to the interval (0.8, 1.25). The reference group is Asian not from Japan subjects with BC with 57.8 kg baseline body weight, 30 U/L baseline aspartate aminotransferase, and 8 µmol/L baseline total bilirubin.

2.3.3. Pharmacodynamics

Mechanism of action

No new mechanism of action study has been submitted to support this application.

Primary and secondary pharmacology

QT analyses

There are no additional studies or analyses regarding QT intervals.

Immunogenicity

Immunogenicity data at baseline and post-treatment, including the incidence of treatment-emergent ADA-positive results and treatment-emergent NAb-positive results are summarized across all studies in Table 13. Overall, across the 11 clinical studies, the incidence of immunogenicity was low.

Table 13: Summary of clinical immunogenicity data for T-DXd

Statistic		Clinical Study											Overall
		J101	J102	A103	A104	U201	J202	U204	U205	U206	U302	U303	
Baseline Assessment													
	N	287	51	12	40	252	169	180	75	148	249	352	1815
ADA-positive at baseline	n (%)	5 (1.7)	3 (5.9)	0	1 (2.5)	13 (5.2)	13 (7.7)	15 (8.3)	5 (6.7)	6 (4.1)	15 (6.0)	20 (5.7)	96 (5.3)
NAb-positive at baseline	n (%)	0	0	0	0	1 (0.4)	0	0	0	0	1 (0.4)	1 (0.3)	3 (0.2)
Post-Baseline Assessment													
	N	289	51	12	39	249	167	172	76	143	294	358	1850
ADA-positive post-baseline[a]	n (%)	1 (0.3)	1 (2.0)	0	0	5 (2.0)	12 (7.2)	9 (5.2)	2 (2.6)	3 (2.1)	10 (3.4)	13 (3.6)	56 (3.0)
NAb-positive post-baseline[b]	n (%)	0	0	0	0	0	0	0	0	0	1 (0.3)	1 (0.3)	2 (0.1)
ADA-positive at baseline and post-baseline	n (%)	1 (0.3)	1 (2.0)	0	0	3 (1.2)	1 (0.6)	3 (1.8)	0	2 (1.4)	3 (1.2)	6 (1.8)	20 (1.1)
NAb-positive at baseline and post-baseline	n (%)	0	0	0	0	0	0	0	0	0	0	0	0
Treatment-emergent ADA-positive incidence[c]	n (%)	0	0	0	0	3 (1.2)	11 (6.6)	7 (4.1)	2 (2.6)	1 (0.7)	8 (2.7)	7 (2.0)	39 (2.1)
Treatment-induced ADA-positive[d]	n (%)	0	0	0	0	2 (0.8)	11 (6.6)	6 (3.5)	2 (2.6)	1 (0.7)	7 (2.4)	7 (2.0)	36 (1.9)
Treatment-boosted ADA-positive[e]	n (%)	0	0	0	0	1 (0.4)	0	1 (0.6)	0	0	1 (0.3)	0	3 (0.2)
Treatment-emergent NAb-positive incidence[f]	n (%)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	1 (0.1)

ADA = anti-drug antibody; N = number of subjects; NAb = neutralizing antibody; T-DXd = trastuzumab deruxtecan.

[a] Includes all subjects who were ADA-positive post-baseline regardless of baseline ADA status.

[b] Includes all subjects who were NAb-positive post-baseline regardless of baseline NAb status.

[c] Includes all subjects who were ADA-negative at baseline and became ADA-positive post-treatment or subjects who had missing ADA data at baseline and ADA-positive post-treatment.

[d] Includes all subjects who were ADA-negative at baseline and became ADA-positive post-treatment.

[e] Includes all subjects who were ADA-positive at baseline and post-treatment but had an increase in ADA titer from baseline to post-treatment.

[f] Includes all subjects who were NAb-negative at baseline and became NAb-positive post-treatment or subjects who had missing NAb data at baseline and NAb positive post-treatment

2.3.4. PK/PD modelling

Efficacy-response analyses

E-R analysis was conducted for confirmed ORR among subjects with HER2-mutant NSCLC across Studies U206, U204, and J101, using T-DXd average serum concentration over Cycle 1 and Cycle 2 (Cavg,Cycle 2) as the exposure metric under logistic regression framework using a linear exposure logit ORR relationship. The existing model for ORR was updated with data from U204 and U206. Several covariates were included: albumin (ALB), time since diagnosis (TSD), sum of diameters (SOD), liver metastasis, prior platinum therapy (PLAT), prior platinum and anti PD(L)-1 therapy (PDL1), and race-country. Body weight was included as an exploratory covariate. None of the tested covariate effects were significant (See Figure 12). Residual plots and PPCs did not indicate model deficiencies (See Figure 13).

Asian subjects were associated with higher ORRs than non-Asian subjects, larger baseline target tumour size were associated with lower ORRs and lower exposure than smaller baseline target tumour size. Simulations comparing T-DXd doses indicated no clinically relevant difference in ORR.

Figure 12: ORR final model: forest plot of typical value predictions for ORR for covariates pre-identified as predictive

Covariates in the exposure-response model were varied one at a time from the reference subject. Numbers on right-hand side of plot represent median and 95% credible interval. Perturbations in calculations of typical value predictions were considered for all categorical covariate levels and at the approximate 5th, 25th, 75th, and 95th percentiles of exposure and continuous covariate values, with the approximate 50th percentile and mode of the categorical covariates representing the reference subject. See Table 16 for perturbations of continuous covariates used and definition of reference subject.

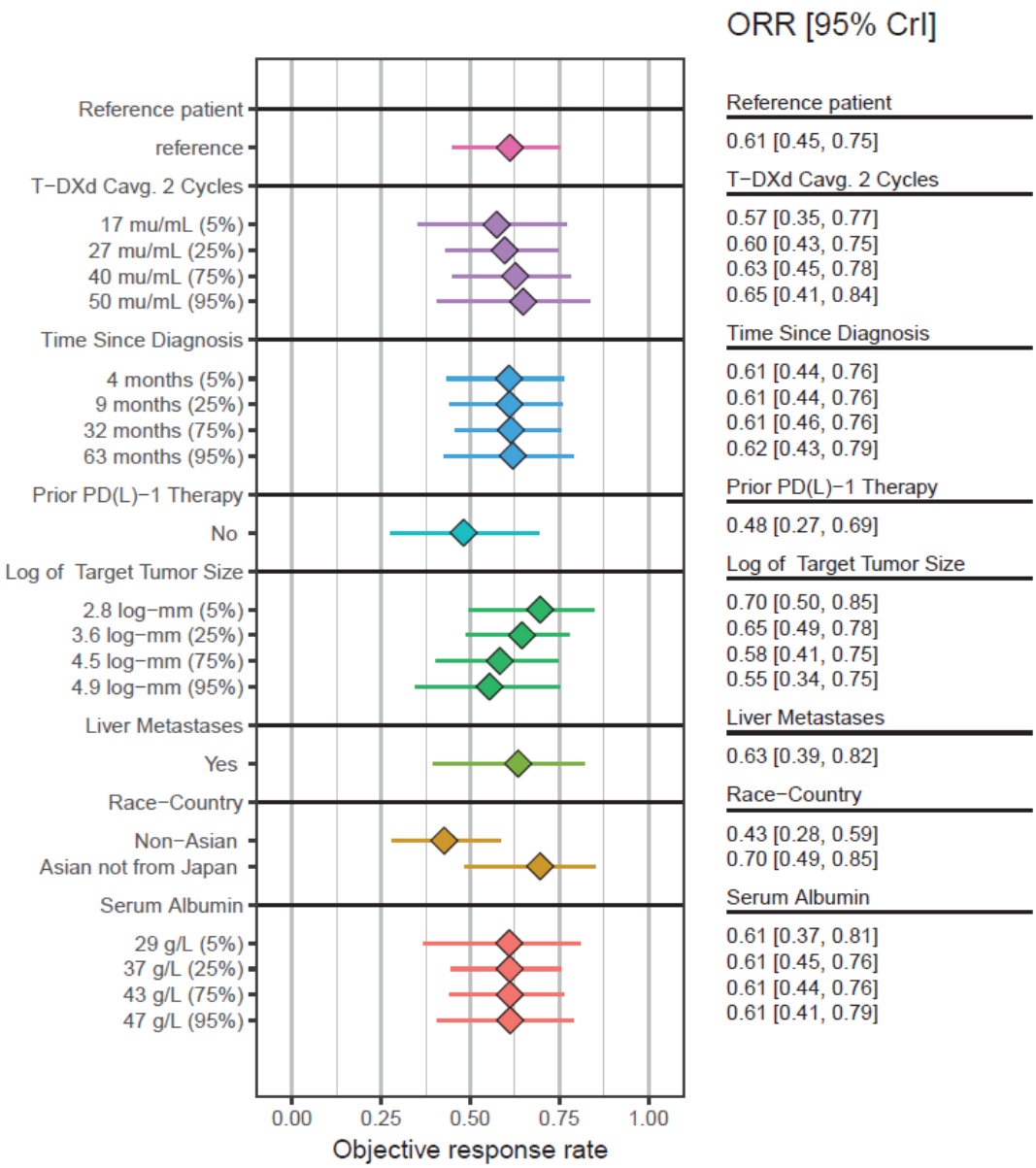
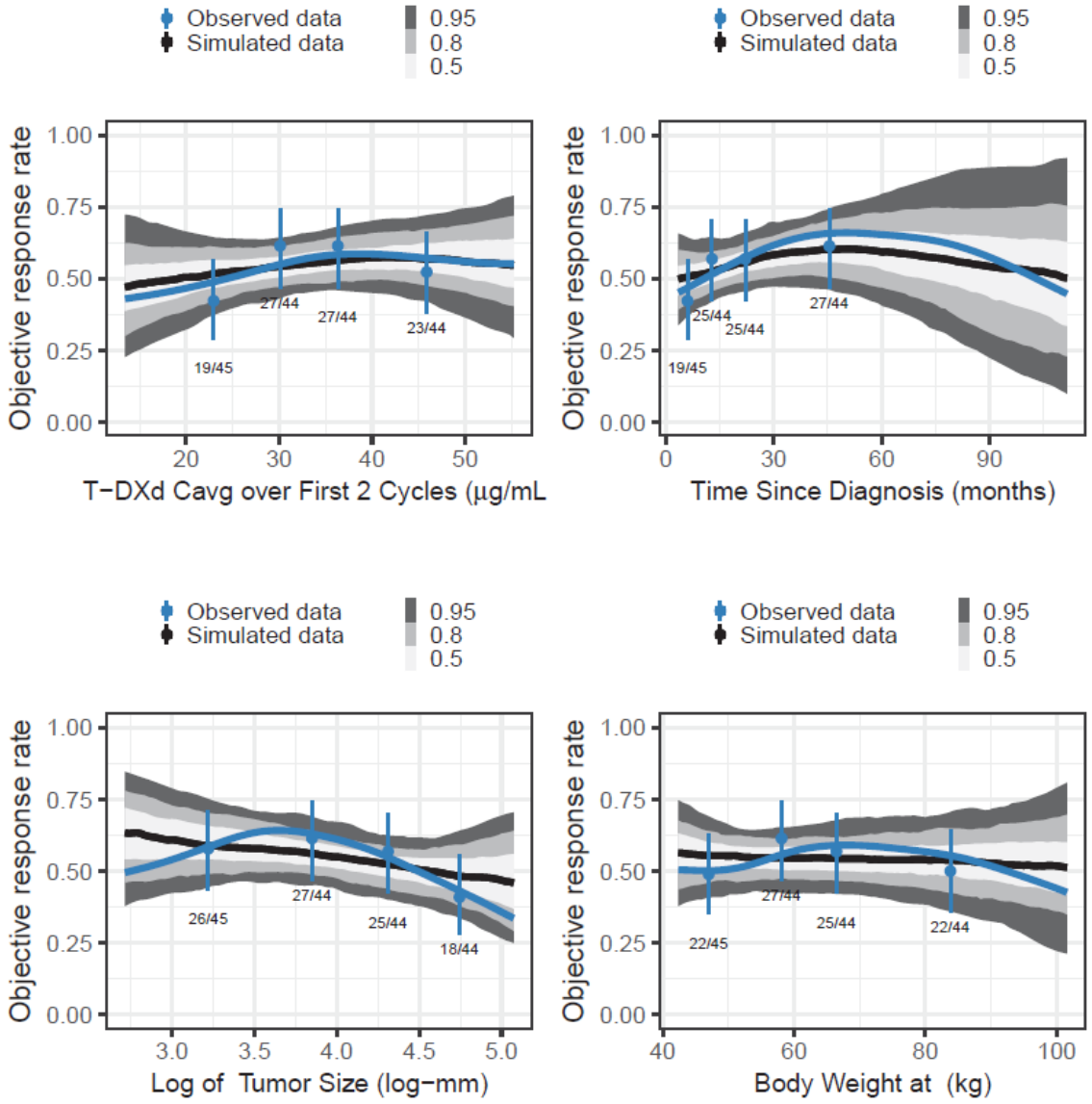


Figure 13: ORR final model: PPCs plots of T-DXd Cavg, Cycle2, BWT, TSD, and SOD.

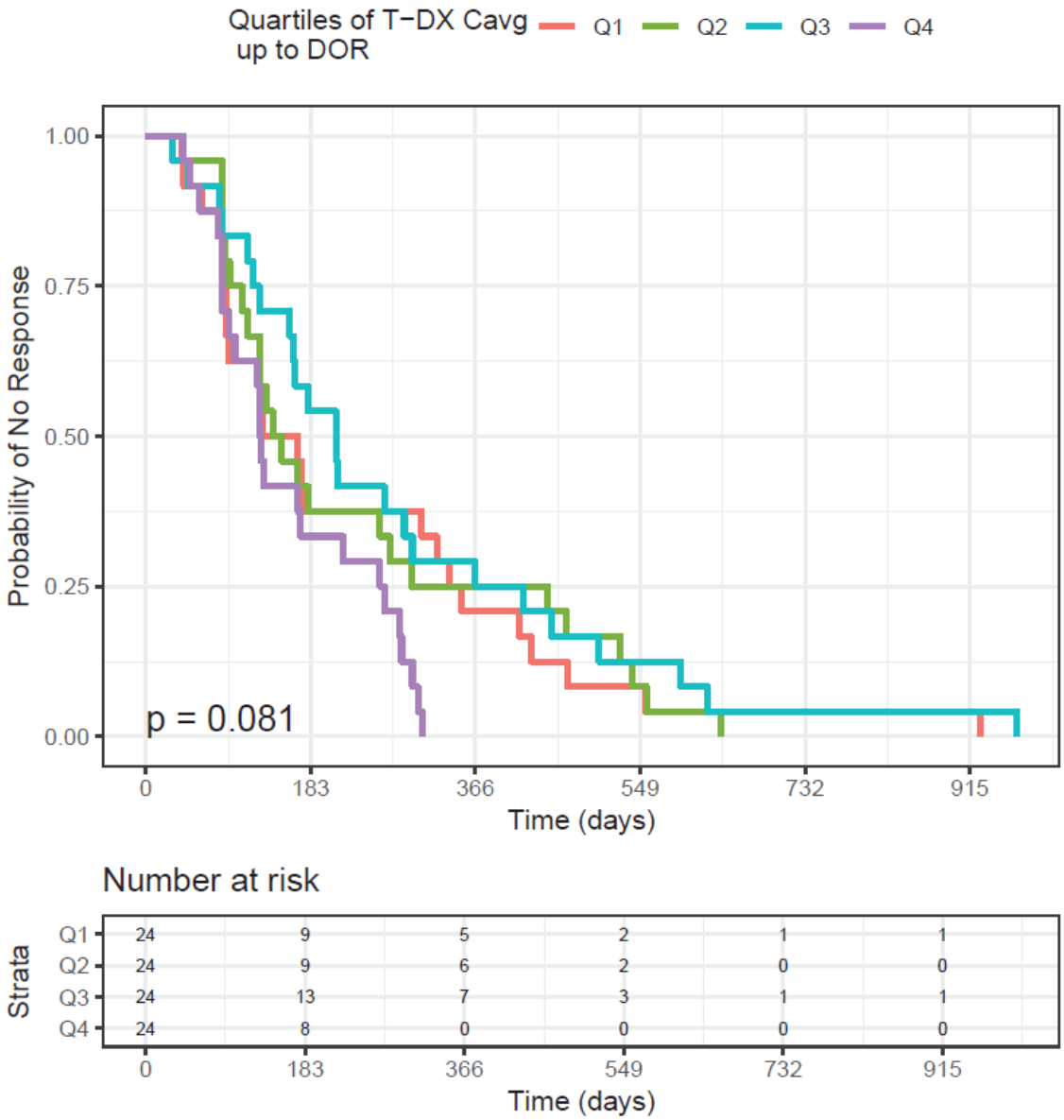
The solid blue line represents a smooth (univariate GAM) of the original data. The solid black line (simulation median) and shaded regions (50%, 80%, and 95% prediction intervals) represent the distribution of smooths fit to replicate data sets simulated using the estimated model. Vertical points and bars represent observed proportion and 95% confidence intervals at quartiles of covariate. Numbers represent responders and total subjects within each quartile.



Graphical assessment of the ER relationship for DOR, PFS, and OS in the HER2 mutant NSCLC population were performed using Kaplan-Meier curves stratified by quartiles of T-DXd Cavg up to time of event. In addition, p-values from the log-rank test of the null hypothesis of no differences among the grouped quartiles were computed. No apparent E-R relationships were noted for DoR, PFS, or OS. The Kaplan-Meier plot for DoR vs T-DXd Cavg quartiles are displayed in Figure 13.

Figure 14: Exposure-efficacy exploratory analysis: duration of response (DoR) Kaplan-Meier curves

Kaplan-Meier curve of efficacy time to event for different quartiles (colors) of C_{avg} up to time-to-event. Shaded area is 95% confidence interval of relationship. Number represents p-value of log-rank test.



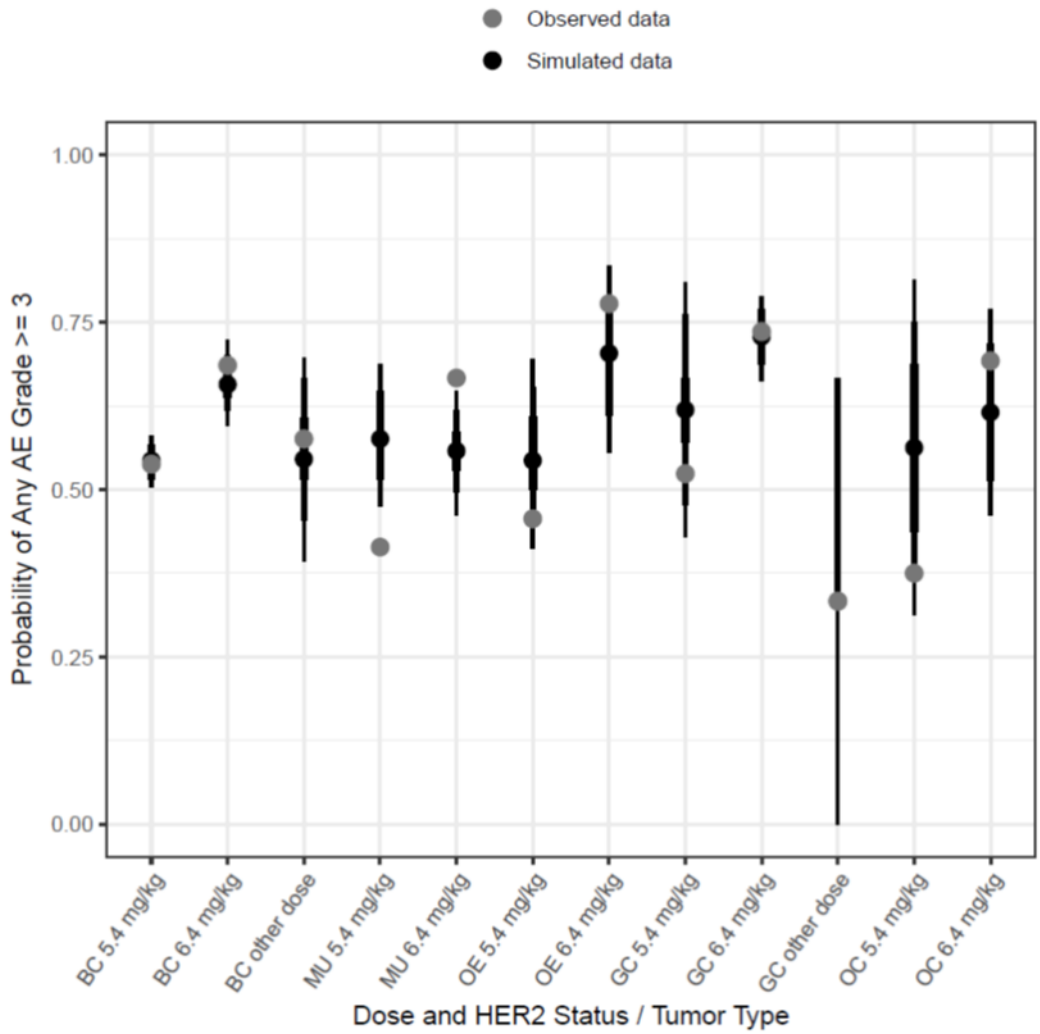
Safety-response analysis

The data set for the exposure-safety analyses and for the Pop PK analyses came from the same studies. Evaluation of the exposure-safety relations were performed by logistic regression, except for interstitial lung disease (ILD) which was analysed by a parametric time-to-event (TTE) model. The exposure metrics selected for the final models were similar to prior E-R analyses including the initial BC application. Tumor type / HER2 status and prior checkpoint inhibitor were included for each safety point. Additional explorative covariates were evaluated and included if warranted by the diagnostics.

The investigated safety endpoints were: Adverse events (AEs) associated with discontinuation of study drug, AEs associated with dose reduction of study drug, Grade ≥3 AEs, Serious AEs (SAEs), Any grade and Grade ≥3 (lab-defined) anemia (only Grade ≥3), Any grade and Grade ≥3 drug-related ILD and Grade ≥2 left ventricular ejection fraction (LVEF) decreased.

Model-predicted AE rates were generally comparable in NSCLC subjects at the same dose independent of HER2 status and were lower (up to 9%) after the 5.4 mg/kg dose compared to 6.4 mg/kg.

Figure 15: **Exposure-safety analysis of any AE, grade≥ 3: PPC of the final model by tumor type, race-country, and dose.**



Black point represents median of posterior simulations, and black lines represents 50%, 80%, and 95% prediction intervals of posterior simulations. Blue point is mean of observed data. BC: Breast cancer, MU: HER2-mutant NSCLC, OE: HER2-overexpressing NSCLC, GC: Gastic cancer, OC: Other cancer.

Dose selection

The recommended dosing regimen for T-DXd in adult subjects with unresectable or metastatic HER2-mutant NSCLC who have received ≥1 prior systemic therapy is 5.4 mg/kg Q3W.

Results from Studies J101 and U204 demonstrate that a T-DXd dose of 6.4 mg/kg has clinical activity in subjects with HER2-mutant NSCLC and has an acceptable and generally manageable safety profile in this population of subjects with NSCLC (see sections 2.4 Clinical efficacy and section 2.5 Clinical safety).

PK, safety, and efficacy data as well as E-R analyses for efficacy and safety endpoints for T-DXd in subjects with BC supported that the 5.4 mg/kg dose of T-DXd has a more optimal benefit-risk profile in

subjects with metastatic BC. These data along with PK similarity between NSCLC and BC subjects also supported that a 5.4 mg/kg dose would have clinical benefit in subjects with NSCLC.

2.3.5. Discussion on clinical pharmacology

No new analytical methods were used for the data analyses. Final documentation for analyses of the data from U206 are recommended to be provided when finalized (REC).

The existing Pop PK model for T-DXd and DXd was updated with data from Study U206 (data cut-off 24 Mar 2022) from patients with HER2-mutant NSCLC (n=147). Overall, the diagnostic plots indicated the model could predict the observed data. Observed DXd exposure values following 5.4 mg/kg trastuzumab deruxtecan administration seem somewhat higher in subjects with NSCLC compared to subjects with breast cancer and seemed to be underpredicted by popPK analysis. The GoF plots for DXd indicated an underprediction of the individual DXd concentrations especially at the higher plasma concentrations. Shrinkage of the IIV values was rather high for DXd. However, as individual exposure-response data were only supportive in this procedure, no update of the DXd popPK model is requested for this procedure.

The PK of NSCLC patients (Study U204 and U206) were comparable at each dose level and seemed independent of HER2 status. Study J101 also contributed data to the NSCLC population (n=18). The pooled NCA based PK analyses are not considered acceptable due to different PK sampling of the two investigated doses. A few NSCLC subjects from Study U204 had abnormal high Tmax values e.g. 211.4 hours post-infusion due to concentration data right after infusion being missing or BLQ. Body weight had impact on both T-DXd and DXd exposures even the dose is weight based. The predicted AUC of DXd varied less over the investigated body weight span after 6.4 mg/kg compared to after 5.4 mg/kg in NSCLC-mutant subjects. Comparing the exposure in NSCLC patients by HER2 status with BC patients, based on the model predicted exposure metrics, the exposure ratios are close to 1 for each dose level. From a PK perspective, the rationale for selecting the lower 5.4 mg/kg dose Q3W over the 6.4 m/kg dose Q3W for HER2-mutant NSCLC patients can be supported if the exposure in NSCLC patients is comparable to BC patients. as indicated by post-hoc derived exposure metrics.

There are no additional studies or analyses regarding QT intervals. The incidence of ADAs was low across cancer types and low in the studies including NSCLC patients. Immunogenicity is not expected to have any effect on exposure, efficacy or safety.

2.3.6. Conclusions on clinical pharmacology

Overall, the clinical pharmacology of T-DXd in HER2 mutant patients is considered well described. However, final reports for bioanalyses conducted in Study U206 are recommended be provided (REC).

2.4. Clinical efficacy

Table 14 summarises the key study design features of the 3 previously described studies:

Table 14: Tabular listing of clinical studies included in the dossier

Study Identifier	Objectives of the Study	Study Design and Type of Control	Test Product(s)	Number of Subjects	Geographies Diagnosis of Patients
DS8201-A-U206	To evaluate confirmed ORR of T-DXd in HER2-mutant NSCLC subjects treated at 5.4 and 6.4 mg/kg doses	Phase 2, multicenter, randomized, 2-arm study No controls	T-DXd dosing: **Arm 1:** 5.4 mg/kg Q3W **Arm 2:** 6.4 mg/kg Q3W	**Planned:** Arm 1: n = 100 Arm 2: n = 50 **Actual (Full Analysis Set):** Arm 1: n = 102 Arm 2: n = 50 **Actual (Pre-specified Early Cohort):** Arm 1: n = 52 Arm 2: n = 28	**Geographies:** Asia, North America, Europe, Australia **Subject Diagnosis:** HER2-mutant, metastatic NSCLC
DS8201-A-U204	To evaluate the ORR of T-DXd in HER2-overexpressing and/or HER2-mutant advanced NSCLC subjects	Phase 2, multicenter, open-label, nonrandomized, 2-cohort study No controls	T-DXd dosing: **Cohort 1:** 6.4 mg/kg Q3W **Cohort 1a:** 5.4 mg/kg Q3W **Cohort 2:** 6.4 mg/kg Q3W	**Planned:** Cohort 1: n = 40 Cohort 1a: n = 40 Cohort 2: n = 90 **Actual:** Cohort 1: n = 49 Cohort 1a: n = 41 Cohort 2: n = 91	**Geographies:** US, Japan, and EU **Subject Diagnosis:** Cohorts 1 and 1a: HER2-overexpressing (IHC 3+ or IHC 2+), unresectable and/or metastatic NSCLC Cohort 2: HER2-mutant, unresectable and/or metastatic NSCLC
DS8201-A-J101	**Part 1:** To assess the safety and tolerability of T-DXd To determine the MTD or the RP2D of T-DXd **Part 2**: To assess the stability and tolerability of T-DXd at the MTD/RP2D To evaluate the efficacy of T-DXd at the MTD/RP2D	Phase 1, two-part, multicenter, nonrandomized, open-label, multiple-dose, first-in-human study of T-DXd	T-DXd dosing: **Part 1 dosing:** 0.8, 1.6, 3.2, 5.4, 6.4, and 8.0 mg/kg **Part 2 dosing:** 5.4 and 6.4 mg/kg	**Planned**: Part 1: n = 18 Part 2a: n = 100 Part 2b: n = 40 Part 2c: n = 20 to 40 Part 2d: n = 60 Part 2e: n = 20 **Actual**: Part 1: n = 27 Part 2a: n = 103 Part 2b: n = 41 Part 2c: n = 40 Part 2d: n = 60 (18 subjects with NSCLC [7 HER2-expressing and 11 HER2-mutant]) Part 2e: n = 21	**Geographies:** Japan and US **Subject Diagnosis:** Subjects with advanced solid tumors

Study U206 is considered the main study, whereas Studies U204 and J101 the supportive one. In the T-Dxd 5.4 mg/kg arm of Study U206, patients were treated with the dose intended for marketing in the NSCLC indication, i.e., 5.4 mg/kg Q3W. Patients from the other arm of this trial and from both supportive trials received a higher dose of Enhertu: 6.4 mg/kg Q3W.

2.4.1. Dose response study(ies)

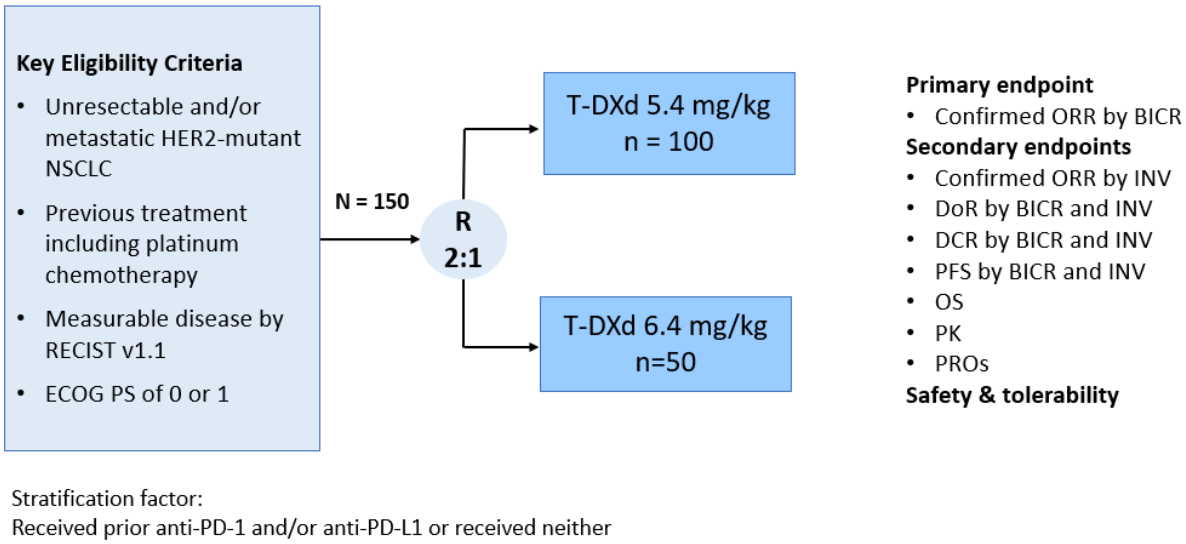
Refer to section 2.3.4

2.4.2. Main study

Study U206 (DESTINY-Lung02)

Study U206 is an ongoing, global, multicentre, open-label, randomized, 2 arm, Phase 2 study to evaluate the safety and efficacy of 2 doses of T-DXd, 5.4 mg/kg and 6.4 mg/kg, in subjects with metastatic, centrally-confirmed HER2 mutant NSCLC who had disease recurrence or progressed during or after at least 1 regimen of prior anti-cancer therapy that must have contained platinum-based chemotherapy. The study design is presented in Figure 16.

Figure 16: Study U206 (DESTINY-Lung02) Design



Methods

Study participants

Key inclusion criteria:

- Age ≥18 years (followed local regulatory requirements if legal age of consent for study participation was >18 years).
- Pathologically documented metastatic NSCLC with a known documented activating HER2 mutation (refer to list in Table 15, below) from an archival or fresh tumour tissue sample analysed by a CLIA certified laboratory or equivalent laboratory performing testing to Good Laboratory Practice standard. Any validated local test was acceptable for the HER2 mutation status assessment, including next-generation sequencing, polymerase chain reaction, mass spectrometry, or other platforms. HER2 mutation documented only from a liquid biopsy sample could not be used.

Table 15: **List HER2 (ERBB2) mutations**

HER2 mutations
Exon 20 insertion (any)
Tyr772_Ala775dup (Ala771_Tyr772insTyrValMetAla, Glu770_Ala771insAlaTyrValMet Ala775_Gly776insTyrValMetAla)
Ala775_Gly776insVal
Ala775_Gly776insThrValMetAla (Tyr772_Val773insValMetAlaThr)
Gly776delinsLeuCys
Gly776delinsValCys
Gly776_Val777insLeu
Gly778_Ser779insCysValGly (Gly776_Val777insValGlyCys)
Val777_Gly778insCysGly (Gly776_Val777delinsCysValCysGly),
Val777_Ser779dup (Gly776_Val777insValGlySer , Ser779_Pro780insValGlySer)
Gly778_Ser779insLeuProSer
Gly778dup (Val777_Gly778insGly)
Gly778_Pro780dup (Val777_Gly778insGlySerPro, Pro780_Tyr781insGlySerPro)
Ser310Phe
Ser310Tyr
Arg678Gln
Thr733Ile
Leu755Ala
Leu755Met
Leu755Pro
Leu755Ser
Leu755Trp
Ile767Met
Asp769Asn
Asp769His
Asp769Tyr
Gly776Cys
Gly776Ser
Gly776Val
Val777Leu
Val777Met
Val842Ile
Thr862Ile
Leu869Arg
Arg896Cys
Arg896His
Gly778_Ser779insCysProGly (Val777_Gly778insGlyCysPro)
Leu755_Glu757delinsSer
Leu755_Thr759del
Val777_Gly778insCysVal
Ile767Phe
Thr798Ile

- Had previous treatment including platinum therapy in the metastatic/locally advanced setting, were not amenable to curative surgery or radiation, and must have progressed during or after last treatment regimen or discontinued because of unacceptable toxicity.
- Patient is willing and able to provide an adequate archival tumour tissue sample. A fresh biopsy is required if an archival tumour tissue sample cannot be supplied. Resection and core needle biopsy are acceptable. Other tissue samples, e.g., fine needle aspirates or cell block are not acceptable.
- Presence of at least 1 measurable lesion confirmed by blinded ICR based on Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST v1.1).
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.
- Has LVEF ≥ 50% within 28 days before randomization.

- Adequate organ function within 14 days before randomization

Key exclusion criteria:

- Known driver mutation in the EGFR, BRAF, or MET exon 14 gene or a known ALK, ROS1, RET, or NTRK fusion.
- Uncontrolled or significant cardiovascular disease.
- History of non-infectious interstitial lung disease (ILD)/pneumonitis that required steroids, current ILD/pneumonitis, or instances where ILD/pneumonitis could not be ruled out by imaging at Screening.
- 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. Subjects with clinically inactive brain metastases could have been included in the study. Subjects with treated brain metastases that were no longer symptomatic and who required no treatment with corticosteroids or anticonvulsants could have been included in the study if they had recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks had to have elapsed between the end of brain radiotherapy and study randomization.
- Known HIV infection, active hepatitis B or C.
- Prior complete pneumonectomy.
- Lung-specific intercurrent clinically significant illnesses, e.g., pulmonary emboli within three months of the study randomization, severe asthma, severe COPD, restrictive lung disease, pleural effusion, etc.
- Prior treatment with any agent, including an ADC, containing a chemotherapeutic agent targeting topoisomerase I.

Treatments

Table 6.1: Study Drug Dosing Information

Study Drug Name	Trastuzumab Deruxtecan
Dosage Formulation	Trastuzumab deruxtecan for injection 100 mg will be provided as a sterile lyophilized powder containing 100 mg of Trastuzumab deruxtecan in a glass vial (Lyo-DP). Each glass vial should be reconstituted with 5 mL water for injection to a concentration of 20 mg/mL (ie, 100 mg/5 mL).
Dosage Level(s)	5.4 mg/kg 6.4 mg/kg
Route of Administration	Trastuzumab deruxtecan will be administered with 5% dextrose as an IV infusion.
Dosing [Instructions/Regimen]	Each vial is designed for single use only and is not to be used to treat more than one subject. Refer to Pharmacy Instructions.
Duration	The study drug will be administered as an IV infusion over 90 min (± 10 min) Q3W ± 2 days.
Packaging	Trastuzumab deruxtecan for injection 100 mg will be labeled in compliance with regulatory requirements and packaged.
Labeling	The packaging will clearly display the name of the study drug, the lot number, storage condition, and other required information in accordance with local regulations.

min = minutes; PO = oral

Duration of treatment: During the Treatment Period, subjects were to receive the assigned dose of study drug Q3W until progression of disease or until the subject meets one of the discontinuation criteria (death, adverse event, progressive disease, clinical progression, withdrawal by subject, physician decision, lost to follow-up, pregnancy, protocol deviation, study termination by sponsor or other).

Guidelines for dose modification:

The investigator was to evaluate which toxicities are attributed to the study drug and adjust the dose of the drug as recommended below for study drug. All dose modifications were to be based on the worst preceding toxicity (Common Terminology Criteria for Adverse Events [CTCAE] version 5.0). Specific criteria for interruption, re-initiation, dose reduction and/or discontinuation of trastuzumab deruxtecan are listed in table below, which is applicable only to TEAEs that were assessed as related to use of trastuzumab deruxtecan by the investigator(s).

Once the dose of trastuzumab deruxtecan has been reduced because of toxicity, all subsequent cycles should be administered at that lower dose level unless further dose reduction is required. More than 2 dose reductions are not allowed and the subject will be withdrawn from the study treatment if further toxicity meeting the requirement for dose reduction occurs. The adjustments for reduced dosing of trastuzumab deruxtecan depending on the initial starting dose are shown in Table 16.

Table 16: Sample dose reduction levels of trastuzumab deruxtecan

Starting Dose	Dose Level -1	Dose Level -2
6.4 mg/kg	5.4 mg/kg	4.4 mg/kg
5.4 mg/kg	4.4 mg/kg	3.2 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 subject was assessed as requiring a dose delay of longer than 28 days, the subject was to be withdrawn from the study. Treatment cycles for a subject for whom trastuzumab deruxtecan dosing was temporarily withheld for any reason may have future cycles scheduled based on the date of the last trastuzumab deruxtecan dose.

Investigators may consider dose reductions or discontinuations of the study drug according to the subject's condition and after discussion with the Sponsor Medical Monitor. For Grade 3 or Grade 4 events, monitoring (including local laboratory tests when appropriate) should be performed at intervals no greater than 7 days until AE is determined to be resolving or subject is discontinued at EOT. Prophylactic or supportive treatment for expected toxicities, including management of study drug-induced AEs was to be as per treating physician discretion and institutional guidelines.

Objectives

The primary objective of the study was to evaluate confirmed ORR based on blinded ICR of tumor scans in subjects with HER2-mutant NSCLC. Confirmation of response was required.

Outcomes/endpoints

The main objectives and endpoints are described in the following table.

Table 17: Description of objectives, outcome measure and endpoints

Objectives	Outcome Measure	Endpoints	Category
Primary			
To evaluate confirmed ORR of trastuzumab deruxtecan in HER2-mutated NSCLC subjects treated at 5.4 and 6.4 mg/kg doses.	**Title:** Confirmed ORR **Description:** Complete response (CR) and partial response (PR) rate as assessed by blinded data review and based on Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1 **Time frame:** At least 9 months after the last subject is randomized	The primary efficacy endpoint is confirmed ORR, defined as the proportion of subjects with CR or PR, assessed by BICR based on RECIST version 1.1	Efficacy
Secondary			
To evaluate the clinical efficacy of trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses by confirmed ORR by investigator assessment	**Title:** Clinical Efficacy **Description:** Evaluation of the clinical efficacy of trastuzumab deruxtecan at 5.4 and 64 mg/kg doses by confirmed ORR by investigator assessment **Time frame:** At least 9 months after the last subject is randomized	• Confirmed ORR as indicated above assessed by investigator assessment based on RECIST v.1.1.	Efficacy
To evaluate the clinical efficacy of trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses by DoR.	**Title:** Clinical Efficacy **Description:** Evaluation of the clinical efficacy of trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses by DoR **Time frame:** At least 9 months after the last subject is randomized	• DoR, defined as time from the initial response (CR or PR) by BICR and investigator assessment until documented tumor progression or death from any cause.	Efficacy

To evaluate further the clinical efficacy of trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses by DCR, Progression-free survival (PFS) and Overall survival (OS)	**Title:** Clinical Efficacy **Description:** Further evaluation of the clinical efficacy of trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses by DCR, PFS and OS **Time frame:** At least 9 months after the last subject is randomized Note: PFS and OS will be updated at the final database lock (approximately 31 months).	• DCR, defined as the proportion of subjects who achieve CR, PR, or SD during study treatment. DCR based on BICR and DCR based on investigator assessments will both be determined. • PFS, defined as the time from date of randomization until first objective radiographic tumor progression or death from any cause, based on BICR and investigator assessment. • OS, defined as the time from date of randomization until death from any cause.	Efficacy
To evaluate safety of trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses.	**Title:** Safety **Description:** The number and percentage of any TEAEs collected between first dose and database lock points **Time frame:** At least 9 months after the last subject is randomized Note: Safety will be updated at the final database lock (approximately 31 months).	• AEs including TEAEs, SAEs, and AESIs that will be graded according to the CTCAE Version 5.0 • Physical examination findings that may include ECOG PS, vital sign measurements, ophthalmologic findings, standard clinical laboratory parameters, ECG parameters, echocardiogram (ECHO)/MUGA findings, and radiologic findings.	Safety

Sample size

The sample size in this study was determined on the basis of the probability evaluation that the 95% Clopper-Pearson CI exceeds and excludes the ORR benchmark of 26.4%.

