Amsterdam, 14 November 2024
EMA/67925/2025
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Datopotamab deruxtecan Daiichi Sankyo

International non-proprietary name: datopotamab deruxtecan

Procedure No. EMEA/H/C/006081/0000

Note

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
AE	adverse event
AGA	actionable genomic alteration
ALK	anaplastic lymphoma kinase
BCRP	breast cancer resistance protein
BICR	blinded independent central review
BLA	Biologics License Application (FDA-term; relates to DCO 29.03.2023)
BOR	best overall response
BRAF	proto-oncogene B-raf
CBR	clinical benefit rate
CI	confidence interval
CR	complete response
CRF	case report form
CSR	clinical study report
CYP3A	cytochrome P450, family 3, subfamily A
Dato-DXd	datopotamab deruxtecan; DS-1062a, investigational drug; an antibody-drug conjugate that comprises a humanized anti-TROP2 IgG1κ monoclonal antibody, MAAP-9001a, which is covalently conjugated to a drug-linker, MAAA-1162a, via thioether bonds
DCO	data cut-off
DCR	disease control rate
DoR	duration of response
120-DSU	120-Day Safety Update (relates to DCO 13.10.2023)
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	epidermal growth factor receptor
EOI	End of infusion
ER	exposure-response
FAS	Full Analysis Set
HR	hazard ratio
ID	identification
INV	investigator
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of safety
IV	intravenous
LFT	Liver function tests
KRAS	Kirsten rat sarcoma viral oncogene homologue
MET	mesenchymal-epithelial transition
MTD	maximum tolerated dose

Abbreviation	Definition
NSCLC	non-small cell lung cancer
NTRK	neurotrophic tyrosine receptor kinase
OATP1B	organic anion transporting polypeptide 1B
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-(L)1	programmed cell death (ligand) 1
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome(s)
Q3W	every 3 weeks
RDE	recommended dose for expansion
RECIST v1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RET	rearranged during transfection
ROS1	ROS proto-oncogene 1
SAP	Statistical Analysis Plan
SCE	Summary of clinical efficacy
SCS	Summary of clinical safety
SD	stable disease
SoD	sum of diameters
TL01	TROPION-Lung01; DS1062-A-U301
TL05	TROPION-Lung05; DS1062-A-U202
TNBC	triple-negative breast cancer
TP01	TROPION-PanTumor01; DS1062-A-J101
TROP2	trophoblast cell surface protein 2
TTD	time to deterioration
TTR	time to response
US	United States

1. Joint Rapporteur CHMP Recommendation

Based on the review of the data and the applicant's response to the list of questions on quality, safety, efficacy, the application for Datopotamab deruxtecan Daiichi Sankyo in the treatment of adult patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) who have received prior systemic therapy is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time.

The details of these major objections are provided in the list of outstanding issues (Section VII).

1.1. Questions to be posed to additional experts

1.2. Inspection issues

1.3. Inspection issues

1.3.1. GMP inspection(s)

All sites involved in manufacturing and QC testing have a valid proof of GMP compliance.

GCP inspection(s)

No GCP inspection issues have been identified during assessment of the corresponding documents.

1.4. New active substance status

Based on the review of the data, it is concluded that the active substance datopotamab deruxtecan contained in the medicinal product Datopotamab deruxtecan Daiichi Sankyo is qualified as a new active substance.

1.5. Additional data exclusivity / marketing protection

Not applicable

1.6. Similarity with authorised orphan medicinal products

Not applicable

1.7. Derogation(s) from market exclusivity

Not applicable

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

Locally advanced or metastatic NSCLC requiring systemic therapy in 2L+ setting. In this disease setting, the aim of treatment is to prolong progression-free survival and overall-survival, and/or to improve symptoms.

The proposed indication:

Datopotamab deruxtecan Daiichi Sankyo as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) who require systemic therapy following prior treatment:

- *Patients without known actionable genomic alterations previously treated with platinum-based chemotherapy in the advanced or metastatic setting and programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor, either in combination or sequentially*
- *Patients with actionable genomic alterations (as listed in section 5.1) previously treated with prior platinum-based therapy and targeted therapy for the detected alteration*

2.1.2. Epidemiology

Lung cancer is the second most common cancer and the leading cause of cancer-related mortality worldwide, with an estimated 2.2 million new cases in 2020 (11.4% of all new cancer cases) and 1.8 million deaths (18.0% of all cancer deaths) globally, based on GLOBOCAN 2020 data. More than half of lung cancers are diagnosed at an advanced stage, and the 5-year relative survival rate is approximately 22% (SEER 2018). NSCLC is the most common type of lung cancer, accounting for approximately 80% to 85% of all lung cancers; small cell lung cancer comprises the remaining approximately 15% to 20% of lung cancers (GLOBOCAN 2020).

2.1.3. Biologic features

Distinguishing among the different histologic subtypes of NSCLC is important for the selection of best treatment option for patients and the identification of patients who are more likely to respond to newer targeted therapies. Non-squamous NSCLC, which accounts for approximately 60% of all lung cancers, are recommended to undergo molecular testing, while squamous NSCLC, which accounts for approximately 25% to 30% of lung cancers, are suggested to consider molecular testing since genomic alterations are less frequent in this patient population (ESMO 2023 and NCCN 2022 guidelines). Patients should be tested for biomarkers including sensitizing EGFR mutations, ALK gene rearrangements, ROS proto-ROS1 rearrangements, BRAF point mutations, NTRK gene fusions, MET factor exon 14 skipping mutations, RET, ERBB2 and KRAS (NCCN guidelines 2022). Patients with oncogene-driven NSCLC have in general better prognosis than those without any genomic alterations and are usually younger, non-smokers, however higher risk of brain metastasis is observed, especially in patients with EGFR/ALK mutations (Shin 2014; Zhang 2016).

2.1.4. Clinical presentation

Clinical presentation of lung cancer varies, and some case might be diagnosed during routine screening. Symptoms may result from tumour invasion locally, regionally or distant; Paraneoplastic syndromes not related to metastases can also be observed. The most common symptoms at presentation are cough, dyspnoea, pain, weight loss (Kocher 2015).

2.1.5. Management

Approximately 70% of NSCLCs present with advanced disease that is not curable by surgical resection, either locally advanced (stage IIIB) or often with metastatic disease (stage IV) (Cagle 2013). The landscape of the treatment of advanced NSCLC evolved with development of targeted therapies and checkpoint inhibitors. Following diagrams (ESMO guidelines: Hendriks et al, 2023) show treatment choices for advanced NSCLC depending on histology and eligibility for immunotherapy:

Unmet medical need:

Limited treatment options exist for patients who progressed on 1L therapy. There is an unmet medical need to improve outcomes for patients who progressed on first line treatment since the available therapies only slightly prolong overall survival and progression-free survival (benefit of about 3–6 months compared to best supportive care; source table 1.1 Clinical Overview).

2.2. About the product

Dato-DXd is an antibody-drug conjugate (ADC) that comprises a recombinant humanized anti TROP2 immunoglobulin G1 (IgG1) monoclonal antibody (MAb), MAAP-9001a, which is covalently conjugated to a drug linker (D-L), MAAA 1162a, via thioether bonds. The payload (released drug), DXd (MAAA-1181a), inhibits DNA topoisomerase I and leads to apoptosis of the target cells.

Treatment would be given 6 mg/kg once every 21 days (Q3W), until disease progression or unacceptable toxicity.

2.3. The development programme/compliance with guidance/scientific advice

The clinical development program for Dato-DXd in the intended indication is straightforward and involved a pan-tumour phase I trial in heavily pre-treated patients for dose determination (TP01), a phase II single-arm trial in pre-treated NSCLC (TL05) for initial evaluation efficacy/safety and a phase III randomised controlled trial in selected pre-treated patients with NSCLC (TL01).

The initial design of TL01 (aka DS1062-A-U301), the phase III trial intended to provide comprehensive data in the proposed therapeutic indication for Dato-DXd, was discussed with CHMP in a SA procedure in November 2020. It was not upfront disclosed whether this trial would be open-label, and it was proposed that PFS, as assessed by investigator, would be the primary endpoint. The overall design, including population (patients with advanced squamous/non-squamous NSCLC without actionable genomic alterations in progression after platinum-based chemotherapy and checkpoint immunotherapy) and comparator arm, were found acceptable by the CHMP, but it was recommended that PFS, if retained as primary endpoint, were assessed by BICR, to partially mitigate bias from the likely open-label design. Regarding the choice of primary endpoints in this clinical setting, the CHMP did not favor PFS as an independent primary endpoint and insisted that OS should be the prioritized primary endpoint: "a positive primary PFS analysis, if not supported by positive OS results, cannot be viewed as sufficient for a MAA."

In a follow-up scientific advice in March 2022, the applicant disclosed a major amendment in the protocol –during study conduct– that allowed inclusion of patients with AGA (not allowed in the original protocol) while keeping the original intended sample size. By the time this amendment took place (~24-NOV-2021), about a quarter (161 out of planned n=590) of patients had been enrolled. The CHMP was overall cautious regarding this major amendment to an ongoing open-label trial, and pointed out that the heterogeneity of the additional subpopulation (which also implied an added stratification factor) may pose interpretation challenges for efficacy in the subgroup (with AGAs) as a whole. Importantly, concerns were raised upon the consideration that patients with KRAS+ tumors were included in the "AGA-negative" subgroup, since Lumykras (sotorasib) had received conditional marketing authorization for patients with KRAS G12C mutations in January 2022.

Overall, the proposed therapeutic indication –restricted to non-squamous histology– reflects the population recruited per inclusion criteria (AGA+ and AGA- and their required prior treatments), and specific clarifications on KRAS+ patients will be provided in 5.1.

The clinical studies supporting the current application are presented in the following table:

Table 1: Clinical studies

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
Pivotal study: **TL01** (TROPION-Lung01; DS1062-A-U301)	Enrolment status: completed on 07 Nov 2022 Planned: Dato-DXd: 295 Docetaxel: 295 Treated: Dato-DXd: 299 Docetaxel: 305 Ongoing Primary analysis DCO: 29 Mar 2023	NSCLC Monotherapy Phase 3, global, multicenter, randomized, active-controlled, open label study of Dato DXd vs docetaxel Dual Primary Endpoints: •PFS (BICR) •OS Secondary endpoints: •PFS (inv) •ORR (BICR/inv) •DoR (BICR/inv) •TTR (BICR/inv) •DCR (BICR/inv) •PRO included TTD	Day 1 of each 21-day cycle Dato-DXd: 6 mg/kg Docetaxel: 75 mg/m2	Adult subjects with advanced NSCLC who progressed after prior treatment with platinum-based chemotherapy and also received: a. anti-PD-(L)1 monoclonal antibody, either in combination, or sequentially (subjects without AGA); OR b. prior targeted therapy for the documented activating tumor genomic alteration (subjects with AGA: EGFR, ALK, ROS1, NTRK, BRAF, MET exon 14 skipping, or RET). Subjects with KRAS mutations, in the absence of above genomic alterations were eligible and must have met the prior therapy requirements as described for

				subjects without AGAs.
Supportive: **TL05** (TROPION-Lung05; DS1062 A-U202))	Complete Primary analysis DCO: 14 Dec 2022 Planned: Approximately 150 Treated: 137	NSCLC Monotherapy Phase 2, global, multicenter, single-arm, open-label study of Dato DXd monotherapy Primary endpoint: •ORR (BICR) Secondary endpoints: •ORR (inv) •DoR (BICR/inv) •Best percentage change in SoD of measurable tumors (BICR/inv) •DCR (BICR/inv) •CBR (BICR/inv) •PFS (BICR/inv) •TTR (BICR/inv) •OS	Day 1 of each 21-day cycle Dato-DXd: 6 mg/kg	Adult subjects with advanced or metastatic NSCLC with AGA (ie, EGFR, ALK, ROS1, NTRK, BRAF, MET exon 14 skipping, or RET) and previously treated with applicable targeted therapy and platinum-based chemotherapy with or without prior anti PD (L)1 therapy. Subjects with KRAS mutations, in the absence of above alterations, were excluded from the study.
Supportive: **TP01** (TROPION-PanTumor01; DS1062 A J101)	Study status: complete for NSCLC cohort Primary analysis DCO: 30 Jul 2021 Planned: Approximately 40 subjects at each selected dose level at or below the MTD of 8.0 mg/kg Treated:	NSCLC Monotherapy First-in-Human (NSCLC and Other Solid Tumors) Phase 1, 2 part (dose escalation and dose expansion), multicenter, open-label, multiple-dose study of Dato-DXd monotherapy Efficacy endpoints: • ORR (BICR/inv)	Day 1 of each 21-day cycle Dose Escalation: Dose levels from 0.27 to 10 mg/kg Dose Expansion: 4 mg/kg 6 mg/kg 8 mg/kg	Adult subjects with advanced solid tumors (advanced unresectable NSCLC or other solid tumors) and progression after prior therapy with SoC Adult subjects with advanced solid tumors (advanced unresectable NSCLC or other solid tumors) and progression after prior therapy with SoC.

	210	• DoR (BICR/inv) • DCR (BICR/inv) • TTR (BICR/inv) • PFS (BICR/inv) • OS		

The Paediatric Committee, having assessed the waiver application in accordance with Article 13 of Regulation (EC) No 1901/2006 as amended, granted on 9 July 2021 a product-specific waiver (EMA/317764/2021) for all subsets of the paediatric population and the above-mentioned condition(s) in accordance with Article 11(1)(b) of said Regulation, on the grounds that the disease or condition for which the specific medicinal product is intended occurs only in adult populations.
The Norwegian Paediatric Committee member agrees with the above-mentioned recommendation of the Paediatric Committee.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

All sites involved in manufacturing and QC testing have a valid proof of GMP compliance.

GLP

Safety pharmacology investigations as well as the pivotal toxicity studies were conducted under an extensive GLP audit program and in general appeared to be GLP-compliant.

GCP

The applicant stated that the study was conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP; CPMP/ICH/135/95), and applicable regulatory requirement(s) including the following:

- European Commission Directive (2001/20/EC Apr 2001) and/or
- European Commission Directive (2005/28/EC Apr 2005) and/or
- United States (US) Food and Drug Administration GCP Regulations: Code of Federal Regulations Title 21, parts 11, 50, 54, 56 and 312 as appropriate and/or
- Japanese Ministry of Health, Labor and Welfare Ordinance No. 28 of 27 March 1997 and/or
- The Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics No. 1 of 25 November 2014
- Other applicable local regulations

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

2.5.2. PRIME

Not applicable.

2.5.3. Accelerated assessment

Not applicable.

2.5.4. Conditional marketing authorisation

Not applicable.

2.5.5. Marketing authorisation under exceptional circumstances

Not applicable.

2.5.6. Biosimilarity

Not applicable.

2.5.7. Additional data exclusivity/ marketing protection

Not applicable.

2.5.8. New active substance status

The applicant requested the active substance {*active substance*} contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Assessment of this claim is appended.

2.5.9. Orphan designation

Not applicable.

2.5.10. Similarity with orphan medicinal products

Not applicable.

2.5.11. Derogation(s) from orphan market exclusivity

Not applicable.

2.5.12. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) on the granting of a product specific waiver for datopotamab deruxtecan (EMEA-002976-PIP01-21).

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

Datopotamab deruxtecan is an antibody-drug conjugate that contains a humanised anti-TROP2 IgG1 monoclonal antibody (produced in CHO cells), covalently linked to DXd, an exatecan derivative and a topoisomerase I inhibitor, via a tetrapeptide-based cleavable linker. Datopotamab deruxtecan is a powder for solution for infusion.

The drug product is presented as a lyophilized powder in a glass vial without preservatives. Each vial is intended for reconstitution with 5 mL of Water for Injection to provide a solution of 20 mg/mL datopotamab deruxtecan.

All manufacturing sites for production and QC testing of datopotamab, MAAA-1162a drug-linker, DS and DP have valid GMP certificates.