Consistent with the primary objective, for each of the two single arm treatment groups, the probability that the resulting Clopper-Pearson 95% CI will exceed and exclude the ORR benchmark of 26.4% will be evaluated. This benchmark is the upper bound of the 95% CI (ORR 22.9; 95% CI: 19.7 to 26.4) in ramucirumab plus docetaxel arm in the REVEL trial that was investigated as a second-line treatment for patients with stage IV NSCLC after platinum-based therapy. One hundred and fifty subjects will be randomized in a 2:1 ratio to receive T-DXd at the 5.4 mg/kg or 6.4 mg/kg dose level, respectively.

With 100 subjects to receive T-DXd at 5.4 mg/kg, the probability to exclude the ORR benchmark of 26.4% is at least 80% when the true ORR is 40%. Assuming 50 subjects will be randomized in the 6.4 mg/kg concurrent arm, the probability to exclude the ORR benchmark of 26.4% is at least 80% when the true ORR is 45%. Details of the probability evaluation under different true ORR values are shown in Table 18.

The resulting 95% CIs using exact (Clopper-Pearson) method under several scenarios of observed ORR are provided in

Table 19, indicating that with 50 subjects and 42% observed ORR, the 95% CI excludes the benchmark of 26.4% ORR. With 100 subjects and 36% observed ORR, the 95% CI excludes the benchmark of 26.4% ORR.

With 100 subjects at 5.4 mg/kg and 50 subjects at the 6.4 mg/kg dose level, if the higher dose true ORR is at least 12.3% higher than that of the lower dose, the probability of observing the ORR difference between dose levels being 5% or more is at least 80%.

Assuming 100 subjects at 5.4 mg/kg and 50 subjects at the 6.4 mg/kg dose level, the 95% CI of the ORR difference between dose levels is expected to extend approximately 16% from the observed difference in proportions to either confidence limit.

Table 18: Probability that the resulting Clopper-Pearson 95% confidence interval (CI) will exclude the benchmark of 26.4% ORR

True ORR (%)	Probability evaluated for N=100 (%)	Probability evaluated for N=50 (%)
36	53.8	32.6
37	61.9	38.1
38	69.4	43.8
39	76.2	49.6
40	82.1	55.4
45	97.3	80.3
50	99.8	94.1
55	99.9	98.8

CI = confidence interval; ORR = objective response rate
Calculations were made using R package of binom.

Table 19: CI with 50 and 100 subjects under scenarios of observed ORR

N=100		N=50	
Observed ORR (%)	95% CI using exact method (%)	Observed ORR (%)	95% CI using exact method (%)
35	(25.7, 45.2)	36	(22.9, 50.8)
36	(26.6, 46.2)	42	(28.2, 56.8)
45	(35.0, 55.3)	44	(30.0, 58.7)
50	(39.8, 60.2)	54	(39.3, 68.2)
55	(44.7, 64.9)	58	(43.2, 71.8)
60	(49.7, 69.7)	60	(45.2, 73.6)
65	(54.8, 74.3)	64	(49.2, 77.1)

CI = confidence interval; ORR = objective response rate
Calculations were made using R package of binom.

Randomisation

Once all screening procedures have been completed and study eligibility has been confirmed, approximately 150 subjects were to be enrolled in the study and centrally randomized in a 2:1 ratio to receive trastuzumab deruxtecan at a dose of either 5.4 mg/kg or 6.4 mg/kg. Randomization was stratified by history of prior treatment with anti-PD 1 and/or anti-PD-L1 (yes, no).

Randomization was to be managed through an Interactive Response Technology (IRT) for subjects meeting all eligibility criteria.

After randomization, the first dose of study treatment should occur as soon as possible and no more than 7 days after the randomization date.

Subjects who have dropped out were not to be replaced.

Blinding (masking)

The treatment assignment was to remain blinded to study subjects, Investigators, study site personnel (except the unblinded pharmacist and other unblinded staff members as deemed necessary for site operations to maintain the blind), central imaging readers and the ILD Adjudication Committee. The Sponsor and the CRO were not blinded to the treatment assignment of subjects.

The randomization schedule was to be kept securely.

Statistical methods

Summary statistics will be presented by treatment group, 5.4 mg/kg and 6.4 mg/kg doses, and overall, across all subjects (5.4 and 6.4 mg/kg doses) for safety analysis set and summaries of disposition and demographics and baseline characteristics, while it will be presented only by treatment group, 5.4 mg/kg and 6.4 mg/kg doses, for full analysis set (FAS), pharmacokinetic analysis set and immunogenicity analysis set.

Assessment of change from baseline to post-treatment or the ratio of post-treatment to baseline will include only those subjects with both baseline and post-treatment measurements. The last non-missing value of a variable taken before the first dose of the study treatment will be used as the baseline value, unless otherwise specified. In general, missing or dropout data will not be imputed for the purpose of data analysis, unless otherwise specified.

In the protocol amendment (Version 3.0 Date 01 DEC 2021), an early cohort of subjects is prespecified and defined as those who have been randomized 4.5 months (137 days) before the DCO. If not discontinued treatment early, subjects in this pre-specified early cohort should have at least 3 post-baseline tumour assessments and approximately 4.5-month follow up on safety and efficacy. Statistical analyses will be performed on this pre-specified early cohort to provide more robust assessment of efficacy and safety.

At the time of developing the IA SAP was planned to have "at least 75 subjects", at the DCO of 24 MAR 2022 82 subjects are included in the pre-specified early cohort.

Efficacy analyses will be performed on the full analysis set (~n=150) and the pre-specified early cohort (~n=100). Safety analyses will be performed using the safety analysis set and the pre-specified early cohort. PK analysis will be based on the PK analysis set and the pre-specified early cohort. In general, the pre-specified early cohort will be analysed within each full analysis set, safety analysis set, and PK

analysis set unless otherwise specified. All other exploratory analyses will be performed based on the full analysis set and safety analysis set.

Analysis sets

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

Safety Analysis Set: The safety analysis set will include all randomized subjects who received at least 1 dose of study treatment. Subjects will be summarized according to the treatment actually received.

Response Evaluable Set: Not Applicable to the interim analysis.

Pharmacokinetic Analysis Set: The PK analysis set will include all subjects who received at least 1 dose of T-DXd and had any measurable post-dose serum concentrations of T-DXd, total anti-HER2 antibody, and

MAAA-1181a.

Immunogenicity (ADA and NAb) Analysis Set: The Immunogenicity analysis set will include all subjects who received at least one dose of the study drug and who had at least one baseline or post baseline immunogenicity assessment.

Prespecified early Cohort Analysis Set: The pre-specified early cohort analysis set within the FAS will include all subjects who have been randomized 4.5 months (137 days) before the DCO. The pre-specified early cohort analysis set within the safety analysis set will include all subjects who have been randomized 4.5 months (137 days) before the DCO and received at least 1 dose of study treatment. The pre-specified early cohort analysis set within the PK analysis set will include all subjects who received at least 1 dose of T-DXd and had any measurable post-dose serum concentrations of T-DXd, total anti-HER2 antibody, and MAAA 1181a.

Multiple comparisons/multiplicity

The evaluation of the study results at DCOs for both IAs and primary analysis will be based primarily on point estimation and 95% CI. For both IAs, there is no plan to stop the trial in response to the efficacy results. Hence, multiplicity adjustment is not applicable.

Interim analyses and data monitoring

Two IAs are planned for this study. The first IA will be performed when a total of at least 75 subjects have been randomized to receive a dose of trastuzumab deruxtecan (5.4 mg/kg or 6.4 mg/kg) and have had at least 4.5 months of follow-up before the DCO or have discontinued treatment. This dataset will be named "Pre-Specified Early Cohort".

The main purpose of the interim analyses (IA) was to evaluate the safety and efficacy of each dose without the intent to modify the study design and study conduct. There was no plan for stopping the trial for efficacy. The evaluation of the study results will be based primarily on point estimation and 95% CI. Hence, futility and efficacy stopping boundaries are not defined for both IAs. A PK assessment will also be performed. Additionally, exposure-response analyses (ER) for key efficacy and safety endpoints may be performed at the time of these IAs.

For each dose, the primary efficacy endpoint of confirmed ORR by BICR will be summarized using descriptive statistics including 2-sided exact 95% CI (Clopper-Pearson). Other efficacy endpoints based on response rates will be summarized by dose level using the same methodology as the primary efficacy endpoint. For time-to-event endpoints such as DoR, Kaplan-Meier (K-M) estimates of median and their corresponding 95% CIs using Brookmeyer and Crowley method will be provided. Safety data related to AEs will be summarized using descriptive statistics. For the first and second IAs, in addition to analysing

and presenting the FAS for efficacy and SAS for safety with respect to both DCO dates, data from the subset of subjects who were randomized at least 4.5 months before the DCO will also be analysed and presented to allow for a more robust assessment of the efficacy and safety data from this pre-defined subset.

Efficacy analyses

Efficacy analyses will be performed for the FAS and the pre-specified early cohort analysis set within the FAS. Point estimates will be accompanied with 2-sided 95% CIs, unless specified otherwise.

Analysis of the Primary Efficacy Endpoint – cORR:

Primary Analysis: The primary efficacy endpoint is confirmed ORR, defined as the sum of CR and PR rate, assessed by the BICR based on RECIST version 1.1. The best overall response of CR/PR cannot be determined unless it is confirmed, no earlier than 4 weeks (28 days) from the time a response of CR/PR is first suspected.

The primary analysis of ORR will be performed for FAS. The ORR for each dose level will be estimated along with the two-sided Clopper-Pearson 95% CIs. A swimmer plot for response over time will be also prepared.

The ORR difference between dose levels will be estimated and provided with 95% CI using a stratified analysis for prior anti PD-1/PD-L1 treatment, where the strata-adjusted ORR difference is computed, and each stratum is weighted according to the inverse of variance, which is the reciprocals of the variances of the stratum-specific differences. This inverse of variance weighting strategy assigns a larger weight to strata in which treatment differences have been estimated with greater precision, and they yield an estimate of ORR difference that has minimum variance. Note that the randomization stratification factor (prior treatment of anti PD-1/PD-L1 or not) as recorded in IRT will be used for the stratified analysis.

Analysis of the Secondary Efficacy Endpoint – DOR:

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. DoR based on BICR will be summarized with median duration and its two-sided 95% CI for the median using Brookmeyer and Crowley method for each treatment group. Kaplan-Meier estimates of the distribution of DoR will be calculated and presented graphically by treatment group. The censoring rules are described in the following table:

Event or censoring for DoR analyses will be as follows:

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

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

DoR will be calculated only for subjects with a best overall response of CR or PR. The same analysis will be performed for DoR based on investigator assessment.

Changes to the statistical analyses specified in protocol

Changes in the planned analyses are described below.

- The imputation rules for incomplete date of prior medications described in Section 8.3.3.2 of the IA SAP (v1.0, 17 Feb 2022) were not followed during the execution of the analyses. Instead, the T-DXd program convention was followed, and the imputation rules described in Section 8.3.3.3 of the IA SAP (v1.0, 17 Feb 2022) were Interim Analysis 1 Study Report DS8201-A-U206 used to impute the incomplete date of prior medication. The incomplete dates were not imputed for post anticancer therapies.
- To follow T-DXd program convention, the derivation of Number of Lines of Prior Systemic Therapy for Advanced/Metastatic Disease (≤2, >2) included the following:
  - Therapies intended for "Locally Advanced" or "Metastatic" or "Other" (palliative)

- Therapies intended for "Neo-Adjuvant", "Adjuvant", or "Maintenance" with PD within 6 months since the end of the therapy only if end of therapy date and PD date are present after imputation
- Any regimens in sequential lines of therapy according to eCRF entry with identical combination of agent names were subtracted

- The number and percentage of subjects who were positive for neutralizing antibody (NAb) of T-DXd were not summarized due to delay in receiving the NAb data.

Results

The interim analysis (IA) was conducted after at least 75 subjects had been randomised to receive at least 1 dose and had at least 4.5 months of follow-up before the IA DCO. The DCO for the IA was 24-MAR-2022.

According to the protocol, the primary analysis (PA) occurred 9 months after the last subject was randomized and treated as per protocol, with a DCO on 23-DEC-2022. The timing of the DCO was driven by when the primary endpoint, confirmed ORR by BICR, was considered mature.

Only results from the primary analysis are presented in this report.

Participant flow

As of the DCO date, 152 subjects (T-DXd 5.4 mg/kg: 102 subjects; T-DXd 6.4 mg/kg: 50 subjects) were randomized and 151 subjects received treatment with T-DXd. One subject discontinued from the study before starting treatment with T-DXd 5.4 mg/kg due to a SARSCoV-2 infection. As of the DCO, the majority of subjects in both dose groups had discontinued study drug (T-DXd 5.4 mg/kg: 74/102 [73.3%] subjects; T-DXd 6.4 mg/kg: 36/50 [72.0%] subjects). Overall, 27.2% of subjects were still receiving study drug (T-DXd 5.4 mg/kg: 27/102 [26.7%] subjects; T-DXd 6.4 mg/kg: 14/50 [28.0%] subjects).

The disposition of subjects is summarised in Table 20.

Table 20: Disposition of subjects (all screened subjects), Study U206, DCO 23-DEC-2022

Parameter	All Screened Subjects		
	T-DXd 5.4 mg/kg (N = 102)	T-DXd 6.4 mg/kg (N = 50)	Overall (N = 152)
Number of subjects screened	-	-	177
Number of subjects screen failed	-	-	25
Randomized (n [%])	102 (100)	50 (100)	152 (100)
Treated	101 (99.0)	50 (100)	151 (99.3)
Randomized but not treated	1 (1.0)	0	1 (0.7)
Analysis set (n [%])			
Full Analysis Set	102 (100)	50 (100)	152 (100)
Safety Analysis Set	101 (99.0)	50 (100)	151 (99.3)
Response Evaluable Set	101 (99.0)	50 (100)	151 (99.3)
PK Analysis Set	101 (99.0)	50 (100)	151 (99.3)
Immunogenicity Analysis Set	101 (99.0)	50 (100)	151 (99.3)
Treatment status in the Safety Analysis Set (n [%])[a]			
Ongoing at DCO	27 (26.7)	14 (28.0)	41 (27.2)
Discontinued	74 (73.3)	36 (72.0)	110 (72.8)

Parameter	All Screened Subjects		
	T-DXd 5.4 mg/kg (N = 102)	T-DXd 6.4 mg/kg (N = 50)	Overall (N = 152)
Primary reason for discontinuation from study treatment (n [%])[a]			
Death	3 (3.0)	2 (4.0)	5 (3.3)
Adverse event	15 (14.9)	12 (24.0)	27 (17.9)
Progressive disease	47 (46.5)	19 (38.0)	66 (43.7)
Clinical progression	4 (4.0)	1 (2.0)	5 (3.3)
Withdrawal by subject	1 (1.0)	2 (4.0)	3 (2.0)
Physician decision	3 (3.0)	0	3 (2.0)
Lost to follow-up	0	0	0
Pregnancy	0	0	0
Protocol deviation	0	0	0
Study terminated by Sponsor	0	0	0
Other	1 (1.0)	0	1 (0.7)
Study status in the Full Analysis Set (n [%])			
Ongoing at DCO	60 (58.8)	31 (62.0)	91 (59.9)
Discontinued	42 (41.2)	19 (38.0)	61 (40.1)
Primary reason for discontinuation from the study (n [%])			
Death	36 (35.3)	14 (28.0)	50 (32.9)
Lost to follow-up	0	0	0
Withdrawal by subject	5 (4.9)	5 (10.0)	10 (6.6)
Study terminated by Sponsor	0	0	0
Other	1 (1.0)	0	1 (0.7)
Duration of follow-up (months)			
n	102	50	152
Mean	10.97	10.97	10.97
Standard deviation	4.558	4.537	4.536
Median	11.52	11.78	11.61
Min, max	1.1, 20.6	0.6, 21.0	0.6, 21.0

DCO = data cut-off; max = maximum; min = minimum; N = number of subjects in the Full Analysis Set; PK = pharmacokinetic; T-DXd = trastuzumab deruxtecan

Duration of follow-up (months) was defined as (last visit date − randomization date + 1) ÷ 365.25 × 12. Last visit date was the date of last clinical visit for ongoing subjects, date of death for subjects who died, or the last known contact date in survival follow-up for other subjects who discontinued study treatment.

Percentages were based on the number of subjects (N in column headers) in the Full Analysis Set, which includes all subjects who signed a main informed consent form and were randomized.

[a] Percentages were calculated based on the number of subjects in the Safety Analysis Set.

DCO: 23 Dec 2022

Source: DS8201-A-U206 Table 14.1.1.1

Recruitment

The first subject was randomized on 19 Mar 2021. Enrolment in this study was completed on 24 Mar 2022. The study recruited patients in 47 sites from USA, Canada, Netherlands, France, Spain, Italy, Australia, Japan, South Korea and Taiwan.

At DCO (23-DEC-2022), median follow-up was 11.6 months for the 152 enrolled patients.

Conduct of the study

Changes in the Conduct of the Study

Changes in the conduct of the study were documented in a protocol amendment. Written approval of all protocol amendments was obtained from the IRB or IEC. The study was initiated from Amendment 1 (Protocol v2.0).

Amendment 1 (Protocol v2.0) - 22 October 2020

The primary changes made by Amendment 1 were as follows:

- Updated protocol design, increasing the sample size from 100 to 150 subjects in total to better characterize the efficacy and safety profiles of the 5.4 mg/kg dose group, with a focus on subjects who had disease recurrence or progression during/after at least one regimen of prior platinum-based anticancer therapy.
- An estimate of the number of sites was provided.
- Blinding procedures were described.
- The time frame of the study was increased from approximately 7.5 to at least 9 months after the last subject was randomized. The anticipated total duration of the study was increased from 25 to 31 months.
- The description of the stratified subgroups was updated.
- The schedule for the HEOR assessments was updated.
- Bone scan was added to the list of "Treatment response/disease assessments."
- Enhanced data collection for ILD adjudication was guided by a set of pre-defined list of PTs as per the Event Adjudication Site Manual.
- Updated several sections to align with the updated study design and latest safety information.
- Subjects having first, second-line, and later therapies were removed from the list of subgroups for the exploratory analyses.
- Statistical analysis to assess the impact of SARS-CoV-2 infection (ie, COVID-19) was added.

Amendment 2 (Protocol v3.0) - 01 December 2021

The primary changes made by Amendment 2 were as follows:

- Incorporated interim analyses for early assessment of the efficacy and safety of the 2 doses administered in the study.
- The primary analysis DCO time frame was updated.
- Inclusion and exclusion criteria were updated to provide clarification and align with the latest safety information.

- Efficacy data from an interim analysis of the results of the DS8201-A-U204 study were updated.
- Lung cancer of the subject population was specified.
- The description of the duration of study administration was updated.
- Description of the preparation of the study drug for infusion was updated.
- Duration of infusion was adjusted in case of no IRR. For cases of IRR, reference to management guidelines was provided.
- Hy's Law text was updated.
- The management guidelines for Grades 2, 3, and 4 ILD/pneumonitis were updated.
- Exceptions to the prohibited corticosteroids were updated.
- The purpose for analyzing banked samples was updated.
- The storage and disposal of specimens were updated.
- The list of HER2 mutations was updated.
- Death resulting from disease progression was removed from the list of events exempted from SAE reporting.
- The list of prior and concomitant medications relating to SARS-CoV-2 was removed.
- SARS-CoV-2 assessment(s) was updated.

Major protocol deviations

Table 21: Major protocol deviations, Study U206, DCO 23-DEC-2022

Category/Deviation	T-DXd 5.4 mg/kg (N = 102) n (%)	T-DXd 6.4 mg/kg (N = 50) n (%)	Overall (N = 152) n (%)
Subjects with any major protocol deviations	32 (31.4)	19 (38.0)	51 (33.6)
COVID-19 related	1 (1.0)	0	1 (0.7)
Concomitant and prohibited medications or non-drug therapy/Prohibited medication administered/taken	1 (1.0)	0	1 (0.7)
Eligibility criteria/Subject did not meet inclusion criteria but was enrolled in the study	8 (7.8)	4 (8.0)	12 (7.9)
Eligibility criteria/Subject met exclusion criteria and enrolled in the study	1 (1.0)	0	1 (0.7)
Informed consent/Administered consent does not include updates or information required and approved by IRB	3 (2.9)	1 (2.0)	4 (2.6)
Informed consent/Consent form misplaced or lost	0	1 (2.0)	1 (0.7)
Informed consent/Consent was not obtained prior to any study procedures being performed	3 (2.9)	1 (2.0)	4 (2.6)
Informed consent/Failure to obtain informed consent/assent	3 (2.9)	2 (4.0)	5 (3.3)

IP/IP was not dispensed/administered as per protocol	7 (6.9)	3 (6.0)	10 (6.6)
SAE reporting/SAE not reported to the IRB/IEC	1 (1.0)	0	1 (0.7)
SAE reporting/SAE not reported within the 24-hour timeline	10 (9.8)	5 (10.0)	15 (9.9)
SAE reporting/SUSAR not reported within the required timeline	0	1 (2.0)	1 (0.7)
Study procedures/(Non-IP related) Randomization procedure not conducted as per protocol	1 (1.0)	0	1 (0.7)
Study procedures/Visits, assessments, or procedures not performed per protocol	19 (18.6)	12 (24.0)	31 (20.4)
COVID-19 related	1 (1.0)	0	1 (0.7)

COVID-19 = coronavirus disease 2019; DCO = data cutoff date; IEC = independent ethics committee; IP = investigational product; IRB = institutional review board; SAE = serious adverse event; SUSAR = suspected unexpected serious adverse reaction; T-DXd = trastuzumab deruxtecan

Baseline data

Table 22: Demographic characteristics, Study U206, DCO 23-DEC-2022

Parameter	Full Analysis Set		
	T-DXd 5.4 mg/kg (N = 102)	T-DXd 6.4 mg/kg (N = 50)	Overall (N = 152)
Age (years)[a]			
n	102	50	152
Mean	59.8	59.5	59.7
Standard deviation	11.59	12.14	11.73
Median	59.4	61.3	60.4
Min, max	31, 84	28, 86	28, 86
Age group (n [%])			
<18	0	0	0
≥18, <40	4 (3.9)	2 (4.0)	6 (3.9)
≥40, <65	58 (56.9)	33 (66.0)	91 (59.9)
≥65, <75	32 (31.4)	10 (20.0)	42 (27.6)
≥75	8 (7.8)	5 (10.0)	13 (8.6)
<65	62 (60.8)	35 (70.0)	97 (63.8)
≥65	40 (39.2)	15 (30.0)	55 (36.2)
<75	94 (92.2)	45 (90.0)	139 (91.4)
≥75	8 (7.8)	5 (10.0)	13 (8.6)
Sex (n [%])			
Male	37 (36.3)	16 (32.0)	53 (34.9)
Female	65 (63.7)	34 (68.0)	99 (65.1)
Sex and age group (n [%])			

Male			
<18	0	0	0
≥18, <40	2 (2.0)	1 (2.0)	3 (2.0)
≥40, <65	22 (21.6)	9 (18.0)	31 (20.4)
≥65, <75	9 (8.8)	4 (8.0)	13 (8.6)
≥75	4 (3.9)	2 (4.0)	6 (3.9)
Sex and age group (n [%]) (cont.)			
Female			
<18	0	0	0
≥18, <40	2 (2.0)	1 (2.0)	3 (2.0)
≥40, <65	36 (35.3)	24 (48.0)	60 (39.5)
≥65, <75	23 (22.5)	6 (12.0)	29 (19.1)
≥75	4 (3.9)	3 (6.0)	7 (4.6)
Race (n [%])			
American Indian or Alaska Native	0	0	0
Asian	65 (63.7)	31 (62.0)	96 (63.2)
Black or African American	0	2 (4.0)	2 (1.3)
Native Hawaiian or Other Pacific Islander	0	0	0
White	23 (22.5)	5 (10.0)	28 (18.4)
Other	14 (13.7)	12 (24.0)	26 (17.1)
Ethnicity (n [%])			
Hispanic or Latino	1 (1.0)	1 (2.0)	2 (1.3)
Not Hispanic or Latino	89 (87.3)	41 (82.0)	130 (85.5)
Unknown	12 (11.8)	8 (16.0)	20 (13.2)
Weight at Baseline (kg)			
n	102	50	152
Mean	63.6	63.4	63.5
Standard deviation	15.13	13.91	14.69
Median	60.9	63.6	61.1
Min, max	40.0, 111.1	40.9, 105.0	40.0, 111.1
Body mass index at Baseline (kg/m^2)			
n	101	48	149
Mean	23.4	23.6	23.5
Standard deviation	4.63	4.42	4.54
Median	23.0	23.1	23.0
Min, max	15.8, 42.0	16.8, 38.6	15.8, 42.0
Geographic region (n [%])			
Asia	63 (61.8)	30 (60.0)	93 (61.2)
North America	4 (3.9)	2 (4.0)	6 (3.9)
Europe	33 (32.4)	17 (34.0)	50 (32.9)
Australia	2 (2.0)	1 (2.0)	3 (2.0)

DCO = data cut-off; max = maximum; min = minimum; n = number of subjects in the Full Analysis Set who had ≥1 post baseline tumor assessment; N = number of subjects in the Full Analysis Set; T-DXd = trastuzumab deruxtecan
Body mass index = Weight (kg) / Height (m)^2. Percentage was calculated using the number of subjects in the column heading as the denominator.
[a] Subject's age was the age at the date of signing the informed consent form.
DCO: 23 Dec 2022

Table 23: Baseline disease characteristics, Study U206, DCO 23-DEC-2022

Parameter	Full Analysis Set		
	T-DXd 5.4 mg/kg (N = 102)	T-DXd 6.4 mg/kg (N = 50)	Overall (N = 152)
ECOG performance status at Baseline (n [%])			
0	29 (28.4)	19 (38.0)	48 (31.6)
1	73 (71.6)	31 (62.0)	104 (68.4)
12-Lead ECG at Baseline (n [%])			
Normal	59 (57.8)	24 (48.0)	83 (54.6)
Abnormal, not clinically significant	43 (42.2)	26 (52.0)	69 (45.4)
Clinically significant finding	0	0	0
Not performed	0	0	0
ECHO/MUGA at Baseline			
Normal	85 (83.3)	38 (76.0)	123 (80.9)
Abnormal, not clinically significant	17 (16.7)	11 (22.0)	28 (18.4)
Clinically significant finding	0	0	0
Not performed	0	1 (2.0)	1 (0.7)
Creatinine clearance at Baseline (mL/min)			
n	102	50	152
Mean	83.3	80.0	82.2
Standard deviation	29.26	18.85	26.28
Median	80.0	77.1	79.1
Min, max	30.2, 191.8	36.5, 131.6	30.2, 191.8
Renal function at Baseline (n [%])			
Normal renal function	38 (37.3)	16 (32.0)	54 (35.5)
Mild renal impairment	41 (40.2)	29 (58.0)	70 (46.1)
Moderate renal impairment	23 (22.5)	5 (10.0)	28 (18.4)
Severe renal impairment	0	0	0
Hepatic function at Baseline (n [%])			
Normal hepatic function	76 (74.5)	39 (78.0)	115 (75.7)
Mild hepatic impairment	26 (25.5)	11 (22.0)	37 (24.3)
Moderate hepatic impairment	0	0	0
Severe hepatic impairment	0	0	0
Strata (from IRT) (n [%])			
Subjects who received prior anti-PD-1 and/or anti-PD-L1 treatment	74 (72.5)	36 (72.0)	110 (72.4)
Those who received neither	28 (27.5)	14 (28.0)	42 (27.6)
Type of HER2 mutation (n [%])			

Kinase domain	99 (97.1)	50 (100)	149 (98.0)
Extracellular domain	3 (2.9)	0	3 (2.0)
Unknown	0	0	0
Other	0	0	0
Histology (n [%])			
Adenocarcinoma	100 (98.0)	50 (100)	150 (98.7)
Squamous	1 (1.0)	0	1 (0.7)
Large cell	0	0	0
Small cell	0	0	0
Other[a]	1 (1.0)	0	1 (0.7)
Not done	0	0	0
Number of lines of prior systemic therapy for advanced/metastatic disease (n [%])			
≤2	69 (67.6)	32 (64.0)	101 (66.4)
>2	33 (32.4)	18 (36.0)	51 (33.6)
CNS metastasis at Baseline (n [%])			
Yes	35 (34.3)	22 (44.0)	57 (37.5)
No	67 (65.7)	28 (56.0)	95 (62.5)
Liver metastasis at Baseline (n [%])			
Yes	24 (23.5)	15 (30.0)	39 (25.7)
No	78 (76.5)	35 (70.0)	113 (74.3)
Pleural effusion at Baseline (n [%])			
Yes	2 (2.0)	3 (6.0)	5 (3.3)
No	100 (98.0)	47 (94.0)	147 (96.7)
Prior lung resection (n [%])			
Yes	22 (21.6)	12 (24.0)	34 (22.4)
No	80 (78.4)	38 (76.0)	118 (77.6)
Smoking status (n [%])			
Never	55 (53.9)	29 (58.0)	84 (55.3)
Former	47 (46.1)	21 (42.0)	68 (44.7)
Current	0	0	0

[a] Subject No. 81022006 reported as "Other: carcinoma."
DCO: 23 Dec 2022

Table 24: Types of HER2 Mutation, Other Gene Abnormality Status, and Test Types Used to Assess HER2 Mutations, Study U206, DCO 23-DEC-2022

	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 102)	U206 HER2-mut NSCLC T-DXd 6.4 mg/kg (N =50)
HER2 type of mutation, n (%)[a]		
Kinase domain	99 (97.1)	50 (100.0)
p.Ala775_Gly776insThrValMetAla	8 (7.8)	1 (2.0)
p.Ala775_Gly776insVal	1 (1.0)	0
p.Ala775_Gly776insValValMetAla	0	1 (2.0)
p.Asp769His	0	0
p.Gly776Ser	0	0
p.Gly776_Val777delinsValCysAsp	1 (1.0)	0
p.Gly776delinsCysVal	1 (1.0)	0
p.Gly776delinsLeuCys	0	1 (2.0)
p.Gly776delinsValCys	14 (13.7)	8 (16.0)
p.Gly776delinsValVal	1 (1.0)	0
p.Gly778_Pro780dup	9 (8.8)	2 (4.0)
p.Gly778_Ser779insLeuProSer	1 (1.0)	0
p.Leu755Ala	1 (1.0)	2 (4.0)
p.Leu755Met	1 (1.0)	0
p.Leu755Pro	1 (1.0)	1 (2.0)
p.Leu755Ser	0	0
p.Leu869Arg	1 (1.0)	0
p.Ser779_Pro780insArgSer	1 (1.0)	0
p.Tyr772_Ala775dup	57 (55.9)	33 (66.0)
p.Val777Leu	0	1 (2.0)
p.Val777_Gly778insCysGly	1 (1.0)	0
Extracellular domain	3 (2.9)	0
p.Asp277Tyr	0	0
p.Ser310Phe	3 (2.9)	0
p.Ser310Tyr	0	0
Transmembrane domain	0	0
p.Gly660Asp	0	0
Other gene abnormality status, n (%)		
EGFR/ALK/Ros1/BRAF	1 (1.0)	3 (6.0)
No EGFR/ALK/Ros1/BRAF	101 (99.0)	47 (94.0)
Missing	0	0
Test type to assess HER2 mutation, n (%)		
NGS	93 (91.2)	49 (98.0)
PCR	4 (3.9)	1 (2.0)
Mass spectrometry	5 (4.9)	0
Pyrosequencing	0	0
Unknown	0	0

DCO = data cut-off; HER2 = human epidermal growth factor receptor 2; NGS = next generation sequencing; NSCLC = non-small cell lung cancer; PCR = polymerase chain reaction; T-DXd = trastuzumab deruxtecan

[a] A subject may be counted for multiple categories. (DCO date: 23 Dec 2022)

Table 25: Prior cancer treatments, Study U206, DCO 23-DEC-2022

	Full Analysis Set		
	T-DXd 5.4 mg/kg (N=102)	T-DXd 6.4 mg/kg (N=50)	Overall (N=152)
Any Prior Systemic Cancer Therapy (n [%])			
Yes	102 (100)	50 (100)	152 (100)
Platinum-based Therapy	102 (100)	50 (100)	152 (100)
Docetaxel Treatment	30 (29.4)	17 (34.0)	47 (30.9)
Anti PD-1 Treatment	59 (57.8)	29 (58.0)	88 (57.9)
Anti PD-L1 Treatment	23 (22.5)	12 (24.0)	35 (23.0)
Anti PD-(L)1 Treatment	75 (73.5)	39 (78.0)	114 (75.0)
Platinum and Anti PD-(L)1 Therapy But Not in Combination	24 (23.5)	10 (20.0)	34 (22.4)
Platinum Therapy in Combination with Anti PD-(L)1 Therapy	51 (50.0)	29 (58.0)	80 (52.6)
No	0	0	0
Intended for [a] (n [%])			
Neo-Adjuvant	3 (2.9)	1 (2.0)	4 (2.6)
Adjuvant	12 (11.8)	4 (8.0)	16 (10.5)
Locally Advanced/Metastatic	45 (44.1)	21 (42.0)	66 (43.4)
Metastatic	66 (64.7)	31 (62.0)	97 (63.8)
Preventative	0	0	0
Maintenance	22 (21.6)	9 (18.0)	31 (20.4)
Other	1 (1.0)	3 (6.0)	4 (2.6)
If Locally Advanced or Metastatic, Line of Therapy [b] (n [%])			
1st Line	102 (100)	49 (98.0)	151 (99.3)
2nd Line	58 (56.9)	35 (70.0)	93 (61.2)
3rd Line	30 (29.4)	15 (30.0)	45 (29.6)
4th+ Line	21 (20.6)	10 (20.0)	31 (20.4)
Number of Prior Therapy Regimens (n [%])			
0	0	0	0
1	31 (30.4)	10 (20.0)	41 (27.0)
2	34 (33.3)	21 (42.0)	55 (36.2)
3	11 (10.8)	7 (14.0)	18 (11.8)
4	9 (8.8)	10 (20.0)	19 (12.5)
5	8 (7.8)	0	8 (5.3)
>5	9 (8.8)	2 (4.0)	11 (7.2)
Number of Prior Therapy Regimens			
n	102	50	152
Mean	2.7	2.5	2.7
Standard Deviation	2.12	1.31	1.89
Median	2.0	2.0	2.0
Min, Max	1, 12	1, 7	1, 12
Prior Systemic Cancer Therapy and Intended for [a] Group (n [%])			
Platinum-based Therapy			
Locally Advanced/Metastatic	43 (42.2)	20 (40.0)	63 (41.4)
Metastatic	61 (59.8)	29 (58.0)	90 (59.2)
Best Response to Most Recent Prior Therapy [c] (n [%])			
Complete Response (CR)	1 (1.0)	1 (2.0)	2 (1.3)
Partial Response (PR)	24 (23.5)	11 (22.0)	35 (23.0)
Stable Disease (SD)	38 (37.3)	22 (44.0)	60 (39.5)
Progressive Disease (PD)	25 (24.5)	10 (20.0)	35 (23.0)
Unknown (UNK)	12 (11.8)	5 (10.0)	17 (11.2)
Not Applicable (NA)	2 (2.0)	1 (2.0)	3 (2.0)
Reason for Discontinuation of Most Recent Prior Therapy [c] (n [%])			
Disease Progression	76 (74.5)	42 (84.0)	118 (77.6)
Adverse Event	7 (6.9)	1 (2.0)	8 (5.3)
Completed Therapy	6 (5.9)	2 (4.0)	8 (5.3)
Investigator Decision	5 (4.9)	2 (4.0)	7 (4.6)
Cost	0	0	0
Patient Choice	3 (2.9)	0	3 (2.0)
Regimen Availability	1 (1.0)	1 (2.0)	2 (1.3)
Unknown	3 (2.9)	0	3 (2.0)
Other	1 (1.0)	2 (4.0)	3 (2.0)

Prior Radiation Therapy (n [%])			
Yes	58 (56.9)	25 (50.0)	83 (54.6)
No	44 (43.1)	25 (50.0)	69 (45.4)
Prior Cancer Surgery (n [%])			
Yes	25 (24.5)	13 (26.0)	38 (25.0)
No	77 (75.5)	37 (74.0)	114 (75.0)

Notes: Percentages are based on the number of subjects in the Full Analysis Set.
Most recent prior therapy is the last prior therapy before first dose of study drug.
[a] A subject may receive multiple therapies intended for different purposes.
[b] Lines of prior systemic therapy for advanced/metastaic include: 1) Therapies intended for "Locally Advanced" or "Metastatic" or "other" (palliative), 2) Therapies intended for "Neo-Adjuvant", "Adjuvant", or "Maintenance" with PD within 6 months since the end of the therapy only if end of therapy date and PD date are present after imputation and 3) Any regimens in sequential lines of therapy according to eCRF entry with identical combination of agent names will be subtracted.
[c] The percentage is based on the number of subjects with the corresponding prior cancer systemic therapy.
Source Data: adam.adsl; Listings 16.2.4.4.2, 16.2.4.4.3, 16.2.4.4.4

Numbers analysed

Table 7.1: Data Sets Analyzed (All Screened Subjects and Pre-specified Early Cohort Analysis Set)

	All Screened Subjects			Pre-Specified Early Cohort[a]		
Analysis Sets	T-DXd 5.4 mg/kg (N = 102)	T-DXd 6.4 mg/kg (N = 50)	Overall (N = 152)	T-DXd 5.4 mg/kg (N = 52)	T-DXd 6.4 mg/kg (N = 28)	Overall (N = 80)
Full Analysis Set (FAS)	102 (100)	50 (100)	152 (100)	52 (100)	28 (100)	80 (100)
Safety Analysis Set	101 (99.0)	50 (100)	151 (99.3)	51 (98.1)	28 (100)	79 (98.8)
PK Analysis Set	99 (97.1)	49 (98.0)	148 (97.4)	51 (98.1)	28 (100)	79 (98.8)
Immunogenicity Analysis Set	99 (97.1)	49 (98.0)	148 (97.4)	51 (98.1)	28 (100)	79 (98.8)

DCO = data cut-off; PK = pharmacokinetics; T-DXd = trastuzumab deruxtecan
[a] An early cohort of subjects was pre-specified and defined as those who have been randomized at least 4.5 months (137 days) before the DCO.
DCO: 24 Mar 2022

Outcomes and estimation

Primary endpoint – ORR by BICR:

Parameter	Full Analysis Set		
	T-DXd 5.4 mg/kg (N = 102)	T-DXd 6.4 mg/kg (N = 50)	Difference in % (6.4 mg/kg – 5.4 mg/kg)
Best overall response (confirmed) (n [%])			
CR	1 (1.0)	2 (4.0)	-
PR	49 (48.0)	26 (52.0)	-
SD	45 (44.1)	18 (36.0)	-
PD	4 (3.9)	2 (4.0)	-
Non-evaluable	3 (2.9)	2 (4.0)	-
Confirmed ORR			
n (%)	50 (49.0)	28 (56.0)	6.7[b]

95% CI	(39.0, 59.1)[a]	(41.3, 70.0)[a]	(-9.5, 22.9)[b]
DCR where confirmation of CR/PR is required			
n (%)	95 (93.1)	46 (92.0)	-3.5[b]
95% CI	(86.4, 97.2) [a]	(80.8, 97.8) [a]	(-14.1, 7.0)[b]
Best overall response (unconfirmed) (n [%])			
CR	1 (1.0)	2 (4.0)	-
PR	54 (52.9)	28 (56.0)	-
SD	40 (39.2)	16 (32.0)	-
PD	4 (3.9)	2 (4.0)	-
Non-evaluable	3 (2.9)	2 (4.0)	-
ORR (unconfirmed)			
n (%)	55 (53.9)	30 (60.0)	5.6[c]
95% CI	(43.8, 63.8)[a]	(45.2, 73.6)[a]	(-10.6, 21.7)[c]
DCR (unconfirmed)			
n (%)	95 (93.1)	46 (92.0)	-3.5[c]
95% CI	(86.4, 97.2)[a]	(80.8, 97.8)[a]	(-14.1, 7.0)[c]

CI = confidence interval; CR = complete response; DCO = data cut-off; DCR = disease control rate; IRT = interactive response technology; n = number of subjects in the Full Analysis Set who had ≥1 post baseline tumor assessment; N = number of subjects in the Full Analysis Set; ORR = objective response rate; PD = progressive disease; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SD = stable disease; T-DXd = trastuzumab deruxtecan

Percentages were based on the number of subjects in the Full Analysis Set.

Overall response was determined by blinded 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. "Unconfirmed" means confirmation was not required.