Datopotamab monoclonal antibody (intermediate)

General information

Datopotamab is a recombinant humanized anti-trophoblast cell surface antigen 2 (TROP2) immunoglobulin G1 (IgG1) monoclonal antibody. Datopotamab consists of 2 heavy chains and 2 kappa light chains each containing intrachain disulphide bonds, covalently linked through interchain disulphide bonds.

Manufacture, process controls and characterisation

The manufacturing process and process controls for the datopotamab intermediate are described in detail.

The datopotamab process consists of thawing of the WCB and upscaling of the cells, expression of datopotamab in the production bioreactor, harvesting, clarification, a series of chromatography steps, viral inactivation, viral filtration, UF/DF, final filtration and filling. Quality of intermediates is adequately controlled by in-process controls.

Raw materials are described and properly controlled. Compositions of culture media and buffers are provided. The generation of the recombinant cell clone expressing datopotamab is described. A two-tiered cell bank system consisting of a MCB and WCB has been generated. The cell bank has been properly qualified, including testing on end-of-production cells. Also, genetic stability of the cell bank was demonstrated. Apart from the WCB cells, no animal-derived materials are used in the process. The applicant has removed the *in vivo* viral assay from the qualification specifications of future WCBs.

An overview is provided of all critical and key process parameters as well as of all IPCs. It is confirmed that any harvest test result that is positive for mycoplasma or virus contamination will result in rejection of the corresponding batch of datopotamab.

The manufacturing process of the datopotamab monoclonal antibody has been appropriately validated. PPQ data from validation batches showed that the CPP results were within the acceptance ranges and that all IPC and release test results complied with the specifications. Also, temperature-conditioned transport of the datopotamab mAb has been validated. Reprocessing of the viral filtration and final filtration were validated Also, the reuse of UF membrane and of the resins used in the protein A chromatography and cation exchange chromatography has been validated at small scale. The small-scale process has been extensively and adequately qualified. Both reprocessing and column/UF lifetime will also be verified at commercial scale. Validation protocols have been provided and are deemed acceptable.

The applicant has described the control strategy for CQAs of datopotamab which is comprised of multiple control elements that were established based on process development experiments and data generated during the process characterization studies. Findings from these studies were used to define a commercial manufacturing process, including CPPs, KPPs and IPCs. An overview was provided of all process variants used during clinical development. Extensive comparability studies were performed which confirmed that datopotamab from all process variants was highly similar.

Extensive characterisation has been performed for datopotamab using a combination of different analytical methods to reveal the structural and physico-chemical properties of the molecule. Physico-chemical characterisation included analysis of primary structure, disulphide bonds, glycosylation, charge variants, size variants including LMWS and HMWS, protein concentration, secondary and tertiary structure. Also, biological characterisation was performed including ADCC, CDC, cell growth inhibition, antigen binding activity, FcgammaRIIIa binding, FcRn binding and C1q binding. Datopotamab does not show any CDC activity or cell growth inhibitory activity. *In vitro* ADCC activity was observed for datopotamab; however, no *in vivo* ADCC activity was detected when using an *in vivo* model, thereby indicating that ADCC is not relevant for the mechanism of action of the drug product.

Impurities have been investigated in detailiIt is agreed that impurities are efficiently removed to levels that are very low and safe.

Clearance studies have been performed.

The applicant provided a risk assessment confirming that there is no risk for nitrosamine impurities.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The specifications for datopotamab include control of identity, purity, potency and other general tests. The proposed tests are deemed sufficient for the release testing of datopotamab.

All release testing methods have been described. Non-compendial methods were appropriately validated. Batch data are provided for clinical lots, PPQ lots and the commercial batches produced thus far. Release test results are very consistent between batches and confirm compliance with the specifications.

The applicant has provided detailed information on the reference materials used during clinical development and those intended for commercial product testing. A two-tiered system has been established consisting of a primary and secondary reference standard. All reference standards have been properly qualified. Protocols have been included to produce and qualify future primary and secondary reference standards. The qualification protocols and specifications are deemed acceptable.

The applicant provided a detailed description of the container used for datopotamab storage. Specifications are provided. The materials in contact with the datopotamab comply with the respective Ph. Eur requirements. Extractables and leachables testing were performed but did not reveal any

compounds of concerns. The proposed containers are properly qualified and deemed acceptable for storage of datopotamab.

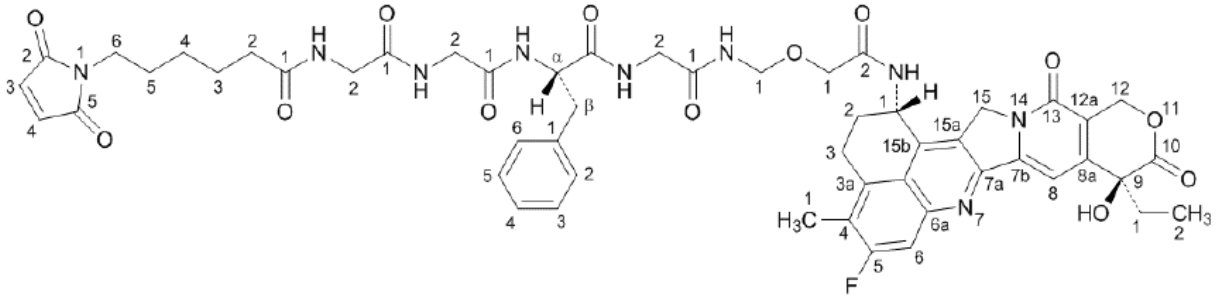
Stability

Long term stability studies have been performed, as well as stability studies under accelerated and stressed conditions. The currently available stability data justify the proposed shelf life for datopotamab intermediate when stored under the long-term storage condition.

MAAA-1162a drug-linker (intermediate)

General information

The molecular structure of the MAAA-1162a drug-linker is shown below.



Manufacture, process controls and characterisation

The manufacturing process and process controls for the MAAA-1162a drug-linker are described in detail. The MAAA-1162a drug-linker manufacturing consists of several chemical synthesis steps.

MAAA-1162a is synthesized by coupling drug intermediate and linker intermediate.

The control of materials including starting materials, reagents, solvents, catalysts and other auxiliary materials are appropriate. Adequate justifications of starting materials have been provided as well as discussions on the observed impurities. No animal-derived materials are used in the process. The control of critical steps and specifications of intermediates are deemed adequate and in-process controls (IPCs) and operational controls are suitably justified.

The manufacturing process was optimised during development to improve the manufacturing efficiency while maintaining the desired quality of the drug-linker. The discussion on manufacturing process development outlines the optimisation of the manufacturing process. Comparability studies were performed to qualify the changes introduced in the process.

The structure of MAAA-1162a was confirmed using elemental analysis, infrared (IR), ultra-violet (UV), ^{1}H and ^{13}C nuclear magnetic resonance (NMR), mass spectrometry (MS) and single crystal X-ray structure analysis. The methods employed are appropriate for structure elucidation of MAAA-1662a.

An exhaustive list and discussion of observed and potential impurities was provided. The control strategy for the impurities including organic impurities, stereoisomers, residual solvents, elemental impurities and mutagenic impurities (including nitrosamines) for MAAA-1162a was provided. With reference to ICH Q3A (R2) "Impurities in New Drug Substances", each step of the MAAA-1162a drug-linker synthetic process was examined for observed and potential impurities. Potential impurities, which might be present in each isolated intermediate and MAAA-1162a drug-linker were identified. Observed impurities in each isolated intermediate were identified based upon testing according to their specifications. The applicant provided a risk assessment confirming that there is no risk in relation to nitrosamine impurities.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The specifications of MAAA-1162a include tests for description, identification by IR, specific optical rotation, assay and related substances by reversed phase high performance liquid chromatography (RP-HPLC) and residual solvents by gas chromatography (GC). The proposed limits are acceptable and are based on ICH Q3A, ICH Q6A and batch data.

Suitably described and validated analytical methods are used and are adequate to control MAAA-1162a on a routine basis. The assay and related substances methods are appropriately validated and were shown to be stability indicating. Batch analysis data are provided. All batches complied with the specifications. The reference standard has been adequately described and qualified.

MAAA-1162a is suitably packaged. Materials in contact with the product comply with relevant EU requirements. The suitability and compatibility of MAAA-1162a with the primary packaging components were evaluated and confirmed by the registration stability studies conducted under ICH long-term and accelerated storage conditions.

Stability

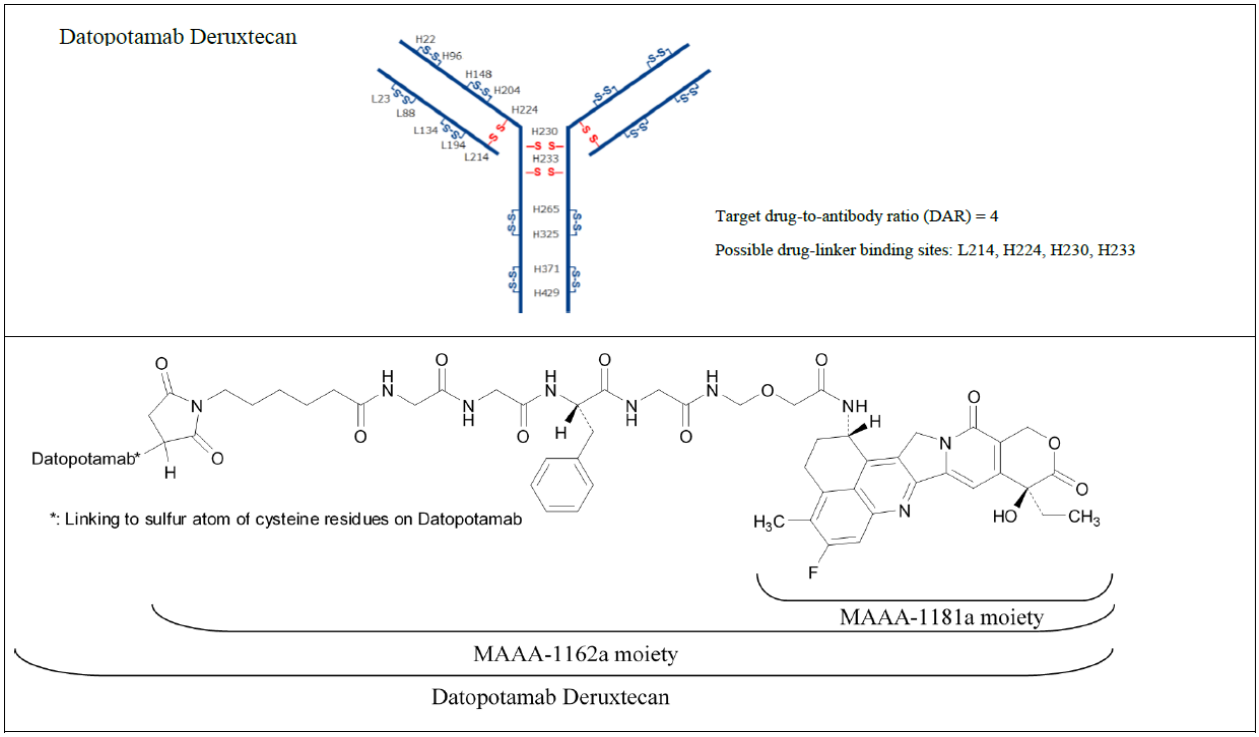
Stability data from long-term and accelerated stability studies are provided for MAAA-1162a manufactured at the commercial manufacturing sites. Stability studies were conducted according to ICH guidance (Q1A, Q1B and Q1E) at 25°C/60% RH (long term) and at 40°C/75% RH (accelerated). No significant changes or trends were observed in tested parameters. Stress testing studies as well as photostability studies have been conducted. The proposed retest period is supported by the stability data.

Active substance

General information

Datopotamab deruxtecan is an antibody-drug conjugate (ADC) comprised of a recombinant humanized anti-trophoblast cell surface antigen 2 (TROP2) immunoglobulin G1 (IgG1) monoclonal antibody, datopotamab, covalently conjugated to a drug-linker, MAAA-1162a, via thioether bonds. The structure is shown below.

Figure 1 Schematic Structures of Datopotamab Deruxtecan



Manufacture, process controls and characterisation

The manufacturing process and process controls for the datopotamab deruxtecan DS are described in detail. The DS manufacturing process includes thawing of datopotamab intermediate, reduction of datopotamab, conjugation of reduced datopotamab with MAAA-1162a drug-linker, quenching of reaction mixture, purification, formulation, filtration and filling.

Starting materials are the datopotamab monoclonal antibody and the MAAA-1162a drug linker, for which detailed information on their synthesis and control has been provided. Raw materials are described and are adequately controlled. No animal-derived materials are used in the process. An overview is provided of all critical and key process parameters as well as of all IPCs. The overall control strategy has been explained and is deemed acceptable.

Process validation was successfully performed. All process parameter results fell within the acceptance criteria; DS test results complied with the IPC and release specifications and confirmed the high consistency of the DS quality. Extensive hold time studies were performed which confirmed that the proposed hold times can be considered as properly validated. The lifetime of the UF/DF membrane has been adequately validated. Also transport of the DS has been adequately validated.

The development of the DS manufacturing process and the different process variants have been described. Comparability analyses have been performed to justify the process changes introduced during clinical development. Comparability test results confirmed that Phase 3 clinical lots from the clinical site and DP lots from the commercial site were highly comparable.

Extensive process characterisation has been performed to identify the CPPs and to establish an appropriate control strategy for the DS manufacturing process. The proposed strategy and the combination of IPC and release testing is deemed acceptable.

In-depth characterisation has been performed for datopotamab deruxtecan using a combination of different analytical methods to reveal the structural and physico-chemical properties of the molecule. Physico-chemical characterisation included analysis of primary structure, disulphide bonds, glycosylation, charge variants, size variants including LMWS and HMWS, protein concentration, drug-linker distribution analysis, secondary and tertiary structure. Also, biological characterisation was performed including ADCC, CDC, cell growth inhibition, antigen binding activity, FcgammaRIIIa binding, FcRn binding and C1q binding.

The DS shows *in vitro* ADCC activity that is similar to that of datopotamab mAb. However, ADCC is not considered as an important mechanism of action of the DS or DP since only datopotamab deruxtecan was able to reduce tumor growth in the *in vivo* model whereas datopotamab mAb showed no inhibitory effect on tumor growth *in vivo*.

Both product-related and process-related impurities have been described. The most important impurities have been described. Overall, all impurities are adequately controlled during manufacturing and/or DS release testing.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The specification for datopotamab deruxtecan active substance includes control of identity, purity and impurities, potency, drug-to-antibody ratio (DAR) and other general tests.

Overall, the parameters included in the active substance specification are found adequate to control the quality of the active substance.

Analytical methods for DS release testing are described and were adequately validated. Batch analysis data are provided for clinical DS lots and PPQ DS lots. All test results comply with the specifications and confirm the high consistency of the DS quality. Specifications limits have been sufficiently justified.

The applicant has provided detailed information on the reference materials. A two-tiered system has been established consisting of a primary and secondary standard. All standards have been properly qualified. Protocols have been included to produce and qualify future primary and secondary standards. The qualification protocols and specifications are deemed acceptable.

The applicant provided a detailed description of the container for datopotamab deruxtecan drug substance, which is a single-use bag. Specifications are provided. The materials in contact with the DS comply with the respective Ph. Eur requirements. Extractables and leachables testing were performed and did not reveal any compounds of concerns. The proposed containers are properly qualified and deemed acceptable for storage of datopotamab deruxtecan drug substance.

Stability

Long term stability studies have been performed, as well as stability studies under accelerated and stressed conditions. Under the long-term storage conditions, it was observed that datopotamab deruxtecan drug substance remains stable. No trends were observed for any of the quality parameters. Datopotamab deruxtecan drug substance also remained stable at accelerated conditions. Some degradation was observed under stressed conditions. The currently available stability data justify the proposed DS shelf life when stored under long-term storage condition.