[a] For each dose group, the 2-sided 95% CIs were based on the exact (Clopper-Pearson) method for binomial distribution.

[b] The ORR or DCR difference between dose levels was estimated and provided with a 95% CI using a stratified analysis for prior anti-PD-1/PD-L1 treatment, where the strata-adjusted ORR or DCR difference was computed, and each stratum was weighted according to the inverse of variance, which was the reciprocals of the variances of the stratum specific differences. Note that the randomized stratification factor (prior treatment of anti-PD-1/PD-L1 or not) as recorded in IRT were used for the stratified analysis.

[c] Sensitivity Analysis: The ORR or DCR was assessed where confirmation of CR/PR is not required. The ORR or DCR difference between dose levels was estimated along with the 95% CI using a stratified analysis as in footnote [b] based on the strata constructed through IRT.

DCO: 23 Dec 2022

Median time to initial response was 1.8 months in the 5.4 mg/kg arm and 1.6 months in the 6.4 mg/kg arm.

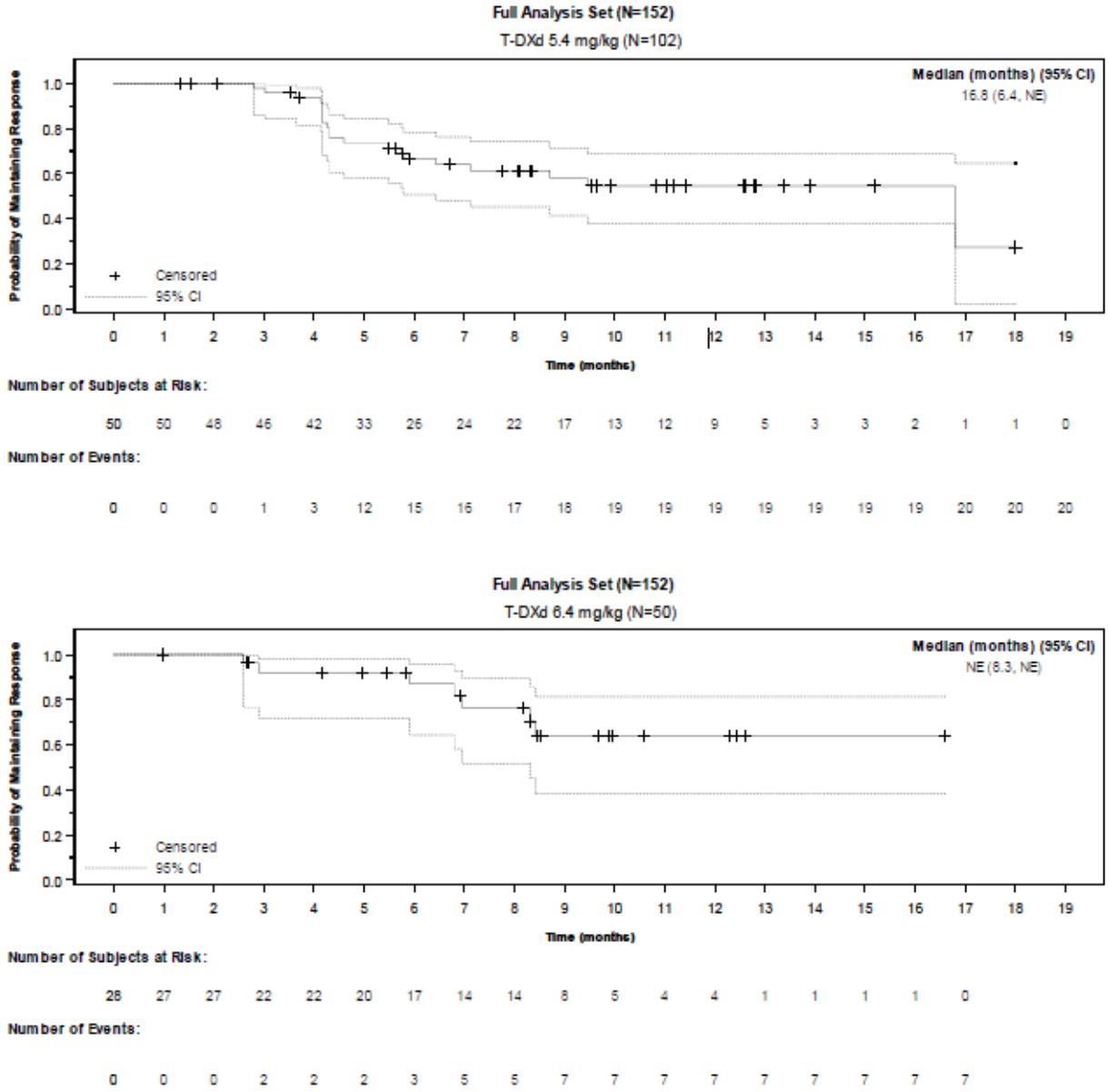
Secondary endpoint – DOR by BICR:

Parameter	Full Analysis Set	
	T-DXd 5.4 mg/kg (N = 102)	T-DXd 6.4 mg/kg (N = 50)
DoR of confirmed CR or PR (months)		
Subjects with confirmed CR/PR	50	28
Subjects with events (%)	20 (40.0)	7 (25.0)
PD	17 (34.0)	7 (25.0)
Death	3 (6.0)	0
Subjects without events (censored) (%)	30 (60.0)	21 (75.0)
New anticancer therapy	5 (10.0)	4 (14.3)
Event after missing 2 consecutive assessments	0	0
Lost to follow-up	0	0
Withdrew consent from study	2 (4.0)	4 (14.3)
Ongoing without event	21 (42.0)	12 (42.9)
Adequate tumor assessment no longer available	2 (4.0)	1 (3.6)
DoR estimates and 95% CI (months)		
25th percentile	4.6	8.3
95% CI[a]	(4.2, 7.1)	(2.9, NE)
Median	16.8	NE
95% CI[a]	(6.4, NE)	(8.3, NE)
75th percentile	NE	NE
95% CI[a]	(16.8, NE)	(NE, NE)
Estimated proportion of responders maintaining response (%) at 3 months	97.9	92.1
95% CI[b]	(85.8, 99.7)	(71.9, 98.0)
Estimated proportion of responders maintaining response (%) at 6 months	66.5	87.0
95% CI[b]	(50.6, 78.3)	(64.4, 95.7)
Estimated proportion of responders maintaining response (%) at 12 months	54.4	64.1
95% CI[b]	(37.6, 68.5)	(38.2, 81.4)
Number of subjects with DoR >6 months		
n (%)	26 (52.0)	17 (60.7)
Number of subjects with DoR >12 months		
n (%)	9 (18.0)	4 (14.3)

Percentage was calculated using number of subjects with CR/PR as the denominator. For the rows of number of subjects with DoR >6 months (alternatively >12), only those with observed DoR >6 (or >12) months were counted.
Best overall response of CR/PR with confirmation was assessed by blinded independent central review using RECIST criteria v1.1.
Median, 25th percentile, 75th percentile, and estimated proportion of responders maintaining response at 3, 6, and 12 months for DoR were based on Kaplan-Meier estimate.

[a] 95% CIs for median, 25th, and 75th percentiles are from Kaplan-Meier analysis and computed using the Brookmeyer-Crowley method.
[b] 95% CI is from Kaplan-Meier analysis.
DCO: 23 Dec 2022

Figure 17: **Kaplan Meir plot of DOR by BICR, DCO 23-DEC-2022**

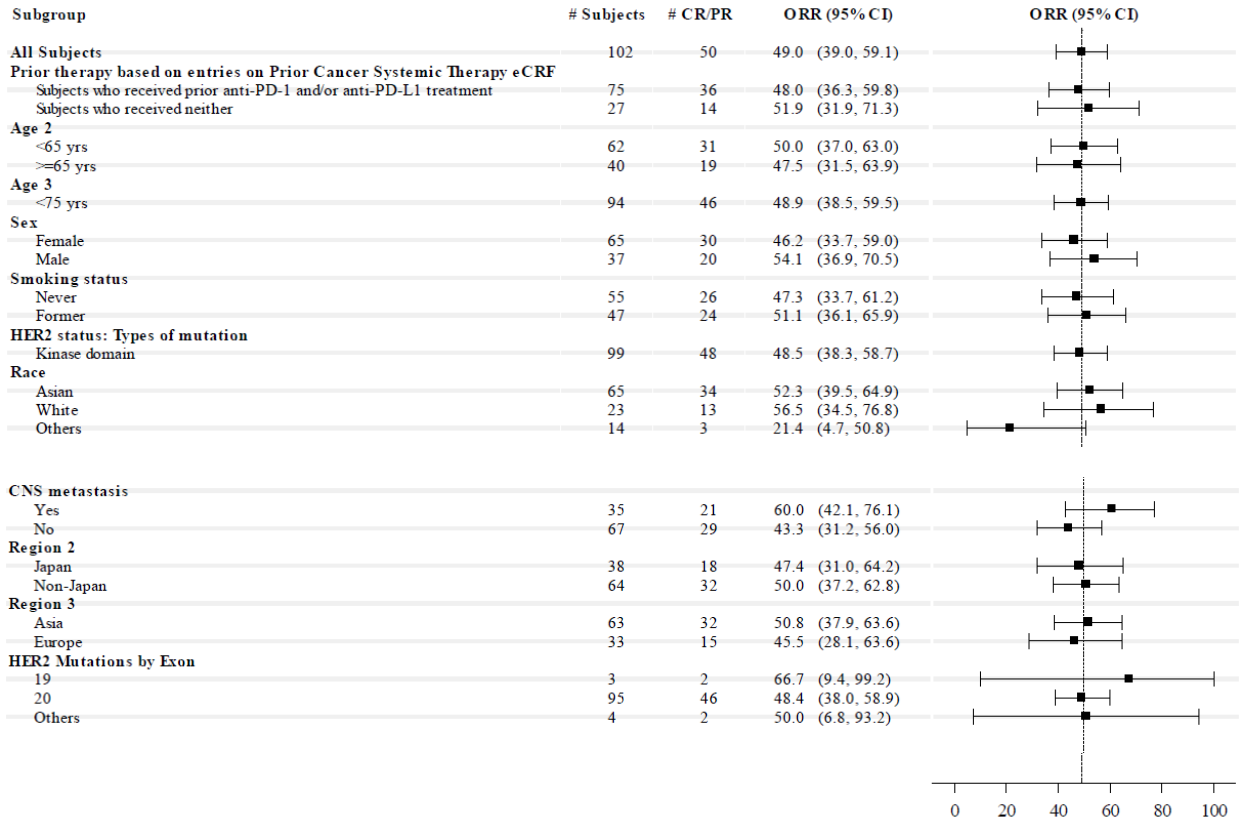


CI = confidence interval; DCO = data cut-off; N = number of subjects in the Full Analysis Set; NE = not estimable; PD = progressive disease; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; T-DXd = trastuzumab deruxtecan
Notes: PD was assessed by blinded independent central review using RECIST v1.1.
Solid line reflects duration of response estimate referenced in y-axis label over time.
DCO: 23 Dec 2022

Ancillary analyses

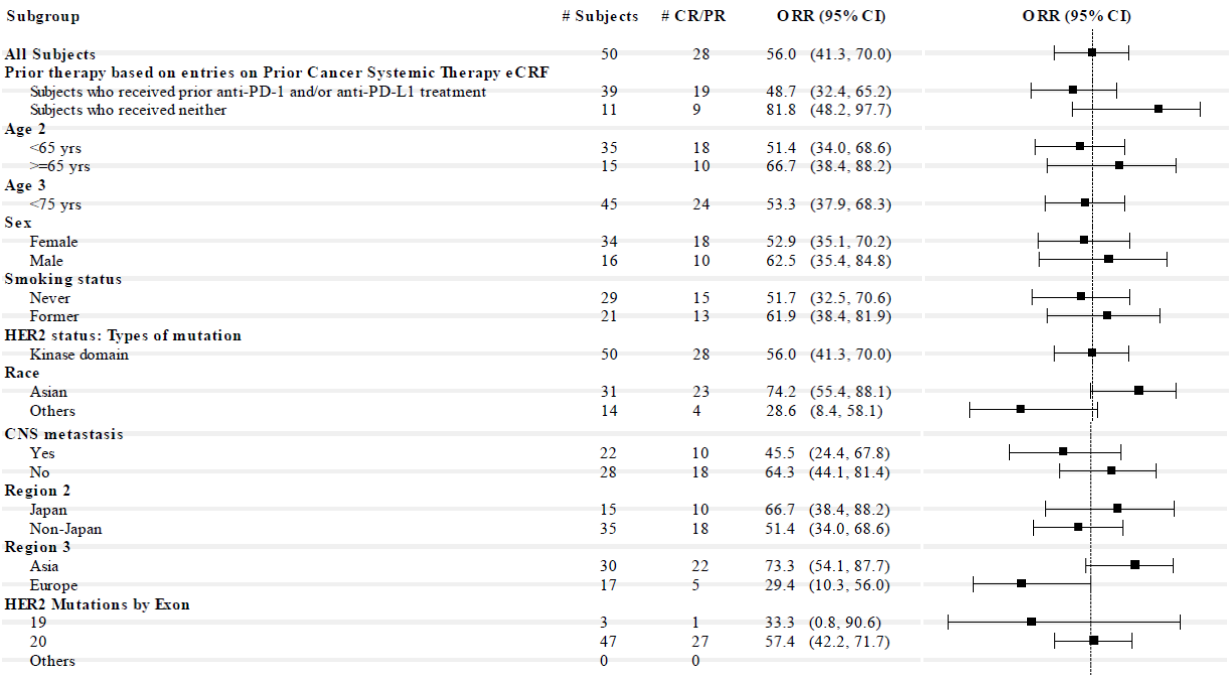
Subgroup analyses:

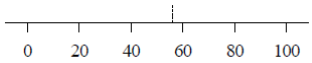
Figure 18: Forest plot of objective response rate based on blinded independent central review in arm T-DXd 5.4 mg/kg, DCO 23-DEC-2022



ORR results are not presented in the forest plots for subgroups of <10 subjects, except for the subgroups of subjects with HER2 exon 19 mutations (n = 3 in in each treatment group) and HER2 other exon mutations (n = 4 in the T DXd 5.4 mg/kg group).The 2-sided 95% CI are based on the exact (Clopper-Pearson) binomial distribution. If sample size is too small (n <10) in a subgroup (except for the HER2 mutations exon 19 and others subgroups), the results for the subgroup are not presented.
Note: Age 2: <65 and ≥65; Age 3: <75 and ≥75; Region 2: Japan vs. Non-Japan; Region 3: Asia, North America and Australia, Europe.

Figure 19: Forest plot of objective response rate based on blinded independent central review in arm T-DXd 6.4 mg/kg, DCO 23-DEC-2022





ORR results are not presented in the forest plots for subgroups of <10 subjects, except for the subgroups of subjects with HER2 exon 19 mutations (n = 3 in in each treatment group) and HER2 other exon mutations (n = 4 in the T DXd 5.4 mg/kg group).The 2-sided 95% CI are based on the exact (Clopper-Pearson) binomial distribution. If sample size is too small (n <10) in a subgroup (except for the HER2 mutations exon 19 and others subgroups), the results for the subgroup are not presented.
Note: Age 2: <65 and ≥65; Age 3: <75 and ≥75; Region 2: Japan vs. Non-Japan; Region 3: Asia, North America and Australia, Europe.

Table 26: Subgroup Analyses of Objective Response Rate by Blinded Independent Central Review (Study U206, Full Analysis Set)- CNS at baseline yes/no

	Full Analysis Set	
	T-DXd 5.4 mg/kg (N = 102)	**T-DXd 6.4 mg/kg (N = 50)**
CNS metastasis at Baseline		
CNS metastasis: Yes, n	35	22
Confirmed ORR, n (%)	21 (60.0)	10 (45.5)
95% CI[a]	42.1, 76.1	24.4, 67.8
CNS metastasis: No, n	67	28
Confirmed ORR, n (%)	29 (43.3)	18 (64.3)
95% CI[a]	31.2, 56.0	44.1, 81.4

BICR = blinded independent central review; CI = confidence interval; CNS = central nervous system; DCO = data cut-off; ORR = objective response rate; RECIST = Response Evaluation Criteria in Solid Tumours; T-DXd = trastuzumab deruxtecan
[a] The 2-sided 95% confidence intervals are based on the exact (Clopper-Pearson) method for binomial distribution.
Notes: Overall response is determined by BICR based on RECIST version 1.1.
Percentage is calculated using n as the denominator where n is number of subjects for each subgroup. DCO date: 23 Dec 2022

Table 27: Subgroup Analyses of Duration of Response by Blinded Independent Central Review (Study U206, Full Analysis Set) -CNS at baseline Yes/no

	Full Analysis Set	
	T-DXd 5.4 mg/kg (N = 102)	**T-DXd 6.4 mg/kg (N = 50)**
CNS metastasis at Baseline		
CNS metastasis: Yes		
Number of confirmed responders, n	21	10
Confirmed responders with PD/death, n (%)	15 (71.4)	3 (30.0)
Median DoR (95% CI[a]), months	4.6 (4.2, 6.4)	8.3 (2.6, NE)
CNS metastasis: No		
Number of confirmed responders, n	29	18

Confirmed responders with PD/death, n (%)	5 (17.2)	4 (22.2)
Median DoR (95% CI[a]), months	16.8 (16.8, NE)	NE (7.0, NE)

CI = confidence interval; CR = complete response; DCO = data cut-off; DoR = duration of response; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; T-DXd = trastuzumab deruxtecan
[a] 95% CI for median is computed using the Brookmeyer-Crowley method.
Notes: Percentage is calculated using the number of subjects with CR/PR (confirmed responders) as the denominator. Best overall response (CR/PR) with confirmation was assessed by blinded independent central review using RECIST version 1.1. Median is from Kaplan-Meier estimate.

Table 28: Subgroup Analyses of Objective Response Rate by Blinded Independent Central Review (Study U206, Full Analysis Set) -prior immunotherapy Yes/NO

	Full Analysis Set	
	T-DXd 5.4 mg/kg (N = 102)	**T-DXd 6.4 mg/kg (N = 50)**
Subjects who received prior anti-PD1 and/or ant PD-L1 treatment		
Yes	**75**	**39**
Confirmed ORR, n (%)	36 (48.0)	19 (48.7)
95% CI[a]	36.3, 59.8	32.4, 65.2
No	**27**	**11**
Confirmed ORR, n (%)	14 (51.9)	9 (81.8)
95% CI[a]	31.9, 71.3	48.2, 97.7

BICR = blinded independent central review; CI = confidence interval; CNS = central nervous system;
DCO = data cut-off; ORR = objective response rate; RECIST = Response Evaluation Criteria in Solid Tumours;
T-DXd = trastuzumab deruxtecan
a The 2-sided 95% confidence intervals are based on the exact (Clopper-Pearson) method for binomial distribution.
Notes: Overall response is determined by BICR based on RECIST version 1.1.
Percentage is calculated using n as the denominator where n is number of subjects for each subgroup. DCO date: 23 Dec 2022

Table 29: Subgroup Analyses of Duration of Response by Blinded Independent Central Review (Study U206, Full Analysis Set)

	Full Analysis Set	
	T-DXd 5.4 mg/kg (N = 102)	**T-DXd 6.4 mg/kg (N = 50)**
Subjects who received prior anti-PD1 and/or ant PD-L1 treatment		
YES	**75**	**39**
Number of confirmed responders, n	36	19
Confirmed responders with PD/death, n (%)	14 (38.9)	5 (26.3)
Median DoR (95% CI[a]), months	16.8 (5.8, NE)	NE (7.0, NE)
NO	**27**	**11**
Number of confirmed responders, n	14	9
Confirmed responders with PD/death, n (%)	6 (42.9)	2 (22.2)
Median DoR (95% CI[a]), months	NE (4.2, NE)	NE (2.9, NE)

CI = confidence interval; CR = complete response; DCO = data cut-off; DoR = duration of response; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; T-DXd = trastuzumab deruxtecan
a 95% CI for median is computed using the Brookmeyer-Crowley method.
Notes: Percentage is calculated using the number of subjects with CR/PR (confirmed responders) as the denominator.
Best overall response (CR/PR) with confirmation was assessed by blinded independent central review using RECIST version 1.1.
Median is from Kaplan-Meier estimate.

Table 30: Subgroup Analysis of Objective Response Rate by Blinded Independent Central Review (Study U206, Full Analysis Set): HER2 mutation exon 19 or 20 Yes/No

	Full Analysis Set	
	T-DXd 5.4 mg/kg (N = 102)	**T-DXd 6.4 mg/kg (N = 50)**
HER2 mutation: exon 19 or exon 20		
Subjects with HER2 mutation in exon 19 or exon 20, n	98	50
Confirmed ORR, n (%)	48 (49.0)	28 (56.0)
95% CI[a]	38.7, 59.3	41.3, 70.0

BICR = blinded independent central review; CI = confidence interval; CNS = central nervous system; DCO = data cut-off; ORR = objective response rate; RECIST = Response Evaluation Criteria in Solid Tumours; T-DXd = trastuzumab deruxtecan
[a] The 2-sided 95% confidence intervals are based on the exact (Clopper-Pearson) method for binomial distribution.
Notes: Overall response is determined by BICR based on RECIST version 1.1.
Percentage is calculated using n as the denominator where n is number of subjects for each subgroup. DCO date: 23 Dec 2022

Table 31: Subgroup Analysis of Duration of Response by Blinded Independent Central Review (Study U206, Full Analysis Set) HER2 mutation exon 19/20 at baseline Yes/No

	Full Analysis Set	
	T-DXd 5.4 mg/kg (N = 102)	**T-DXd 6.4 mg/kg (N = 50)**
HER2 mutation: exon 19 or exon 20		
Subjects with HER2 mutation in exon 19 or exon 20, n	98	50
Number of confirmed responders, n	48	28
Confirmed responders with PD/death, n (%)	19 (39.6)	7 (25.0)
Median DoR (95% CI[a]), months	16.8 (5.8, NE)	NE (8.3, NE)

CI = confidence interval; CR = complete response; DCO = data cut-off; DoR = duration of response; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; T-DXd = trastuzumab deruxtecan
[a] 95% CI for median is computed using the Brookmeyer-Crowley method.
Notes: Percentage is calculated using the number of subjects with CR/PR (confirmed responders) as the denominator.
Best overall response (CR/PR) with confirmation was assessed by blinded independent central review using RECIST version 1.1.
Median is from Kaplan-Meier estimate.

Table 32: Subgroup Analysis of Objective Response Rate by Blinded Independent Central Review Full Analysis Set (5.4 mg/kg)

Total	**Subjects in group (n) 102**	**Confirmed ORR (n (%) 50 (49.0)**	**95% CI 39.0, 59.1**
Subgroup: Race			
Asian	65	34 (52.3)	39.5, 64.9
White	23	13 (56.5)	34.5, 76.8
Others	14	3 (21.4)	4.7, 50.8
Subgroup: Region			
Japan	38	18 (47.4)	31.0, 64.2
Non-Japan	64	32 (50.0)	37.2, 62.8
Subgroup: Region			
Asia	63	32 (50.8)	37.9, 63.6
Europe	33	15 (45.5)	28.1, 63.6

Notes: Overall Response is determined by Blinded Independent Central Review based on RECIST, Version 1.1. ORR = Objective Response Rate

Percentage is calculated using n as the denominator where n is number of subjects for each subgroup.
[a] The 2-sided 95% confidence intervals are based on the exact (Clopper-Pearson) method for binomial distribution.
Region 2: Japan vs. Non-Japan; Region 3: Asia, North America and Australia, Europe.

Table 33: Subgroup Analysis of Objective Response Rate by Blinded Independent Central Review Full Analysis Set (6.4 mg/kg)

	Subjects in group (n)	Confirmed ORR (n, %)	95%
Total	**50**	**28 (56.0) %**	**(41.3, 70.0)**
Subgroup: Race			
Asian	31	23 (74.2)	55.4, 88.1
White	5	1 (20.0)	0.5, 71.6
Others	14	4 (28.6)	8.4, 58.1
Subgroup: Region 2			
Japan	15	10 (66.7)	38.4, 88.2
Non-Japan	35	18 (51.4)	34.0, 68.6
Subgroup: Region 3			
Asia	30	22 (73.3)	54.1, 87.7
Europe	17	5 (29.4)	10.3, 56.0

Notes: Overall Response is determined by Blinded Independent Central Review based on RECIST, Version 1.1. ORR = Objective Response Rate Percentage is calculated using n as the denominator where n is number of subjects for each subgroup.

[a] The 2-sided 95% confidence intervals are based on the exact (Clopper-Pearson) method for binomial distribution.

Region 2: Japan vs. Non-Japan; Region 3: Asia, North America and Australia, Europe.

Table 34: Subgroup analyses of DoR by blinded independent central review Full analyses set 5.4 mg/kg

	No of confirmed responders in subgroup (n)	Confirmed responders with PD/death (%)	Confirmed responders censored	DoR (median (95% CI) months
Total	50	20 (40.0)	30 (60.0)	16.8 (6.4- NE)
Subgroup: Race				
Asian	34	12 (35.3)	22 (64.7)	16.8 (7.1- NE)
White	13	7 (53.8)	6 (46.2)	5.7 (4.1- NE)
Others	3	1 (33.3)	2 (66.7)	NE (4.3, -NE)
Subgroup: Region 2				
Japan	18	7 (38.9)	11 (61.1)	16.8 (7.1- NE)
Non-Japan	32	13 (40.6)	19 (59.4)	NE (4.3-NE)
Subgroup: Region 3				
Asia	32	12 (37.5)	20 (62.5)	16.8 (7.1- NE)
Europe	15	8 (53.3)	7 (46.7)	6.4 (4.2- NE)

Notes: Percentage is calculated using number of subjects with CR/PR (confirmed responders) as the denominator.
CR = Complete Response, DOR = Duration of Response, NE = Not Estimable, PR = Partial Response, PD = Progressive Disease. Best overall response (CR/PR) with confirmation was assessed by Blinded Independent Central Review using RECIST, Version 1.1. Median is from Kaplan-Meier Estimate.
[a] 95% CI for median is computed using the Brookmeyer-Crowley method.
Region 2: Japan vs. Non-Japan; Region 3: Asia, North America and Australia, Europe.

Table 35: Subgroup analyses of DoR by blinded independent central review Full analyses set 6.4 mg/kg

	No of confirmed responders in subgroup (n)	Confirmed responders with PD/death (%)	Confirmed responders censored	DoR (median (95% CI) months
Total	28	7 (25.0)	21 (75.0)	NE (8.3-NE)
Subgroup: Race				
Asian	23	6 (26.1)	17 (73.9)	NE (8.3,NE)
White	1	1 (100)	0	7.0 (NE, NE)
Others	4	0	4 (100)	NE
Region 2				
Japan	10	2 (20)	8 (80)	NE (2.6, NE)
Non-Japan	18	5 (27.8)	13 (7.2)	NE (5.9, NE)
Subgroup: Region 3				
Asia	22	6 (27.3)	16 (72.7)	NE (6.8, NE)
Europe	5	1 (20)	4 (80)	NE 97.0, NE)

Notes: Percentage is calculated using number of subjects with CR/PR (confirmed responders) as the denominator.
CR = Complete Response, DOR = Duration of Response, NE = Not Estimable, PR = Partial Response, PD = Progressive Disease. Best overall response (CR/PR) with confirmation was assessed by Blinded Independent Central Review using RECIST, Version 1.1. Median is from Kaplan-Meier Estimate.
[a] 95% CI for median is computed using the Brookmeyer-Crowley method.
Note Region 2: Japan vs. Non-Japan; Region 3: Asia, North America and Australia, Europe

Sensitivity analyses:

ORR by INV and concordance between BICR and INV

Table 36 Best Overall Response, Objective Response Rate and Disease Control Rate by Investigator Assessment Full Analysis Set (DCO 24 March 2022)

Table 14.2.2.1.1: Best Overall Response, Objective Response Rate and Disease Control Rate by Investigator Assessment
Full Analysis Set

	FAS			Pre-Specified Early Cohort*		
	T-DXd 5.4 mg/kg (N=102)	T-DXd 6.4 mg/kg (N=50)	Difference in % (6.4 mg/kg - 5.4 mg/kg)	T-DXd 5.4 mg/kg (N=52)	T-DXd 6.4 mg/kg (N=28)	Difference in % (6.4 mg/kg - 5.4 mg/kg)
Best Overall Response (Confirmed) (n [%])						
Complete Response (CR)	1 (1.0)	0		1 (1.9)	0	
Partial Response (PR)	27 (26.5)	16 (32.0)		21 (40.4)	11 (39.3)	
Stable Disease (SD)	59 (57.8)	25 (50.0)		24 (46.2)	13 (46.4)	
Progressive Disease (PD)	6 (5.9)	3 (6.0)		3 (5.8)	2 (7.1)	
Non-Evaluable (NE)	9 (8.8)	6 (12.0)		3 (5.8)	2 (7.1)	
Confirmed Objective Response Rate (ORR)						
n (%)	28 (27.5)	16 (32.0)	5.8 [b]	22 (42.3)	11 (39.3)	-1.9 [b]
95% CI	(19.1, 37.2) [a]	(19.5, 46.7) [a]	(-9.5, 21.1) [b]	(28.7, 56.8) [a]	(21.5, 59.4) [a]	(-23.6, 19.7) [b]
			4.5 [c]			-3.0 [c]
			(-10.3, 20.6) [c]			(-24.4, 19.7) [c]
			5.6 [d]			-1.8 [d]
			(-9.8, 20.9) [d]			(-23.4, 19.8) [d]

Notes: ORR = Objective Response Rate (Best overall response of CR or PR), DCR = Disease Control Rate (Best overall response of CR, PR or SD).
Percentages are based on the number of subjects in the Full Analysis Set.
Overall Response was determined by investigator assessment based on RECIST, Version 1.1. To derive best overall response, time-point response of Non-CR/Non-PD is considered as SD. 'Unconfirmed' means confirmation is not required.
* An early cohort of subjects is pre-specified and defined as those who have been randomized 4.5 months (137 days) before the DCO.

Table 37 Concordance of Confirmed Best Overall Response between Blinded Independent Centra Review and Investigator Assessment (Pre-specified Early Cohort Analysis Set) (DCO 24 March 2022)

Table 8.2: Concordance of Confirmed Best Overall Response between Blinded Independent Central Review and Investigator Assessment (Pre-specified Early Cohort Analysis Set)

		Confirmed Best Overall Response by Blinded Independent Central Review, n (%)						
Treatment Arm	**Confirmed Best Overall Response By Investigator Assessment**	**CR**	**PR**	**SD**	**PD**	**NE**	**Total**	**Concordance Rate**
Pre-specified Early Cohort[a]								
T-DXd 5.4 mg/kg (N = 52)	Complete Response (CR)	0	1 (1.9)	0	0	0	1 (1.9)	—
	Partial Response (PR)	0	20 (38.5)	1 (1.9)	0	0	21 (40.4)	—
	Stable Disease (SD)	1 (1.9)	6 (11.5)	16 (30.8)	1 (1.9)	0	24 (46.2)	—
	Progressive Disease (PD)	0	0	2 (3.8)	1 (1.9)	0	3 (5.8)	—
	Not Evaluable	0	0	0	0	3 (5.8)	3 (5.8)	—
	Total	1 (1.9)	27 (51.9)	19 (36.5)	2 (3.8)	3 (5.8)	52 (100)	40 (76.9)
T-DXd 6.4 mg/kg (N = 28)	Complete Response (CR)	0	0	0	0	0	0	—
	Partial Response (PR)	1 (3.6)	9 (32.1)	1 (3.6)	0	0	11 (39.3)	—
	Stable Disease (SD)	0	1 (3.6)	12 (42.9)	0	0	13 (46.4)	—
	Progressive Disease (PD)	0	1 (3.6)	1 (3.6)	0	0	2 (7.1)	—
	Not Evaluable	0	0	0	1 (3.6)	1 (3.6)	2 (7.1)	—
	Total	1 (3.6)	11 (39.3)	14 (50.0)	1 (3.6)	1 (3.6)	28 (100)	22 (78.6)

DCO = data cut-off; T-DXd = trastuzumab deruxtecan
[a] An early cohort of subjects was pre-specified and defined as those who have been randomized at least 4.5 months (137 days) before the DCO.
Notes: Percentages were based on the row total number of subjects in the dose group. Concordance rate (%) was derived as the number of subjects that are concordant for confirmed best overall response between blinded independent central review and investigator assessment divided by the total number of subjects assessed for each dose level.
DCO: 24 Mar 2022

DOR sensitivity analysis based on treatment policy estimand

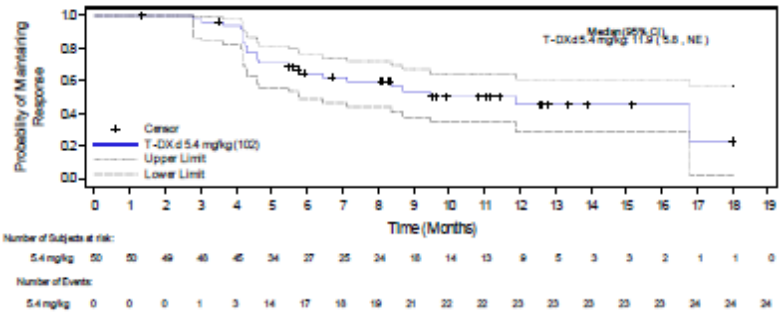
According to this analysis, all PD/deaths were treated as events, regardless of the intercurrent event, such as the start of new anticancer therapy.

For responders without PD/death, DoR was censored at the last tumour assessment before the first new anticancer therapy if the subject received new anticancer therapy after T-DXd or censored at the last tumour assessment if the subject did not.

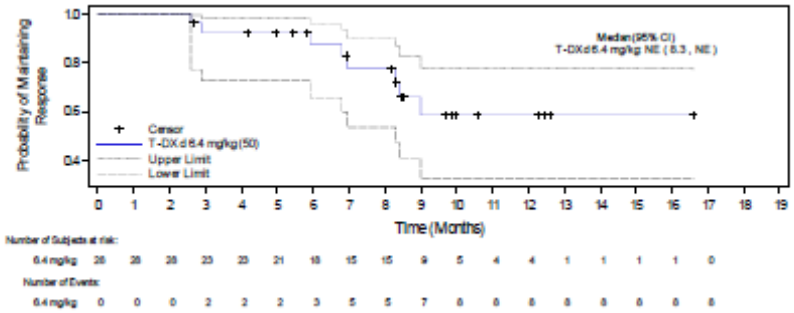
Median DoR was 11.9 months (95% CI: 5.8, NE) in 50 responders in the T-DXd 5.4 mg/kg group and NE (95% CI: 8.3, NE) in 28 responders in the T-DXd 6.4 mg/kg group.

Figure 20: **Kaplan-Meier Plot for Duration of Response by Blinded Independent Central Review – Supplementary Analysis Using Alternative Event/Censoring Rules; Method 1 (Study U206; Full Analysis Set)**

5.4 mg/kg



6.4 mg.kg



CI = confidence interval; DoR = duration of response; NE = not evaluable; PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumours; T-DXd = trastuzumab deruxtecan
Note: The analysis was based on a treatment policy estimand strategy. All PD/Deaths are treated as events. For responders without PD/Death, DoR is censored at the last tumour assessment before the first new anti-cancer therapy started if the subject had post-T-DXd-treatment new anti-cancer therapy and the last tumour assessment if otherwise. PD was assessed by independent central review using RECIST version 1.1.
Solid line reflects survival estimate referenced in y-axis label over time.

DOR sensitivity analysis based on a composite estimand strategy

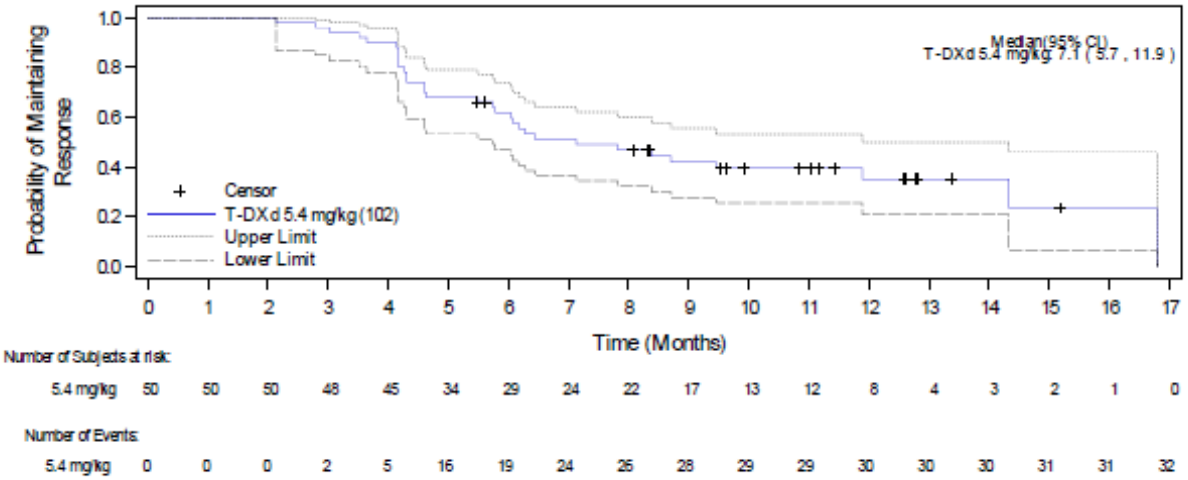
According to this analysis, all PD/deaths were treated as events.
For responders without PD/death, the date of start of a new anticancer therapy or of discontinuation from study drug was used as the event date for determining the end of DoR.

For other responders with ongoing T-DXd treatment, DoR was censored at the last tumour assessment.

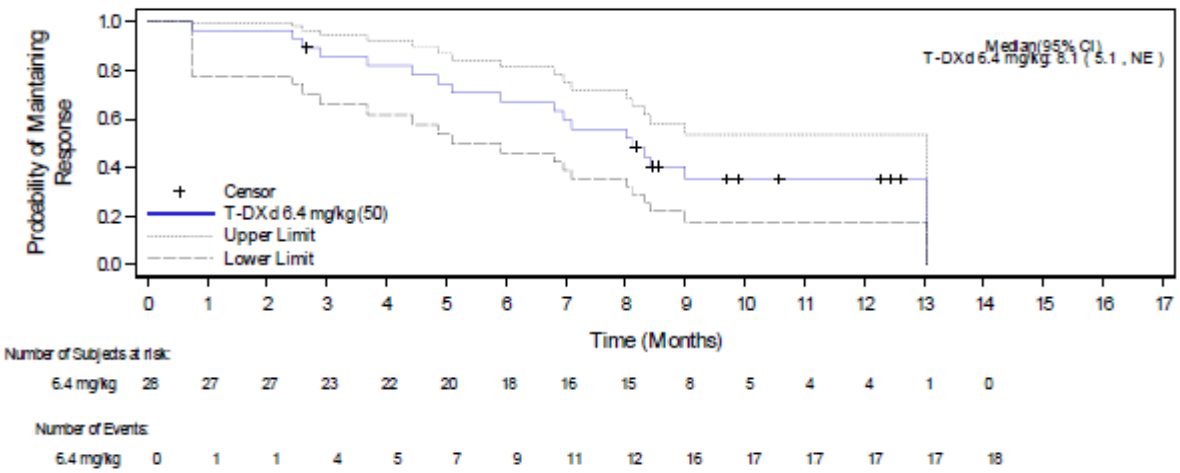
Median DoR was 7.1 months (95% CI: 5.7, 11.9) in 50 responders in the T-DXd 5.4 mg/kg group and 8.1 months (95% CI: 5.1, NE) in 28 responders in the T-DXd 6.4 mg/kg group.

Figure 21: **Kaplan-Meier Plot for Duration of Response by Blinded Independent Central Review – Supplementary Analysis Using Alternative Event/Censoring Rules; Method 2 (Study U206; Full Analysis Set)**

5.4 mg/kg



6.4 mg/kg



BICR = blinded independent central review; CI = confidence interval; DoR = duration of response; NE = not evaluable; PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumours; T-DXd = trastuzumab deruxtecan
Note: The analysis was based on any deaths or PD after the last dose was counted as an event (i.e., a treatment policy strategy) and a composite estimand strategy was applied for the use of new anticancer therapy or discontinuation. All PD/Deaths are treated as events. For responders without PD/Death, if the subject started new anti-cancer therapy or discontinued from study treatment, the date was used as the DoR event date. For other responders who have ongoing T-DXd treatment, DoR is censored at the last tumour assessment. PD was assessed by BICR using RECIST version 1.1.
Solid line reflects survival estimate referenced in y-axis label over time.

DOR sensitivity analysis combining the BICR and investigator assessments.