Finished Medicinal Product

Description of the product and pharmaceutical development

Datopotamab deruxtecan is an antibody-drug conjugate that contains a humanised anti-TROP2 IgG1 monoclonal antibody, covalently linked to DXd, an exatecan derivative and a topoisomerase I inhibitor, via a tetrapeptide-based cleavable linker. Datopotamab deruxtecan is a powder for solution for infusion. The drug product is presented as a lyophilized powder in a glass vial without preservatives. Each vial is intended for reconstitution with 5 mL of Water for Injection to provide a solution of 20 mg/mL datopotamab deruxtecan. 100 mg datopotamab deruxtecan is formulated with well-known compendial excipients: Sucrose, L-Histidine, L-Histidine hydrochloride monohydrate and polysorbate 80.

Manufacture of the product and process controls

A detailed description has been provided for the manufacturing process and process controls for the datopotamab deruxtecan DP. The DP process consists of DS thawing, mixing, sterile filtration, filling and lyophilisation. No animal-derived materials are used in the process. Quality of intermediates is adequately controlled by in-process controls.

The composition of the DP has been provided. All excipients are of compendial grade. No excipients derived from human or animal origin are used and no novel excipients are included.

The pharmaceutical development of datopotamab deruxtecan DP is described in detail. Early phase clinical trials were performed using a liquid formulation. A lyophilised presentation was developed for later stage clinical trials and commercial production. Comparability analyses have demonstrated comparability of DP manufactured during development. Formulation studies were performed to justify the composition of the DP. Process development studies were performed to define the optimal process parameters. Critical process parameters were identified.

The use of inline filters is recommended; compatibility of these filters has been properly validated. A description was provided for the container closure system and its compatibility was demonstrated. Extractables and leachables studies were performed which did not reveal any compounds of concern.

The DP manufacturing process was appropriately validated. Supporting validation studies were provided.

Product specification, analytical procedures, batch analysis

Drug product specifications and acceptance limits as well as corresponding analytical methods have been described.
The specification for datopotamab deruxtecan includes control of identity, purity and impurities, potency, quantity and other general tests. The general tests for release includes appearance before and after reconstitution (color and clarity), osmolality, pH, water content, reconstitution time as well as tests for safety (visible particles, subvisible particulate matter, bacterial endotoxins and sterility). The tests are performed according to compendial requirements and/or by visual observation.

Analytical methods have been adequately validated. DP batch data were provided; the results complied with the specifications. Specification acceptance criteria have been sufficiently justified.

The applicant has described the reference materials that are used during DP release testing.

Risk assessments were performed demonstrating that the risk for elemental impurities or nitrosamines can be considered negligible to non-existing.

The container closure system for the lyophilized DP is a Type I glass amber vial, closed with a fluoro-resin laminated butyl rubber stopper and secured with an aluminium seal with polypropylene flip-off cap. Vial and stopper materials are compliant with respective Ph.Eur. monographs.

Stability of the product

The applicant provided long term, accelerated and stressed stability data of representative DP lots. The available stability data support the proposed shelf life of 36 months for the drug product when stored at 2-8°C.

Post approval change management protocol(s)

The applicant has presented PACMPs for introducing additional manufacturing sites of the datopotamab antibody intermediate and the datopotamab deruxtecan drug substance. A comparability analysis will be performed according to ICH Q5E to demonstrate equivalence of the material form the registered site(s) and the new site. Material from the new site will be included in stability studies. Analytical methods will be transferred to the new sites; compendial methods will be verified; non-compendial methods will be partially revalidated.

Adventitious agents

The safety of datopotamab with respect to adventitious agents is assured by complementary approaches consisting of risk assessment of raw materials, testing of the cell bank, LIVCA bank, and unprocessed bulks for adventitious agents, and demonstration of the purification process viral clearance capabilities with respect to inactivation and removal of representative model viruses.

Safety assessment confirmed that there is no risk for TSE/BSE.

GMO

Not applicable.

Discussion and conclusions on chemical, pharmaceutical and biological aspects

Datopotamab monoclonal antibody intermediate

The manufacturing process and process controls for the datopotamab intermediate are described in detail. The datopotamab process consists of thawing of the WCB and upscaling of the cells, expression of datopotamab in the production bioreactor, harvesting, clarification, series of chromatography steps, viral inactivation, viral filtration, UF/DF, final filtration and filling. Quality of intermediates is adequately controlled by in-process controls.

Raw materials are described and properly controlled. Compositions of culture media and buffers are provided. The generation of the recombinant cell clone expressing datopotamab is described. A two-

tiered cell bank system consisting of a MCB and WCB has been generated. The cell bank has been properly qualified, including testing on end-of-production cells. Also genetic stability of the cell bank was demonstrated. Apart from the WCB cells, no animal-derived materials are used in the process.

An overview is provided of all critical and key process parameters as well as of all IPCs.

The manufacturing process of the datopotamab monoclonal antibody has been appropriately validated.

An overview was provided of all process variants used during clinical development. Comparability studies were performed which confirmed that datopotamab from all process variants was highly similar.

Extensive characterisation has been performed for datopotamab using a combination of different analytical methods to reveal the structural and physico-chemical properties of the molecule. Also, biological characterisation was performed. Datopotamab does not show any CDC activity or cell growth inhibitory activity. *In vitro* ADCC activity was observed for datopotamab; however, no *in vivo* ADCC activity was detected when using an *in vivo* model, thereby indicating that ADCC is not relevant for the mechanism of action of the drug product.

Impurities have been investigated in detail. Product-related impurities are controlled via the release specifications of datopotamab. Process-related impurities include HCP, host cell DNA, residual protein A and residual cell culture components. The other impurities were shown to be efficiently removed to levels that are very low and safe present and therefore do not require routine testing. The applicant also provided a risk assessment confirming that there is no risk for nitrosamine impurities.

The applicant has proposed specifications and acceptance limits for datopotamab. The proposed tests are deemed sufficient for the release testing of datopotamab. All release testing methods have been described. Non-compendial methods were appropriately validated. Batch data are provided for clinical lots, PPQ lots and the commercial batches produced thus far. Release test results are very consistent between batches and confirm compliance with the specifications.

The applicant has provided detailed information on the reference materials used during clinical development and those intended for commercial product testing.

The container used for datopotamab storage is a single-use bag. Specifications are provided. The materials in contact with the datopotamab comply with the respective Ph. Eur requirements. Extractables and leachables testing were performed but did not reveal any compounds of concerns. The proposed containers are properly qualified and deemed acceptable for storage of datopotamab.

Long term stability studies have been performed, as well as stability studies under accelerated and stressed conditions. Under the long-term storage conditions, it was observed that datopotamab remains stable The currently available stability data justify the proposed shelf life for datopotamab intermediate when stored under the long-term storage condition.

MAAA-1162a drug-linker intermediate

The manufacturing process and process controls for the MAAA-1162a drug-linker are described in detail. The MAAA-1162a drug-linker manufacturing consists of several chemical synthesis steps. The control of materials including starting materials, reagents, solvents, catalysts and other auxiliary materials are appropriate. Adequate justifications of starting materials have been provided as well as discussions on the observed impurities. No animal-derived materials are used in the process. The control of critical steps and specifications of intermediates are deemed adequate and in-process controls (IPCs) and operational controls are suitably justified.

The manufacturing process was optimised during development to improve the manufacturing efficiency while maintaining the desired quality of the drug-linker. Comparability studies were performed to qualify the changes introduced in the process.

The structure of MAAA-1162a was confirmed using elemental analysis, infrared (IR), ultra-violet (UV), ^{1}H and ^{13}C nuclear magnetic resonance (NMR), mass spectrometry (MS) and single crystal X-ray structure analysis. Impurities were evaluated in detail.

The specification of MAAA-1162a includes tests for description, identification by IR, specific optical rotation, assay and related substances by reversed phase high performance liquid chromatography (RP-HPLC) and residual solvents by gas chromatography (GC). The proposed limits are acceptable and are based on ICH Q3A, ICH Q6A and batch data. The applicant provided a risk assessment confirming that there is no risk in relation to nitrosamine impurities.

Suitably described and validated analytical methods are used and are adequate to control MAAA-1162a on a routine basis. Batch analysis data are provided. All batches complied with the specifications. The reference standard has been adequately described and qualified.

MAAA-1162a is suitably packaged. Materials in contact with the product comply with relevant EU requirements.

Stability data from long-term and accelerated stability studies are provided for MAAA-1162a manufactured at the commercial manufacturing sites. Stability studies were conducted according to ICH guidance (Q1A, Q1B and Q1E) at 25°C/60% RH (long term) and at 40°C/75% RH (accelerated). No significant changes or trends were observed in tested parameters. Stress testing studies as well as photostability studies have been conducted. The proposed retest period is supported by the stability data.

Datopotamab deruxtecan drug substance

The manufacturing process and process controls for the datopotamab deruxtecan DS are described in detail. The DS manufacturing process includes thawing of datopotamab intermediate, reduction of datopotamab, conjugation of reduced datopotamab with MAAA-1162a drug-linker, quenching of reaction mixture, purification, concentration, formulation, filtration and filling. Starting materials are the datopotamab mAb and the MAAA-1162a drug linker, for which detailed information on their synthesis and control has been provided in separate sections. Raw materials are described and are adequately controlled. No animal-derived materials are used in the process. An overview is provided of all critical and key process parameters as well as of all IPCs.

Process validation was successfully performed. All process parameter results fell within the acceptance criteria; DS test results complied with the IPC and release specifications and confirmed the high consistency of the DS quality. Also hold times and DS transport have been adequately validated.

Extensive process characterisation has been performed to identify the CPPs and to establish an appropriate control strategy for the DS manufacturing process. The development of the DS manufacturing process and the different process variants have been described. Comparability analyses confirmed that DS from different process variants were comparable.

In-depth characterisation has been performed for datopotamab deruxtecan using a combination of different analytical methods to reveal the structural and physico-chemical properties of the molecule. Also biological characterisation was performed. The DS shows *in vitro* ADCC activity that is similar to that of datopotamab mAb. However, ADCC is not considered as an important mechanism of action of the DS or DP since only datopotamab deruxtecan was able to reduce tumor growth in an *in vivo* model whereas datopotamab mAb showed no inhibitory effect on tumor growth *in vivo*. Product-related impurities as well as drug substance without conjugated drug-linker are controlled via the release

specification. Process-related impurities include residual MAAA-1162a drug-linker as well as reagents, by-products and degradation products. The most important impurities have been described. Overall, all impurities are adequately controlled during manufacturing and/or release testing.

The applicant has proposed specifications and acceptance limits for the datopotamab deruxtecan drug substance. Analytical methods used for DS release testing are described and have been adequately validated. Batch analysis data are provided for clinical DS lots and PPQ DS lots. All test results comply with the specifications and confirm the high consistency of the DS quality. The applicant also provided detailed information on the reference materials.

The container used for datopotamab deruxtecan drug substance storage is a single-use bag. Specifications are provided. The materials in contact with the DS comply with the respective Ph. Eur requirements. Extractables and leachables testing were performed and did not reveal any compounds of concerns. The proposed containers are properly qualified and deemed acceptable for storage of datopotamab deruxtecan drug substance.

Long term stability studies have been performed, as well as stability studies under accelerated and stressed conditions. Under the long-term storage conditions, it was observed that datopotamab deruxtecan drug substance remains stable f The currently available stability data justify the proposed DS shelf life when stored under the long-term storage condition.

Datopotamab deruxtecan drug product

A detailed description has been provided for the manufacturing process and process controls for the datopotamab deruxtecan DP. The DP process consists of DS thawing, mixing, sterile filtration, filling and lyophilisation. No animal-derived materials are used in the process. Quality of intermediates is adequately controlled by in-process controls.

The composition of the DP has been provided. All excipients are of compendial grade. No excipients derived from human or animal origin are used and no novel excipients are included.

The pharmaceutical development of datopotamab deruxtecan DP is described in detail. Early phase clinical trials were performed using a liquid formulation. A lyophilised presentation was developed for later stage clinical trials and commercial production. Comparability analyses have demonstrated comparability of DP manufactured during development. Formulation studies were performed to justify the composition of the DP. Process development studies were performed to define the optimal process parameters. Critical process parameters were identified.

A description was provided for the container closure system and its compatibility was demonstrated. Extractables and leachables studies were performed which did not reveal any compounds of concern.

The DP manufacturing process was appropriately validated. Supporting validation studies were provided including validation of aseptic processing and validation of sterile filtration. In addition, also validation of sterilisation of container components as well as validation of shipment was provided.

Drug product specifications and acceptance limits as well as corresponding analytical methods have been described. Methods have been adequately validated. DP batch data were provided; the results complied with the specifications. The applicant has also described the reference materials that are used during DP release testing. Risk assessments were performed demonstrating that the risk for elemental impurities or nitrosamines can be considered negligible to non-existing.

The container closure system for the lyophilized DP is a Type I glass amber vial, closed with a fluoro-resin laminated butyl rubber stopper and secured with an aluminium seal with polypropylene flip-off cap. Vial and stopper materials are compliant with respective Ph.Eur. monographs.

The applicant provided long term, accelerated and stressed stability data of representative DP lots. The available stability data support the proposed shelf life of 36 months for the drug product when stored at 2-8°C.

Safety assessment confirmed that there is no risk for TSE/BSE.

The applicant has presented PACMPs for introducing additional manufacturing sites of the datopotamab antibody intermediate and the datopotamab deruxtecan drug substance.

Conclusion

No major objections had been observed for quality. However, several other concerns had been identified. Most of these concerns have been properly addressed. However, there are still a few issues that need to be updated/resolved. Therefore, based on the review of the quality data provided, the marketing authorisation application for datopotamab deruxtecan could be approvable from the quality point of view provided the applicant adequately addresses the concerns as detailed in the list of questions.

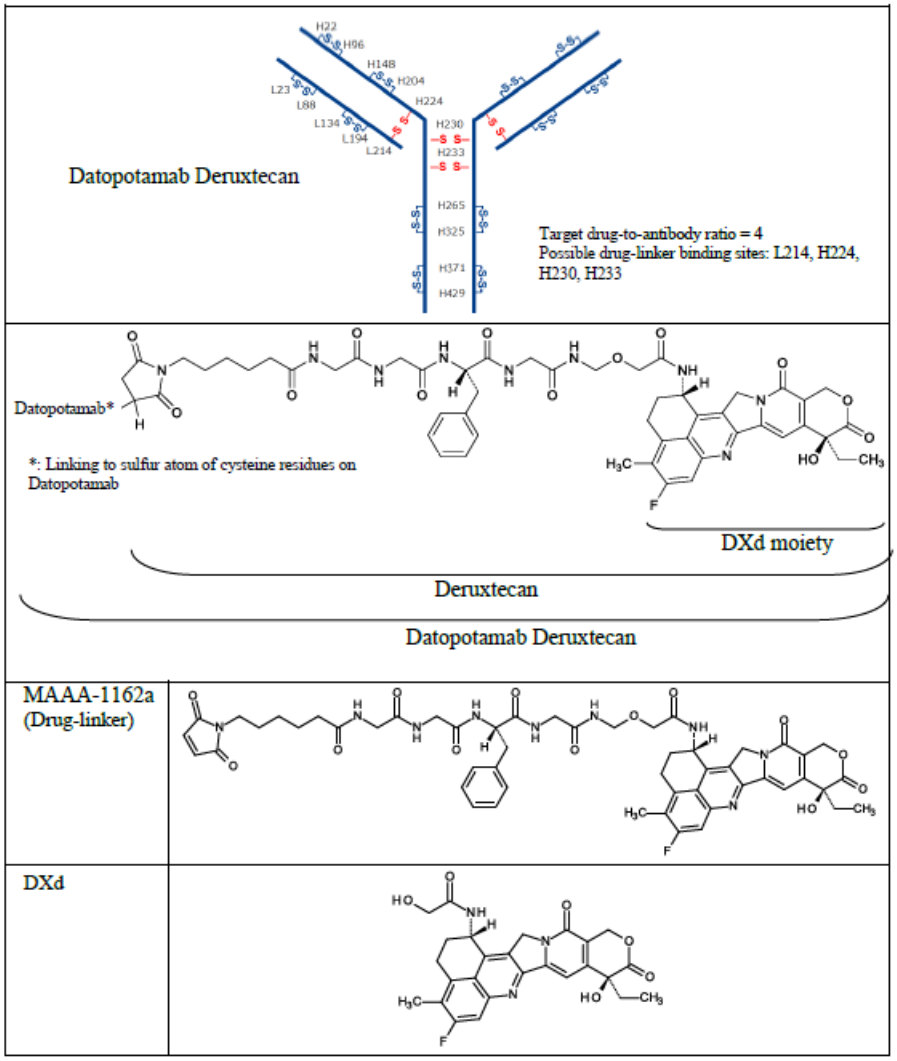
3.2. Non-clinical aspects

3.2.1. Introduction

Datopotamab deruxtecan is an antibody-drug conjugate (ADC) composed of a humanised anti-trophoblast cell surface antigen (TROP) 2 immunoglobulin G1 monoclonal antibody, datopotamab, covalently linked to the membrane-permeable deoxyribonucleic acid (DNA) topoisomerase I inhibitor DXd via a stable tetrapeptide-based linker. The average drug-to-antibody ration of Dato-DXd is four.