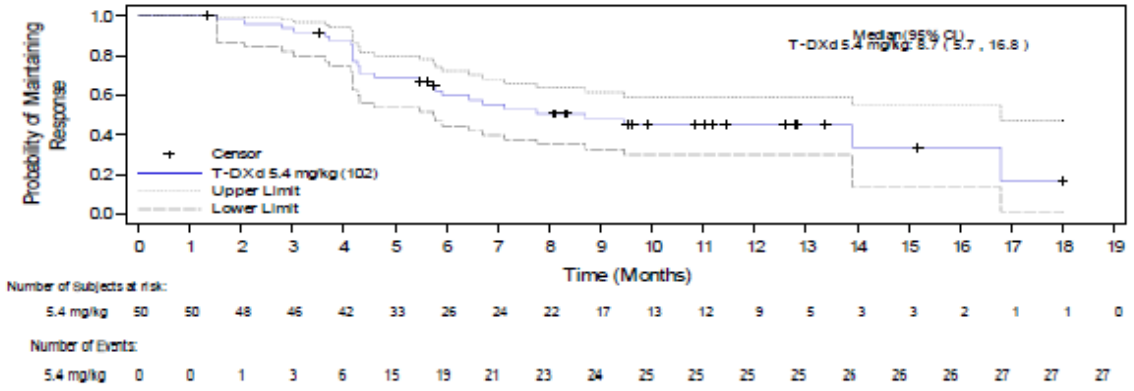
According to this analysis, the earliest of the PD event dates between the BICR and investigator assessments was taken as DoR event date if at least 1 assessment resulted in an event.

If an event of PD, either by BICR or by investigator assessment, occurred on/after the start date of DoR, the earlier PD date between the BICR and investigator assessment was taken into account to determine the end of DoR Otherwise, DoR was the same as DoR by BICR.

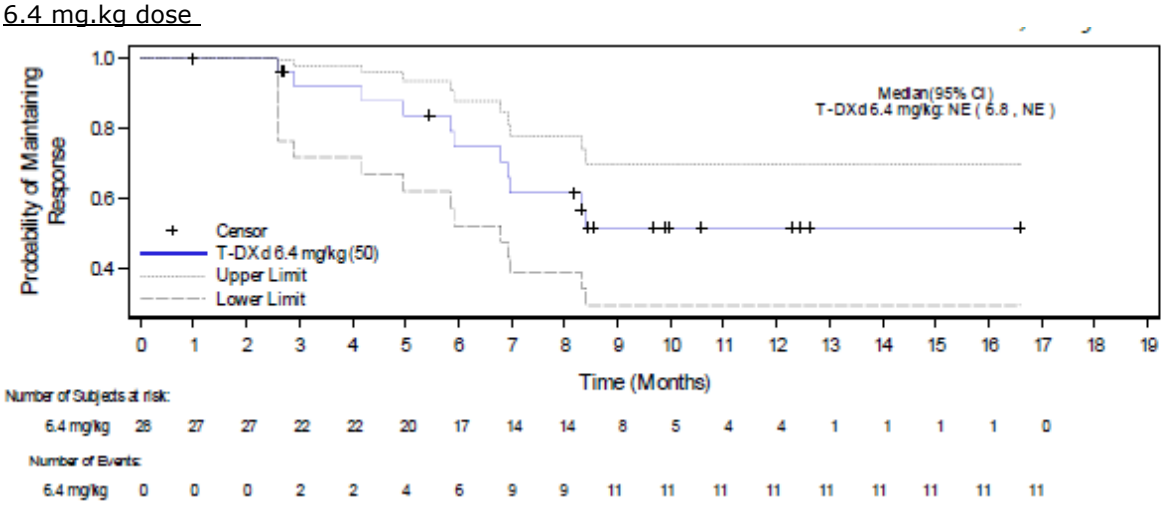
Median DoR was 8.7 months (95% CI: 5.7, 16.8) in 50 responders in the T-DXd 5.4 mg/kg group and NE (95% CI: 6.8, NE) in 28 responders in the T-DXd 6.4 mg/kg group.

Figure 22: **Kaplan-Meier Plot for Duration of Response by Blinded Independent Central Review and Investigator Assessment - Supplementary Analysis Using Alternative Event Rule; Method 3 (Study U206; Full Analysis Set)**

5.4 mg/kg dose



6.4 mg.kg dose



BICR = blinded independent central review; CI = confidence interval; DoR = duration of response; NE= not evaluable; PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumours; T-DXd = trastuzumab deruxtecan
Note: DoR event/censoring in Method 3 combines BICR and investigator assessments. The earlier PD date from BICR and investigator assessment is taken as the DoR event date if the PD date from investigator assessment occurs on/after the start date of DoR by BICR. Otherwise, DoR is the same as DoR by BICR. PD was assessed by independent central review using RECIST version 1.1.
Solid line reflects survival estimate referenced in y-axis label over time.

Summary of main study

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

Table 38: Summary of Efficacy for trial U206

Title: A Phase 2, multicenter, randomized study of trastuzumab deruxtecan in subjects with HER2-mutated metastatic non-small cell lung cancer (NSCLC) (DESTINY-Lung02)	
Study identifier	Sponsor's Protocol Number: DS8201-A-U206 NCT04644237
Design	Partially blinded, randomised, 2 arm, Phase 2 study

Hypothesis	The null hypothesis of objective response rate (ORR) equaling 26.4% was tested by comparing the lower limit of 95% confidence interval (CI; Clopper-Pearson) against 26.4% for each of 5.4- and 6.4-mg/kg doses as a single arm at the primary analysis.		
Treatment groups	HER2-mut NSCLC T-DXd 5.4 mg/kg		T-DXd 5.4 mg/kg intravenous (IV) infusion Q3W 102 subjects randomized
	HER2-mut NSCLC T-DXd 6.4 mg/kg		T-DXd 6.4 mg/kg IV infusion Q3W 50 subjects randomized
Endpoints and definitions	Primary endpoint	ORR by blinded independent central review (BICR)	Confirmed ORR, defined as the proportion of subjects who achieved a best overall response (BOR) of complete response (CR) or partial response (PR), assessed by BICR based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).
	Secondary endpoints	ORR by investigator (Ix)	Confirmed ORR, defined as the proportion of subjects who achieved a BOR of CR or PR, assessed by Ix based on RECIST v1.1.
		Duration of response (DoR) by BICR and Ix	DoR, defined as time from initial response (CR or PR) based on both BICR and Ix assessment until documented tumor progression or death from any cause. DoR was calculated only for subjects with BOR of CR or PR.
		Disease control rate (DCR) by BICR and Ix	DCR, defined as the proportion of subjects who achieve CR, PR, or stable disease based on both BICR and Ix assessment during study treatment. Confirmation of CR and PR was required.
		Progression-free survival (PFS) by BICR and Ix	PFS, defined as the time from date of randomization until first objective radiographic tumor progression or death from any cause based on both BICR and Ix assessment.
		Overall survival (OS)	OS, defined as the time from date of randomization until death from any cause.
Database lock	Data cut-off (DCO) date for the primary analysis: 23 Dec 2022.		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (ie, all randomized subjects). DCO date: 23 Dec 2022		
Descriptive statistics and estimate variability	**Treatment group**	**HER2-mut NSCLC T-DXd 5.4 mg/kg**	**HER2-mut NSCLC T-DXd 6.4 mg/kg**
	Number of subjects	102	50
	Primary endpoint		
	Confirmed ORR by BICR, %	49.0	56.0
	95% CI[a]	39.0, 59.1	41.3, 70.0
	Secondary endpoints		
	DoR by BICR (months), median	16.8	NE
	95% CI[b]	6.4, NE	8.3, NE
	DCR by BICR, %	93.1	92.0
	95% CI[a]	86.4, 97.2	80.8, 97.8
	PFS by BICR (months), median	9.9	15.4
	95% CI[b]	7.4, NE	8.3, NE

	OS (months), median	19.5	NE
	95% CI[b]	13.6, NE	12.1, NE
	Confirmed ORR by Ix, %	46.1	56.0
	95% CI[a]	36.2, 56.2	41.3, 70.0
	DoR by Ix (months), median	9.9	19.4
	95% CI[b]	7.2, 17.0	5.0, 19.4
	DCR by Ix, %	90.2	88.0
	95% CI[a]	82.7, 95.2	75.7, 95.5
	PFS by Ix (months), median	9.7	9.5
	95% CI[b]	8.2, 11.3	6.5, 21.0
Effect estimate per comparison	Not applicable		
Notes	Abbreviations: NE = not estimable [a] The 2-sided 95% CIs were based on the exact (Clopper-Pearson) method for binomial distribution. [b] The 95% CI for median was from the Kaplan-Meier analysis computed by using the Brookmeyer-Crowley method.		

Analysis performed across trials (pooled analyses and meta-analysis)

ORR and DOR across patients with HER2-mutant NSCLC in the trials from the current application

Table 39: Confirmed ORR by ICR in HER2-mutant NSCLC across U206, U204 and J101 – 01 Aug 2019 for Study J101, 03 Dec 2021 for Study U204, and 24 Mar 2022 for Study U206

Parameter	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 52)	U206 HER2-mut NSCLC T-DXd 6.4 mg/kg (N = 28)	J101 HER2-mut NSCLC T-DXd 6.4 mg/kg (N = 11)	U204 HER2-mut NSCLC T-DXd 6.4 mg/kg (N = 91)	Overall HER2-mut NSCLC Pool T-DXd 6.4 mg/kg (N = 130)
BOR (confirmed) (n [%])					
CR	1 (1.9)	1 (3.6)	0	1 (1.1)	2 (1.5)
PR	27 (51.9)	11 (39.3)	8 (72.7)	49 (53.8)	68 (52.3)
SD	19 (36.5)	14 (50.0)	2 (18.2)	34 (37.4)	50 (38.5)
PD	2 (3.8)	1 (3.6)	1 (9.1)	3 (3.3)	5 (3.8)
NE	3 (5.8)	1 (3.6)	0	4 (4.4)	5 (3.8)
Confirmed ORR					
n (%)	28 (53.8)	12 (42.9)	8 (72.7)	50 (54.9)	70 (53.8)
95% CI [a]	(39.5, 67.8)	(24.5, 62.8)	(39.0, 94.0)	(44.2, 65.4)	(44.9, 62.6)

Pooled data includes 11 subjects from Study J101, 91 subjects from Study U204, and 28 subjects from Study U206. For Study U206, only subjects who have been randomized at least 4.5 months (137 days) before the DCO were included in the analyses.
Percentages are based on the number of subjects in the FAS.
[a] The 2-sided 95% CIs are based on the exact (Clopper-Pearson) method for binomial distribution.
Overall response is determined by ICR based on RECIST v1.1. To derive best overall response, time-point response of Non-CR/Non-PD is considered as SD.
DCOs: 01 Aug 2019 for Study J101, 03 Dec 2021 for Study U204, and 24 Mar 2022 for Study U206

Based on pooled data at 6.4 mg/kg dose in subjects with HER2-mutant NSCLC, confirmed ORR (N=130) based on independent central review was achieved in 53.8% (95% CI: 44.9, 62.6) subjects with median DoR of 9.9 months (95% CI: 7.0, 14.7), the median PFS (N=102) was 8.3 months (95% CI: 6.8, 11.9) and median OS was 18.6 months (95% CI: 14.8, 25.8). At the 5.4 mg/kg dose in subjects with HER2-mutant NSCLC (N = 52) in Study U206, cORR based on independent central review was achieved in 53.8% (95% CI: 39.5, 67.8), with median DoR not estimated.

Table 40: Objective Response Rate, Best Overall Response, Disease Control Rate, and Duration of Response by Independent Central Review in HER2-mutant Non-small Cell Lung Cancer (Full Analysis Set) DCO study 206 is 23 Dec 2022

Parameter	**U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 102)**	**U206 HER2-mut NSCLC T-DXd 6.4 mg/kg (N = 50)**	**J101 HER2-mut NSCLC T-DXd 6.4 mg/kg (N = 11)**	**U204 HER2-mut NSCLC T-DXd 6.4 mg/kg (N = 91)**	**Overall HER2-mut NSCLC Pool T-DXd 6.4 mg/kg (N = 152)**
BOR (confirmed) (n [%])					
CR	1 (1.0)	2 (4.0)	0	1 (1.1)	3 (2.0)
PR	49 (48.0)	26 (52.0)	8 (72.7)	49 (53.8)	83 (54.6)
SD	45 (44.1)	18 (36.0)	2 (18.2)	34 (37.4)	54 (35.5)
PD	4 (3.9)	2 (4.0)	1 (9.1)	3 (3.3)	6 (3.9)
NE	3 (2.9)	2 (4.0)	0	4 (4.4)	6 (3.9)
Confirmed ORR					
n (%)	**50 (49.0)**	**28 (56.0)**	**8 (72.7)**	**50 (54.9)**	**86 (56.6)**
95% CI[a]	**(39.0, 59.1)**	**(41.3, 70.0)**	**(39.0, 94.0)**	**(44.2, 65.4)**	**(48.3, 64.6)**
DCR where confirmation of CR or PR is required					
n (%)	95 (93.1)	46 (92.0)	10 (90.9)	84 (92.3)	140 (92.1)
95% CI[a]	(86.4, 97.2)	(80.8, 97.8)	(58.7, 99.8)	(84.8, 96.9)	(86.6, 95.9)
ORR (confirmation not required)					
n (%)	55 (53.9)	30 (60.0)	8 (72.7)	56 (61.5)	94 (61.8)
95% CI[a]	(43.8, 63.8)	(45.2, 73.6)	(39.0, 94.0)	(50.8, 71.6)	(53.6, 69.6)
DCR where confirmation of CR or PR is not required					
n (%)	95 (93.1)	46 (92.0)	10 (90.9)	84 (92.3)	140 (92.1)
95% CI[a]	(86.4, 97.2)	(80.8, 97.8)	(58.7, 99.8)	(84.8, 96.9)	(86.6, 95.9)
DoR of confirmed CR or PR					
Median (months)	**16.8**	**NE**	**9.9**	**10.6**	**11.1**
95% CI[b]	**(6.4, NE)**	**(8.3, NE)**	**(6.9, NE)**	**(5.8, 17.7)**	**(8.5, 17.7)**

BOR = best overall response; CI = confidence interval; CR = complete response; DCO = data cut-off date; DCR = disease control rate; FAS = Full Analysis Set; HER2 = human epidermal growth factor receptor 2; ICR = independent central review; mut = mutant; NE = non-evaluable; NSCLC = non-small cell lung cancer; ORR = objective response rate; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SCE = summary of clinical efficacy; SD = stable disease;

T-DXd = trastuzumab deruxtecan; v = version

[a] the 2-sided 95% CIs are based on the exact (Clopper-Pearson) method for binomial distribution.

[b] the 95% CIs are computed using the Brookmeyer-Crowley method.

Notes: Pooled data include 11 subjects from Study J101, 91 subjects from Study U204, and 50 subjects from Study U206. Percentages are based on the number of subjects in the FAS. Overall response is determined by ICR based on RECIST v1.1. To derive best overall response, time-point response of non-

CR/non-PD is considered as SD.

DCOs: 01 Aug 2019 for Study J101, 03 Dec 2021 for Study U204, and 23 Dec 2022 for Study U206

Clinical studies in special populations

Table 41: Elderly subjects with HER2-mutant NSCLC in controlled and noncontrolled studies

	Age 65 to 74 years elderly subject number/total number (%)	**Age 75 to 85 years elderly subject number/total number (%)**	**Age 85+ years elderly subject number/total number (%)**
T-DXd 5.4 mg/kg			
Noncontrolled study (U206)	32/102 (31.4)	8/102 (7.8)	0/102 (0.0)
T-DXd 6.4 mg/kg			
Noncontrolled studies (U206, U204, J101)	38/152 (25.0)	15/152 (9.9)	2/152 (1.3)

HER2 = human epidermal growth factor receptor 2; NSCLC = non-small cell lung cancer; T-DXd = trastuzumab deruxtecan

In vitro biomarker test for patient selection for efficacy

Subjects enrolled in Study U206 and randomized to the T-DXd 5.4 mg/kg group with available archival and/or freshly collected tumor tissue processed into formalin-fixed paraffin-embedded (FFPE) samples were tested retrospectively at a central laboratory with the to-be-marketed companion diagnostic Oncomine™ Dx Target Test (hereafter referred to as ODxTT). ODxTT is a qualitative in vitro diagnostic that uses targeted, high throughput, parallel sequencing technology to detect HER2 SNVs and exon 20 insertions for Enhertu NSCLC indication in nucleic acid isolated from FFPE tumor tissue specimens using a reference hotspot file. The clinical validity of ODxTT was assessed by evaluating the concordance between the results obtained with ODxTT and the results obtained with the local assays used for the enrollment in Study U206.

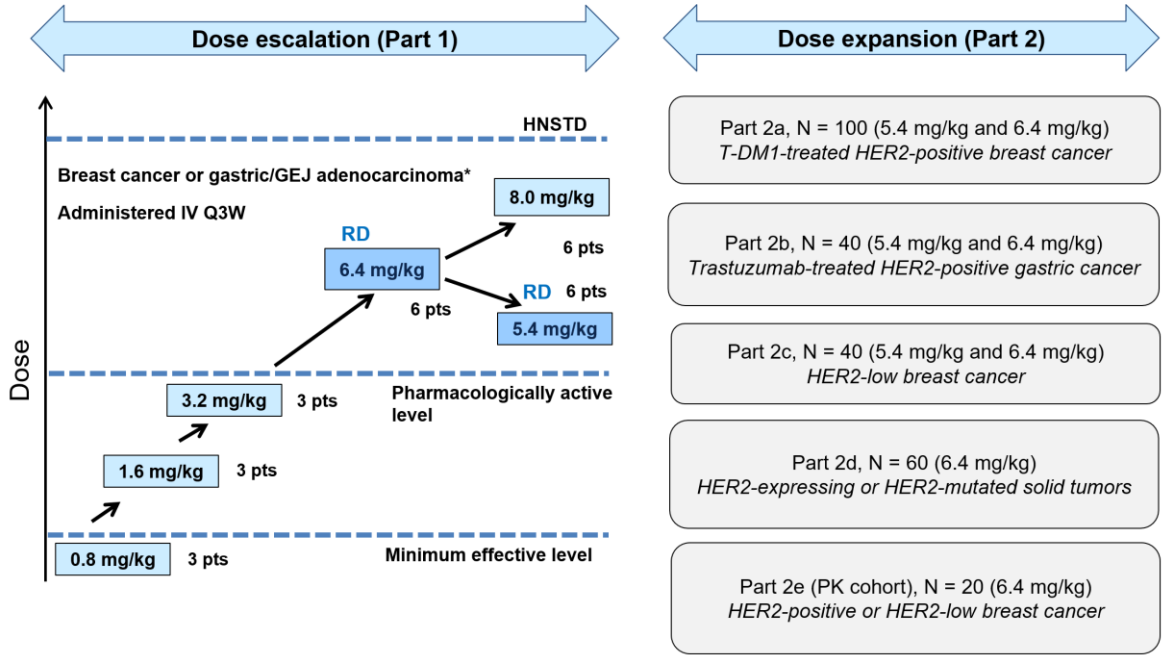
In vitro biomarker test for patient selection for efficacy: Out of 102 samples (deemed to be HER2-mutant positive by local assays) corresponding to the patients randomised to arm 5.4 mg/kg of trial U206, 29 were deemed insufficient for central testing using the to-be marketed CDx (Oncomine Dx Target Test, aka ODxTT). From the remaining 73 samples which were tested, 59 were positive, 2 were negative and 12 were labelled as "unknown". While the MAH claims for concordant results between local assays and ODxTT based on the positive (59/61) and negative (107/117) samples, it is noted that ~12% (22/190) of the samples tested with ODxTT corresponded to the "unknown" category, which could become an important proportion for the commercial application of this CDx. Upon these limited sample of centrally confirmed samples, concordance cannot be claimed.

Supportive studies

Study J101:

Study J101 was a Phase 1, multicenter, 2-part (dose escalation followed by dose expansion), open-label, nonrandomized, multiple-dose, first-in-human study of T-DXd in subjects with advanced solid tumors with HER2 expression or mutations refractory to standard treatments or for which no standard treatments were available, with study sites in Japan and the US (see study design in Figure 23).

Figure 23: Study J101 Design



- HER2 status was assessed on archival tissue in both Parts 1 and 2

Dose Escalation (Part 1, 27 subjects enrolled) was intended to identify the maximum tolerated dose (MTD) or the recommended Phase 2 dose (RP2D) of T-DXd. Part 1 consisted of modified continuous reassessment method with escalation with overdose control design and included at least 3 subjects evaluable for assessment of dose-limiting toxicity per dose level (ie, 0.8, 1.6, 3.2, 5.4, 6.4, and 8.0 mg/kg).

Dose Expansion (Part 2, 265 subjects enrolled) was intended to further assess the safety, tolerability, and efficacy of T-DXd at the MTD/RP2D (5.4 mg/kg and 6.4 mg/kg) and was conducted in 5 cohorts of subjects.

The submitted SCE presented efficacy data from 11 subjects with NSCLC whose tumors had a HER2 mutation and who were treated with T-DXd 6.4 mg/kg from Part 2d of Study J101.

Results

Of the 11 subjects with HER2-mutant NSCLC from Part 2d, 8 (72.7%) subjects were female and 7 (63.6%) subjects were <65 years of age. Seven (63.6%) of the 11 subjects were White. The majority of subjects (72.7%) had an ECOG PS of 1 at baseline and had received >2 lines of prior systemic therapy for advanced/metastatic disease (81.8%). Among these subjects, specific mutations included: 8 (72.7%) subjects with a kinase domain mutation; 1 (9.1%) subject with an extracellular domain mutation; 2 (18.2%) subjects with a transmembrane domain mutation.

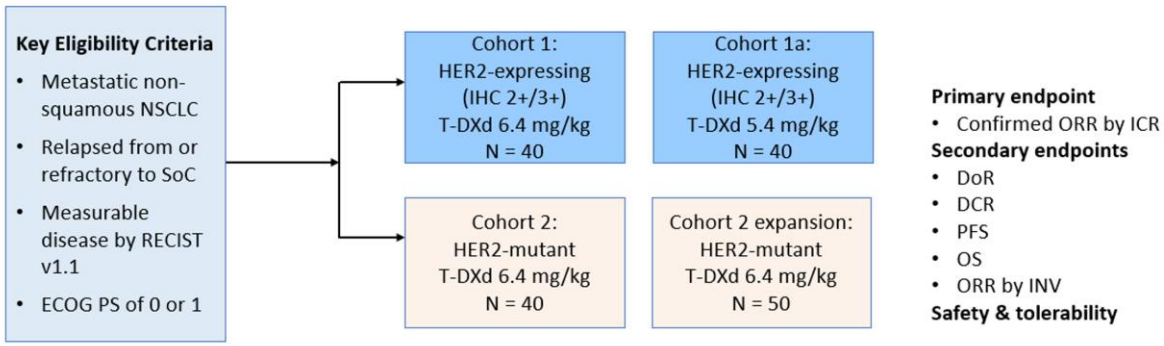
At DCO on 01-AUG-2019, for the 11 subjects with HER2-mutant NSCLC from Part 2d, a confirmed ORR by ICR was achieved in 8 (72.7%) subjects (95% CI: 39.0, 94.0), with all 8 (72.7%) subjects achieving confirmed PR. The median DoR by ICR was 9.9 months (95% CI: 6.9, NE), and the median PFS by ICR was 11.3 months (95% CI: 8.2, NE). Median OS was not estimable in these 11 subjects, with 7 (63.6%) subjects censored at the time of DCO.

<u>Study U204:</u>

Study U204 was a Phase 2, open-label, multicenter, 2-cohort study to evaluate the safety and efficacy of T-DXd in subjects with HER2-overexpressing (ie, IHC 3+ or IHC 2+) or HER2-mutant (defined as a known

documented activating HER2 mutation) NSCLC. To be enrolled in Study U204, subjects had to have pathologically documented unresectable and/or metastatic NSCLC that was relapsed from or was refractory to standard treatment or for which no standard treatment was available. Subjects had at least 1 measurable lesion assessed by the investigator based on RECIST v1.1, had an ECOG PS of 0 to 1, and were willing and able to comply with protocol visits and procedures. The study was conducted in North America, Japan, and Europe, with a planned sample size of approximately 170 subjects. Study design is provided in Figure 24.

Figure 24: Study U204 (DESTINY-Lung01) Design



A total of 181 subjects were enrolled in the study: 49 subjects in Cohort 1, 41 subjects in Cohort 1a, and 91 subjects in Cohort 2. The submitted SCE presents results from the HER2-mutant NSCLC subjects treated with T-DXd 6.4 mg/kg Q3W from Cohort 2.

The primary efficacy endpoint was confirmed ORR assessed by ICR. The primary analysis was to be performed when subjects in Cohort 2 had a minimum of 6 months follow-up past onset of response for all subjects who had a response by ICR. Of note, 1 subject was a late responder and did not have a minimum follow-up duration of 6 months after the onset of response.

No IA was planned in the original protocol. Three IAs were conducted to guide the future strategy for T-DXd in this population.

Results

In Cohort 2, the FAS (all enrolled subjects) included 91 subjects. All enrolled subjects received at least 1 dose of study drug. At the 03 Dec 2021 DCO, the median duration of follow-up was 16.7 months (range: 0.7 to 36.9), and 11 (12.1%) subjects were ongoing on treatment. A total of 80 (87.9%) subjects discontinued treatment, with the 2 most common reasons for discontinuation being PD (37 [40.7%] subjects) and adverse event (AE) (28 [30.8%] subjects).

The majority (65.9%) of the subjects were female (34.1% were male) and the median age was 60.0 years (range: 29 to 88). Forty (44.0%) subjects were White, and 31 (34.1%) subjects were Asian. For 20 (22.2%) subjects, race was reported as "Other". The median body mass index was 22.5 kg/m^2 (range: 15.3 to 38.8). All enrolled subjects in Cohort 2 had an activating HER2 (ERBB2) mutation. At baseline (based on the FAS), 33.0% of subjects had >2 lines of prior systemic therapy for advanced/metastatic disease and 65.9% had prior treatment with an anti-PD-1/PD-L1 inhibitor. Thirty-three (36.3%) subjects had a history of central nervous system (CNS) metastasis, 20 (22.0%) subjects had a history of pneumonectomy, and 7 (7.7%) subjects had a history of pleural effusion. The specific mutations in Cohort 2 included: 85 (93.4%) subjects with a kinase domain mutation; 6 (6.6%) subjects with an extracellular domain mutation; none of the subjects had a transmembrane domain mutation.

At DCO 03-DEC-2021, in subjects with HER2-mutant NSCLC (Cohort 2), the primary efficacy endpoint of ORR by ICR was achieved in 54.9% (50/91 subjects; 95% CI: 44.2, 65.4), with 1 (1.1%) subject achieving confirmed CR and 49 (53.8%) achieving confirmed PR. The ORR by investigator assessment was achieved in 61.5% (56/91 subjects), with 3 (3.3%) subjects achieving confirmed CR and 53 (58.2%) achieving confirmed PR.

The median DoR based on ICR was 10.6 months (95% CI: 5.8, 17.7), 21 of 50 (42.0%) subjects were censored for the DoR analysis, including 8 of 50 (16.0%) subjects who were ongoing without an event. Of the 50 subjects with confirmed CR or PR, 26 (52.0%) subjects maintained a response with the observed DoR at ≥6 months and 17 (34.0%) subjects maintained a response with the observed DoR at ≥12 months.

The median PFS by ICR was 8.3 months (95% CI: 6.0, 11.9) and the median OS estimated by Kaplan-Meier method was 18.6 months (95% CI: 13.8, 25.8). The estimated 6-month and 12-month OS rates were 83.3% and 68.8%, respectively.

2.4.3. Discussion on clinical efficacy

This application is to extend the indication of Enhertu (trastuzumab deruxtecan, T-DXd) to include the treatment of unresectable or metastatic HER2-mutant NSCLC in patients who have received prior systemic therapy. The intended posology for this indication (5.4 mg/kg) is based on the primary analysis of ORR from phase II trial U206. Results from similar patient cohorts treated with T-DXd at 6.4 mg/kg from trials J101 and U204 were submitted as supportive evidence of efficacy.

Design and conduct of clinical studies

Study U206 is an ongoing partially blinded phase 2 study that randomised patients from the targeted population to T-DXd at 5.4 mg/kg or 6.4 mg/kg in a 2:1 ratio. The overall design of this trial is followed, noting that the two arms were different posologies of T-DXd, hence uncontrolled. Of note, both patients and investigators knew about treatment with T-DXd, the blinded portion was the dose. The rationale for randomisation is followed: Phase I J101 identified the two potential RP2D for T-DXd (5.4 and 6.4 mg/kg Q3W), and these were investigated in NSCLC patients in phase II U204, albeit the 5.4 mg/kg dose was only investigated in HER2-overexpressing patients. The paucity of data on Enhertu 5.4 mg/kg in HER2-mutant NSCLC patients prompted evaluation of this dose in another phase II trial, namely U206. Since no statistical hypothesis testing between both arms of U206 was considered and the dose proposed for marketing is 5.4 mg/kg, the assessment of efficacy results from this trial focuses on the T-DXd 5.4 mg/kg arm from U206. The study planned to randomise ~100 patients to the 5.4 mg/kg arm and ~50 to the 6.4 mg/kg arm.

The main limitation of the trial derives from its uncontrolled nature, hampering the ability to draw conclusions on clinical benefit in terms of the time-to-event endpoints PFS and OS. Further, the lack of a standard-of-care (SoC) control arm also results in uncertainty on the observed treatment effect as patient selection may have occurred, though in general, patients with HER2-mutant NSCLC seem to have a poorer prognosis than patients with non-oncogene-addicted NSCLC.

Results from the primary analysis, which occurred 9 months after the last subject was randomised and treated as per protocol, are presented and discussed in this report. The timing of the DCO (23-DEC-2022) was dependent on maturity of primary endpoint (confirmed ORR by BICR). This is endorsed since these results provide sufficiently mature of treatment effect from T-DXd 5.4 mg/kg in subjects with advanced HER2-mutant NSCLC.

Study participants: Patients with metastatic NSCLC whose tumours presented activating HER2 mutations documented in tissue via NGS, PCR or mass spectrometry (among others) in local laboratories could be enrolled in the trial. Central confirmation for the presence of such mutation was carried on some of the samples from the recruited patients, but since no conclusions of concordance can be drawn upon these limited data, the related SmPC statement on central confirmation of the biomarker has been removed (see further data on the concordance study below).

Inclusion of patients who had discontinued previous treatment because of toxicity (in addition to those who had discontinued because of progression) was added as of protocol V3, while recruitment was ongoing.

To appropriately reflect the inclusion/exclusion criteria from the targeted population, in particular in consideration of prior treatments (disease recurrence or progression during or after at least 1 regimen of prior anti-cancer therapy that must have contained platinum-based chemotherapy), and to align with similar indications in the oncogene-addicted NSCLC field, the MAH was requested to modify the originally sought therapeutic indication in section 4.1 of the SmPC. The following wording was agreed to better represent the population intended for treatment: *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*

The term "advanced" in therapeutic indications for oncogene-addicted NSCLC is understood to encompass patients with metastatic (stage IV) disease and locally advanced unresectable disease (i.e., stage IIIA/B/C) that for diverse reasons cannot receive concurrent chemoradiotherapy (1L approach) or have already received it and present locoregional –i.e., non-metastatic– progression (such as in this 2L+ setting), and would then be approached with systemic therapy *as if* metastatic. Acknowledging that performing a specific trial in such rare subgroup of incurable patients would face recruitment issues and would thus likely be unfeasible, and expecting similar benefits as their metastatic counterparts on account of the predictive potential from the biomarker, this extrapolation of benefit has been allowed in this specific oncogene-addicted setting for multiple products.

Treatments: The T-DXd schemes as proposed (5.4 or 6.4 mg/kg Q3W) in U206 were based on results from studies J101 and U204. Dose reduction schedule and dose modification approach for the dose intended for marketing in advanced HER2-mutant NSCLC (5.4 mg/kg Q3W) are appropriately described in section 4.2 of the SmPC. Duration of treatment (until disease progression or unacceptable toxicity) is also adequately described in sections 4.2 and 5.1.

Objectives/endpoints: The primary objective of U206 was to evaluate the antitumour activity of T-DXd as measured per confirmed ORR assessed by BICR. Assessment of images by blinded review partly mitigates the open-label nature of the trial, but concordance with investigator assessment is expected. Duration of response (DOR) was a secondary objective. Both ORR and DOR are considered appropriate endpoints to evaluate efficacy in this rare oncogene-addicted NSCLC setting, since spontaneous regression is not anticipated. However, considering the limitations from these endpoints, the results should be outstanding in relation to what can be achieved with approved existing therapeutic options.

Statistical methods: The differences in the IA SAP and main study SAP do not affect the calculations for the primary endpoints. The amended version of the main study SAP (V2, 13-FEB-2023) correctly defines the efficacy dataset as patients from the ITT, in comparison to the "Response Evaluable Set" (patients with measurable disease at baseline), as the previous version declared.

The MAH has reasonably demonstrated that no actions were taken on the final SAP based on the interim analysis. A series of sensitivity analyses on DOR were requested and their results are discussed under the results section. Regarding sample size, the choice of benchmark (ORR 26.4%), albeit stemming from an unselected (oncogene-agnostic) 2L+ NSCLC population, is regarded as relevant for the indication

pursued, noting a similar approach in other trials for advanced oncogene-addicted NSCLC in the 2L+ setting.

Recruitment and participant flow: Between March 2021 and March 2022 the trial completed recruitment (N=152), and data on ORR and DOR have been submitted with a DCO of 23-DEC-2022, which is considered sufficient follow-up to assess and confirm response. As expected in this advanced 2L+ NSCLC setting, about half the patients had discontinued treatment because of progressive disease. Of note, about a quarter of patients (27 out of 110 = 24.5%) discontinued treatment because of adverse events, with a slight predominance in the 6.4 mg/kg arm. 81% (50 out of 61) of patients who discontinued the study had died, whereas the rest withdrew voluntarily. 12 patients did not fulfil eligibility criteria and were registered as major protocol deviations.

Baseline data: HER2-mutant NSCLC is rare and predominantly occurs in a relatively younger, female predominant and non-smoker population, in nearly all cases with tumours of adenocarcinoma histology. In U206, the recruited population across arms corresponds to most expectations (median age 60 years, 65% women, 99% adenocarcinoma), albeit the proportion of former smokers (45%) was higher than anticipated. Of note, about two thirds of patients were recruited in Asia. Regarding specific disease characteristics, HER2 mutations occurred in the kinase domain and in exons 19/20 in nearly all patients. Two thirds of the patients had received 1 prior systemic treatment for advanced disease (2L setting) and the remaining, two or more lines (3L+ setting). All patients had received prior platinum-based treatment, 75% of patients had received prior anti-PD-1/PD-L1 therapy and 31% prior docetaxel. 37.5% of patients had a history of brain metastases at the time of enrolment. The reason for discontinuation of most recent prior therapy in 76% of patients was disease progression, while 5% had discontinued because of adverse events, and the rest for other reasons.

Efficacy data and additional analyses

At the final analysis (DCO 23-DEC.2022) and with median follow-up of 11.6 months for the ITT population (N=152), confirmed ORR as assessed by BICR was 49% in the T-DXd 5.4 mg/kg arm and 56% in the 6.4 mg/kg arm. Most of the responses were partial in nature. 5 subjects were considered non-evaluable (3 in the 5.4 mg/kg arm and 2 in the 6.4 mg/kg arm) because they discontinued T-DXd before the first post-baseline assessment, and there were no tumour scans after study treatment initiation. In any case, these patients are considered as non-responders. Median DoR was ~17 months for the 50 responders in the 5.4 mg/kg arm and it was not reached in the 6.4 mg/kg arm.

To understand the clinical background for this specific disease, it is noted that experience with other therapies in HER2-mutant NSCLC is limited and none of the HER2-directed products has a specific indication for lung cancer, even if several prospective trials showed a degree of antidisease activity: ORR 44% for T-DM1 (n=18, Li et al JCO 2018) and 29% for trastuzumab + pertuzumab + docetaxel (n=65, Mazieres et al JCO 2022).

Subgroup analysis of ORR-BICR in the 5.4 mg/kg arm does not show specific trends, noting similar response rates across diverse categories of age, gender, smoking status, race, presence of CNS metastases, region of the world and HER2 mutations. Noticeably, ORR was slightly higher in patients with CNS metastases (ORR 60%), than those without (ORR 43%). Although similar results were observed in arm 6.4 mg/kg, the smaller size of the subgroups seems to cause higher variability. Concerning patients with baseline CNS metastases, CNS response (as per brain imaging) was not systematically collected in the pivotal trial. Regarding asian and non-asian patients, ORR seems comparable across arms, although slight differences were observed for DOR. However, considering the small number of patients, results must be interpreted with caution.

Sensitivity analyses: ORR by investigator (INV) was numerically lower at 42%, noting concordance INV-BICR rate at ~80% for both 5.4 and 6.4 mg/kg arms. All the requested sensitivity analyses on DOR (treatment policy estimand, alternative censoring rules, combination of BICR and investigator assessments) resulted in a shorter mDOR, ranging from 7.1 to 11.9 months. It is, therefore, considered plausible that censoring for anticancer therapy and missed assessments resulted in an upward bias (overestimation) of the mDOR in the 5.4 mg/kg arm and that the median DoR is somewhere between 8 and 12 months, rather than the originally estimated 16.8 months.

Supportive results: Response rates in the T-DXd 6.4 mg/kg cohorts across trials U206, J101 and U204 are comparable to ORR in the pivotal 5.4 mg/kg cohort from U206. Of note, confirmed ORR by ICR in the 6.4 mg/kg pool (53.4%, 70 responders from 130 patients) is identical to that of the 5.4 mg/kg cohort. Responses in the 6.4 mg/kg cohorts seem durable, approaching 10 months in median.

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

Although response rate and duration of responses for T-DXd 5.4 mg/kg in advanced HER2-mutant NSCLC 2L+ from the uncontrolled study U206 are regarded as promising and have been confirmed with updated results, these endpoints are not surrogate endpoints for OS and PFS in HER2-mutant NSCLC, and thus the totality of currently available data are not considered comprehensive enough for a full approval in the new intended indication. The MAH will submit the results of Study DESTINY-Lung04 (a phase 3, open-label, randomised, controlled trial of T-DXd vs. standard-of-care immunochemotherapy in the first line treatment of patients with advanced HER2-mutant NSCLC) as a new specific obligation (SOB) by Q4 2025. The study started in October 2021 and is close to finishing recruitment (252 subjects enrolled up to July 2023, out of targeted sample size of 264), and it is therefore realistic that interpretable results of time-to-event endpoints in this biomarker-driven population will be eventually provided.

2.4.4. Conclusions on the clinical efficacy

Trastuzumab deruxtecan shows promising activity in terms of response rate in patients with advanced HER2-mutant NSCLC, a setting for which no HER2-targeted treatments hold an approved indication. Responses seem durable, but could be overestimated, as suggested by additional sensitivity analyses. The data supporting this extension of indication come from an uncontrolled trial and are not considered as comprehensive. However, the requirements for a conditional marketing authorisation are considered fulfilled for this extension of indication (See section on Additional consideration on the benefit-risk balance).

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 advanced NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy, the MAH should submit the results of the study DESTINY-Lung04, Open-label, Randomized, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Trastuzumab Deruxtecan as First-line Treatment of Unresectable, Locally Advanced, or Metastatic NSCLC Harboring HER2 Exon 19 or 20 Mutations.

2.5. Clinical safety

Introduction

Enhertu (T-DXd) as monotherapy is currently approved in the EU for advanced HER2+ BC 2L+, advanced HER2-low BC after chemotherapy and advanced HER2+ gastric/gastroesophageal cancer after an anti-HER2-based regimen.

The safety profile for T-DXd was determined in patients who received at least one dose of Enhertu 5.4 mg/kg (n = 573) across multiple tumour types in clinical studies. The median duration of treatment in this pool was 11.3 months (range: 0.7 to 37.9 months).

Safety datasets

To provide an analysis of the safety profile of T-DXd in HER2-mutant NSCLC, a review of the safety data was conducted in NSCLC subjects treated with T-DXd 5.4 mg/kg and 6.4 mg/kg doses from Studies J101, U204, and U206. The following pooled data were presented in the SCS:

- HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool, which includes 152 subjects with HER2-mutant NSCLC treated with T-DXd 6.4 mg/kg in Studies J101 (n = 11), U204 (n = 91), and U206 (n = 50)
- NSCLC T-DXd 5.4 mg/kg Pool, which includes 142 subjects with NSCLC (HER2-mutant or HER2-overexpressing) treated with T-DXd 5.4 mg/kg in Studies U204 (n = 41), and U206 (n = 101)
- NSCLC T-DXd 6.4 mg/kg Pool, which includes 208 subjects with NSCLC (HER2-mutant or HER2-overexpressing) treated with T-DXd 6.4 mg/kg in Studies J101 (n = 18), U204 (n = 140), and U206 (n = 50)

The applicant has also provided data from 2 safety pools that include subjects from several studies irrespective of tumor type.

- All Tumor Types T-DXd 5.4 mg/kg Pool, which includes 1045 subjects assigned to T-DXd 5.4 mg/kg across all tumor types. This pool included: Study J101: 91 subjects; Study U201: 184 subjects; Study U204: 41 subjects; Study U206: 101 subjects; Study U302: 257 subjects; Study U303: 371 subjects.
- All Tumor Types T DXd ≥5.4 mg/kg Pool, which includes 1741 subjects assigned to T DXd ≥5.4 mg/kg across all tumor types. This pool included: Study J101: 280 subjects; Study J202: 169 subjects; Study U201: 253 subjects; Study U204: 181 subjects; Study U205: 79 subjects; Study U206: 151 subjects; Study U302: 257 subjects; Study U303: 371 subjects.

The following table contains the trials included in this pool and the underlined highlighted subpopulations treated with T-DXd 5.4 mg/kg.