Deruxtecan, the drug-linker compound (MAAA-1162a) is similar to the one used in Enhertu® (trastuzumab deruxtecan; publicly available EPAR: EMA/CHMP/636117/2022). Parts of the dossier for datopotamab deruxtecan are therefore identical to those previously submitted as part of the marketing authorisation application dossier for Enhertu®.

Figure 2 Structure of datopotamab deruxtecan (antibody-drug conjugate/Dato-DXd), deruxtecan (drug-linker/MAAA-1162a) and DXd (drug/MAAA-1181a).



Datopotamab deruxtecan is indicated for the treatment of adult patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) who have received prior systemic therapy.

The recommended dose of datopotamab deruxtecan is 6.0 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

A list of terminology used in the non-clinical dossier is included below in table below.

Table 2 List of terminology

TERM	DEFINITION
^{14}C-DXd	^{14}C-labeled DXd
Dato	MAAP-9001a; the antibody component of Dato-DXd, a humanized anti-TROP2 immunoglobulin G1 monoclonal antibody, also known as datopotamab
Dato-DXd	DS-1062a; an antibody-drug conjugate comprised of a humanized anti-TROP2 immunoglobulin G1 monoclonal antibody, MAAP-9001a, which is covalently conjugated to a drug-linker, MAAA-1162a, via thioether bonds; the target drug-to-antibody ratio is 4, also known as datopotamab deruxtecan
DXd	MAAA-1181a; the drug component of Dato-DXd, a derivative of exatecan, a topoisomerase I inhibitor
MAAA-1162a	drug-linker, the complex of DXd and a maleimide tetrapeptide linker
MAAP-9002b	an antibody-drug conjugate comprised of same antibody, linker, and drug as those of Dato-DXd; the average drug-to-antibody ratio was approximately 7.
total anti-TROP2 antibody[a]	the sum of drug conjugated and unconjugated anti-TROP2 antibody

[a] Total anti-TROP2 antibody is referred to as total antibody in the nonclinical study reports.

3.2.2. Pharmacology

The following mechanism of action was proposed for datopotamab deruxtecan (Dato-DXd): After binding of datopotamab deruxtecan (Dato-DXd) to TROP2, it undergoes internalisation and intracellular linker cleavage in the lysosomes to release the DXd (MAAA-1181a). DXd induces DNA damage and apoptotic cell death.

The non-clinical pharmacology program for datopotamab deruxtecan was composed of several primary in vitro and in vivo pharmacodynamic studies to support the anticipated mechanism of action. Secondary pharmacodynamics for the DXd was addressed in vitro in an off-target panel of 86 receptors, channels, transporters or enzymes. Safety pharmacology was evaluated in two dedicated safety studies; a hERG study and an in vivo study in telemetered male cynomolgus monkeys assessing cardiovascular, respiratory and CNS endpoints. Both safety studies were GLP-compliant in accordance to guideline requirement (ICH S7A).

3.2.2.1. Primary pharmacodynamic studies

In vitro pharmacodynamic studies

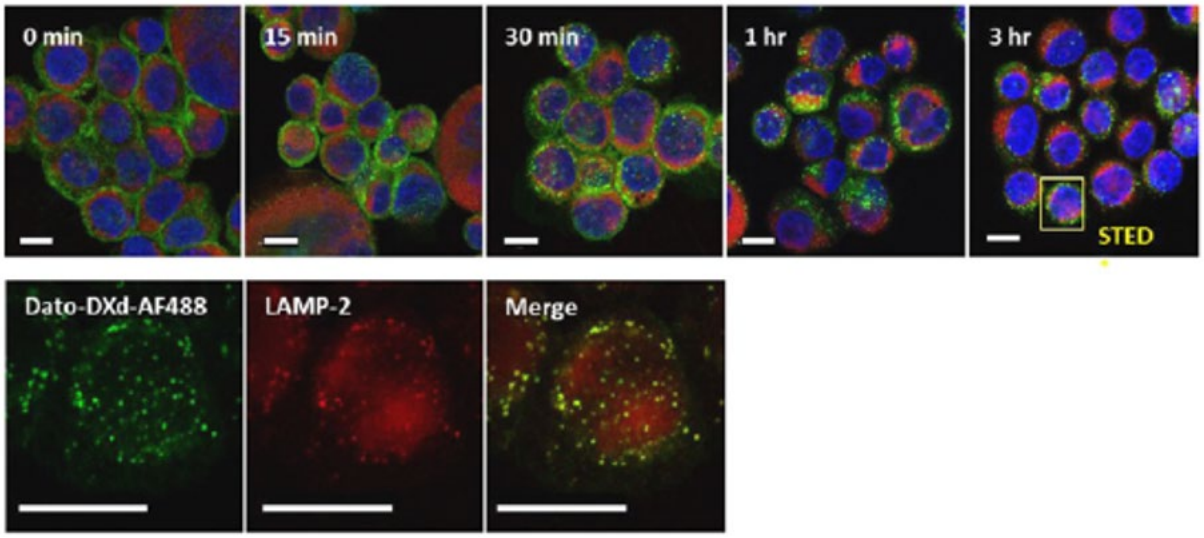
Target binding activity and specificity of datopotamab deruxtecan (CR16-H0009-R01 and CR16-H0009-R02)

Target binding activity of datopotamab deruxtecan (Dato-DXd) to human TROP family proteins (EpCAM and TROP2) was evaluated by ELISA at doses of 1 µg/mL (CR16-H0009-R01). The study showed, that datopotamab deruxtecan (Dato-Dxd) binds specifically to the intended target TROP2 and not to EpCAM.

Species cross-reactivity and binding affinity were evaluated by ELISA in CHO-K1 cells overexpressing mouse, rat, cynomolgus monkey and human TROP2 (CR16-H0009-R02). Datopotamab deruxtecan (Dato-DXd) specifically bound to both human and cynomolgus TROP2 with EC_{50} (95% CLs) values of 110.42 ng/mL (80.32 to 151.79 ng/mL) and 97.65 ng/mL (77.70 to 122.72 ng/mL), respectively. No binding was seen to mouse or rat TROP2. **Internalisation and trafficking to lysosome** (publication by Okajima et al. from 2021)

Datopotamab deruxtecan (Dato-DXd) internalisation and intracellular trafficking to the lysosomes were shown in BxPC3 cells by immunofluorescence imaging (Figure 3). BxPC-3 cells treated with Alexa 488-labeled Dato-DXd (green) were co-stained with anti-LAMP2 antibody (red) and DAPI (blue), and analysed by confocal microscopy. Lysosomal transport of datopotamab deruxtecan (Dato-DXd) was illustrated by showing co-localisation of Alexa 488-labeled datopotamab deruxtecan (Dato-DXd) (green) with the lysosomal marker anti-LAMP2 antibody (red) in BxPC-3 cells.

Figure 3 Intracellular trafficking of datopotamab deruxtecan (Dato-DXd) to lysosome



Bars represent 10 mm for confocal images (top) and Stimulated emission depletion (STED) images (bottom).