Table 42: Studies that constitute the All tumor types T-DXd 5.4 mg/kg Pool

Study Number Phase/Status[a]	Data Cut-off Date	Study Title	Number of Subjects Treated
DS8201-A-J101 Phase 1/Completed	01 Aug 2019	Phase 1, Two-Part, Multicenter, Non-Randomized, Open-Label, Multiple-Dose First-in-Human Study of DS-8201a in Subjects with Advanced Solid Malignant Tumors	Total: 280 subjects treated with T-DXd: • 91 subjects treated with T-DXd 5.4 mg/kg • 183 subjects treated with T-DXd 6.4 mg/kg (18 subjects with NSCLC [7 HER2-expressing and 11 HER2-mutant]) • 6 subjects treated with T-DXd 8.0 mg/kg

Study Number Phase/Status[a]	Data Cut-off Date	Study Title	Number of Subjects Treated
DS8201-A-U201 Phase 2/Completed	08 Jun 2020	A Phase 2, Multicenter, Open-Label Study of DS-8201a, an Anti-HER2-ADC for HER2-Positive, Unresectable and/or Metastatic Breast Cancer Subjects Previously Treated with T-DM1 (DESTINY-Breast01)	Total: 253 subjects treated with T-DXd: • 184 subjects treated with T-DXd 5.4 mg/kg • 48 subjects treated with T-DXd 6.4 mg/kg • 21 subjects treated with T-DXd 7.4 mg/kg
DS8201-A-U204 Phase 2/Completed	03 Dec 2021 DCO for SAE line listing: 19 Jun 2022	A Phase 2, Multicenter, Open-Label, 2-Cohort Study of T-DXd (DS-8201a), an Anti-HER2 ADC, for HER2-Overexpressing or -Mutated, Unresectable and/or Metastatic NSCLC (DESTINY-Lung01)	Total: 181 subjects treated with T-DXd: Subjects with HER2-overexpressing NSCLC: • 49 subjects treated with T-DXd 6.4 mg/kg (Cohort 1) • 41 subjects treated with T-DXd 5.4 mg/kg (Cohort 1a) Subjects with HER2-mutant NSCLC: • 91 subjects treated with T-DXd 6.4 mg/kg (Cohort 2)
DS8201-A-U206 Phase 2/Ongoing	24 Mar 2022 (IA) DCO for SAE line listing: 19 Jun 2022	A Phase 2, Multicenter, Randomized Study of T-DXd in Subjects with HER2-Mutated Metastatic NSCLC (DESTINY-Lung02)	Total: 151 subjects treated with T-DXd: • 101 subjects treated with T-DXd 5.4 mg/kg • 50 subjects treated with T-DXd 6.4 mg/kg
DS8201-A-U302 Phase 3/Completed	07 Sep 2021	A Phase 3, Multicenter, Randomized, Open-label, 2-arm, Active-controlled Study in Subjects with Unresectable and/or Metastatic HER2-positive BC previously Treated with Trastuzumab and a Taxane (DESTINY-Breast03)	Total: 518 subjects; 257 subjects treated with T-DXd: • 257 subjects treated with T-DXd 5.4 mg/kg • 261 subjects treated with T-DM1 3.6 mg/kg
DS8201-A-U303 Phase 3/Ongoing	11 Jan 2022	A Phase 3, Multicenter, Randomized, Open-label, Active-controlled Study of T-DXd (DS-8201a), an anti-HER2 ADC, versus TPC for HER2-low, unresectable and/or metastatic BC subjects (DESTINY-Breast04)	Total: 543 subjects; 371 subjects treated with T-DXd: • 371 subjects treated with T-DXd 5.4 mg/kg • 172 subjects treated with TPC 3.6 mg/kg

ADC = antibody-drug conjugate; AUC = area under the concentration-time curve; BC = breast cancer; DCO = data cut-off; DS-8201a = trastuzumab deruxtecan product code; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; IA = interim analysis; IV = intravenous; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; Q3W = every 3 weeks; SAE = serious adverse event; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice.

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

Notable differences in baseline characteristics between the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg group and the All Tumor Types T-DXd 5.4 mg/kg Pool were:

- A higher proportion of subjects with ECOG PS of 1 in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg group than in the All Tumor Types T-DXd 5.4 mg/kg Pool:
  - ECOG PS of 0: 30/101 (29.7%) subjects vs. 551/1045 (52.7%) subjects
  - ECOG PS of 1: 71/101 (70.3%) subjects vs. 493/1045 (47.2%) subjects

Patient exposure

Table 43: Summary of Exposure with Updated Study U206 Data (DCO 23 Dec 2022; Safety Analysis Set)

Parameter	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
Duration of treatment (months)[f]						
Mean	8.09	9.07	7.48	8.28	11.03	9.84
Std dev	5.077	6.847	5.064	6.792	7.509	7.465
Median	7.66	7.44	6.90	6.31	9.59	7.82
Min, max	0.7, 20.8	0.7, 33.8	0.7, 20.8	0.7, 33.8	0.7, 37.9	0.7, 41.0
Duration of treatment category (months)[f], n (%)						
0 to ≤3	22 (21.8)	35 (23.0)	40 (28.2)	59 (28.4)	167 (16.0)	366 (21.0)
>3 to ≤6	20 (19.8)	29 (19.1)	26 (18.3)	41 (19.7)	175 (16.7)	335 (19.2)
>6 to ≤9	17 (16.8)	26 (17.1)	24 (16.9)	34 (16.3)	165 (15.8)	283 (16.3)
>9 to ≤12	16 (15.8)	17 (11.2)	21 (14.8)	20 (9.6)	122 (11.7)	184 (10.6)
>12 to ≤18	22 (21.8)	26 (17.1)	27 (19.0)	31 (14.9)	192 (18.4)	280 (16.1)
>18 to ≤24	4 (4.0)	16 (10.5)	4 (2.8)	18 (8.7)	167 (16.0)	203 (11.7)
>24	0	3 (2.0)	0	5 (2.4)	57 (5.5)	90 (5.2)
≥12	26 (25.7)	45 (29.6)	31 (21.8)	54 (26.0)	416 (39.8)	573 (32.9)
Cumulative dose (mg/kg)[g]						
Mean	58.877	72.978	54.508	66.561	78.285	72.818
Std dev	37.5824	53.7331	37.5777	53.9622	52.7402	53.5967
Median	54.998	57.820	48.600	49.923	69.048	59.414
Min, max	5.40, 162.28	6.23, 274.08	5.40, 162.28	6.23, 274.08	5.30, 262.70	5.30, 274.08
Number of cycles						
Mean	11.2	12.3	10.3	11.2	15.1	13.4
Std dev	7.05	9.38	7.06	9.27	10.22	10.10
Median	10.0	10.0	10.0	8.0	13.0	11.0
Min, max	1, 30	1, 47	1, 30	1, 47	1, 51	1, 53
Dose intensity (mg/kg/3 weeks)[h]						
Mean	5.071	5.706	5.085	5.736	5.036	5.330
Std dev	0.4894	0.6718	0.5085	0.7168	0.8370	0.8895
Median	5.254	5.833	5.275	5.922	5.221	5.355
Min, max	2.87, 5.80	3.76, 6.87	2.81, 5.80	3.54, 6.99	2.50, 22.68	2.50, 22.68
Relative dose intensity[i], n (%)						
≥90%	78 (77.2)	82 (53.9)	111 (78.2)	118 (56.7)	935 (89.5)	1325 (76.1)
<90% to ≥80%	16 (15.8)	39 (25.7)	21 (14.8)	49 (23.6)	60 (5.7)	235 (13.5)
<80% to ≥60%	6 (5.9)	30 (19.7)	8 (5.6)	38 (18.3)	41 (3.9)	160 (9.2)
<60%	1 (1.0)	1 (0.7)	2 (1.4)	3 (1.4)	9 (0.9)	21 (1.2)

DCO = data cut-off; HER2-mut = human epidermal growth factor receptor 2 mutated; max = maximum; min = minimum; NSCLC = non-small cell lung cancer; Std dev = standard deviation; T-DXd = trastuzumab deruxtecan

[a] Includes 11 subjects from Study J101, 91 subjects from Study U204, and 50 subjects from Study U206.

[b] Includes 41 subjects with HER2-overexpressing NSCLC from Study U204 and 101 subjects with HER2-mutant NSCLC from Study U206.

[c] Includes 11 subjects with HER2-mutant and 7 subjects with HER2-expressing NSCLC from Study J101, 91 subjects with HER2-mutant and 49 subjects with HER2-overexpressing NSCLC from Study U204, and 50 subjects with HER2-mutant NSCLC from Study U206.

[d] Includes 91 subjects from Study J101, 184 subjects from Study U201, 41 subjects from Study U204, 101 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

[e] Includes 280 subjects from Study J101, 169 subjects from Study J202, 253 subjects from Study U201, 181 subjects from Study U204, 79 subjects from Study U205, 151 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

[f] Duration of treatment (months) = (date of the last dose – date of the first dose + 21) ÷ 30.44; 1 month = 365.25 ÷ 12 = 30.44 days.

[g] Cumulative dose (mg/kg) = sum of actual dose level received (mg/kg).

[h] Dose intensity = cumulative dose ÷ (duration of treatment [days] ÷ 21).

[i] Relative dose intensity (%) = dose intensity ÷ assigned dose level (mg/kg/3 weeks) x 100.

Data are included as of data cut-off of 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study U201, 03 Dec 2021 for Study U204, 09 Apr 2021 for Study U205, 23 Dec 2022 for Study U206, 07 Sep 2021 for Study U302, and 11 Jan 2022 for Study U303.

Adverse events

Table 44: Grouped Terms for Adverse Events

Grouped Term	Selected MedDRA Preferred Terms
Abdominal pain	abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain
Anemia	anaemia, haemoglobin decreased, haematocrit decreased, red blood cell count decreased
Blood bilirubin increased	blood bilirubin increased, hyperbilirubinaemia, bilirubin conjugated increased, blood bilirubin unconjugated increased
Blood potassium decreased	hypokalaemia, blood potassium decreased
Fatigue	fatigue, asthenia, malaise, lethargy
Headache	headache, migraine, sinus headache
Leukopenia	leukopenia, white blood cell count decreased
Lymphopenia	lymphopenia, lymphocyte count decreased
Musculoskeletal pain	back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, neck pain, musculoskeletal chest pain, limb discomfort
Neutropenia	neutropenia, neutrophil count decreased
Rash	rash, rash pustular, rash maculo-papular, rash papular, rash macular, rash pruritic
Skin hyperpigmentation	skin hyperpigmentation, skin discolouration, pigmentation disorder
Stomatitis	stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, oral mucosal blistering, oral mucosal eruption
Thrombocytopenia	thrombocytopenia, platelet count decreased
Transaminases increased	transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal, liver function test increased
Upper respiratory tract infection	upper respiratory tract infection, influenza, influenza-like illness, nasopharyngitis, pharyngitis, sinusitis, rhinitis, laryngitis
Vision blurred	vision blurred, visual impairment

MedDRA = Medical Dictionary for Regulatory Activities, version 24.1

Overview of treatment-emergent AEs:

Table 45: Overview of Treatment-emergent Adverse Events with Updated Study U206 Data (DCO 23 Dec 2022; Safety Analysis Set)

Parameter	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
Treatment duration (months)						
Mean	8.09	9.07	7.48	8.28	11.03	9.84
Std dev	5.077	6.847	5.064	6.792	7.509	7.465
Median	7.66	7.44	6.90	6.31	9.59	7.82
Min, max	0.7, 20.8	0.7, 33.8	0.7, 20.8	0.7, 33.8	0.7, 37.9	0.7, 41.0

Parameter	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
Adverse events, n (%)						
Subjects with any TEAE	101 (100.0)	152 (100.0)	142 (100.0)	208 (100.0)	1040 (99.5)	1736 (99.7)
TEAEs with CTCAE ≥Grade 3	53 (52.5)	104 (68.4)	74 (52.1)	147 (70.7)	563 (53.9)	1063 (61.1)
TE SAEs	37 (36.6)	60 (39.5)	53 (37.3)	88 (42.3)	279 (26.7)	543 (31.2)
TE SAEs with CTCAE ≥Grade 3	28 (27.7)	53 (34.9)	42 (29.6)	78 (37.5)	215 (20.6)	444 (25.5)
TEAEs associated with study drug discontinuation	15 (14.9)	49 (32.2)	22 (15.5)	65 (31.3)	165 (15.8)	335 (19.2)
TEAEs associated with dose reduction	18 (17.8)	53 (34.9)	25 (17.6)	71 (34.1)	225 (21.5)	454 (26.1)
TEAEs associated with study drug interruption	45 (44.6)	82 (53.9)	55 (38.7)	108 (51.9)	434 (41.5)	771 (44.3)
TEAEs associated with an outcome of death	6 (5.9)	15 (9.9)	13 (9.2)	26 (12.5)	45 (4.3)	105 (6.0)
Subjects with drug-related TEAEs	97 (96.0)	149 (98.0)	135 (95.1)	200 (96.2)	1016 (97.2)	1695 (97.4)
Drug-related TEAEs with CTCAE ≥Grade 3	39 (38.6)	78 (51.3)	48 (33.8)	107 (51.4)	453 (43.3)	851 (48.9)
Drug-related TE SAEs	14 (13.9)	31 (20.4)	17 (12.0)	42 (20.2)	130 (12.4)	259 (14.9)
Drug-related TE SAEs with CTCAE ≥Grade 3	9 (8.9)	22 (14.5)	11 (7.7)	30 (14.4)	84 (8.0)	180 (10.3)
Drug-related TEAEs associated with study drug discontinuation	14 (13.9)	35 (23.0)	17 (12.0)	46 (22.1)	150 (14.4)	282 (16.2)
Drug-related TEAEs associated with dose reduction	17 (16.8)	52 (34.2)	24 (16.9)	69 (33.2)	209 (20.0)	427 (24.5)
Drug-related TEAEs associated with study drug interruption	27 (26.7)	58 (38.2)	31 (21.8)	77 (37.0)	322 (30.8)	579 (33.3)
Drug-related TEAEs associated with an outcome of death	1 (1.0)	2 (1.3)	1 (0.7)	4 (1.9)	12 (1.1)	25 (1.4)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events, version 5.0; DCO = data cut-off; HER2-mut = human epidermal growth factor receptor 2 mutated; max = maximum; min = minimum; NSCLC = non-small cell lung cancer; SAE = serious adverse event; Std dev = standard deviation; T-DXd = trastuzumab deruxtecan; TE = treatment-emergent; TEAE = treatment-emergent adverse event

[a] Includes 11 subjects from Study J101, 91 subjects from Study U204, and 50 subjects from Study U206.

[b] Includes 41 subjects with HER2-overexpressing NSCLC from Study U204 and 101 subjects with HER2-mutant NSCLC from Study U206.

[c] Includes 11 subjects with HER2-mutant and 7 subjects with HER2-expressing NSCLC from Study J101, 91 subjects with HER2-mutant and 49 subjects with HER2-overexpressing NSCLC from Study U204, and 50 subjects with HER2-mutant NSCLC from Study U206.

[d] Includes 91 subjects from Study J101, 184 subjects from Study U201, 41 subjects from Study U204, 101 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

[e] Includes 280 subjects from Study J101, 169 subjects from Study J202, 253 subjects from Study U201, 181 subjects from Study U204, 79 subjects from Study U205, 151 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.
Notes: A TEAE was defined as an AE that occurred, having been absent before the first dose of study drug, or had worsened in severity or seriousness after the initiation of the study drug until 47 days (for all studies except Study J101 [28 days]) after the last dose of study drug. SAEs with an onset or worsening 48 days (29 days for Study J101) or more after the last dose of study drug, if considered related to the study drug, were also TEAEs. If relationship was missing, the TEAE was also considered to be related to the study drug. If a subject had both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade was treated as the lowest severity grade. Percentages were calculated using the number of subjects in each treatment group as the denominator.
Data are included as of data cut-off of 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study 201, 03 Dec 2021 for Study U204, 09 Apr 2021 for Study U205, 23 Dec 2022 for Study U206, 07 Sep 2021 for Study U302, and 11 Jan 2022 for Study U303. (U206 DCO 23 Dec 2022)

Common AEs

Table 46: Treatment-emergent Adverse Events in ≥10% of Subjects from Study U206 with HER2-mutant NSCLC at T-DXd 5.4 mg/kg by Preferred Term or Grouped Term with Updated Study U206 Data (DCO 23 Dec 2022; Safety Analysis Set)

MedDRA Preferred Term or Grouped Term	Number (%) of Subjects					
	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
Subjects with Any TEAE	101 (100.0)	152 (100.0)	142 (100.0)	208 (100.0)	1040 (99.5)	1736 (99.7)
Nausea	68 (67.3)	119 (78.3)	98 (69.0)	154 (74.0)	793 (75.9)	1292 (74.2)
Fatigue[f]	45 (44.6)	86 (56.6)	74 (52.1)	120 (57.7)	577 (55.2)	986 (56.6)
Neutropenia[f]	43 (42.6)	66 (43.4)	47 (33.1)	82 (39.4)	368 (35.2)	675 (38.8)
Decreased appetite	40 (39.6)	63 (41.4)	59 (41.5)	91 (43.8)	352 (33.7)	718 (41.2)
Anemia[f]	37 (36.6)	65 (42.8)	48 (33.8)	79 (38.0)	369 (35.3)	677 (38.9)
Constipation	37 (36.6)	57 (37.5)	47 (33.1)	73 (35.1)	361 (34.5)	587 (33.7)
Vomiting	32 (31.7)	71 (46.7)	45 (31.7)	91 (43.8)	454 (43.4)	728 (41.8)
Leukopenia[f]	29 (28.7)	43 (28.3)	31 (21.8)	51 (24.5)	258 (24.7)	465 (26.7)
Thrombocytopenia[f]	28 (27.7)	33 (21.7)	31 (21.8)	44 (21.2)	257 (24.6)	473 (27.2)
Diarrhoea	23 (22.8)	59 (38.8)	38 (26.8)	75 (36.1)	301 (28.8)	548 (31.5)
Alopecia	22 (21.8)	64 (42.1)	27 (19.0)	78 (37.5)	391 (37.4)	639 (36.7)
Transaminases increased[f]	22 (21.8)	37 (24.3)	27 (19.0)	45 (21.6)	286 (27.4)	455 (26.1)
Musculoskeletal pain[f]	17 (16.8)	38 (25.0)	28 (19.7)	47 (22.6)	269 (25.7)	405 (23.3)
Stomatitis[f]	16 (15.8)	13 (8.6)	18 (12.7)	20 (9.6)	161 (15.4)	264 (15.2)
COVID-19	14 (13.9)	9 (5.9)	14 (9.9)	10 (4.8)	27 (2.6)	41 (2.4)
Dizziness	13 (12.9)	12 (7.9)	16 (11.3)	23 (11.1)	111 (10.6)	166 (9.5)
Hypokalemia[f]	13 (12.9)	19 (12.5)	16 (11.3)	28 (13.5)	128 (12.2)	217 (12.5)
Pyrexia	13 (12.9)	23 (15.1)	17 (12.0)	24 (11.5)	127 (12.2)	261 (15.0)
Weight decreased	11 (10.9)	32 (21.1)	19 (13.4)	45 (21.6)	150 (14.4)	288 (16.5)

AE = adverse event; COVID-19 = coronavirus disease 2019; DCO = data cut-off; HER2-mut = human epidermal growth factor receptor 2 mutated; MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer;
SAE = serious adverse event; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event
[a] Includes 11 subjects from Study J101, 91 subjects from Study U204, and 50 subjects from Study U206.
[b] Includes 41 subjects with HER2-overexpressing NSCLC from Study U204 and 101 subjects with HER2-mutant NSCLC from Study U206.
[c] Includes 11 subjects with HER2-mutant and 7 subjects with HER2-expressing NSCLC from Study J101, 91 subjects with HER2-mutant and 49 subjects with HER2-overexpressing NSCLC from Study U204, and 50 subjects with HER2-mutant NSCLC from Study U206.
[d] Includes 91 subjects from Study J101, 184 subjects from Study U201, 41 subjects from Study U204, 101 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.
[e] Includes 280 subjects from Study J101, 169 subjects from Study J202, 253 subjects from Study U201, 181 subjects from Study U204, 79 subjects from Study U205, 151 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.
[f] Group terms.
A TEAE was defined as an AE that occurred, having been absent before the first dose of study drug, or had worsened in severity or seriousness after the initiation of the study drug until 47 days (for all studies except Study J101 [28 days]) after the last dose of study drug.
Common TEAEs were defined as ≥10% of subjects from Study U206 with HER2-mutant NSCLC at T-DXd 5.4 mg/kg.
If a subject had multiple preferred terms or grouped terms, the subject was counted in each of those different terms. If a subject had multiple occurrences of the same grouped term or preferred term, the subject was counted once for that specific term.

Percentages were calculated using the number of subjects in each treatment group as the denominator.
Preferred terms/grouped terms were sorted by descending frequency in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg column.
Data are included as of data cut-off of 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study 201, 03 Dec 2021 for Study U204, 09 Apr 2021 for Study U205, 23 Dec 2022 for Study U206, 07 Sep 2021 for Study U302, and 11 Jan 2022 for Study U303.

Treatment-related AEs

Table 47: Drug-related Treatment-emergent Adverse Events by Preferred Term or Grouped Term Reported for ≥5% of Subjects from Study U206 with HER2-mutant NSCLC at T-DXd 5.4 mg/kg with Updated Study U206 Data (DCO 23 Dec 2022; Safety Analysis Set)

MedDRA Preferred Term or Grouped Term	Number (%) of Subjects					
	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
Subjects with Any Drug-related TEAE	97 (96.0)	149 (98.0)	135 (95.1)	200 (96.2)	1016 (97.2)	1695 (97.4)
Nausea	66 (65.3)	113 (74.3)	96 (67.6)	146 (70.2)	765 (73.2)	1236 (71.0)
Neutropenia[f]	43 (42.6)	66 (43.4)	47 (33.1)	81 (38.9)	361 (34.5)	665 (38.2)
Fatigue[f]	37 (36.6)	76 (50.0)	57 (40.1)	105 (50.5)	511 (48.9)	883 (50.7)
Decreased appetite	36 (35.6)	55 (36.2)	48 (33.8)	79 (38.0)	314 (30.0)	641 (36.8)
Anemia[f]	34 (33.7)	55 (36.2)	44 (31.0)	63 (30.3)	326 (31.2)	567 (32.6)
Vomiting	29 (28.7)	64 (42.1)	41 (28.9)	81 (38.9)	392 (37.5)	628 (36.1)
Constipation	28 (27.7)	36 (23.7)	34 (23.9)	46 (22.1)	225 (21.5)	365 (21.0)
Leukopenia[f]	28 (27.7)	41 (27.0)	30 (21.1)	48 (23.1)	251 (24.0)	454 (26.1)
Thrombocytopenia[f]	25 (24.8)	33 (21.7)	28 (19.7)	43 (20.7)	243 (23.3)	453 (26.0)
Alopecia	21 (20.8)	64 (42.1)	26 (18.3)	78 (37.5)	377 (36.1)	619 (35.6)
Diarrhoea	20 (19.8)	44 (28.9)	31 (21.8)	58 (27.9)	242 (23.2)	437 (25.1)
Transaminases increased[f]	19 (18.8)	28 (18.4)	23 (16.2)	35 (16.8)	228 (21.8)	353 (20.3)
Stomatitis[f]	15 (14.9)	11 (7.2)	16 (11.3)	18 (8.7)	142 (13.6)	237 (13.6)
Interstitial lung disease (adjudicated drug-related)[g]	13 (12.9)	41 (27.0)	15 (10.6)	53 (25.5)	128 (12.2)	255 (14.6)
Dyspepsia	6 (5.9)	7 (4.6)	7 (4.9)	7 (3.4)	78 (7.5)	102 (5.9)
Lymphopenia[f]	6 (5.9)	12 (7.9)	7 (4.9)	17 (8.2)	86 (8.2)	163 (9.4)
Weight decreased	6 (5.9)	19 (12.5)	9 (6.3)	26 (12.5)	106 (10.1)	185 (10.6)
Abdominal pain[f]	5 (5.0)	11 (7.2)	7 (4.9)	13 (6.3)	115 (11.0)	151 (8.7)
Hypokalemia[f]	5 (5.0)	8 (5.3)	5 (3.5)	9 (4.3)	70 (6.7)	114 (6.5)

AE = adverse event; DCO = data cut-off; HER2-mut = human epidermal growth factor receptor 2 mutated; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; PT = preferred term; SAE = serious adverse event; SMQ = standardised MedDRA query; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event

[a] Includes 11 subjects from Study J101, 91 subjects from Study U204, and 50 subjects from Study U206.
[b] Includes 41 subjects with HER2-overexpressing NSCLC from Study U204 and 101 subjects with HER2-mutant NSCLC from Study U206.
[c] Includes 11 subjects with HER2-mutant and 7 subjects with HER2-expressing NSCLC from Study J101, 91 subjects with HER2-mutant and 49 subjects with HER2-overexpressing NSCLC from Study U204, and 50 subjects with HER2-mutant NSCLC from Study U206.
[d] Includes 91 subjects from Study J101, 184 subjects from Study U201, 41 subjects from Study U204, 101 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.
[e] Includes 280 subjects from Study J101, 169 subjects from Study J202, 253 subjects from Study U201, 181 subjects from Study U204, 79 subjects from Study U205, 151 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.
[f] Group terms.
[g] Interstitial lung disease includes events that were adjudicated as ILD and considered study drug related by the ILD Adjudication Committee (includes cases of potential ILD/pneumonitis, based on MedDRA for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure).

Notes: A TEAE was defined as an AE that occurred, having been absent before the first dose of study drug, or had worsened in severity or seriousness after the initiation of the study drug until 47 days (for all studies except Study J101 [28 days]) after the last dose of study drug.

Any SAEs with an onset or worsening 48 days (29 days for Study J101) or more after the last dose of study drug, if considered related to the study drug, were also TEAEs.
If a subject had multiple PTs or grouped terms, the subject was counted in each of those terms. If a subject had multiple occurrences of the same grouped term or PT, the subject was counted once for that term.
If relationship was missing, the TEAE was considered to be related to the study drug.
Percentages were calculated using the number of subjects in each treatment group as the denominator.
Preferred terms/grouped terms were sorted by descending frequency in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg column.
Data are included as of data cut-off of 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study 201, 03 Dec 2021 for Study U204, 09 Apr 2021 for Study U205, 23 Dec 2022 for Study U206, 07 Sep 2021 for Study U302, and 11 Jan 2022 for Study U303.

High-grade (≥G3) treatment-emergent AEs

Table 48: Treatment-emergent Adverse Events of CTCAE Grade ≥3 by Preferred Term or Grouped Term Reported for ≥5% of Subjects from Study U206 with HER2-mutant NSCLC at T-DXd 5.4 mg/kg with Updated Study U206 Data (DCO 23 Dec 2022; Safety Analysis Set)

MedDRA Preferred Term or Grouped Term	Number (%) of Subjects					
	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
Subjects with Any TEAE with CTCAE Grade ≥3	53 (52.5)	104 (68.4)	74 (52.1)	147 (70.7)	563 (53.9)	1063 (61.1)
Neutropenia[f]	19 (18.8)	37 (24.3)	19 (13.4)	50 (24.0)	173 (16.6)	373 (21.4)
Anemia[f]	11 (10.9)	20 (13.2)	14 (9.9)	24 (11.5)	99 (9.5)	255 (14.6)
Fatigue[f]	8 (7.9)	11 (7.2)	11 (7.7)	18 (8.7)	79 (7.6)	142 (8.2)
Hypokalemia[f]	7 (6.9)	4 (2.6)	9 (6.3)	6 (2.9)	40 (3.8)	70 (4.0)
Thrombocytopenia[f]	6 (5.9)	10 (6.6)	6 (4.2)	12 (5.8)	62 (5.9)	128 (7.4)
Leukopenia[f]	5 (5.0)	13 (8.6)	5 (3.5)	16 (7.7)	64 (6.1)	156 (9.0)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; DCO = data cut-off; HER2-mut = human epidermal growth factor receptor 2 mutated; MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; SAE = serious adverse event; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event
[a] Includes 11 subjects from Study J101, 91 subjects from Study U204, and 50 subjects from Study U206.
[b] Includes 41 subjects with HER2-overexpressing NSCLC from Study U204 and 101 subjects with HER2-mutant NSCLC from Study U206.
[c] Includes 11 subjects with HER2-mutant and 7 subjects with HER2-expressing NSCLC from Study J101, 91 subjects with HER2-mutant and 49 subjects with HER2-overexpressing NSCLC from Study U204, and 50 subjects with HER2-mutant NSCLC from Study U206.
[d] Includes 91 subjects from Study J101, 184 subjects from Study U201, 41 subjects from Study U204, 101 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.
[e] Includes 280 subjects from Study J101, 169 subjects from Study J202, 253 subjects from Study U201, 181 subjects from Study U204, 79 subjects from Study U205, 151 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.
[f] Group terms.
Notes: A TEAE was defined as an AE that occurred, having been absent before the first dose of study drug, or had worsened in severity or seriousness after the initiation of the study drug until 47 days (for all studies except Study J101 [28 days]) after the last dose of study drug.
SAEs with an onset or worsening 48 days (29 days for Study J101) or more after the last dose of study drug, if considered related to the study drug, were also TEAEs.
If a subject had multiple preferred terms or grouped terms, the subject was counted in each of those terms. If a subject had multiple occurrences of the same grouped term or preferred term, the subject was counted once for that term using the worst grade.
If a subject had both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade was treated as the lowest severity grade.
Percentages were calculated using the number of subjects in each treatment group as the denominator.
Preferred terms/grouped terms were sorted by descending frequency in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg column.
Data are included as of data cut-off of 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study 201, 03 Dec 2021 for Study U204, 09 Apr 2021 for Study U205, 23 Dec 2022 for Study U206, 07 Sep 2021 for Study U302, and 11 Jan 2022 for Study U303.

Adverse events of special interest (AESIs)

At the beginning of the T-DXd clinical program, AESIs included ILD, left ventricular ejection fraction (LVEF) decrease, QT prolongation, and IRR. On 09 Jul 2019, based on the comprehensive review of the safety data, and taking into consideration biological plausibility, QT prolongation and IRR were no longer considered AESIs for the T-DXd clinical program. In addition, on 06 Apr 2020, "left ventricular ejection

fraction decreased" was renamed to "left ventricular (LV) dysfunction" to reflect that this is a clinical concept rather than a laboratory finding.

Table 49: Selected Preferred Terms in Adverse Events of Special Interest

Category	Selected Preferred Terms for Review
ILD/pneumonitis	Events of potential ILD/pneumonitis from PTs triggering adjudication, based on the current study MedDRA version for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure. ILD was summarized based on the ILD adjudicated outcomes as per the ILD AC Charter
Left ventricular dysfunction	Acute left ventricular failure Acute right ventricular failure Cardiac failure Cardiac failure acute Cardiac failure chronic Cardiac failure congestive Chronic left ventricular failure Chronic right ventricular failure Ejection fraction decreased Left ventricular dysfunction Left ventricular failure Right ventricular failure Ventricular failure

AC = Adjudication Committee; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SMQ = standardised MedDRA query.

Interstitial lung disease events:

Table 50: Interstitial Lung Disease Events by CTCAE Grade Adjudicated by the Interstitial Lung Disease Adjudication Committee with Updated Study U206 Data (DCO 23 Dec 2022; Safety Analysis Set)

CTCAE Grade Reported by Adjudication Committee[a]	Number (%) of Subjects					
	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[b] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[c] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[d] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[e] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[f] (N = 1741)
Subjects with any AE adjudicated as ILD	13 (12.9)	41 (27.0)	15 (10.6)	53 (25.5)	133 (12.7)	265 (15.2)
Grade 1	4 (4.0)	8 (5.3)	4 (2.8)	11 (5.3)	32 (3.1)	70 (4.0)
Grade 2	7 (6.9)	25 (16.4)	8 (5.6)	30 (14.4)	76 (7.3)	143 (8.2)
Grade 3	1 (1.0)	5 (3.3)	1 (0.7)	5 (2.4)	10 (1.0)	21 (1.2)
Grade 4	0	0	0	0	1 (0.1)	2 (0.1)
Grade 5	1 (1.0)	3 (2.0)	2 (1.4)	7 (3.4)	14 (1.3)	29 (1.7)
≥Grade 3	2 (2.0)	8 (5.3)	3 (2.1)	12 (5.8)	25 (2.4)	52 (3.0)
Subjects with any AE adjudicated as drug-related ILD	13 (12.9)	41 (27.0)	15 (10.6)	53 (25.5)	128 (12.2)	255 (14.6)
Grade 1	4 (4.0)	8 (5.3)	4 (2.8)	11 (5.3)	32 (3.1)	67 (3.8)
Grade 2	7 (6.9)	25 (16.4)	8 (5.6)	30 (14.4)	74 (7.1)	140 (8.0)
Grade 3	1 (1.0)	5 (3.3)	1 (0.7)	5 (2.4)	10 (1.0)	20 (1.1)
Grade 4	0	0	0	0	0	1 (0.1)
Grade 5	1 (1.0)	3 (2.0)	2 (1.4)	7 (3.4)	12 (1.1)	27 (1.6)
≥Grade 3	2 (2.0)	8 (5.3)	3 (2.1)	12 (5.8)	22 (2.1)	48 (2.8)
Subjects with any AE adjudicated as not drug-related ILD	0	0	0	0	5 (0.5)	10 (0.6)
Grade 1	0	0	0	0	0	3 (0.2)
Grade 2	0	0	0	0	3 (0.3)	4 (0.2)

CTCAE Grade Reported by Adjudication Committee[a]	Number (%) of Subjects					
	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[b] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[c] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[d] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[e] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[f] (N = 1741)
Grade 3	0	0	0	0	0	1 (0.1)
Grade 4	0	0	0	0	0	0
Grade 5	0	0	0	0	2 (0.2)	2 (0.1)
≥Grade 3	0	0	0	0	2 (0.2)	3 (0.2)
Adjudicated as not ILD	4 (4.0)	2 (1.3)	5 (3.5)	4 (1.9)	30 (2.9)	46 (2.6)
Pending adjudication[a]	0	0	0	0	5 (0.5)	6 (0.3)
Grade 1	0	0	0	0	2 (0.2)	3 (0.2)
Grade 2	0	0	0	0	2 (0.2)	2 (0.1)
Grade 3	0	0	0	0	1 (0.1)	1 (0.1)
Grade 4	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0
≥Grade 3	0	0	0	0	1 (0.1)	1 (0.1)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events, version 5.0; DCO = data cut-off; HER2-mut = human epidermal growth factor receptor 2 mutated; ILD = interstitial lung disease; NSCLC = non-small cell lung cancer; T-DXd = trastuzumab deruxtecan

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

[b] Includes 11 subjects from Study J101, 91 subjects from Study U204, and 50 subjects from Study U206.

[c] Includes 41 subjects with HER2-overexpressing NSCLC from Study U204 and 101 subjects with HER2-mutant NSCLC from Study U206.

[d] Includes 11 subjects with HER2-mutant and 7 subjects with HER2-expressing NSCLC from Study J101, 91 subjects with HER2-mutant and 49 subjects with HER2-overexpressing NSCLC from Study U204, and 50 subjects with HER2-mutant NSCLC from Study U206.

[e] Includes 91 subjects from Study J101, 184 subjects from Study U201, 41 subjects from Study U204, 101 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

[f] Includes 280 subjects from Study J101, 169 subjects from Study J202, 253 subjects from Study U201, 181 subjects from Study U204, 79 subjects from Study U205, 151 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

Notes: Each subject was counted only in 1 of the summary blocks. For subjects having ILD cases across multiple summary blocks, the subject was counted in the block according to the preceding order presented in the table.

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

Percentages of ILD grades were calculated using the number of subjects with each treatment group with non-missing investigator-reported ILD grade as the denominator.

This table includes all events that were submitted to the ILD Adjudication Committee for adjudication.

Data are included as of data cut-off of 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study 201, 03 Dec 2021 for Study U204, 09 Apr 2021 for Study U205, 23 Dec 2022 for Study U206, 07 Sep 2021 for Study U302, and 11 Jan 2022 for Study U303.

Table 51: Overview of Adjudicated Drug-related Interstitial Lung Disease Events with Updated Study U206 Data (DCO 23 Dec 2022; Safety Analysis Set)

CTCAE Grade Reported by Adjudication Committee	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
Subjects with any event adjudicated as drug-related ILD, n (%)	13 (12.9)	41 (27.0)	15 (10.6)	53 (25.5)	128 (12.2)	255 (14.6)
ILD ≥Grade 3	2 (2.0)	8 (5.3)	3 (2.1)	12 (5.8)	22 (2.1)	48 (2.8)
Serious ILD	4 (4.0)	13 (8.6)	5 (3.5)	18 (8.7)	41 (3.9)	82 (4.7)
ILD associated with dose reduction	0	2 (1.3)	0	2 (1.0)	8 (0.8)	11 (0.6)
ILD associated with study drug interruption	5 (5.0)	15 (9.9)	5 (3.5)	17 (8.2)	31 (3.0)	63 (3.6)
ILD associated with study drug discontinuation	10 (9.9)	25 (16.4)	11 (7.7)	35 (16.8)	90 (8.6)	182 (10.5)
Median (range) time to first ILD adjudicated as drug-related ILD onset date (days)[f]	88.0 (40, 421)	125.0 (14, 461)	80.0 (40, 421)	124.0 (-16, 461)	162.0 (26, 710)	134.0 (-16, 710)
Median[g,h] (range) duration of first adjudicated drug-related ILD (days)	67.0 (22.0, 86.0)	43.0 (29.0, 94.0)	67.0 (22.0, 86.0)	41.0 (31.0, 94.0)	66.0 (40.0, 86.0)	78.0 (50.0, 111.0)

CTCAE = Common Terminology Criteria for Adverse Events, version 5.0; DCO = data cut-off; HER2-mut = human epidermal growth factor receptor 2 mutated; ILD = interstitial lung disease; NSCLC = non-small cell lung cancer; T-DXd = trastuzumab deruxtecan

[a] Includes 11 subjects from Study J101, 91 subjects from Study U204, and 50 subjects from Study U206.

[b] Includes 41 subjects with HER2-overexpressing NSCLC from Study U204 and 101 subjects with HER2-mutant NSCLC from Study U206.

[c] Includes 11 subjects with HER2-mutant and 7 subjects with HER2-expressing NSCLC from Study J101, 91 subjects with HER2-mutant and 49 subjects with HER2-overexpressing NSCLC from Study U204, and 50 subjects with HER2-mutant NSCLC from Study U206.

[d] Includes 91 subjects from Study J101, 184 subjects from Study U201, 41 subjects from Study U204, 101 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

[e] Includes 280 subjects from Study J101, 169 subjects from Study J202, 253 subjects from Study U201, 181 subjects from Study U204, 79 subjects from Study U205, 151 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

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

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

[h] Median was based on Kaplan-Meier estimate.

Notes: Adjudicated drug-related ILD includes ILD events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as both ILD and related to T-DXd by the ILD Adjudication Committee; adjudicated drug-related ILD was summarized based on the ILD adjudicated outcomes (CTCAE grade, drug-related) by the ILD Adjudication Committee.

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

Data are included as of data cut-off of 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study 201, 03 Dec 2021 for Study U204, 09 Apr 2021 for Study U205, 23 Dec 2022 for Study U206, 07 Sep 2021 for Study U302, and 11 Jan 2022 for Study U303. (U206 DCO 23 Dec 2022)

Table 52: Outcome and Treatment of Adjudicated Drug-related Interstitial Lung Disease Events with Updated Study U206 Data (DCO 23 Dec 2022; Safety Analysis Set)

	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
Outcome of drug-related ILD event with worst CTCAE grade[f], n (%)						
Subjects with adjudicated drug-related ILD	13	41	15	53	128	255
Fatal	1 (7.7)	2 (4.9)	1 (6.7)	4 (7.5)	9 (7.0)	20 (7.8)
Not recovered/not resolved	3 (23.1)	14 (34.1)	5 (33.3)	17 (32.1)	35 (27.3)	87 (34.1)

	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
Ongoing	0	0	0	0	1 (0.8)	1 (0.4)
Recovering/resolving	1 (7.7)	1 (2.4)	1 (6.7)	1 (1.9)	8 (6.3)	20 (7.8)
Recovered/resolved with sequelae	0	2 (4.9)	0	2 (3.8)	5 (3.9)	10 (3.9)
Recovered/resolved	8 (61.5)	21 (51.2)	8 (53.3)	27 (50.9)	67 (52.3)	112 (43.9)
Missing/unknown	0	1 (2.4)	0	2 (3.8)	3 (2.3)	5 (2.0)
Treatment of adjudicated drug-related ILD[g], n (%)						
Steroid(s)	11 (10.9)	33 (21.7)	13 (9.2)	42 (20.2)	85 (8.1)	172 (9.9)
Antibiotic(s)	6 (5.9)	15 (9.9)	7 (4.9)	21 (10.1)	38 (3.6)	79 (4.5)
Steroid(s) and antibiotic(s)	6 (5.9)	13 (8.6)	7 (4.9)	19 (9.1)	34 (3.3)	71 (4.1)

CTCAE = Common Terminology Criteria for Adverse Events, version 5.0; DCO = data cut-off; HER2-mut = human epidermal growth factor receptor 2 mutated; ILD = interstitial lung disease; NSCLC = non-small cell lung cancer; T-DXd = trastuzumab deruxtecan

[a] Includes 11 subjects from Study J101, 91 subjects from Study U204, and 50 subjects from Study U206.

[b] Includes 41 subjects with HER2-overexpressing NSCLC from Study U204 and 101 subjects with HER2-mutant NSCLC from Study U206.

[c] Includes 11 subjects with HER2-mutant and 7 subjects with HER2-expressing NSCLC from Study J101, 91 subjects with HER2-mutant and 49 subjects with HER2-overexpressing NSCLC from Study U204, and 50 subjects with HER2-mutant NSCLC from Study U206.

[d] Includes 91 subjects from Study J101, 184 subjects from Study U201, 41 subjects from Study U204, 101 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

[e] Includes 280 subjects from Study J101, 169 subjects from Study J202, 253 subjects from Study U201, 181 subjects from Study U204, 79 subjects from Study U205, 151 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

[f] The outcome of the worst ILD event denominator was based on the adjudicated drug-related ILD.

[g]Treatment of ILD included the antibiotics/steroids used/reported by investigators for subjects with adjudicated drug-related ILD events. Adjudicated drug-related ILD includes ILD events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as both ILD and related to T-DXd by the ILD Adjudication Committee; adjudicated drug-related ILD was summarized based on the ILD adjudicated outcomes (CTCAE grade, drug-related) by the ILD Adjudication Committee.

Percentages were calculated using the number of subjects with any event adjudicated as drug-related ILD as the denominator.

Data are included as of data cut-off of 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study U201, 03 Dec 2021 for Study U204, 09 Apr 2021 for Study U205, 23 Dec 2022 for Study U206, 07 Sep 2021 for Study U302, and 11 Jan 2022 for Study U303. (U206 DCO 23 Dec 2022)

Left ventricular dysfunction

The MAH reviewed the selected PTs in the AESI of LV dysfunction to determine whether the event was related to LVEF decrease per echocardiogram (ECHO)/multigated acquisition (MUGA) scan.

In the U206 HER2 mutant NSCLC T DXd 5.4 mg/kg group, 1/101 (1.0%) subject reported TEAEs indicating LV dysfunction. Among the relevant PTs included in the case definition of LV dysfunction (Table 53), only the PT of ejection fraction decreased was reported. A brief narrative of this case is presented below:

- A middle-aged male treated with T DXd 5.4 mg/kg in Study U206, had a nonserious Grade 1 event of ejection fraction decreased on Day 42 of the study that was considered not related to the study drug by the investigator. The study drug was interrupted and the outcome was not recovered at the time of the DCO.

On 06 Apr 2020, "left ventricular ejection fraction decreased" was renamed to "left ventricular (LV) dysfunction" to reflect that this is a clinical concept rather than a laboratory finding.

Table 53: Analysis of Left Ventricular Ejection Fraction with Updated Study U206 Data (DCO 23 Dec 2022; Safety Analysis Set)

Parameter	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
Subjects with worst LVEF CTCAE grade post-baseline, n (%)						
Non-missing, n[f]	90	129	117	172	964	1588
Grade 2	9 (10.0)	17 (13.2)	14 (12.0)	23 (13.4)	148 (15.4)	240 (15.1)
Subjects with LVEF measurement since worst grade	4	11	7	15	110	175
Recovered from worst grade to ≥90% of baseline, n (%)[g,h]	1 (25.0)	8 (72.7)	3 (42.9)	11 (73.3)	83 (75.5)	129 (73.7)
Grade 3	0	4 (3.1)	1 (0.9)	6 (3.5)	8 (0.8)	16 (1.0)
Subjects with LVEF measurement since worst grade	0	3	1	5	7	13
Recovered from worst grade to ≥90% of baseline, n (%)[g,h]	0	1 (33.3)	0	1 (20.0)	5 (71.4)	6 (46.2)
Grade 4	0	0	0	0	0	0
LVEF measurement at baseline						
n	101	151	142	207	1044	1739
Mean	65.3	64.5	64.7	64.4	64.3	64.6
Std dev	6.06	6.47	6.14	6.59	6.26	6.31
Median	65.0	65.0	64.5	65.0	64.0	65.0
Min, max	51, 80	50, 85	51, 80	50, 85	50, 86	50, 86
40% to 49%	0	0	0	0	0	0
20% to 39%	0	0	0	0	0	0
<20%	0	0	0	0	0	0
Lowest LVEF measurement post-baseline						
n	90	130	117	173	965	1590
Mean	62.4	60.9	62.0	60.8	60.6	61.0
Std dev	6.14	6.51	6.27	7.61	5.92	6.25
Median	62.0	61.0	62.0	61.0	60.0	61.0
Min, max	50, 79	34, 75	47, 79	22, 77	37, 79	22, 82
40% to 49%	0	2/130 (1.5)	1/117 (0.9)	3/173 (1.7)	25/965 (2.6)	36/1590 (2.3)
20% to 39%	0	1/130 (0.8)	0	3/173 (1.7)	2/965 (0.2)	6/1590 (0.4)
<20%	0	0	0	0	0	0
Maximum LVEF decrease from baseline						
N	59	98	75	124	682	1109
Mean	5.7	6.3	5.9	6.7	6.2	6.3
Std dev	3.54	5.46	4.13	6.56	4.36	4.66
Median	5.0	5.0	5.0	5.0	5.0	5.0
Min, max	1, 18	1, 34	1, 21	1, 40	1, 36	1, 40
10% to 19% decrease	9/59 (15.3)	16/98 (16.3)	14/75 (18.7)	21/124 (16.9)	136/682 (19.9)	224/1109 (20.2)
≥20% decrease	0	4/98 (4.1)	1/75 (1.3)	6/124 (4.8)	7/682 (1.0)	15/1109 (1.4)
Highest LVEF measurement post-baseline						
N	90	130	117	173	965	1590
Mean	66.5	66.8	66.0	66.3	66.9	67.0

Parameter	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
Std dev	6.80	6.74	6.92	6.77	6.62	6.68
Median	66.0	67.0	66.0	67.0	67.0	67.0
Min, max	52, 81	34, 82	51, 81	34, 82	43, 90	34, 90
Maximum LVEF increase from baseline						
n	46	73	60	93	599	970
Mean	5.2	6.0	5.2	5.6	5.9	5.7
Std dev	3.97	5.17	3.97	4.84	4.23	4.18
Median	3.0	5.0	3.5	5.0	5.0	5.0
Min, max	1, 14	1, 25	1, 14	1, 25	1, 22	1, 25
10% to 19% increase	9/46 (19.6)	13/73 (17.8)	11/60 (18.3)	15/93 (16.1)	111/599 (18.5)	172/970 (17.7)
≥20% increase	0	2/73 (2.7)	0	2/93 (2.2)	3/599 (0.5)	6/970 (0.6)

CTCAE = Common Terminology Criteria for Adverse Events, version 5.0; DCO = data cut-off; HER2-mut= human epidermal growth factor receptor 2 mutated; LVEF = left ventricular ejection fraction, NSCLC = non-small cell lung cancer; Std dev = standard deviation; T-DXd = trastuzumab deruxtecan

[a] Includes 11 subjects from Study J101, 91 subjects from Study U204, and 50 subjects from Study U206.

[b] Includes 41 subjects with HER2-overexpressing NSCLC from Study U204 and 101 subjects with HER2-mutant NSCLC from Study U206.

[c] Includes 11 subjects with HER2-mutant and 7 subjects with HER2-expressing NSCLC from Study J101, 91 subjects with HER2-mutant and 49 subjects with HER2-overexpressing NSCLC from Study U204, and 50 subjects with HER2-mutant NSCLC from Study U206.

[d] Includes 91 subjects from Study J101, 184 subjects from Study U201, 41 subjects from Study U204, 101 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

[e] Includes 280 subjects from Study J101, 169 subjects from Study J202, 253 subjects from Study U201, 181 subjects from Study U204, 79 subjects from Study U205, 151 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

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

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

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

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

Data are included as of data cut-off of 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study U201, 03 Dec 2021 for Study U204, 09 Apr 2021 for Study U205, 23 Dec 2022 for Study U206, 07 Sep 2021 for Study U302, and 11 Jan 2022 for Study U303. (U206 DCO 23 Dec 2022)

Table 54: Subjects in Study U206 HER2-mutant 5.4 mg/kg with Grade 2 LVEF Decrease

Subject	Status	ECHO/MUGA Date	%LVEF (Change from BL)	Relevant Medical Conditions	Relevant Concomitant Medications
Case 1	Discontinued ondue to AE (pulmonary toxicity, Grade 1). Died2022	Oct 2021(BL)	70	History of ongoing pericardial effusion since 2021. AE of **Ejection fraction decreased** (Grade 1) onDec 2021. Treatment was interrupted. Patient had pleural effusion recurrence and thoracoscopy with talc indicated. Pleuroscopy on Jan 2022.	No relevant concomitant medications.
		Dec 2021 (C2D1)	55 (-15)		
		Jan 2022 (EOT)	58 (-12) 83% of baseline.		
Case 2	Died on 2022 due to disease progression.	Dec 2021 (BL)	63	History of chest pain since 2021. No AE concerning LVEF reported.	No relevant concomitant medications.
		Mar 2022 (C5D1)	53 (-10) 84% of baseline.		
Case 3	Ongoing treatment.	Sep 2021 (BL)	66	None reported. No AE concerning LVEF reported.	Prednisolone for AE of cough COVID-19 vaccinea nd boosters
		Dec 2021 (C5D1)	60 (-6)		
		Mar 2022 (C9D1)	55 (-11)		
		Jun 2022 (C13D1)	55 (-11)		
		Sep 2022 (C17D1)	56 (-10)		
		Nov 2022 (unscheduled)	55 (-11) 83% of baseline.		
Case 4	Discontinued on Jul 2022 due to progressive disease.	Aug 2021 (BL)	66	None reported. No AE concerning LVEF reported.	No relevant concomitant medications
		Dec 2021 (C5D1)	60 (-6)		
		Feb 2022 (C9D1)	64 (-2)		
		May 2022 (C13D1)	56 (-10)		
		Jul 2022 (EOT)	59 (-7) 89% of baseline.		
Case 5	Ongoing treatment.	Jan 2022 (BL)	75	None reported. No AE concerning LVEF reported.	No relevant concomitant medications
		Apr 2022 (C5D1)	73 (-2)		
		Jul 2022 (C9D1)	71 (-4)		
		Nov 2022 (C13D1)	64 (-11) 85% of baseline.		
Case 6	Discontinued on Jul 2021 due to progressive disease.	May 2021 (BL)	79	None reported. No AE concerning LVEF reported.	No relevant concomitant medications
		Jul 2021 (EOT)	69 (-10) 87% of baseline.		
Case 7	Ongoing treatment.	Aug 2021 (BL)	80	Dyslipidaemia since 2016 and hypertension since 2019. No AE concerning LVEF reported.	No relevant concomitant medications
		Nov 2021 (C5D1)	67 (-13)		
		Feb 2022 (C9D1)	71 (-9)		
		May 2022 (C13D1)	71 (-9)		
		Aug 2022 (C17D1)	63 (-17)		
		Nov 2022 (C21D1)	62 (-18) 78% of baseline.		
CAse 8	Discontinued on Apr 2022 due to progressive disease.	Oct 2021 (BL)	66	None reported. No AE concerning LVEF reported.	No relevant concomitant medications
		Jan 2022 (C5D1)	64 (-2)		
		Apr 2022 (EOT)	56 (-10) 85% of baseline.		
Case 9	Ongoing treatment.	Dec 2021 (BL)	69	Hyperlipidaemia since 2016 and hyperglycaemia and	No relevant concomitant medications
		Mar 2022 (C5D1)	73 (4)		
		Jun 2022 (C9D1)	62 (-7)		
		Sep 2022 (C13D1)	57 (-12)		

Subject	Status	ECHO/MUGA Date	%LVEF (Change from BL)	Relevant Medical Conditions	Relevant Concomitant Medications
		Nov 2022 (C17D1)	81 (12) 117% of baseline.	hypertension since 2018. No AE concerning LVEF reported.	

AE = adverse event; BL = baseline; C = cycle; COVID-19 = coronavirus disease 2019; D = day; ECHO/MUGA = echocardiogram/multigated acquisition; EOT = end of treatment; HER2-mut = human epidermal growth factor receptor 2 mutated; LVEF = left ventricular ejection fraction

Combined Elevations of Aminotransferases and Bilirubin

Two of 99 subjects (2.0%) of the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg group had post-baseline liver function tests that met the biochemical criteria for potential Hy's Law (ALT or AST ≥3 × upper limit of normal [ULN] and TBL ≥2 × ULN) (Table 55). One subject had ongoing Gilbert syndrome and the other had elevated ALP at baseline and during T-DXd treatment.

Results of the liver function tests were similar between the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg group and the All Tumor Types T-DXd 5.4 mg/kg Pool, with the exception of the following notable differences:

- A lower proportion of subjects with baseline AST ≥ULN in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg group (28/101 [27.7%] subjects) than in the All Tumor Types T-DXd 5.4 mg/kg Pool (404/1036 [39.0%] subjects)
- A lower proportion of subjects with baseline ALT or AST ≥ULN in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg group (31/101 [30.7%] subjects) than in the All Tumor Types T-DXd 5.4 mg/kg Pool (429/1036 [41.4%] subjects)

A total of 19 of 1036 subjects (1.8%) in the All Tumor Types T-DXd 5.4 mg/kg Pool had post-baseline liver function tests that met the biochemical criteria for potential Hy's Law.

Table 55: Hepatic Function Abnormalities with Updated Study U206 Data (DCO 23 Dec 2022; Safety Analysis Set)

Hepatic Parameter	Number (%) of Subjects					
	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
ALT						
Non-missing, n	101	152	141	205	1036	1728
Baseline ≥ULN	17 (16.8)	12 (7.9)	22 (15.6)	15 (7.3)	228 (22.0)	323 (18.7)
Maximum post-baseline value						
≥3 × ULN	6 (5.9)	8 (5.3)	6 (4.3)	8 (3.9)	69 (6.7)	100 (5.8)
≥5 × ULN	2 (2.0)	0	2 (1.4)	0	11 (1.1)	24 (1.4)
≥8 × ULN	0	0	0	0	1 (0.1)	3 (0.2)
≥10 × ULN	1 (1.0)	0	1 (0.7)	0	3 (0.3)	5 (0.3)
≥20 × ULN	0	0	0	0	0	4 (0.2)
AST						
Non-missing, n	101	152	141	205	1036	1728
Baseline ≥ULN	28 (27.7)	23 (15.1)	31 (22.0)	30 (14.6)	404 (39.0)	604 (35.0)
Maximum post-baseline value						
≥3 × ULN	7 (6.9)	8 (5.3)	8 (5.7)	8 (3.9)	85 (8.2)	136 (7.9)
≥5 × ULN	0	1 (0.7)	0	1 (0.5)	20 (1.9)	40 (2.3)

Hepatic Parameter	Number (%) of Subjects					
	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
≥8 × ULN	0	0	0	0	4 (0.4)	5 (0.3)
≥10 × ULN	1 (1.0)	0	1 (0.7)	0	5 (0.5)	13 (0.8)
≥20 × ULN	0	0	0	0	3 (0.3)	4 (0.2)
ALT or AST						
Non-missing, n	101	152	141	205	1036	1728
Baseline ≥ULN	31 (30.7)	24 (15.8)	36 (25.5)	31 (15.1)	429 (41.4)	641 (37.1)
Maximum post-baseline value						
≥3 × ULN	8 (7.9)	14 (9.2)	9 (6.4)	14 (6.8)	109 (10.5)	176 (10.2)
≥5 × ULN	2 (2.0)	1 (0.7)	2 (1.4)	1 (0.5)	30 (2.9)	53 (3.1)
≥8 × ULN	0	0	0	0	4 (0.4)	6 (0.3)
≥10 × ULN	1 (1.0)	0	1 (0.7)	0	5 (0.5)	11 (0.6)
≥20 × ULN	0	0	0	0	3 (0.3)	7 (0.4)
TBL						
Non-missing, n	101	152	141	205	1038	1729
Baseline ≥ULN	2 (2.0)	2 (1.3)	2 (1.4)	3 (1.5)	29 (2.8)	47 (2.7)
Maximum post-baseline value						
≥1.5 × ULN	1 (1.0)	5 (3.3)	1 (0.7)	5 (2.4)	37 (3.6)	56 (3.2)
≥2 × ULN	2 (2.0)	2 (1.3)	2 (1.4)	2 (1.0)	19 (1.8)	37 (2.1)
≥3 × ULN	1 (1.0)	1 (0.7)	1 (0.7)	1 (0.5)	14 (1.3)	32 (1.9)
ALP						
Non-missing, n	101	152	141	205	1038	1730
Baseline ≥ULN	42 (41.6)	39 (25.7)	49 (34.8)	46 (22.4)	348 (33.5)	581 (33.6)
Maximum post-baseline value						
≥1.5 × ULN	13 (12.9)	29 (19.1)	14 (9.9)	34 (16.6)	162 (15.6)	275 (15.9)
≥2 × ULN	31 (30.7)	26 (17.1)	35 (24.8)	31 (15.1)	259 (25.0)	429 (24.8)
Concurrent TBL elevation with ALT or AST elevation[f]						
Non-missing, n	101	152	141	205	1036	1727
ALT or AST ≥3 × ULN and TBL ≥2 × ULN	2 (2.0)	2 (1.3)	2 (1.4)	2 (1.0)	19 (1.8)	36 (2.1)
Concurrent TBL elevation with ALT or AST elevation and ALP <2 × ULN[f]						
Non-missing, n	101	152	141	205	1036	1726
ALT or AST ≥3 × ULN, ALP <2 × ULN, and TBL ≥2 × ULN	1 (1.0)	1 (0.7)	1 (0.7)	1 (0.5)	10 (1.0)	14 (0.8)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DCO = data cut-off; HER2-mut = human epidermal growth receptor 2 mutated; NSCLC = non-small cell lung cancer; TBL = total bilirubin; T-DXd = trastuzumab deruxtecan; ULN = upper limit of normal

[a] Includes 11 subjects from Study J101, 91 subjects from Study U204, and 50 subjects from Study U206.

[b] Includes 41 subjects with HER2-overexpressing NSCLC from Study U204 and 101 subjects with HER2-mutant NSCLC from Study U206.

[c] Includes 11 subjects with HER2-mutant and 7 subjects with HER2-expressing NSCLC from Study J101, 91 subjects with HER2-mutant and 49 subjects with HER2-overexpressing NSCLC from Study U204, and 50 subjects with HER2-mutant NSCLC from Study U206.

[d] Includes 91 subjects from Study J101, 184 subjects from Study U201, 41 subjects from Study U204, 101 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

[e] Includes 280 subjects from Study J101, 169 subjects from Study J202, 253 subjects from Study U201, 181 subjects from Study U204, 79 subjects from Study U205, 151 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

[f] To be considered concurrent, abnormalities must have occurred within a 28-day window.

Baseline value was defined as the last non-missing value before initial administration of study drug.

Non-missing n was the number of subjects with both baseline and post-baseline non-missing data.

Percentage was calculated using the non-missing n as the denominator.

Each subject was counted only for the worst case observed post-baseline.

Data are included as of data cut-off of 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study U201, 03 Dec

2021 for Study U204, 09 Apr 2021 for Study U205, 23 Dec 2022 for Study U206, 07 Sep 2021 for Study U302, and 11 Jan 2022 for Study U303.
Source: (U206 DCO 23 Dec 2022)

Adverse drug reactions:

During the assessment period the MAH has provided safety data from further 404 patients included in Study U301 and treated with T-DXd 5.4 mg/kg. Study U301 was a Phase 3, randomized, 2-arm, open-label, multicenter study designed to compare the safety and efficacy of T-DXd vs TPC in HER2positive, unresectable and/or metastatic BC subjects who were resistant or refractory to TDM1. The safety data of these patients were added to All Tumor Types T-DXd 5.4 mg/kg Pool (N=1449) and presented in the SmPC.

Table 56: All adverse drug reactions in Subject from the All Tumor Types T-DXd 5.4 mg/kg Pool and the All Tumor Types T-DXd 6.4 mg/kg Pool bt MedDRA System organ Class and Preferred term or Grouped Term (Safety Analysis Set)

	Number (%) of Subjects									
	All Tumor Types Pool T-DXd 5.4 mg/kg[a] (N = 1449)					All Tumor Types Pool T-DXd 6.4 mg/kg[b] (N = 669)				
		CTCAE Grade					CTCAE Grade			
MedDRA SOC/PT or Grouped Term	Frequency[c]	All	3 or 4	5	SAE	Frequency[c]	All	3 or 4	5	SAE
Subjects with Any ADR	Not applicable	1438 (99.2)	644 (44.4)	20 (1.4)	208 (14.4)	Not applicable	665 (99.4)	413 (61.7)	18 (2.7)	147 (22.0)
Gastrointestinal disorders										
Nausea	Very common	1087 (75.0)	85 (5.9)	0	16 (1.1)	Very common	483 (72.2)	39 (5.8)	0	11 (1.6)
Vomiting	Very common	610 (42.1)	39 (2.7)	0	22 (1.5)	Very common	268 (40.1)	16 (2.4)	0	12 (1.8)
Constipation	Very common	507 (35.0)	6 (0.4)	0	4 (0.3)	Very common	216 (32.3)	1 (0.1)	0	1 (0.1)
Diarrhoea	Very common	417 (28.8)	29 (2.0)	0	6 (0.4)	Very common	240 (35.9)	15 (2.2)	0	6 (0.9)
Abdominal pain[d]	Very common	280 (19.3)	13 (0.9)	0	5 (0.3)	Very common	95 (14.2)	6 (0.9)	0	5 (0.7)
Stomatitis[d]	Very common	214 (14.8)	10 (0.7)	0	2 (0.1)	Very common	98 (14.6)	4 (0.6)	0	2 (0.3)
Dyspepsia	Very common	163 (11.2)	0	0	0	Common	35 (5.2)	0	0	0
Abdominal distension	Common	52 (3.6)	0	0	0	Common	25 (3.7)	2 (0.3)	0	2 (0.3)
Gastritis	Common	31 (2.1)	2 (0.1)	0	1 (0.1)	Common	10 (1.5)	0	0	0
Flatulence	Common	26 (1.8)	0	0	0	Common	11 (1.6)	0	0	0
General disorders and administration site conditions										
Fatigue[d]	Very common	831 (57.3)	122 (8.4)	0	11 (0.8)	Very common	391 (58.4)	56 (8.4)	1 (0.1)	9 (1.3)
Pyrexia	Very common	189 (13.0)	6 (0.4)	0	13 (0.9)	Very common	130 (19.4)	2 (0.3)	0	5 (0.7)
Oedema peripheral	Common	120 (8.3)	2 (0.1)	0	3 (0.2)	Very common	69 (10.3)	1 (0.1)	0	1 (0.1)
Blood and lymphatic system disorders										
Neutropenia[d]	Very common	510 (35.2)	246 (17.0)	0	4 (0.3)	Very common	291 (43.5)	192 (28.7)	0	3 (0.4)
Anemia[d]	Very common	498 (34.4)	137 (9.5)	0	14 (1.0)	Very common	299 (44.7)	151 (22.6)	0	11 (1.6)
Thrombocytopenia[d]	Very common	355 (24.5)	73 (5.0)	0	7 (0.5)	Very common	206 (30.8)	61 (9.1)	0	14 (2.1)
Leukopenia[d]	Very common	343 (23.7)	93 (6.4)	0	0	Very common	196 (29.3)	89 (13.3)	0	0
Lymphopenia[d]	Very common	154 (10.6)	70 (4.8)	0	0	Very common	86 (12.9)	46 (6.9)	0	0
Febrile neutropenia	Uncommon	13 (0.9)	12 (0.8)	1 (0.1)	9 (0.6)	Common	20 (3.0)	19 (2.8)	1 (0.1)	6 (0.9)
Skin and subcutaneous tissue disorders										
Alopecia	Very common	545 (37.6)	3 (0.2)	0	0	Very common	237 (35.4)	0	0	0
Rash[d]	Common	138 (9.5)	1 (0.1)	0	0	Common	53 (7.9)	0	0	0
Pruritus	Common	73 (5.0)	1 (0.1)	0	0	Common	42 (6.3)	0	0	0
Skin hyperpigmentation[d]	Common	69 (4.8)	0	0	1 (0.1)	Common	18 (2.7)	0	0	0
Metabolism and nutrition disorders										
Decreased appetite	Very common	479 (33.1)	25 (1.7)	0	2 (0.1)	Very common	358 (53.5)	52 (7.8)	0	27 (4.0)
Hypokalemia[d]	Very common	168 (11.6)	55 (3.8)	0	7 (0.5)	Very common	86 (12.9)	29 (4.3)	0	0
Dehydration	Common	43 (3.0)	7 (0.5)	0	5 (0.3)	Common	26 (3.9)	5 (0.7)	0	6 (0.9)
Investigations										
Weight decreased	Very common	235 (16.2)	12 (0.8)	0	1 (0.1)	Very common	132 (19.7)	13 (1.9)	0	0
Ejection fraction decreased	Very common	222 (15.3)	16 (1.1)	0	3 (0.2)	Very common	98 (14.6)	8 (1.2)	0	0
Blood alkaline phosphatase increased	Common	123 (8.5)	6 (0.4)	0	0	Common	61 (9.1)	11 (1.6)	0	2 (0.3)
Blood bilirubin increased[d]	Common	114 (7.9)	13 (0.9)	0	4 (0.3)	Common	46 (6.9)	8 (1.2)	0	1 (0.1)
Blood creatinine increased	Common	49 (3.4)	2 (0.1)	0	1 (0.1)	Common	33 (4.9)	1 (0.1)	0	0
Respiratory, thoracic and mediastinal disorders										
Cough	Very common	213 (14.7)	2 (0.1)	0	1 (0.1)	Very common	82 (12.3)	2 (0.3)	0	0
Interstitial lung disease[e]	Very common	181 (12.5)	12 (0.8)	15 (1.0)	53 (3.7)	Very common	120 (17.9)	10 (1.5)	14 (2.1)	39 (5.8)
Dyspnoea	Very common	156 (10.8)	15 (1.0)	1 (0.1)	14 (1.0)	Very common	67 (10.0)	8 (1.2)	1 (0.1)	5 (0.7)
Epistaxis	Very common	152 (10.5)	0	0	0	Common	50 (7.5)	1 (0.1)	0	0
Nervous system disorders										
Headache[d]	Very common	263 (18.2)	3 (0.2)	0	3 (0.2)	Very common	67 (10.0)	2 (0.3)	0	0
Dizziness	Very common	148 (10.2)	4 (0.3)	0	1 (0.1)	Common	55 (8.2)	3 (0.4)	0	0
Dysgeusia	Common	111 (7.7)	0	0	0	Very common	67 (10.0)	0	0	0
Hepatobiliary disorders										

	Number (%) of Subjects									
	All Tumor Types Pool T-DXd 5.4 mg/kg[a] (N = 1449)					All Tumor Types Pool T-DXd 6.4 mg/kg[b] (N = 669)				
		CTCAE Grade					CTCAE Grade			
MedDRA SOC/PT or Grouped Term	Frequency[c]	All	3 or 4	5	SAE	Frequency[c]	All	3 or 4	5	SAE
Transaminases increased[d]	Very common	384 (26.5)	52 (3.6)	0	2 (0.1)	Very common	162 (24.2)	29 (4.3)	1 (0.1)	4 (0.6)
Musculoskeletal and connective tissue disorders										
Musculoskeletal pain[d]	Very common	379 (26.2)	14 (1.0)	0	12 (0.8)	Very common	130 (19.4)	3 (0.4)	0	1 (0.1)
Infections and infestations										
Upper respiratory tract infection[d]	Very common	270 (18.6)	3 (0.2)	0	4 (0.3)	Very common	108 (16.1)	2 (0.3)	0	1 (0.1)
Pneumonia	Common	76 (5.2)	21 (1.4)	3 (0.2)	27 (1.9)	Very common	73 (10.9)	21 (3.1)	1 (0.1)	22 (3.3)
Eye disorders										
Dry eye	Common	78 (5.4)	2 (0.1)	0	0	Common	29 (4.3)	0	0	0
Vision blurred[d]	Common	59 (4.1)	0	0	0	Common	18 (2.7)	0	0	0
Injury, poisoning and procedural complications										
Infusion related reaction[f]	Common	18 (1.2)	0	0	1 (0.1)	Common	7 (1.0)	0	0	0

ADR = adverse drug reaction; CTCAE = Common Terminology Criteria for Adverse Events, version 5.0; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities, version 25.1; PT = preferred term; SAE = serious adverse event; SOC = system organ class; T-DXd = trastuzumab deruxtecan.
For a grouped term, there are multiple PTs, which could be corresponding to different SOCs. The different SOCs were unified to one SOC as displayed in this table first, and then the subjects were summarized in that grouped term and that SOC.
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
SOCs and PTs/grouped terms are sorted by descending frequency in all grades in the All Tumor Types T-DXd 5.4 mg/kg Pool column.
Ejection fraction decreased includes both laboratory parameters of LVEF decrease and AE preferred terms of LVEF. (grouped PT terms for LV dysfunction includes PTs of Acute left ventricular failure, Acute right ventricular failure, Cardiac failure, Cardiac failure acute, Cardiac failure chronic, Cardiac failure congestive, Chronic left ventricular failure, Chronic right ventricular failure, Ejection fraction decreased, Left ventricular failure, Right ventricular failure,
Ventricular failure and Left Ventricular Dysfunction.)
a Includes 91 subjects from Study J101, 184 from Study U201, 41 from Study U204, 101 from Study U206, 404 from Study U301, 257 from Study U302, and
371 from Study U303.
b Includes 183 subjects from Study J101, 169 from Study J202, 48 from Study U201, 140 from Study U204, 79 from Study U205, and 50 from Study U206.
c Very Common >=1/10 subjects; Common >=1/100 to <1/10 subjects; Uncommon >=1/1000 to <1/100 subjects.
e ILD in the All Tumor Types Pool T-DXd 5.4 mg/kg includes events that were adjudicated as ILD: Acute respiratory failure, Alveolitis, Hypersensitivity pneumonitis, Idiopathic interstitial pneumonia, Interstitial lung disease, Lung disorder, Lung infiltration, Lung opacity, Lymphangitis, Organising pneumonia, Pneumonia, Pneumonia fungal, Pneumonitis, Pulmonary fibrosis, Pulmonary mass, Pulmonary toxicity, Radiation pneumonitis, Respiratory failure.
ILD in the All Tumor Types Pool T-DXd 6.4 mg/kg includes events that were adjudicated as ILD: Interstitial lung disease, Lung opacity, Organising pneumonia, Pneumonia, Pneumonitis, Radiation pneumonitis, Respiratory failure.
f Infusion related reaction is defined as any of the pre-selected PTs (Administration related reaction, Anaphylactic reaction, Hypersensitivity, Infusion related hypersensitivity reaction) considered related to the study drug by the investigator and occurred within 24 hours of the completed infusion at any cycle.
Data are included as of data cut-off of 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study U201, 03 Dec 2021 for Study U204, 08 Nov 2021 for Study U205, 23 Dec 2022 for Study U206, 30 Jun 2022 for Study U301, 25 Jul 2022 for Study U302, and 11 Apr 2022 for Study U303.

Serious adverse event/deaths/other significant events

Table 57: Serious Treatment-emergent Adverse Events by Preferred Term or Grouped Term Based on a Cut-off of ≥1% of Subjects from Study U206 with HER2-mutant NSCLC at T-DXd 5.4 mg/kg with Updated Study U206 Data (DCO 23 Dec 2022; Safety Analysis Set)

MedDRA Preferred Term or Grouped Term	Number (%) of Subjects					
	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
Subjects with any TESAE	37 (36.6)	60 (39.5)	53 (37.3)	88 (42.3)	279 (26.7)	543 (31.2)
Pleural effusion	4 (4.0)	3 (2.0)	5 (3.5)	3 (1.4)	11 (1.1)	15 (0.9)
Thrombocytopenia[f]	3 (3.0)	3 (2.0)	3 (2.1)	3 (1.4)	7 (0.7)	21 (1.2)

MedDRA Preferred Term or Grouped Term	Number (%) of Subjects					
	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
Dyspnoea	2 (2.0)	1 (0.7)	4 (2.8)	5 (2.4)	11 (1.1)	17 (1.0)
Interstitial lung disease (adjudicated drug-related)[g]	2 (2.0)	4 (2.6)	2 (1.4)	4 (1.9)	17 (1.6)	32 (1.8)
Lung neoplasm malignant	2 (2.0)	0	2 (1.4)	0	2 (0.2)	2 (0.1)
Malignant neoplasm progression	2 (2.0)	0	2 (1.4)	0	2 (0.2)	4 (0.2)
Myocarditis	2 (2.0)	0	2 (1.4)	0	2 (0.2)	2 (0.1)
Nausea	2 (2.0)	1 (0.7)	2 (1.4)	3 (1.4)	11 (1.1)	22 (1.3)
Pneumonia	2 (2.0)	5 (3.3)	3 (2.1)	9 (4.3)	22 (2.1)	45 (2.6)
Pneumonitis[h]	2 (2.0)	9 (5.9)	3 (2.1)	13 (6.3)	18 (1.7)	46 (2.6)
Pulmonary embolism	2 (2.0)	0	2 (1.4)	1 (0.5)	4 (0.4)	8 (0.5)
Respiratory failure	2 (2.0)	0	2 (1.4)	2 (1.0)	8 (0.8)	11 (0.6)
Troponin I increased	2 (2.0)	1 (0.7)	2 (1.4)	1 (0.5)	2 (0.2)	3 (0.2)
Vomiting	2 (2.0)	4 (2.6)	3 (2.1)	5 (2.4)	16 (1.5)	28 (1.6)
Acute myocardial infarction	1 (1.0)	0	1 (0.7)	0	1 (0.1)	1 (0.1)
COVID-19	1 (1.0)	0	1 (0.7)	0	5 (0.5)	7 (0.4)
COVID-19 pneumonia	1 (1.0)	0	2 (1.4)	0	2 (0.2)	3 (0.2)
Cancer pain	1 (1.0)	0	1 (0.7)	0	1 (0.1)	1 (0.1)
Cerebrovascular accident	1 (1.0)	0	1 (0.7)	0	1 (0.1)	2 (0.1)
Diarrhoea	1 (1.0)	2 (1.3)	2 (1.4)	3 (1.4)	3 (0.3)	9 (0.5)
Duodenal ulcer	1 (1.0)	0	1 (0.7)	0	1 (0.1)	1 (0.1)
Fatigue[f]	1 (1.0)	4 (2.6)	2 (1.4)	5 (2.4)	6 (0.6)	16 (0.9)
General physical health deterioration	1 (1.0)	0	1 (0.7)	0	5 (0.5)	6 (0.3)
Hypothyroidism	1 (1.0)	0	1 (0.7)	0	1 (0.1)	1 (0.1)
Ileus	1 (1.0)	1 (0.7)	1 (0.7)	1 (0.5)	1 (0.1)	2 (0.1)
Intestinal perforation	1 (1.0)	1 (0.7)	1 (0.7)	1 (0.5)	1 (0.1)	3 (0.2)
Intracranial pressure increased	1 (1.0)	0	1 (0.7)	0	1 (0.1)	1 (0.1)
Intracranial tumour haemorrhage	1 (1.0)	0	1 (0.7)	0	1 (0.1)	1 (0.1)
Large intestinal obstruction	1 (1.0)	0	1 (0.7)	0	1 (0.1)	1 (0.1)
Musculoskeletal pain[f]	1 (1.0)	0	2 (1.4)	0	10 (1.0)	11 (0.6)
Neurological symptom	1 (1.0)	1 (0.7)	1 (0.7)	1 (0.5)	1 (0.1)	2 (0.1)
Neutropenia[f]	1 (1.0)	2 (1.3)	1 (0.7)	2 (1.0)	4 (0.4)	7 (0.4)
Optic nerve disorder	1 (1.0)	0	1 (0.7)	0	1 (0.1)	1 (0.1)
Pericardial effusion	1 (1.0)	1 (0.7)	2 (1.4)	1 (0.5)	2 (0.2)	4 (0.2)
Pneumothorax	1 (1.0)	0	1 (0.7)	0	2 (0.2)	2 (0.1)
Pyrexia	1 (1.0)	0	2 (1.4)	0	10 (1.0)	15 (0.9)

MedDRA Preferred Term or Grouped Term	Number (%) of Subjects					
	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
Subdural haemorrhage	1 (1.0)	0	1 (0.7)	0	1 (0.1)	1 (0.1)
Ureteric obstruction	1 (1.0)	0	1 (0.7)	0	1 (0.1)	1 (0.1)
Urinary tract infection	1 (1.0)	1 (0.7)	1 (0.7)	2 (1.0)	9 (0.9)	13 (0.7)

AE = adverse event; COVID-19 = coronavirus disease 2019; DCO = data cut-off; HER2-mut = human epidermal growth factor receptor 2 mutated; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; PT = preferred term; SAE = serious adverse event; SMQ = standardised MedDRA query; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

[a] Includes 11 subjects from Study J101, 91 subjects from Study U204, and 50 subjects from Study U206.

[b] Includes 41 subjects with HER2-overexpressing NSCLC from Study U204 and 101 subjects with HER2-mutant NSCLC from Study U206.

[c] Includes 11 subjects with HER2-mutant and 7 subjects with HER2-expressing NSCLC from Study J101, 91 subjects with HER2-mutant and 49 subjects with HER2-overexpressing NSCLC from Study U204, and 50 subjects with HER2-mutant NSCLC from Study U206.

[d] Includes 91 subjects from Study J101, 184 subjects from Study U201, 41 subjects from Study U204, 101 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

[e] Includes 280 subjects from Study J101, 169 subjects from Study J202, 253 subjects from Study U201, 181 subjects from Study U204, 79 subjects from Study U205, 151 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

[f] Grouped terms.

[g] Interstitial lung disease includes events that were adjudicated as ILD and considered study drug related by the Adjudication Committee (includes cases of potential ILD/pneumonitis, based on MedDRA for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure).

[h] These events were not assessed as drug-related ILD.

A TEAE was defined as an AE that occurred, having been absent before the first dose of study drug, or had worsened in severity or seriousness after the initiation of the study drug until 47 days (for all studies except Study J101 [28 days]) after the last dose of study drug.

SAEs with an onset or worsening 48 days (29 days for Study J101) or more after the last dose of study drug, if considered related to the study drug, were also TEAEs.

If a subject had multiple PTs or grouped terms, the subject was counted in each of those terms. If a subject had multiple occurrences of the same grouped PT, the subject was counted once for the specific PT.

Percentages were calculated using the number of subjects in each treatment group as the denominator.

Preferred terms/grouped terms were sorted by descending frequency in the U206 HER2 mutant NSCLC T-DXd 5.4 mg/kg column.

Data are included as of data cut-off of 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study 201, 03 Dec 2021 for Study U204, 09 Apr 2021 for Study U205, 23 Dec 2022 for Study U206, 07 Sep 2021 for Study U302, and 11 Jan 2022 for Study U303. (U206 DCO 23 Dec 2022)

Deaths:

Table 58: Deaths by Primary Cause with Updated Study U206 Data (DCO 23 Dec 2022; Safety Analysis Set)

Primary Cause of Death	Number (%) of Subjects					
	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
Any death	37 (36.6)	73 (48.0)	60 (42.3)	114 (54.8)	350 (33.5)	704 (40.4)
Primary cause of any death						
Adverse event	1 (1.0)	7 (4.6)	3 (2.1)	12 (5.8)	24 (2.3)	59 (3.4)
Disease progression	33 (32.7)	55 (36.2)	47 (33.1)	87 (41.8)	270 (25.8)	548 (31.5)
Unknown	1 (1.0)	5 (3.3)	4 (2.8)	8 (3.8)	36 (3.4)	63 (3.6)
Other	2 (2.0)	6 (3.9)	6 (4.2)	7 (3.4)	20 (1.9)	34 (2.0)
On-treatment death[f]	11 (10.9)	16 (10.5)	19 (13.4)	26 (12.5)	49 (4.7)	104 (6.0)
Primary cause of on-treatment death						
Adverse event	1 (1.0)	7 (4.6)	2 (1.4)	11 (5.3)	16 (1.5)	40 (2.3)
Disease progression	10 (9.9)	8 (5.3)	15 (10.6)	14 (6.7)	27 (2.6)	57 (3.3)
Unknown	0	1 (0.7)	1 (0.7)	1 (0.5)	3 (0.3)	4 (0.2)
Other	0	0	1 (0.7)	0	3 (0.3)	3 (0.2)

DCO = data cut-off; HER2-mut= human epidermal growth factor receptor 2 mutated; NSCLC = non-small cell lung cancer; T-DXd = trastuzumab deruxtecan

[a] Includes 11 subjects from Study J101, 91 subjects from Study U204, and 50 subjects from Study U206.

[b] Includes 41 subjects with HER2-overexpressing NSCLC from Study U204 and 101 subjects with HER2-mutant NSCLC from Study U206.

[c] Includes 11 subjects with HER2-mutant and 7 subjects with HER2-expressing NSCLC from Study J101, 91 subjects with HER2-mutant and 49 subjects with HER2-overexpressing NSCLC from Study U204, and 50 subjects with HER2-mutant NSCLC from Study U206.

[d] Includes 91 subjects from Study J101, 184 subjects from Study U201, 41 subjects from Study U204, 101 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

[e] Includes 280 subjects from Study J101, 169 subjects from Study J202, 253 subjects from Study U201, 181 subjects from Study U204, 79 subjects from Study U205, 151 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

[f] On-treatment deaths = death between first dose and 28 days (for Study J101) or 47 days (for all other studies) after the last dose.

Percentages were calculated using the number of subjects in each treatment group as the denominator.

Data are included as of data cut-off of 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study U201, 03 Dec 2021 for Study U204, 09 Apr 2021 for Study U205, 23 Dec 2022 for Study U206, 07 Sep 2021 for Study U302, and 11 Jan 2022 for Study U303. (U206 DCO 23 Dec 2022)

One on-treatment death due to an adverse event occurred in study U206: a 73-year-old female treated with T-DXd 5.4 mg/kg in Study U206 had a serious TEAE of pneumonitis on Day 42 of the study that was considered related to T-DXd by the investigator. This event was adjudicated as not ILD. The subject died on Day 44 of the study after receiving the last dose of T-DXd 5.4 mg/kg on Day 24.

Table 59: Treatment-emergent Adverse Events Associated with an Outcome of Death by Preferred Term with Updated Study U206 Data (DCO 23 Dec 2022; Safety Analysis Set)

MedDRA Preferred Term	Number (%) of Subjects					
	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
Subjects with any TEAE associated with an outcome of death (per investigator)	6 (5.9)	15 (9.9)	13 (9.2)	26 (12.5)	45 (4.3)	105 (6.0)

Lung neoplasm malignant	2 (2.0)	0	2 (1.4)	0	2 (0.2)	2 (0.1)
Malignant neoplasm progression	2 (2.0)	0	2 (1.4)	0	2 (0.2)	4 (0.2)
Cerebrovascular accident	1 (1.0)	0	1 (0.7)	0	1 (0.1)	2 (0.1)
Pneumonitis	1 (1.0)[g]	1 (0.7)	1 (0.7)	2 (1.0)	5 (0.5)	12 (0.7)
Acute hepatic failure	0	0	0	0	1 (0.1)	1 (0.1)
Acute kidney injury	0	0	0	0	1 (0.1)	1 (0.1)
Acute pulmonary oedema	0	1 (0.7)	0	1 (0.5)	0	1 (0.1)
Acute respiratory failure	0	0	0	0	1 (0.1)	1 (0.1)
Bronchospasm	0	0	0	1 (0.5)	0	1 (0.1)
COVID-19	0	0	0	0	1 (0.1)	3 (0.2)
Colitis ischaemic	0	0	0	0	1 (0.1)	1 (0.1)
Death	0	0	0	0	1 (0.1)	1 (0.1)
Disease progression	0	7 (4.6)	4 (2.8)	13 (6.3)	11 (1.1)	34 (2.0)
Disseminated intravascular coagulation	0	0	0	0	1 (0.1)	3 (0.2)
Dyspnoea	0	1 (0.7)	1 (0.7)	1 (0.5)	2 (0.2)	3 (0.2)
Fatigue[f]	0	0	0	0	0	1 (0.1)
Febrile neutropenia	0	0	0	0	1 (0.1)	2 (0.1)
General physical condition abnormal	0	1 (0.7)	0	1 (0.5)	0	1 (0.1)
General physical health deterioration	0	0	0	0	2 (0.2)	2 (0.1)
Hydrocephalus	0	0	0	1 (0.5)	0	1 (0.1)
Interstitial lung disease	0	1 (0.7)	0	1 (0.5)	0	3 (0.2)
Intestinal obstruction	0	0	0	0	0	1 (0.1)
Intestinal perforation	0	1 (0.7)	0	1 (0.5)	0	1 (0.1)
Large intestine perforation	0	0	0	0	0	1 (0.1)
Lymphangiosis carcinomatosa	0	0	0	0	0	1 (0.1)
Lymphangitis	0	0	0	0	1 (0.1)	1 (0.1)
Mechanical ileus	0	0	0	0	0	1 (0.1)
Neoplasm malignant	0	0	1 (0.7)	0	1 (0.1)	1 (0.1)
Neoplasm progression	0	0	0	0	0	2 (0.1)
Pleural effusion	0	0	0	0	1 (0.1)	1 (0.1)
Pneumocystis jirovecii pneumonia	0	1 (0.7)	0	1 (0.5)	0	1 (0.1)
Pneumonia	0	0	0	0	1 (0.1)	2 (0.1)
Pneumonia aspiration	0	0	0	0	0	1 (0.1)
Respiratory failure	0	0	0	2 (1.0)	4 (0.4)	6 (0.3)
Seizure	0	1 (0.7)	0	1 (0.5)	0	1 (0.1)
Sepsis	0	0	1 (0.7)	0	3 (0.3)	3 (0.2)
Shock haemorrhagic	0	0	0	0	1 (0.1)	1 (0.1)
Sudden death	0	0	0	0	1 (0.1)	1 (0.1)
Transaminases increased[f]	0	0	0	0	0	1 (0.1)
Upper gastrointestinal haemorrhage	0	0	0	0	0	1 (0.1)

AE = adverse event; COVID-19 = coronavirus disease 2019; DCO = data cut-off; HER2-mut= human epidermal growth factor receptor 2 mutated; NSCLC = non-small cell lung cancer; SAE = serious adverse event; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event

[a] Includes 11 subjects from Study J101, 91 subjects from Study U204, and 50 subjects from Study U206.

[b] Includes 41 subjects with HER2-overexpressing NSCLC from Study U204 and 101 subjects with HER2-mutant NSCLC from Study U206.

[c] Includes 11 subjects with HER2-mutant and 7 subjects with HER2-expressing NSCLC from Study J101, 91 subjects with HER2-mutant and 49 subjects with HER2-overexpressing NSCLC from Study U204, and 50 subjects with HER2-mutant NSCLC from Study U206.

[d] Includes 91 subjects from Study J101, 184 subjects from Study U201, 41 subjects from Study U204, 101 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

[e] Includes 280 subjects from Study J101, 169 subjects from Study J202, 253 subjects from Study U201, 181 subjects from Study U204, 79 subjects from Study U205, 151 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

[f] Grouped term.

[g] Drug-related.

A TEAE was defined as an AE that occurred, having been absent before the first dose of study drug, or had worsened in severity or seriousness after the initiation of the study drug until 47 days (for all studies except Study J101 [28 days]) after the last dose of study drug.

SAEs with an onset or worsening 48 days (29 days for Study J101) or more after the last dose of study drug, if considered related to the study drug, were also TEAEs.

If a subject had multiple preferred terms or grouped terms, the subject was counted in each of those terms.

If a subject had multiple occurrences of the same preferred term, the subject was counted once for the specific preferred term.

Percentages were calculated using the number of subjects in each treatment group as the denominator.

Preferred terms/grouped terms were sorted by descending frequency in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg column.

Data are included as of data cut-off of 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study U201, 03 Dec 2021 for Study U204, 09 Apr 2021 for Study U205, 23 Dec 2022 for Study U206, 07 Sep 2021 for Study U302, and 11 Jan 2022 for Study U303. (U206 DCO 23 Dec 2022)

Laboratory findings

Haematology:

Table 60: Hematological Treatment-emergent Adverse Events of CTCAE Grade ≥3 by Preferred Term or Grouped Term Reported for ≥5% of Subjects from Study U206 with HER2-mutant NSCLC at T-DXd 5.4 mg/kg with Updated Study U206 Data (DCO 23 Dec 2022; Safety Analysis Set)

MedDRA Preferred Term or Grouped Term	Number (%) of Subjects					
	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
Subjects with any TEAE ≥Grade 3	53 (52.5)	104 (68.4)	74 (52.1)	147 (70.7)	563 (53.9)	1063 (61.1)
Neutropenia[f]	19 (18.8)	37 (24.3)	19 (13.4)	50 (24.0)	173 (16.6)	373 (21.4)
Anemia[f]	11 (10.9)	20 (13.2)	14 (9.9)	24 (11.5)	99 (9.5)	255 (14.6)
Thrombocytopenia[f]	6 (5.9)	10 (6.6)	6 (4.2)	12 (5.8)	62 (5.9)	128 (7.4)
Leukopenia[f]	5 (5.0)	13 (8.6)	5 (3.5)	16 (7.7)	64 (6.1)	156 (9.0)

CTCAE = Common Terminology Criteria for Adverse Events; DCO = data cut-off; HER2-mut = human epidermal growth factor receptor 2 mutated; NSCLC = non-small cell lung cancer; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event

[a] Includes 11 subjects from Study J101, 91 subjects from Study U204, and 50 subjects from Study U206.

[b] Includes 41 subjects with HER2-overexpressing NSCLC from Study U204 and 101 subjects with HER2-mutant NSCLC from Study U206.

[c] Includes 11 subjects with HER2-mutant and 7 subjects with HER2-expressing NSCLC from Study J101, 91 subjects with HER2-mutant and 49 subjects with HER2-overexpressing NSCLC from Study U204, and 50 subjects with HER2-mutant NSCLC from Study U206.

[d] Includes 91 subjects from Study J101, 184 subjects from Study U201, 41 subjects from Study U204, 101 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

[e] Includes 280 subjects from Study J101, 169 subjects from Study J202, 253 subjects from Study U201, 181 subjects from Study U204, 79 subjects from Study U205, 151 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

[f] Grouped terms.

Data are included as of data cut-off of 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study U201, 03 Dec 2021 for Study U204, 09 Apr 2021 for Study U205, 23 Dec 2022 for Study U206, 07 Sep 2021 for Study U302, and 11 Jan 2022 for Study U303. (U206 DCO 23 Dec 2022)

Clinical chemistry:

Table 61: Summary of Shifts from Baseline to Worst Post-baseline CTCAE Grade in Serum Creatinine Increased with Updated Study U206 Data (DCO 23 Dec 2022; Safety Analysis Set)

Group	Baseline CTCAE Grade	Number (%) of Subjects with Worst Post-baseline CTCAE Grade					
		Normal	1	2	3	4	Total
U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	Normal	71 (70.3)	7 (6.9)	2 (2.0)	0	0	80 (79.2)
	1	1 (1.0)	15 (14.9)	2 (2.0)	1 (1.0)	0	19 (18.8)
	2	0	0	2 (2.0)	0	0	2 (2.0)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	72 (71.3)	22 (21.8)	6 (5.9)	1 (1.0)	0	101 (100.0)
HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	Normal	105 (69.1)	27 (17.8)	5 (3.3)	1 (0.7)	0	138 (90.8)
	1	0	11 (7.2)	1 (0.7)	0	0	12 (7.9)
	2	0	0	2 (1.3)	0	0	2 (1.3)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	105 (69.1)	38 (25.0)	8 (5.3)	1 (0.7)	0	152 (100.0)
NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142) n = 140	Normal	104 (73.2)	9 (6.3)	2 (1.4)	0	0	115 (81.0)
	1	1 (0.7)	19 (13.4)	3 (2.1)	1 (0.7)	0	24 (16.9)
	2	0	0	2 (1.4)	0	0	2 (1.4)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	105 (73.9)	28 (19.7)	7 (4.9)	1 (0.7)	0	141 (99.3)
	Missing	1	0	0	0	0	1
NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208) n = 205	Normal	146 (71.2)	33 (16.1)	7 (3.4)	1 (0.5)	0	187 (91.2)
	1	0	15 (7.3)	1 (0.5)	0	0	16 (7.8)
	2	0	0	2 (1.0)	0	0	2 (1.0)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	146 (71.2)	48 (23.4)	10 (4.9)	1 (0.5)	0	205 (100.0)
All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045) n = 1039	Normal	790 (76.0)	140 (13.5)	35 (3.4)	3 (0.3)	2 (0.2)	970 (93.4)
	1	3 (0.3)	51 (4.9)	5 (0.5)	2 (0.2)	0	61 (5.9)
	2	0	1 (0.1)	5 (0.5)	1 (0.1)	0	7 (0.7)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	793 (76.3)	192 (18.5)	45 (4.3)	6 (0.6)	2 (0.2)	1038 (99.9)
	Missing	1	0	0	0	0	1
All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741) n = 1732	Normal	1087 (62.8)	440 (25.4)	68 (3.9)	8 (0.5)	3 (0.2)	1606 (92.7)
	1	5 (0.3)	92 (5.3)	15 (0.9)	3 (0.2)	0	115 (6.6)
	2	0	1 (0.1)	8 (0.5)	1 (0.1)	0	10 (0.6)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	1092 (63.0)	533 (30.8)	91 (5.3)	12 (0.7)	3 (0.2)	1731 (99.9)
	Missing	1	0	0	0	0	1

CTCAE = Common Terminology Criteria for Adverse Events, version 5.0; DCO = data cut-off; HER2-mut = human epidermal growth factor receptor 2 mutated; n = number of subjects with both baseline and post-baseline measurements in each treatment group; NSCLC = non-small cell lung cancer; T-DXd = trastuzumab deruxtecan

[a] Includes 11 subjects from Study J101, 91 subjects from Study U204, and 50 subjects from Study U206.

[b] Includes 41 subjects with HER2-overexpressing NSCLC from Study U204 and 101 subjects with HER2-mutant NSCLC from Study U206.

[c] Includes 11 subjects with HER2-mutant and 7 subjects with HER2-expressing NSCLC from Study J101, 91 subjects with HER2-mutant and 49 subjects with HER2-overexpressing NSCLC from Study U204, and 50 subjects with HER2-mutant NSCLC from Study U206.

[d] Includes 91 subjects from Study J101, 184 subjects from Study U201, 41 subjects from Study U204, 101 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

[e] Includes 280 subjects from Study J101, 169 subjects from Study J202, 253 subjects from Study U201, 181 subjects from Study U204, 79 subjects from Study U205, 151 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

Baseline was defined as the last non-missing value taken before the first dose of study drug.
Blood chemistry data were graded according to CTCAE Version 5.0 based on laboratory criteria only.
Percentage was calculated using the number of subjects with both baseline and post-baseline measurements in each treatment group as the denominator.
Data are included as of data cut-off of 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study U201, 03 Dec 2021 for Study U204, 09 Apr 2021 for Study U205, 23 Dec 2022 for Study U206, 07 Sep 2021 for Study U302, and 11 Jan 2022 for Study U303. (U206 DCO 23 Dec 2022)

QT prolongation:

At the beginning of the T-DXd clinical program, AESIs included ILD, left ventricular ejection fraction (LVEF) decrease, QT prolongation, and IRR. On 09 Jul 2019, based on the comprehensive review of the safety data, and taking into consideration biological plausibility, QT prolongation and IRR were no longer considered AESIs for the T-DXd clinical program. In addition, on 06 Apr 2020, "left ventricular ejection fraction decreased" was renamed to "left ventricular (LV) dysfunction" to reflect that this is a clinical concept rather than a laboratory finding.

Table 62: Summary of QT Interval with Updated Study U206 Data (DCO 23 Dec 2022; Safety Analysis Set)

ECG Parameter	Number (%) of Subjects					
	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
QT interval (ms)						
Non-missing, n	88	141	126	194	1026	1703
New >470 (female) or new >450 (male)	0	1 (0.7)	0	1 (0.5)	55 (5.4)	106 (6.2)
New >480	0	0	0	0	27 (2.6)	42 (2.5)
New >500	0	0	0	0	12 (1.2)	18 (1.1)
Increase from baseline >30	18 (20.5)	54 (38.3)	32 (25.4)	68 (35.1)	421 (41.0)	669 (39.3)
Increase from baseline >60	6 (6.8)	15 (10.6)	10 (7.9)	19 (9.8)	111 (10.8)	165 (9.7)
QTcF[f] interval (ms)						
Non-missing, n	88	141	126	194	1026	1703
New >470 (female) or new >450 (male)	2 (2.3)	11 (7.8)	6 (4.8)	14 (7.2)	92 (9.0)	158 (9.3)
New >480	0	5 (3.5)	0	6 (3.1)	45 (4.4)	69 (4.1)
New >500	0	0	0	0	17 (1.7)	24 (1.4)
Increase from baseline >30	7 (8.0)	28 (19.9)	16 (12.7)	33 (17.0)	264 (25.7)	373 (21.9)
Increase from baseline >60	0	5 (3.5)	1 (0.8)	8 (4.1)	51 (5.0)	73 (4.3)

DCO = data cut-off; ECG = electrocardiogram; HER2-mut= human epidermal growth receptor factor receptor 2 mutated; NSCLC = non-small cell lung cancer; QTcF = QT interval corrected for heart rate using Fridericia's formula; T-DXd = trastuzumab deruxtecan

[a] Includes 11 subjects from Study J101, 91 subjects from Study U204, and 50 subjects from Study U206.
[b] Includes 41 subjects with HER2-overexpressing NSCLC from Study U204 and 101 subjects with HER2-mutant NSCLC from Study U206.
[c] Includes 11 subjects with HER2-mutant and 7 subjects with HER2-expressing NSCLC from Study J101, 91 subjects with HER2-mutant and 49 subjects with HER2-overexpressing NSCLC from Study U204, and 50 subjects with HER2-mutant NSCLC from Study U206.
[d] Includes 91 subjects from Study J101, 184 subjects from Study U201, 41 subjects from Study U204, 101 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.
[e] Includes 280 subjects from Study J101, 169 subjects from Study J202, 253 subjects from Study U201, 181 subjects from Study U204, 79 subjects from Study U205, 151 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.
[f] To be considered concurrent, abnormalities must have occurred within a 28-day window.
A subject with multiple occurrences of a new occurring abnormality was counted only once per abnormality.
Baseline value was defined as the last non-missing value before initial administration of study drug.
If multiple ECG measurements were taken at the baseline, the average of all baseline values was used as baseline.
New was defined as an abnormal ECG finding at post-baseline that was not present at baseline.
Non-missing n was number of subjects with both baseline and post-baseline non-missing data.

Percentages were calculated using the non-missing n as the denominator.
Data are included as of data cut-off of 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study U201, 03 Dec 2021 for Study U204, 09 Apr 2021 for Study U205, 23 Dec 2022 for Study U206, 07 Sep 2021 for Study U302, and 11 Jan 2022 for Study U303. (U206 DCO 23 Dec 2022)

Safety in special populations

Age:

Table 63: Overall Summary of Treatment-emergent Adverse Events by Age Group with Updated Study U206 Data (DCO 23 Dec 2022; Safety Analysis Set)

Subgroup Parameter	Number (%) of Subjects					
	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
Age: <65 years						
n	61	97	88	129	780	1205
Subjects with any TEAE	61 (100.0)	97 (100.0)	88 (100.0)	129 (100.0)	775 (99.4)	1200 (99.6)
TEAEs with CTCAE ≥Grade 3	29 (47.5)	64 (66.0)	41 (46.6)	88 (68.2)	394 (50.5)	699 (58.0)
TE SAEs	17 (27.9)	32 (33.0)	26 (29.5)	44 (34.1)	182 (23.3)	324 (26.9)
TEAEs associated with study drug discontinuation	7 (11.5)	27 (27.8)	10 (11.4)	35 (27.1)	109 (14.0)	210 (17.4)
TEAEs associated with dose reduction	8 (13.1)	32 (33.0)	11 (12.5)	42 (32.6)	157 (20.1)	291 (24.1)
TEAEs associated with study drug interruption	21 (34.4)	53 (54.6)	27 (30.7)	66 (51.2)	303 (38.8)	503 (41.7)
TEAEs associated with an outcome of death	3 (4.9)	7 (7.2)	7 (8.0)	11 (8.5)	30 (3.8)	62 (5.1)
Subjects with drug-related TEAEs	59 (96.7)	95 (97.9)	85 (96.6)	126 (97.7)	759 (97.3)	1176 (97.6)
Drug-related TEAEs with CTCAE ≥Grade 3	19 (31.1)	52 (53.6)	23 (26.1)	68 (52.7)	319 (40.9)	560 (46.5)
Drug-related TE SAEs	5 (8.2)	17 (17.5)	6 (6.8)	22 (17.1)	86 (11.0)	153 (12.7)
Drug-related TEAEs associated with study drug discontinuation	7 (11.5)	20 (20.6)	8 (9.1)	26 (20.2)	99 (12.7)	181 (15.0)
Drug-related TEAEs associated with dose reduction	7 (11.5)	32 (33.0)	10 (11.4)	41 (31.8)	151 (19.4)	277 (23.0)
Drug-related TEAEs associated with study drug interruption	12 (19.7)	36 (37.1)	14 (15.9)	45 (34.9)	226 (29.0)	376 (31.2)
Drug-related TEAEs associated with an outcome of death	0	0	0	1 (0.8)	9 (1.2)	16 (1.3)
Age: ≥65 years						
n	40	55	54	79	265	536
Subjects with any TEAE	40 (100.0)	55 (100.0)	54 (100.0)	79 (100.0)	265 (100.0)	536 (100.0)
TEAEs with CTCAE ≥Grade 3	24 (60.0)	40 (72.7)	33 (61.1)	59 (74.7)	169 (63.8)	364 (67.9)
TE SAEs	20 (50.0)	28 (50.9)	27 (50.0)	44 (55.7)	97 (36.6)	219 (40.9)
TEAEs associated with study drug discontinuation	8 (20.0)	22 (40.0)	12 (22.2)	30 (38.0)	56 (21.1)	125 (23.3)
TEAEs associated with dose reduction	10 (25.0)	21 (38.2)	14 (25.9)	29 (36.7)	68 (25.7)	163 (30.4)

Subgroup Parameter	Number (%) of Subjects					
	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
TEAEs associated with study drug interruption	24 (60.0)	29 (52.7)	28 (51.9)	42 (53.2)	131 (49.4)	268 (50.0)
TEAEs associated with an outcome of death	3 (7.5)	8 (14.5)	6 (11.1)	15 (19.0)	15 (5.7)	43 (8.0)
Subjects with drug-related TEAEs	38 (95.0)	54 (98.2)	50 (92.6)	74 (93.7)	257 (97.0)	519 (96.8)
Drug-related TEAEs with CTCAE ≥Grade 3	20 (50.0)	26 (47.3)	25 (46.3)	39 (49.4)	134 (50.6)	291 (54.3)
Drug-related TE SAEs	9 (22.5)	14 (25.5)	11 (20.4)	20 (25.3)	44 (16.6)	106 (19.8)
Drug-related TEAEs associated with study drug discontinuation	7 (17.5)	15 (27.3)	9 (16.7)	20 (25.3)	51 (19.2)	101 (18.8)
Drug-related TEAEs associated with dose reduction	10 (25.0)	20 (36.4)	14 (25.9)	28 (35.4)	58 (21.9)	150 (28.0)
Drug-related TEAEs associated with study drug interruption	15 (37.5)	22 (40.0)	17 (31.5)	32 (40.5)	96 (36.2)	203 (37.9)
Drug-related TEAEs associated with an outcome of death	1 (2.5)	2 (3.6)	1 (1.9)	3 (3.8)	3 (1.1)	9 (1.7)
Age: <75 years						
n	93	135	132	189	999	1644
Subjects with any TEAE	93 (100.0)	135 (100.0)	132 (100.0)	189 (100.0)	994 (99.5)	1639 (99.7)
TEAEs with CTCAE ≥Grade 3	49 (52.7)	91 (67.4)	68 (51.5)	132 (69.8)	539 (54.0)	998 (60.7)
TE SAEs	35 (37.6)	48 (35.6)	50 (37.9)	74 (39.2)	267 (26.7)	499 (30.4)
TEAEs associated with study drug discontinuation	13 (14.0)	39 (28.9)	18 (13.6)	54 (28.6)	155 (15.5)	309 (18.8)
TEAEs associated with dose reduction	15 (16.1)	48 (35.6)	21 (15.9)	65 (34.4)	212 (21.2)	423 (25.7)
TEAEs associated with study drug interruption	41 (44.1)	74 (54.8)	51 (38.6)	98 (51.9)	415 (41.5)	725 (44.1)
TEAEs associated with an outcome of death	5 (5.4)	9 (6.7)	11 (8.3)	20 (10.6)	43 (4.3)	91 (5.5)
Subjects with drug-related TEAEs	89 (95.7)	133 (98.5)	125 (94.7)	182 (96.3)	970 (97.1)	1599 (97.3)
Drug-related TEAEs with CTCAE ≥Grade 3	35 (37.6)	72 (53.3)	43 (32.6)	101 (53.4)	432 (43.2)	800 (48.7)
Drug-related TE SAEs	13 (14.0)	25 (18.5)	16 (12.1)	35 (18.5)	125 (12.5)	239 (14.5)
Drug-related TEAEs associated with study drug discontinuation	12 (12.9)	30 (22.2)	14 (10.6)	40 (21.2)	141 (14.1)	264 (16.1)
Drug-related TEAEs associated with dose reduction	14 (15.1)	47 (34.8)	20 (15.2)	63 (33.3)	200 (20.0)	402 (24.5)
Drug-related TEAEs associated with study drug interruption	24 (25.8)	52 (38.5)	28 (21.2)	70 (37.0)	309 (30.9)	544 (33.1)
Drug-related TEAEs associated with an outcome of death	1 (1.1)	0	1 (0.8)	2 (1.1)	12 (1.2)	22 (1.3)
Age: ≥75 years						

Subgroup Parameter	Number (%) of Subjects					
	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
n	8	17	10	19	46	97
Subjects with any TEAE	8 (100.0)	17 (100.0)	10 (100.0)	19 (100.0)	46 (100.0)	97 (100.0)
TEAEs with CTCAE ≥Grade 3	4 (50.0)	13 (76.5)	6 (60.0)	15 (78.9)	24 (52.2)	65 (67.0)
TE SAEs	2 (25.0)	12 (70.6)	3 (30.0)	14 (73.7)	12 (26.1)	44 (45.4)
TEAEs associated with study drug discontinuation	2 (25.0)	10 (58.8)	4 (40.0)	11 (57.9)	10 (21.7)	26 (26.8)
TEAEs associated with dose reduction	3 (37.5)	5 (29.4)	4 (40.0)	6 (31.6)	13 (28.3)	31 (32.0)
TEAEs associated with study drug interruption	4 (50.0)	8 (47.1)	4 (40.0)	10 (52.6)	19 (41.3)	46 (47.4)
TEAEs associated with an outcome of death	1 (12.5)	6 (35.3)	2 (20.0)	6 (31.6)	2 (4.3)	14 (14.4)
Subjects with drug-related TEAEs	8 (100.0)	16 (94.1)	10 (100.0)	18 (94.7)	46 (100.0)	96 (99.0)
Drug-related TEAEs with CTCAE ≥Grade 3	4 (50.0)	6 (35.3)	5 (50.0)	6 (31.6)	21 (45.7)	51 (52.6)
Drug-related TE SAEs	1 (12.5)	6 (35.3)	1 (10.0)	7 (36.8)	5 (10.9)	20 (20.6)
Drug-related TEAEs associated with study drug discontinuation	2 (25.0)	5 (29.4)	3 (30.0)	6 (31.6)	9 (19.6)	18 (18.6)
Drug-related TEAEs associated with dose reduction	3 (37.5)	5 (29.4)	4 (40.0)	6 (31.6)	9 (19.6)	25 (25.8)
Drug-related TEAEs associated with study drug interruption	3 (37.5)	6 (35.3)	3 (30.0)	7 (36.8)	13 (28.3)	35 (36.1)
Drug-related TEAEs associated with an outcome of death	0	2 (11.8)	0	2 (10.5)	0	3 (3.1)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events, version 5.0; DCO = data cut-off; HER2-mut= human epidermal growth factor receptor 2 mutated; NSCLC = non-small cell lung cancer; SAE = serious adverse event; T-DXd = trastuzumab deruxtecan; TE = treatment-emergent; TEAE = treatment-emergent adverse event

[a] Includes 11 subjects from Study J101, 91 subjects from Study U204, and 50 subjects from Study U206.

[b] Includes 41 subjects with HER2-overexpressing NSCLC from Study U204 and 101 subjects with HER2-mutant NSCLC from Study U206.

[c] Includes 11 subjects with HER2-mutant and 7 subjects with HER2-expressing NSCLC from Study J101, 91 subjects with HER2-mutant and 49 subjects with HER2-overexpressing NSCLC from Study U204, and 50 subjects with HER2-mutant NSCLC from Study U206.

[d] Includes 91 subjects from Study J101, 184 subjects from Study U201, 41 subjects from Study U204, 101 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

[e] Includes 280 subjects from Study J101, 169 subjects from Study J202, 253 subjects from Study U201, 181 subjects from Study U204, 79 subjects from Study U205, 151 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

A TEAE was defined as an AE that occurred, having been absent before the first dose of study drug, or had worsened in severity or seriousness after the initiation of the study drug until 47 days (for all studies except Study J101 [28 days]) after the last dose of study drug.

SAEs with an onset or worsening 48 days (29 days for Study J101) or more after the last dose of study drug, if considered related to the study drug, were also TEAEs.

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

If a subject had both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade was treated as the lowest severity grade.

If the sample size was too small (<10%) in a subgroup, then that was not included in the table.

Percentages were calculated using the number of subjects in each treatment group as the denominator.

Data are included as of data cut-off of 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study U201, 03 Dec 2021 for Study U204, 09 Apr 2021 for Study U205, 23 Dec 2022 for Study U206, 07 Sep 2021 for Study U302, and 11 Jan 2022 for Study U303. (U206 DCO 23 Dec 2022)

Sex:

Regardless of subgroup, for most TEAE parameters, there was a lower proportion of subjects with TEAEs in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg group than in the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool.

The frequency of events in male subjects was similar between the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg group and the All Tumor Types T-DXd 5.4 mg/kg Pool. Notable differences in female subjects were:

- A lower proportion of subjects with ≥Grade 3 TEAEs (overall and drug-related), TEAEs associated with study drug interruption (overall and drug-related), and drug-related TEAEs associated with dose reduction in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg group than in the All Tumor Types T-DXd 5.4 mg/kg Pool.

ECOG:

Table 64: Overall Summary of Treatment-emergent Adverse Events by Baseline ECOG Performance Status with Updated Study U206 Data (DCO 23 Dec 2022; Safety Analysis Set)

Subgroup Parameter	**Number (%) of Subjects**			
	Baseline ECOG Performance Status: 0		**Baseline ECOG Performance Status: 1**	
	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (n = 29)	**All Tumor Types Pool T-DXd 5.4 mg/kg[a] (n = 550)**	**U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (n = 72)**	**All Tumor Types Pool T-DXd 5.4 mg/kg[a] (n = 494)**
Subjects with any TEAE	29 (100.0)	545 (99.1)	72 (100.0)	494 (100.0)
TEAEs with CTCAE ≥Grade 3	11 (37.9)	273 (49.6)	42 (58.3)	289 (58.5)
TE SAEs	4 (13.8)	104 (18.9)	33 (45.8)	174 (35.2)
TEAEs associated with study drug discontinuation	5 (17.2)	87 (15.8)	10 (13.9)	78 (15.8)
TEAEs associated with dose reduction	8 (27.6)	105 (19.1)	10 (13.9)	120 (24.3)
TEAEs associated with study drug interruption	10 (34.5)	223 (40.5)	35 (48.6)	211 (42.7)
TEAEs associated with an outcome of death	0	10 (1.8)	6 (8.3)	34 (6.9)
Subjects with drug-related TEAEs	29 (100.0)	542 (98.5)	68 (94.4)	473 (95.7)
Drug-related TEAEs with CTCAE ≥Grade 3	10 (34.5)	237 (43.1)	29 (40.3)	215 (43.5)
Drug-related TE SAEs	3 (10.3)	60 (10.9)	11 (15.3)	70 (14.2)
Drug-related TEAEs associated with study drug discontinuation	5 (17.2)	83 (15.1)	9 (12.5)	67 (13.6)
Drug-related TEAEs associated with dose reduction	8 (27.6)	101 (18.4)	9 (12.5)	108 (21.9)
Drug-related TEAEs associated with study drug interruption	8 (27.6)	183 (33.3)	19 (26.4)	139 (28.1)
Drug-related TEAEs associated with an outcome of death	0	6 (1.1)	1 (1.4)	6 (1.2)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events, version 5.0; DCO = data cut-off; ECOG = Eastern Cooperative Oncology Group; HER2-mut= human epidermal growth factor receptor 2 mutated; NSCLC = non-small cell lung cancer; SAE = serious adverse event; T-DXd = trastuzumab deruxtecan; TE = treatment-emergent; TEAE = treatment-emergent adverse event
[a] Includes 91 subjects from Study J101, 184 subjects from Study U201, 41 subjects from Study U204, 101 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.

A TEAE was defined as an AE that occurred, having been absent before the first dose of study drug, or had worsened in severity or seriousness after the initiation of the study drug until 47 days (for all studies except Study J101 [28 days]) after the last dose of study drug.
SAEs with an onset or worsening 48 days (29 days for Study J101) or more after the last dose of study drug, if considered related to the study drug, were also TEAEs.
If relationship was missing, the TEAE was also considered to be related to the study drug.
If a subject had both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade was treated as the lowest severity grade.
If the sample size was too small (<10%) in a subgroup, then that was not included in the table.
Percentages were calculated using the number of subjects in each treatment group as the denominator.
Data are included as of data cut-off of 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study U201, 03 Dec 2021 for Study U204, 09 Apr 2021 for Study U205, 23 Dec 2022 for Study U206, 07 Sep 2021 for Study U302, and 11 Jan 2022 for Study U303.(U206 DCO 23 Dec 2022)

Baseline Renal Function

Regardless of subgroup, for most TEAE parameters, there was a lower proportion of subjects with TEAEs in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg group than in the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool.

Regardless of subgroup, for most TEAE parameters, there was a lower proportion of subjects with TEAEs in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg group than in the All Tumor Types T-DXd 5.4 mg/kg Pool.

Baseline Hepatic Function

Regardless of subgroup, for most TEAE parameters, there was a lower proportion of subjects with TEAEs in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg group than in the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool.

The frequency of events was similar between the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg group and the All Tumor Types T-DXd 5.4 mg/kg Pool, with the exception of the following notable differences:

- A lower proportion of subjects with normal hepatic function had ≥Grade 3 TEAEs, TEAEs associated with dose reduction (overall and drug-related), and TEAEs associated with study drug interruption (overall and drug-related) in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg group than in the All Tumor Types T-DXd 5.4 mg/kg Pool
- A lower proportion of subjects with mild hepatic function had ≥Grade 3 TEAEs (overall and drug-related), TEAEs associated with study drug interruption (overall and drug-related), and drug-related TEAEs in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg group than in the All Tumor Types T-DXd 5.4 mg/kg Pool.

Country:

Regardless of subgroup, for most TEAE parameters, there was a lower proportion of subjects with TEAEs in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg group than in the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool.

Regardless of subgroup, for most TEAE parameters, there was a lower proportion of subjects with TEAEs in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg group than in the All Tumor Types T-DXd 5.4 mg/kg Pool.

Region:

Regardless of subgroup (Asia or Europe), for most TEAE parameters, there was a lower proportion of subjects with TEAEs in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg group than in the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool.

The frequency of events was similar between the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg group and the All Tumor Types T-DXd 5.4 mg/kg Pool, with the exception of the following notable differences:

- A lower proportion of subjects from Asia with ≥Grade 3 TEAEs (overall and drug-related), TEAEs associated with study drug interruption (overall and drug-related), and drug-related TEAEs associated with dose reduction in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg group than in the All Tumor Types T-DXd 5.4 mg/kg Pool
- A lower proportion of subjects from Europe with TEAEs associated with dose reduction (overall and drug-related), TEAEs associated with study drug interruption (overall and drug-related), and drug-related ≥Grade 3 TEAEs in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg group than in the All Tumor Types T-DXd 5.4 mg/kg Pool
- A higher proportion of subjects from Europe with SAEs in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg group than in the All Tumor Types T-DXd 5.4 mg/kg Pool

Safety related to drug-drug interactions and other interactions

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

No new information on drug interactions is available since the time of Study DS8201-A-A104.

Discontinuation due to adverse events

Table 65: Treatment-emergent Adverse Events Associated with Study Drug Discontinuation by Preferred Term or Grouped Term Reported for ≥1% of Subjects from Study U206 with HER2-mutant NSCLC at T-DXd 5.4 mg/kg Pool with Updated Study U206 Data (DCO 23 Dec 2022; Safety Analysis Set)

MedDRA PT or Grouped Term	Number (%) of Subjects					
	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
Subjects with any TEAEs associated with study drug discontinuation	15 (14.9)	49 (32.2)	22 (15.5)	65 (31.3)	165 (15.8)	335 (19.2)
Adjudicated drug-related interstitial lung disease[f]	10 (9.9)	25 (16.4)	11 (7.7)	35 (16.8)	90 (8.6)	182 (10.5)
Interstitial lung disease[g]	2 (2.0)	0	2 (1.4)	1 (0.5)	4 (0.4)	6 (0.3)
Hypokalemia[h]	1 (1.0)	0	1 (0.7)	0	3 (0.3)	3 (0.2)
Myocarditis	1 (1.0)	0	1 (0.7)	0	1 (0.1)	1 (0.1)
Pleural effusion	1 (1.0)	0	1 (0.7)	0	4 (0.4)	4 (0.2)
Pneumonitis[g]	0	1 (0.7)	1 (0.7)	1 (0.5)	9 (0.9)	15 (0.9)

AE = adverse event; DCO = data cut-off; HER2-mut= human epidermal growth factor receptor 2 mutated; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; PT = preferred term; SMQ = standardised MedDRA query; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event
a Includes 11 subjects from Study J101, 91 subjects from Study U204, and 50 subjects from Study U206.
b Includes 41 subjects with HER2-overexpressing NSCLC from Study U204 and 101 subjects with HER2-mutant NSCLC from Study U206.
c Includes 11 subjects with HER2-mutant and 7 subjects with HER2-expressing NSCLC from Study J101, 91 subjects with HER2-mutant and 49 subjects with HER2-overexpressing NSCLC from Study U204, and 50 subjects with HER2-mutant NSCLC from Study U206.
d Includes 91 subjects from Study J101, 184 subjects from Study U201, 41 subjects from Study U204, 101 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.
e Includes 280 subjects from Study J101, 169 subjects from Study J202, 253 subjects from Study U201, 181 subjects from Study U204, 79 subjects from Study U205, 151 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.
f Interstitial lung disease includes events that were adjudicated as ILD and considered study drug related by the Adjudication Committee (includes cases of potential ILD/pneumonitis, based on MedDRA for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure).
g These events were not assessed as drug-related ILD.
h Grouped terms.

A TEAE was defined as an AE that occurred, having been absent before the first dose of study drug, or had worsened in severity or seriousness after the initiation of the study drug until 47 days (for all studies except Study J101 [28 days]) after the last dose of study drug.
If a subject had multiple PTs or grouped terms, the subject was counted in each of those terms. If a subject had multiple occurrences of the same grouped PT, the subject was counted once for the specific PT.
Percentages were calculated using the number of subjects in each treatment group as the denominator.
Preferred terms/grouped terms were sorted by descending frequency in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg column.
Data are included as of data cut-off of 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study U201, 03 Dec 2021 for Study U204, 09 Apr 2021 for Study U205, 23 Dec 2022 for Study U206, 07 Sep 2021 for Study U302, and 11 Jan 2022 for Study U303. (U206 DCO 23 Dec 2022)

Table 66: Treatment-emergent Adverse Events Associated with Dose Reduction by Preferred Term or Grouped Term Reported for ≥1% of Subjects from Study U206 with HER2-mutant NSCLC T-DXd 5.4 mg/kg with Updated Study U206 Data (DCO 23 Dec 2022; Safety Analysis Set)

MedDRA Preferred Term or Grouped Term	Number (%) of Subjects					
	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
Subjects with any TEAEs associated with dose reduction	18 (17.8)	53 (34.9)	25 (17.6)	71 (34.1)	225 (21.5)	454 (26.1)
Neutropenia[f]	4 (4.0)	9 (5.9)	4 (2.8)	14 (6.7)	32 (3.1)	77 (4.4)
Decreased appetite	3 (3.0)	1 (0.7)	3 (2.1)	2 (1.0)	14 (1.3)	50 (2.9)
Fatigue[f]	3 (3.0)	19 (12.5)	6 (4.2)	25 (12.0)	41 (3.9)	116 (6.7)
Nausea	2 (2.0)	13 (8.6)	4 (2.8)	16 (7.7)	47 (4.5)	92 (5.3)
Thrombocytopenia[f]	2 (2.0)	3 (2.0)	2 (1.4)	4 (1.9)	24 (2.3)	44 (2.5)
Blood bilirubin increased[f]	1 (1.0)	3 (2.0)	1 (0.7)	3 (1.4)	9 (0.9)	14 (0.8)
COVID-19	1 (1.0)	0	1 (0.7)	0	1 (0.1)	1 (0.1)
Diarrhoea	1 (1.0)	1 (0.7)	1 (0.7)	3 (1.4)	10 (1.0)	19 (1.1)
Transaminases increased[f]	1 (1.0)	1 (0.7)	1 (0.7)	1 (0.5)	8 (0.8)	12 (0.7)
Urinary tract infection	1 (1.0)	0	1 (0.7)	0	1 (0.1)	1 (0.1)
Weight decreased	1 (1.0)	2 (1.3)	1 (0.7)	3 (1.4)	9 (0.9)	17 (1.0)

AE = adverse event; COVID-19 = coronavirus disease 2019; DCO = data cut-off; HER2-mut = human epidermal growth factor receptor 2 mutated; MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer;
T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event
[a] Includes 11 subjects from Study J101, 91 subjects from Study U204, and 50 subjects from Study U206.
[b] Includes 41 subjects with HER2-overexpressing NSCLC from Study U204 and 101 subjects with HER2-mutant NSCLC from Study U206.
[c] Includes 11 subjects with HER2-mutant and 7 subjects with HER2-expressing NSCLC from Study J101, 91 subjects with HER2-mutant and 49 subjects with HER2-overexpressing NSCLC from Study U204, and 50 subjects with HER2-mutant NSCLC from Study U206.
[d] Includes 91 subjects from Study J101, 184 subjects from Study U201, 41 subjects from Study U204, 101 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.
[e] Includes 280 subjects from Study J101, 169 subjects from Study J202, 253 subjects from Study U201, 181 subjects from Study U204, 79 subjects from Study U205, 151 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.
[f] Grouped terms.
A TEAE was defined as an AE that occurred, having been absent before the first dose of study drug, or had worsened in severity or seriousness after the initiation of the study drug until 47 days (for all studies except Study J101 [28 days]) after the last dose of study drug.
If a subject had multiple preferred terms or grouped terms, the subject was counted in each of those terms. If a subject had multiple occurrences of the same grouped preferred term, the subject was counted once for the specific preferred term. SAEs with an onset or worsening 48 days (29 days for Study J101) or more after the last dose of study drug, if considered related to the study drug, were also TEAEs.
Percentages were calculated using the number of subjects in each treatment group as the denominator.
Preferred terms/grouped terms were sorted by descending frequency in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg column.
Data are included as of data cut-off of 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study U201, 03 Dec 2021 for Study U204, 09 Apr 2021 for Study U205, 23 Dec 2022 for Study U206, 07 Sep 2021 for Study U302, and 11 Jan 2022 for Study U303. (U206 DCO 23 Dec 2022)

Table 67: Treatment-emergent Adverse Events Associated with Study Drug Interruption by Preferred Term or Grouped Term Reported for ≥1% of Subjects from Study U206 with HER2-mutant NSCLC at T-DXd 5.4 mg/kg with Updated Study U206 Data (DCO 23 Dec 2022; Safety Analysis Set)

MedDRA PT or Grouped Term	Number (%) of Subjects					
	U206 HER2-mut NSCLC T-DXd 5.4 mg/kg (N = 101)	HER2-mut NSCLC Pool T-DXd 6.4 mg/kg[a] (N = 152)	NSCLC Pool T-DXd 5.4 mg/kg[b] (N = 142)	NSCLC Pool T-DXd 6.4 mg/kg[c] (N = 208)	All Tumor Types Pool T-DXd 5.4 mg/kg[d] (N = 1045)	All Tumor Types Pool T-DXd ≥5.4 mg/kg[e] (N = 1741)
Subjects with any TEAEs associated with study drug interruption	45 (44.6)	82 (53.9)	55 (38.7)	108 (51.9)	434 (41.5)	771 (44.3)
Neutropenia[f]	12 (11.9)	26 (17.1)	12 (8.5)	33 (15.9)	127 (12.2)	243 (14.0)
COVID-19	9 (8.9)	7 (4.6)	9 (6.3)	7 (3.4)	22 (2.1)	30 (1.7)
Adjudicated drug-related interstitial lung disease[g]	5 (5.0)	15 (9.9)	5 (3.5)	17 (8.2)	31 (3.0)	63 (3.6)
Fatigue[f]	5 (5.0)	8 (5.3)	7 (4.9)	13 (6.3)	48 (4.6)	89 (5.1)
Anemia[f]	4 (4.0)	9 (5.9)	5 (3.5)	10 (4.8)	41 (3.9)	97 (5.6)
Pneumonia	3 (3.0)	8 (5.3)	3 (2.1)	11 (5.3)	22 (2.1)	47 (2.7)
Hypokalemia[f]	2 (2.0)	1 (0.7)	2 (1.4)	2 (1.0)	8 (0.8)	14 (0.8)
Pleural effusion	2 (2.0)	0	2 (1.4)	0	3 (0.3)	5 (0.3)
Upper respiratory tract infection[f]	2 (2.0)	4 (2.6)	2 (1.4)	6 (2.9)	24 (2.3)	50 (2.9)
Urinary tract infection	2 (2.0)	1 (0.7)	3 (2.1)	1 (0.5)	9 (0.9)	12 (0.7)
Abdominal pain[f]	1 (1.0)	0	1 (0.7)	1 (0.5)	5 (0.5)	8 (0.5)
Anxiety	1 (1.0)	0	1 (0.7)	0	2 (0.2)	2 (0.1)
COVID-19 pneumonia	1 (1.0)	0	1 (0.7)	0	1 (0.1)	1 (0.1)
Decreased appetite	1 (1.0)	0	1 (0.7)	2 (1.0)	7 (0.7)	33 (1.9)
Dizziness	1 (1.0)	0	1 (0.7)	0	4 (0.4)	4 (0.2)
Dyspnoea	1 (1.0)	2 (1.3)	2 (1.4)	5 (2.4)	14 (1.3)	21 (1.2)
Ejection fraction decreased	1 (1.0)	1 (0.7)	1 (0.7)	1 (0.5)	10 (1.0)	14 (0.8)
General physical health deterioration	1 (1.0)	0	1 (0.7)	0	2 (0.2)	2 (0.1)
Headache[f]	1 (1.0)	0	1 (0.7)	1 (0.5)	1 (0.1)	2 (0.1)
Herpes zoster	1 (1.0)	1 (0.7)	1 (0.7)	1 (0.5)	5 (0.5)	6 (0.3)
Myocarditis	1 (1.0)	0	1 (0.7)	0	1 (0.1)	1 (0.1)
Oropharyngeal pain	1 (1.0)	0	1 (0.7)	0	2 (0.2)	2 (0.1)
Pneumothorax	1 (1.0)	0	1 (0.7)	0	2 (0.2)	3 (0.2)
Pulmonary embolism	1 (1.0)	1 (0.7)	1 (0.7)	1 (0.5)	3 (0.3)	5 (0.3)
Pyrexia	1 (1.0)	2 (1.3)	1 (0.7)	2 (1.0)	18 (1.7)	27 (1.6)
Thrombocytopenia[f]	1 (1.0)	6 (3.9)	1 (0.7)	6 (2.9)	27 (2.6)	48 (2.8)
Troponin I increased	1 (1.0)	1 (0.7)	1 (0.7)	1 (0.5)	1 (0.1)	2 (0.1)
Interstitial lung disease[h]	1 (1.0)	0	1 (0.7)	0	3 (0.3)	4 (0.2)
Respiratory failure[h]	1 (1.0)	0	1 (0.7)	0	2 (0.2)	2 (0.1)
Pneumonitis[h]	0	0	0	0	5 (0.5)	8 (0.5)

AE = adverse event; COVID-19 = coronavirus disease 2019; DCO = data cut-off; HER2-mut= human epidermal growth factor receptor 2 mutated; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; PT = preferred term; SMQ = standardised MedDRA query; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event

[a] Includes 11 subjects from Study J101, 91 subjects from Study U204, and 50 subjects from Study U206.

[b] Includes 41 subjects with HER2-overexpressing NSCLC from Study U204 and 101 subjects with HER2-mutant NSCLC from Study U206.

[c] Includes 11 subjects with HER2-mutant and 7 subjects with HER2-expressing NSCLC from Study J101, 91 subjects with HER2-mutant and 49 subjects with HER2-overexpressing NSCLC from Study U204, and 50 subjects with HER2-mutant NSCLC from Study U206.

[d] Includes 91 subjects from Study J101, 184 subjects from Study U201, 41 subjects from Study U204, 101 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.
[e] Includes 280 subjects from Study J101, 169 subjects from Study J202, 253 subjects from Study U201, 181 subjects from Study U204, 79 subjects from Study U205, 151 subjects from Study U206, 257 subjects from Study U302, and 371 subjects from Study U303.
[f] Grouped terms.
[g] Interstitial lung disease includes events that were adjudicated as ILD and considered study drug related by the Adjudication Committee (includes cases of potential ILD/pneumonitis, based on MedDRA for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure).
[h] These events were not assessed as drug-related ILD.
A TEAE was defined as an AE that occurred, having been absent before the first dose of study drug, or had worsened in severity or seriousness after the initiation of the study drug until 47 days (for all studies except Study J101 [28 days]) after the last dose of study drug.
If a subject had multiple PTs or grouped terms, the subject was counted in each of those terms. If a subject had multiple occurrences of the same grouped PT, the subject was counted once for the specific PT.
Percentages were calculated using the number of subjects in each treatment group as the denominator.
Preferred terms/grouped terms were sorted by descending frequency in the U206 HER2-mutant NSCLC T-DXd 5.4 mg/kg column.
Data are included as of data cut-off of 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study U201, 03 Dec 2021 for Study U204, 09 Apr 2021 for Study U205, 23 Dec 2022 for Study U206, 07 Sep 2021 for Study U302, and 11 Jan 2022 for Study U303.
Source: Module 5.3.5.3 SCS Tables 14.3.2.5.1 and 14.3.2.7.5 (U206 DCO 23 Dec 2022)

Post marketing experience

T-DXd was first approved in the US on 20 Dec 2019 as monotherapy for the treatment of patients with unresectable or metastatic HER2-positive BC who have received 2 or more prior anti-HER2-based regimens.

As of 19 Jun 2022, ENHERTU had been approved in over 40 countries, including in the US and Japan, and in the EU for the treatment of patients with unresectable or metastatic HER2-positive BC who had received 2 or more prior anti-HER2-based regimens. ENHERTU is approved in Japan, the US, Israel, and Singapore for the treatment of patients with locally advanced or metastatic HER2-positive gastric cancer who have received a prior anti-HER2 based regimen. A third indication has been approved in the US for the treatment of adult patients with unresectable or metastatic HER2-positive BC who have received a prior anti HER2-based regimen in either the metastatic setting or in the neoadjuvant or adjuvant setting, and have developed disease recurrence during or within 6 months of completing therapy.

The first 5 Periodic Benefit Risk Evaluation Reports (PBRERs), covering the reporting periods 20 Dec 2019 through 19 Jun 2020, 20 Jun 2020 through 19 Dec 2020, 20 Dec 2020 through 19 Jun 2021, 20 Jun 2021 through 19 Dec 2021, and 20 Dec 2021 through 19 Jun 2022 have been previously submitted.

Spontaneous Events

According to the cumulative summary tabulations of serious and nonserious adverse reactions from post-marketing data (Appendix 3 of the PBRER for reporting period 20 Dec 2021 through 19 Jun 2022), there have been 5247 AEs meeting PBRER criteria reported, of which the majority (4181) were nonserious. AESIs from these 5247 AEs are summarized below.

Adverse Events of Special Interest

ILD and LV dysfunction are AESIs for which targeted questionnaires are used for systematic data collection. Additionally, neutropenia including febrile neutropenia is also an important identified risk for T-DXd.

Interstitial Lung Disease

ILD/Pneumonitis remains an important identified risk for T-DXd and is subject to close monitoring. The following group of MedDRA PTs have been used to define T-DXd-related ILD in the post-marketing setting: pneumonitis, interstitial lung disease, organising pneumonia, and acute interstitial pneumonitis. Further details of identified cases are presented by PBRER period in Table 68

Table 68: Number of Spontaneous T-DXd Cases with at Least One Interstitial Lung Disease Event

Group	2020 Q1/2	2020 Q3/4	2021 Q1/2	2021 Q3/4	2022 Q1/2
Global					
No. of ILD (fatal)	6 (1)	53 (5)	141 (12)	195 (16)	232 (25)
Non-Japan (Europe, North America, ROW)					
No. of ILD (fatal)	4 (1)	15 (2)	29 (1)	94 (9)	107 (15)
Japan					
No. of ILD (fatal)	2 (0)	38 (3)	112 (11)	101 (7)	125 (10)

Notes: Spontaneous Cases and Cases from Post Marketed Studies ENH019-061, ENH019-071 are included.
Cases are selected independent from causality assessment and Case Classification "*No Patient Identifier" is included.
Included PTs: acute interstitial pneumonitis, interstitial lung disease, organising pneumonia, pneumonitis
Period in reference to PBRER-period: Q1/Q2: 20.Dec to 19 Jun, Q3/4: 20 Jun to 19 Dec.
Data Retrieval Date: 17 Jul 2022, MedDRA version 25.0

The proportion of fatal cases to total ILD post-marketing cases was similar to the one observed in clinical studies. It should be noted that the reporting rate of global ILD cases increased from 2020 Q3/4 and peaked in 2021 Q1/2. In the latest reporting period, there was a slight decrease in global ILD reporting rate in comparison to the prior period. The reporting rate for fatal ILD remains stable for the latest reporting period compared to the prior period. Furthermore, most of ILD cases were reported in Japan even though ENHERTU exposure is much higher in the US and Europe than Japan. There were 2 all-case surveys on ILD with ENHERTU treatment conducted in Japan, which could have stimulated the reporting of ILD events.

Overall, evidence from post-marketing spontaneous cases does not alter the risk of ILD/pneumonitis as observed in clinical studies.

Left Ventricular Dysfunction

For the purposes of post-marketing data collection, a potential LV dysfunction event was defined as any of the MedDRA version 25.0 PTs within the narrow scope of the cardiac failure SMQ and the PT of LV dysfunction.

This approach yielded 31 cases cumulatively; 22 reporting ejection fraction (EF) decrease (2 of them accompanied by cardiomyopathy and cardiotoxicity, respectively), 7 cardiac failure, 1 pulmonary edema, and 1 LV dysfunction were received. From the overall 31 cases, 13 cases were serious (mainly cases of cardiac failure, cardiomyopathy, and cardiotoxicity) and 18 cases were non-serious (mainly cases of EF decrease). Cases were often confounded by underlying cardiac/cardiovascular comorbidities and/or disease progression. For 3 cases (2 cardiac failure, 1 EF decrease with pneumonia) a fatal outcome was reported. However, these deaths were associated with progression of the underlying disease.

When information was provided, EF decrease was reported to be mild including isolated cases with EF decrease to 30%. Dose reduction in line with the scheme provided in T-DXd label or drug withdrawal led to improvement of EF decrease, where information was available.

Overall, the limited evidence from post-marketing cases does not alter the risk of LV dysfunction as observed in clinical studies.

Neutropenia, Including Febrile Neutropenia

Post-marketing data as well as clinical study data confirm neutropenia as the most frequently reported hematologic event, with the majority of patients recovered or were recovering. Many patients were able to continue T-DXd with or without dose reduction or interruption, approximately 22% received G-CSFs as treatment. Febrile neutropenia represents a fraction of below 12% of reported neutropenia cases. Fatal cases were mostly reported in patients developing febrile neutropenia associated with severe infections and septic shock or patients experienced neutropenia during treatment but died due to aggravation of the primary disease or pulmonary toxicity. It should be noted that the global reporting rate of neutropenia

cases increased from 2020 Q3/4 and peaked in 2021 Q3/4. There is no further increase in neutropenia reporting rate in the latest PBRER period in comparison to the previous period. Further details of identified cases are presented by PBRER period below.

Table 69: Neutropenia Cases Post-marketing – Cumulative, per PSUR Interval

Group	2020 Q1/2	2020 Q3/4	2021 Q1/2	2021 Q3/4	2022 Q1/2
Global					
No. of Neutropenia (fatal)	3 (0)	41 (0)	109 (3)	161 (4)	210 (4)
No. of Infectious Neutropenia (fatal)	0 (0)	4 (0)	17 (2)	15 (4)	24 (4)

Notes: Spontaneous Cases and Cases from Post Marketed Studies ENH019-061, ENH019-071 are included.
Cases are selected independent from causality assessment and Case Classification "*No Patient Identifier" is included.
Included PTs: cyclic neutropenia, febrile neutropenia, granulocytopenia, idiopathic neutropenia, neutropenia, neutropenic infection, neutropenic sepsis, neutrophil count decreased, autoimmune neutropenia, benign ethnic neutropenia.
Included PTs for infectious neutropenia: febrile neutropenia, neutropenic infection, neutropenic sepsis.
Period in reference to PBRER-period: Q1/Q2: 20 Dec to 19 Jun, Q3/4: 20 Jun to 19 Dec.
Data Retrieval Date: 17 Jul 2022, MedDRA version 25.0

Additional safety data needed in the context of a conditional MA

The size of the safety database in HER2-mutant NSCLC (n=101 on 5.4 mg/kg and n=152 on 6.4 mg/kg) is limited and the lack of a (SoC) control group, hampers the causality assessment and contextualization of the safety profile. The results of study DESTINY-Lung04 (SOB) will address these uncertainties.

2.5.1. Discussion on clinical safety

Albeit the most common adverse events patients experience with Enhertu are chemotherapy-like (nausea/vomiting, fatigue, alopecia, cytopenias, decreased appetite, constipation, etc.) and thus likely related to its cytotoxic component, there are certain HER2-block-related events (e.g., ILD and left ventricular dysfunction) which incidence and seriousness require close attention from clinicians.

To date, most of the clinical experience with T-DXd has been established in patients with HER2-overexpressing tumours, particularly breast (approved dose 5.4 mg/kg Q3W) and gastric/gastroesophageal cancers (approved dose 6.4 mg/kg Q3W). The all tumours 5.4 mg/kg pool (N=1449) consists mainly of patients with HER2+ and HER2-low breast cancer (n=883) and HER2-mutated NSCLC (n=142) treated with Enhertu 5.4 mg/kg Q3W until PD or intolerance. Safety results from the 5.4 mg/kg arm from study U206 in HER2-mutated metastatic NSCLC (n=101), for which the indication is sought, are crucial to understand the toxic impact of Enhertu in this particular patient population: NSCLC is a different oncology entity from the cancer types already indicated for treatment with Enhertu, with a specific pattern of pleuropulmonary-related events. Supportive results from trials U204 and J101 were also provided to characterise the safety profile of T-DXd in lung cancer.

Exposure: Safety data have been provided for 1,741 subjects receiving trastuzumab deruxtecan (T-DXd) ≥5.4 mg/kg across eight clinical trials in various solid tumour types, of which 1,045 subjects received 5.4 mg/kg (safety Pool SmPC). During the assessment period the MAH has provided safety data from further 404 patients included in Study U301 and treated with T-DXd 5.4 mg/kg. Study U301 was a Phase 3, randomized, 2-arm, open-label, multicenter study designed to compare the safety and efficacy of T-DXd vs TPC in HER2positive, unresectable and/or metastatic BC subjects who were resistant or refractory to TDM1. The safety data of these patients were added to All Tumor Types T-DXd 5.4 mg/kg Pool (nr 1449) and presented in the SmPC. but the T-DXd 5.4 mg mg/kg pool assessed in this procedure was still the (N=1045).

With the updated data from study U206, the median exposure in the all tumours 5.4 mg/kg pool (N=1045) is 9.6 months, whereas for the 5.4 mg/kg safety dataset from U206 (N=101) it is 7.7 months, corresponding to a medium number of cycles of 13 and 10, respectively.

Uncertainty arises from the limited size of the safety database in HER2-mutant NSCLC (n=101 on 5.4 mg/kg and n=152 on 6.4 mg/kg) and the lack of a (SoC) control group, hampering the causality assessment and contextualization of the safety profile. The known safety profile of T-DXd aligns with that known for topoisomerase I inhibitors and trastuzumab. The updated data do not raise any new signals in the proposed target population compared to the treatment of other solid tumours (mainly HER2-overexpressed BC). Overall, the safety database may be considered sufficient to characterize the safety profile of T-DXd in the target population with supportive data from other solid tumours for long-term safety as well as identification of less frequently occurring events.

The higher dose of 6.4 mg/kg was less tolerable with numerically more Grade≥ 3 AEs (68.4% vs 52.5%), and AEs leading to dose discontinuations (32.2% vs. 14.9%) (HER2-mutant NSCLC Pool 6.4 mg/kg). These data support the choice of the proposed lower dose of 5.4 mg/kg from a safety perspective. Following an updated results from study U206 5.4 mg/kg arm the event rates increased and were similar to those observed in the all tumour types pool 5.4 mg/kg.

Most commonly reported AEs:

The most common adverse reactions were nausea (75.0%), fatigue (57.3%), vomiting (42.1%), alopecia (37.6%), neutropenia (35.2%), constipation (35.0%), anaemia (34.4%), decreased appetite (33.1%), diarrhoea (28.8%), transaminases increased (26.5%), musculoskeletal pain (26.2%), thrombocytopenia (24.5%) and leukopenia (23.7%).

The most common Grade 3 or 4 adverse reactions were neutropenia (17.0%), anaemia (9.5%), fatigue (8.4%), leukopenia (6.4%), nausea (5.9%), thrombocytopenia (5.0%), lymphopenia (4.8%), hypokalaemia (3.8%), transaminases increased (3.6%), vomiting (2.7%), diarrhoea (2.0%), decreased appetite (1.7%), pneumonia (1.4%) and ejection fraction decreased (1.1%). Grade 5 adverse reactions occurred in 1.4% of patients, including ILD (1.0%).

Dose interruptions due to adverse reactions occurred in 34.3% of patients treated with Enhertu. The most frequent adverse reactions associated with dose interruption were neutropenia (13.3%), fatigue (5.0%), anaemia (4.7%), leukopenia (3.7%), thrombocytopenia (3.0%), upper respiratory tract infection (2.7%) and ILD (2.6%). Dose reductions occurred in 20.6% of patients treated with Enhertu. The most frequent adverse reactions associated with dose reduction were fatigue (5.0%), nausea (4.9%) neutropenia (3.5%) and thrombocytopenia (2.1%). Discontinuation of therapy due to an adverse reaction occurred in 13.0% of patients treated with Enhertu. The most frequent adverse reaction associated with permanent discontinuation was ILD (9.2%).

Most common ADRs were gastrointestinal (GI) or haematologic in nature, and in line with what is already described in the SmPC and known side effects of cytotoxic drugs such as topoisomerase inhibitors.

The various types of adverse events were generally similar between study 206 (5.4 mg/kg) and the all tumours 5.4 mg/kg pool although there was a higher overall SAE frequency in study 206 (5.4 mg/kg).

Not unexpectedly with the doubling of exposure in study 206 (5.4 mg/kg; 7.7 months) the adverse events increased, and particularly neutropenia was higher compared to the all tumours 5.4 mg/kg pool (42.6% vs 35.2%).

With the updated data for study 206 (5.4 mg/kg arm) the frequency of ILD (12.9%) is now in line with the all tumours 5.4 mg/kg pool frequency (12.5%). For the HER2-mutated pool with the dose of 6.4 mg/kg (N=152) a higher frequency (27.0%) of ILD was seen.

The profile of LVEF decreases post-baseline was similar for study U206 (5.4 mg/kg) and the All tumours 5.4 mg/kg Pool. There is no observed dose-response relationship for LVEF decrease.

No new ADRs have been identified.

Interactions – extrinsic/intrinsic factors: AEs evaluated for intrinsic factors (age, sex, baseline ECOG PS, renal function at baseline, and hepatic function at baseline) did not reveal new safety signals. Tolerability appears lower in elderly (subjects ≥65 years of age), as was seen before. AEs evaluated for extrinsic factors (country, geographic region, smoking status, prior therapy, and prior pneumonectomy) did not reveal new safety signals.

2.5.2. Conclusions on clinical safety

No new adverse events or any AEs with a clearly higher frequency or severity were identified in HER2-mutant NSCLC patients (5.4 mg/kg cohort) compared to the all tumours 5.4 mg/kg pool, which mainly consists of breast cancer patients. Incidence and severity of AEs is considerably higher in the lung cancer pools treated at 6.4 mg/kg, supporting a considerably safer profile at the lower dose.

The size of the safety database in HER2-mutant NSCLC (n=101 on 5.4 mg/kg and n=152 on 6.4 mg/kg) is limited and the lack of a (SoC) control group, hampers the causality assessment and contextualization of the safety profile.

The safety profile of Enhertu in the treatment of patients with HER2-mutant NSCLC will be further characterized in the ongoing confirmatory study DESTINY-Lung04 results of which are required as a special obligation for this new indication.

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

The PRAC considered that the risk management plan version 7.0 is acceptable.

Safety concerns

There was no new safety concern identified for T-DXd.

Pharmacovigilance plan

No new additional pharmacovigilance activities were identified. Routine pharmacovigilance activities remain sufficient to mitigate the risks for Enhertu in all approved indications.

Risk minimisation measures

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

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

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern (Continued)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risks		
Embryo-foetal toxicity	Routine risk minimisation measures: SmPC Section 4.4 SmPC Section 4.6 Patient Information Leaflet Section 2 Recommendations for pregnancy monitoring and contraception usage are included in SmPC Section 4.4 and SmPC Section 4.6. Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Product confusion-related medication error	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 6.6 Pack and vials: specific livery for ENHERTU on the packaging and specific colours for vial cap and bottle to distinguish from other trastuzumab containing products Additional risk minimisation activities: HCP Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Missing Information		
Use in patients with moderate or severe hepatic impairment	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 5.2 Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Review of data from ongoing clinical studies Additional pharmacovigilance activities: Analysis of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern (Continued)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing Information		
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

To improve clarity and readability changes have been made in Annex II D of the SmPC to align with the information in Annex 6 of the RMP.

2.6.1. Overall conclusion on the RMP

The changes to the RMP and the changes to the conditions and obligations of the MA are acceptable.

2.7. Update of the Product information

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

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

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:

1. In accordance with articles 59(3) and 61(1) of Directive 2001/83/EC, the MAH completed a full user test of the PL during the review of the initial Marketing Authorisation Application (MAA) for Enhertu in 2020 (EMEA/H/C/005124/0000).
2. 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 are unchanged.
3. 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. Quick Response (QR) code

Not applicable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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.

The intended posology for this indication is 5.4 mg/kg and is based on preliminary results from phase II trial U206.

3.1.2. Available therapies and unmet medical need

Treatment for advanced NSCLC is tailored according to the expression of PD-L1 by IHC or the presence of predictive genomic aberrations, e.g., EGFR/BRAF mutations, ALK/ROS1/RET rearrangements, METex14 skipping or exon 20 insertions. HER2 mutations occur in ~3% of all lung cancers, and are predominantly observed in female patients, non-smokers, and patients with adenocarcinoma subtype.

Considering its relative rarity, clinical experience in HER2-mutant NSCLC is limited and none of the HER2-directed products has a specific indication approved for lung cancer in the EU, although several trials have shown a degree of antidisease activity.

Docetaxel is the current standard-of-care in the 2L+ setting for most patients with advanced non-oncogene-addicted NSCLC (pemetrexed and anti-PD-1/PD-L1 products can also be used if not used in first line), but it also constitutes an appropriate treatment in patients with oncogene-addicted disease for which targeted products are not approved/available. (L. E. Hendriks et al., 2023).

Evidence of efficacy of anti-HER2 products in HER2-mutant NSCLC is limited and mainly consists of real-world data and results from small retrospective cohorts. EUHER2 was a retrospective study (Mazieres et al, Ann Oncol 2016) which reported 44% ORR from conventional chemotherapy (n=93) and 51% from HER2-targeted therapies (among which trastuzumab, neratinib, afatinib, lapatinib, T-DM1)(n=65). T-DM1 (Kadcyla®) showed 44% of responses in the HER2-mutant NSCLC cohort (n=18) from a basket trial (Li et al, JCO 2018). IFCT.1703 R2D2 (Mazieres et al, JCO 2022) reported 29% ORR from trastuzumab + pertuzumab + docetaxel in 45 patients.

3.1.3. Main clinical studies

The current application (T-DXd at 5.4 mg/kg Q3W) is based on preliminary results from phase II trial U206. Results from similar patient cohorts treated with T-DXd at 6.4 mg/kg from trials J101 and U204 were submitted as supportive evidence of efficacy.

Study U206 is an ongoing partially-blinded phase 2 study that randomised patients from the targeted population to T-DXd at 5.4 mg/kg or 6.4 mg/kg in a 2:1 ratio, hence uncontrolled (both patients and investigators were aware of treatment with T-DXd, the blinded portion was the dose). The study planned to randomise ~100 patients to the 5.4 mg/kg arm and ~50 to the 6.4 mg/kg arm. The primary objective was to evaluate confirmed ORR by BICR, and the key secondary objective was DOR.

Enrolment for the pivotal trial Study U206 is currently completed.

3.2. Favourable effects

Results of the primary efficacy analyses based on database lock 23 December 2022 come from a dataset that includes a total of N=152 randomised patients (5.4 mg/kg n=102; 6.4 mg/kg n=50) with median follow-up of 11.6 months.

- Confirmed ORR as assessed by BICR was 49% (95% CI 39.0-59.1) in the T-DXd 5.4 mg/kg arm and 56% (44.9, 62.6) in the 6.4 mg/kg arm.
- Median DoR was ~17 months for the 50 responders in the 5.4 mg/kg arm and it was not reached in the 6.4 mg/kg arm
- Response rates are overall similar in patients with/without baseline CNS metastases, prior or no prior anti-PD-1/PD-L1 treatment and of asian/non-asian ethnicity.

3.3. Uncertainties and limitations about favourable effects

The main limitation to the interpretation of efficacy results is the uncontrolled nature of trial U206. Since the provided dataset is not considered comprehensive. The MAH will submit the results of study DESTINY-Lung04 by Q4 2025, as a new specific obligation to confirm the efficacy and safety of Enhertu in the intended indication (see section below on Additional Consideration on benefit-risk balance).

The applied censoring rules for the DOR primary analysis resulted in an upward bias (overestimation) of the median DOR, and it is therefore considered more plausible than the median DOR is somewhere between 8 and 12 months, rather than the originally estimated 16.8 months. This uncertainty will be addressed by the results of the SOB.

3.4. Unfavourable effects

Safety data have been provided for 1,741 subjects who received trastuzumab deruxtecan (T-DXd) ≥5.4 mg/kg across eight clinical trials in various solid tumour types, of which 1,045 subjects received 5.4 mg/kg, with a median exposure of 9.6 months, whereas for the 5.4 mg/kg safety dataset from U206 (N=101) it is 7.7 months, corresponding to a medium number of cycles of 13 and 10, respectively.

The safety pool in the current SmPC consists of N=1449 patients receiving 5.4 mg/kg including 404 patients from trial U301 (patients metastatic HER2-positive breast cancer) in addition to the 5.4 mg/kg pool assessed in this procedure (N=1045).

The adverse events were generally similar between study U206 (5.4 mg/kg) and the all tumours 5.4 mg/kg pool.

In study U206 (5.4 mg/kg) neutropenia was reported more frequently compared to the all tumours 5.4 mg/kg pool (42.6% vs 35.2%).

With the updated data for study U206 (5.4 mg/kg arm) the frequency of ILD (12.9%) is in line with the all tumours 5.4 mg/kg pool frequency (12.5%). For the HER2-mutated pool a higher frequency (27.0%) of ILD was seen with the dose of 6.4 mg/kg (N=152).

The profile of LVEF decreases post-baseline was similar for study U206 (5.4 mg/kg) and the all tumours 5.4 mg/kg pool.

No new adverse events or AEs with a higher frequency were observed in the HER2-mutant NSCLC patients (5.4 mg/kg cohort, n=101) compared to the all tumours 5.4 mg/kg pool (N=1045). The most

commonly reported ADRs were gastrointestinal (GI) or haematologic in nature, and in line with what is already described in the SmPC and known side effects of cytotoxic drugs such as topoisomerase inhibitors.

The most common SAEs were dyspnoea, adjudicated drug-related ILD, malignant neoplasm progression, nausea, pleural effusion, pneumonitis, thrombocytopenia (grouped term), and troponin I increased (2.0%, each).

In study U206 (5.4 mg/kg arm) the most common AEs associated with study drug discontinuation were adjudicated drug-related ILD (9.9%) Neutropenia (11.9%), and adjudicated drug-related ILD (5.0%) were the most common TEAEs leading to dose interruption whereas neutropenia (4%), decreased appetite, and fatigue were the most common TEAEs associated with dose reduction (3.0%, each).

There were more ≥3 Grade TEAEs and SAEs in patients ≥65 years.

Incidence and severity of AEs is considerably lower in lung cancer patients treated at 5.4 mg/kg as compared to those from the 6.4 mg/kg pools.

3.5. Uncertainties and limitations about unfavourable effects

The size of the safety database in HER2-mutant NSCLC (n=101 on 5.4 mg/kg and n=152 on 6.4 mg/kg) is limited and the lack of a (SoC) control group, hampers the causality assessment and contextualization of the safety profile. The results of study DESTINY-Lung04 (SOB) will address these uncertainties.

3.6. Effects Table

Table 70: Effects Table for trastuzumab deruxtecan in the treatment of patients with advanced HER2-mutant NSCLC after progression to at least one prior therapy, Study 206 at data cut-off 23-DEC-2022.

Effect	Short description	Unit	T-DXd 5.4 mg/kg n=102		Uncertainties / Strength of evidence	References
Favourable Effects						
cORR by BIRC	Confirmed overall response rate by blinded independent central review	% (n) 95% CI	49% (50) 39.0, 59.1		Uncertainty: Uncontrolled trial, Endpoint showing antitumour activity	SCS Tbl. 3.3
mDOR by BICR	Median duration of response by blinded independent central review	Months 95% CI	16.8 6.4, NE		Uncertainties: Uncontrolled trial, potential bias given censoring rules	SCS Tbl. 3.3
Unfavourable Effects:						
			All tumours 5.4 mg/kg pool (N=1045)	**HER2-mt NSCLC 5.4 mg/kg U206 (n=101)**		
Grade ≥3 AEs		%	53.9	52.5	Exposure for study U206: mDoT 7.7 months. All tumours 5.4 mg/kg pool (n=1,045): mDoT 9.6 months. No new safety signals	Table 2/Q28
SAEs		%	26.7	36.6		
AEs leading to discontinuation		%	15.8	14.9		
ILD/pneumonitis[x] All ⩾ Grade 3		%	 12.7 2.3	 12.9 1.0		Table 6/Q28
Left ventricular ejection fraction: - Grade 2 LVEF decrease		%	 15.4	 10.0	[#]Recovered: 83/148 (75.5%) – 1/9 (25%)	Table 9/Q28

Effect	Short description	Unit	T-DXd 5.4 mg/kg n=102		Uncertainties / Strength of evidence	References
- Grade 3 LVEF decrease			0.8	0	5/8 (71%)- NA	
Neutropenia:[+] All ⩾ Grade 3		%	 35.2 16.6	 42.6 18.8		Table 9/Q28

Abbreviations: ILD=Interstitial lung disease, mDoT=median duration of treatment,

Notes:
*Pts. receiving the 5.4 mg/kg dose: Includes 91 subjects from Study J101, 184 from Study U201, 41 from Study U204, 101 from Study U206, 257 from Study U302, and 371 from Study U303 corresponding to 883 Breast cancer patients, 142 NSCLC and 20 Other.
[ϰ]Adjudicated as ILD whether or not considered related.
not all pts had LVEF measured after the AE; denominator were those who had the measurement performed.
[+]neutropenia, neutrophil count decreased

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Lung cancer with HER2 (ERBB2) mutation subtype is rare (~3% of all NSCLC), and mainly affects women and non-smokers. None of the targeted anti-HER2 products is approved for HER2-mutant NSCLC.

Previous results from phase I trial J101 and phase II trial U204, in which T-DXd was evaluated at the 6.4 mg/kg dose, already reported encouraging efficacy in heavily pretreated HER2-mutant NSCLC patients. The design of trial U206 accounted the paucity of data for the 5.4 mg/kg dose in these patients and randomised patients to both dose schemes. The primary endpoint for this single arm trial was ORR which show a treatment-related anti-tumour effect.

In this heavily pre-treated population of patients with advanced HER2-mutant NSCLC (two thirds of them having received ≥2 lines of previous treatments), the reported ORR (49%) and median DoR (~17 months) exceeds treatment effects previously seen in historical data from HER2-mutant NSCLC cohorts in the 2L setting (ORR 5-18%). Besides, while acknowledging the limitations of cross-study comparisons, the results appear comparable to those observed in previous applications for the treatment of advanced oncogene-addicted NSCLC in 2L (ORR 41-60%, median DoR 9-17.5 months). However, it is considered plausible that DOR results are overestimated, and it remains uncertain whether treatment effect in terms of ORR/DOR would reflect into long term benefit (PFS/OS) in this particular setting. Since the totality of presented data is not considered comprehensive for full approval of this extension of indication, the ongoing Study DESTINY-Lung04 in the first line setting has been requested as a new SOB in the context of the conditional marketing authorisation of Enhertu.

Regarding safety, the data from Study U206 indicate that interstitial lung disease is of particular concern: although the frequency is in line with the larger safety pool, ILD presents a larger therapeutic problem in patients with lung cancer (as opposed to breast cancer, which represents the majority in the pool). This is reflected in the percentage of AEs leading to discontinuation (11.9 % vs 9.0%) as well as drug interruption in study U206 (5.4 mg/kg) compared to the one for the all tumour 5.4 mg/kg pool.

Although the currently reported efficacy results seem to be overall comparable between the 5.4 mg/kg dose and the 6.4 mg/kg dose (noting numerically better results in the 6.4 mg/kg arm), T-DXd at 5.4 mg/kg was less toxic and better tolerated than T-DXd at 6.4 mg/kg, supporting the currently intended (5.4 mg/kg Q3W) posology for marketing.

3.7.2. Balance of benefits and risks

Pivotal evidence to ascertain the benefit/risk balance for T-DXd in the targeted population comes from an uncontrolled efficacy dataset. Mature data from ORR and DOR for the intended posology for marketing (5.4 mg/kg Q3W) have been provided, but it is uncertain whether these data could reflect long term benefits in terms of PFS and OS. The study DESTINY-Lung04 will be submitted by Q4 2025 as a new SOB to confirm the efficacy and safety of Enhertu.

The safety profile of T-DXd is non-negligible and ILD/pneumonitis remains an important safety concern. Most frequently occurring GI and haematological adverse events related to the MoA are reversible upon supportive management and/or dose modifications.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

Enhertu is currently authorised as a conditional marketing authorisation. The data supporting the extension of indication to advanced HER2-mutant NSCLC are not considered comprehensive, a conditional marketing authorisation is therefore also proposed for this new indication.

Importantly, 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. Furthermore, the CHMP considers that the new indication for this product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance of T-DXd 5.4 mg/kg Q3W is positive, as the results from Study U206 outline promising response rates in patients with advanced HER2-mutant NSCLC. Responses seem durable and overall efficacy data is supported by results from the 6.4 mg/kg cohorts across trials U206, J101 and U204. The safety profile of T-DXd is well-known and there does not seem to be any new adverse event with a clearly higher frequency or severity in patients with lung cancer.
- It is likely that the applicant will be able to provide comprehensive data. Study DESTINY-Lung04 (DL04) is a phase 3, open-label, randomised, controlled trial of T-DXd vs. standard-of-care immunochemotherapy in the first line treatment of patients with advanced HER2-mutant NSCLC. The study started in October 2021 and is close to finishing recruitment (252 subjects enrolled up to July 2023, targeted sample size is ~264), and will provide interpretable results of time-to-event endpoints in an earlier setting for this biomarker-driven population. Study DL04 has been added as a new SOB with due date Q4 2025.
- T-DXd fulfills an unmet medical need for patients with advanced HER2-mutant NSCLC, since there are no approved HER2-targeted therapies in this setting, particularly after progression to first-line platinum-based chemotherapy. Currently approved treatment options in the second-line setting for NSCLC without actionable oncogenic driver mutations show response rates ranging from 5.5% to 22.9%, and median DoR from 6.3 to 8.4 months. While the limitations related to indirect comparisons between studies are acknowledged, response rate in the current approved treatments are lower than that observed with T-DXd in the pivotal Study U206 (ORR 49% (95% CI 39.0-59.1. Moreover, providing a new treatment option with a new mechanism of action T-DXd is expected to bring relevant therapeutic advantage to patients.
- The benefits to public health of the immediate availability of T-DXd outweigh the risks inherent in the fact that additional data are still required. Patients with advanced NSCLC and activating HER2 mutations have a dismal prognosis and will likely benefit from the availability of a HER2-targeted treatment.

3.8. Conclusions

The overall B/R of Enhertu for the intended treatment of advanced HER2-mutant NSCLC after progression to platinum-based chemotherapy +/- immunotherapy is positive, subject to the specific obligations and conditions imposed in order to obtain further clinical data to generate a comprehensive dataset. Consequently, the ongoing study DESTINY-Lung04, a phase III RCT of T-DXd versus standard-of-care immunochemotherapy in the 1L setting is imposed as a SOB in Annex II of the Opinion.

4. Recommendations

Outcome

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

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

Extension of indication to include the indication treatment of non-small cell lung cancer (NSCLC) for Enhertu (trastuzumab deruxtecan), based on results from study DS8201-A-U206 (DESTINY-Lung02), a phase 2, randomised study evaluating the safety and efficacy of trastuzumab deruxtecan in subjects with HER2-mutated metastatic non-small cell lung cancer.
As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The Annex II and Package Leaflet are updated in accordance.

Version 7.0 of the RMP has also been submitted.

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

Amendments to the marketing authorisation

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

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

Risk management plan (RMP)

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

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

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

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) 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 advanced NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy, the MAH should submit the results of the study DESTINY-Lung04, Open-label, Randomized, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Trastuzumab Deruxtecan as First-line Treatment of Unresectable, Locally Advanced, or Metastatic NSCLC Harboring HER2 Exon 19 or 20 Mutations.	4Q 2025