Inhibition of cell growth in human tumour cells by datopotamab deruxtecan (CR16-H0009-R03)

The effect of datopotamab deruxtecan (Dato-DXd or DS-1062a), datopotamab (Dato or MAAP-9001a) or the DXd payload (MAAA-1181a) on inhibition of cell growth in two human pancreas adenocarcinoma cell lines (CFPAC-1 and BxPC-3) and one human anaplastic carcinoma cell line (Calu-6) were demonstrated using CellTiter-Glo Luminescent Cell Viability Assay and results were correlated with TROP2 cell line expression determined by flow cytometry using a commercially available fluorescent antibody (Anti-Human Trop2 Alexa Fluor 488). An isotype control IgG-DXd was also included for control.

Datopotamab deruxtecan (Dato-DXd or DS-1062a) showed inhibitory activity in the two human pancreas adenocarcinoma cell lines, CFPAC-1 and BxPC-3, with IC_{50} values of 706 and 74.6 ng/mL. No inhibition was seen in the Calu-6 cell line. This corresponded with CFPAC-1 and BxPC-3 being TROP2 positive (TROP2 expression of 22.1 and 47.9 rMFI, respectively) and Calu-6 negative (1.1 rMFI). Additionally, high TROP2 expression levels appeared to be correlated with low IC_{50} values. All three cell lines (CFPAC-1, BxPC-3 and Calu-6) appeared to be sensitive to the DXd payload (MAAA-1181a) (please see table below).

Table 3 Cell growth inhibitory activity of datopotamab deruxtecan (Dato-DXd), datopotamab (Dato), isotype control IgG-DXd, and DXd, and TROP2 expression in human tumour cells.

Cell Line	IC_{50}				TROP2 Expression (rMFI)
	Dato-DXd (ng/mL)	Dato (ng/mL)	Isotype Control IgG-DXd (ng/mL)	DXd (nmol/L)	
CFPAC-1	706	≥20,000	≥20,000	2.82	22.1
BxPC-3	74.6	≥20,000	≥20,000	1.58	47.9
Calu-6	≥20,000	≥20,000	≥20,000	1.15	1.1

IC_{50} = 50% inhibitory concentration; rMFI = relative geometric mean of fluorescence intensity; TROP2 = trophoblast cell surface antigen 2

Human Topoisomerase 1 inhibitory activity of the DXd (CD13-H0072-R05)

Human topoisomerase I is a type IB topoisomerase which can relax positive and negative supercoiled DNA and is an essential enzyme for DNA replication, transcription, and chromatin condensation. Inhibition of topoisomerase I causes cell death. Upon binding to TROP2 and internalisation in the tumour cells, the DXd moiety of deruxtecan (MAAA-1181a) is anticipated to be released from datopotamab deruxtecan (Dato-DXd) and induce cell death of the cell.

The human topoisomerase I inhibitory activity of DXd was evaluated by a topoisomerase I-mediated DNA relaxation assay using supercoiled DNA as a substrate. Recombinant human topoisomerase I was incubated with DXd (MAAA-1181a) at concentrations of 78.125 to 20000 nmol/L for 5 min. Supercoiled pBR322 DNA was then added and incubated at 37°C for 30 minutes. The mixture was electrophoresed on an agarose gel and the amount of the supercoiled DNA was measured.

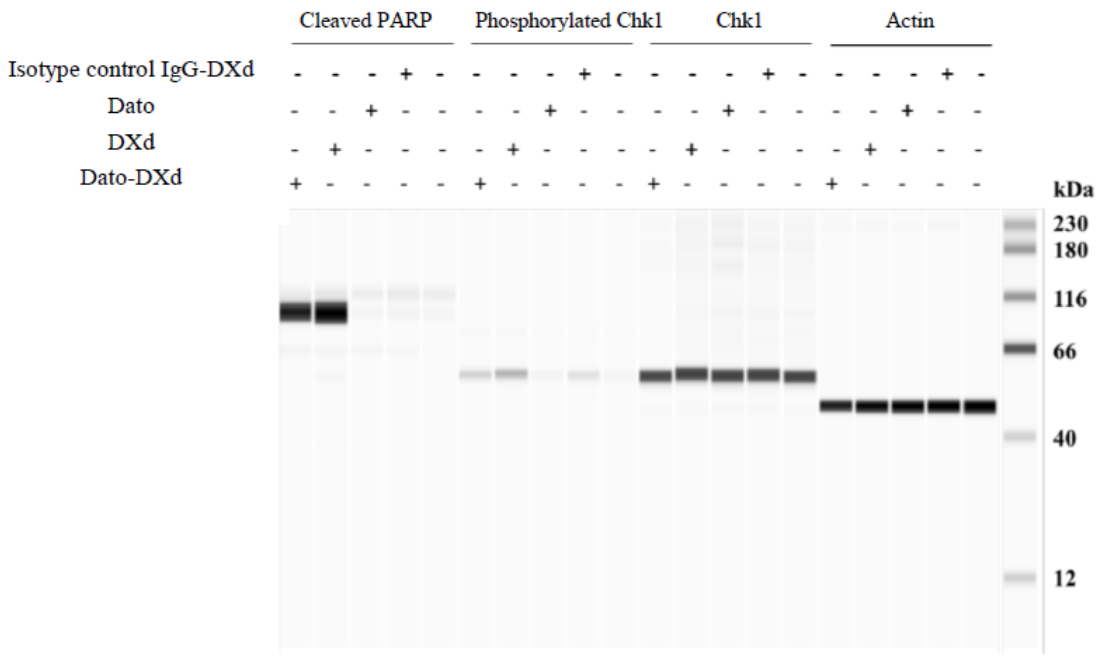
DXd (MAAA-1181a) inhibited the relaxation of supercoiled DNA caused by human topoisomerase I in a dose-dependent manner (IC_{50} value of 3581.19 nmol/L). This result indicated that DXd (MAAA-1181a) has inhibitory activity against human topoisomerase I.

This study has previously been assessed as a part of the marketing authorisation application for Enhertu® and the above study description is therefore harmonised with the EPAR of Enhertu®. Please note, that different terminology was used for the DXd, which are described in the study report as MAAA-1181c (CD13-H0072-R05) and in this dossier as MAAA-1181a. However, in the pharmacology written summary p. 9, it was stated that MAAA-1181c is representative of MAAA-1181a or DXd. MAAA-1181c appears to be an acetonitrile-methanol-water solvate of MAAA-1181a.

Induction of DNA damage and apoptosis by datopotamab deruxtecan (CR16-H0009-R04)

Topoisomerase I inhibitors can induce double-strand DNA-breaks leading to apoptosis. Hence, the ability of datopotamab deruxtecan (Dato-DXd), datopotamab (Dato) and the DXd to induce DNA damage and apoptosis was demonstrated in a human pancreas adenocarcinoma cell line (CFPAC-1) expressing TROP2 using phosphorylation of Chk1 and cleaved PARP as markers, respectively, in a Simple Western system. For cleaved PARP and phosphorylated Chk1, a strong signal was seen for datopotamab deruxtecan (Dato-DXd) and DXd. No signal was observed for datopotamab (Dato) alone for any of the markers but it should be noted that for phosphorylated Chk1 a positive response was seen for the isotype control antibody IgG-DXd, exhibiting a band intensity slightly weaker than for datopotamab deruxtecan (Dato-DXd) (please see Figure 4 below).

Figure 4 Changes in phosphorylated checkpoint kinase 1 (Chk1) and cleaved poly adenosine diphosphate-ribose polymerase (PARP) by treatment with datopotamab deruxtecan (Dato-DXd), isotype control IgG-DXd, datopotamab (Dato), or DXd.



ADC = antibody-drug conjugate; Chk1 = checkpoint kinase 1; DNA = deoxyribonucleic acid; PARP = poly adenosine diphosphate-ribose polymerase
After the CFPAC-1 cells were treated with Dato-DXd (10 μg/mL), DXd (10 nmol/L), Dato (10 μg/mL), or isotype control IgG-DXd (10 μg/mL) for 3 days, DNA damage and apoptosis were evaluated by the detection of phosphorylated Chk1 (56 kDa) and cleaved PARP (89 kDa) using the Simple Western system. The expression levels of total Chk1 (56 kDa) and Actin (45 kDa), which were used as internal controls, were also confirmed.

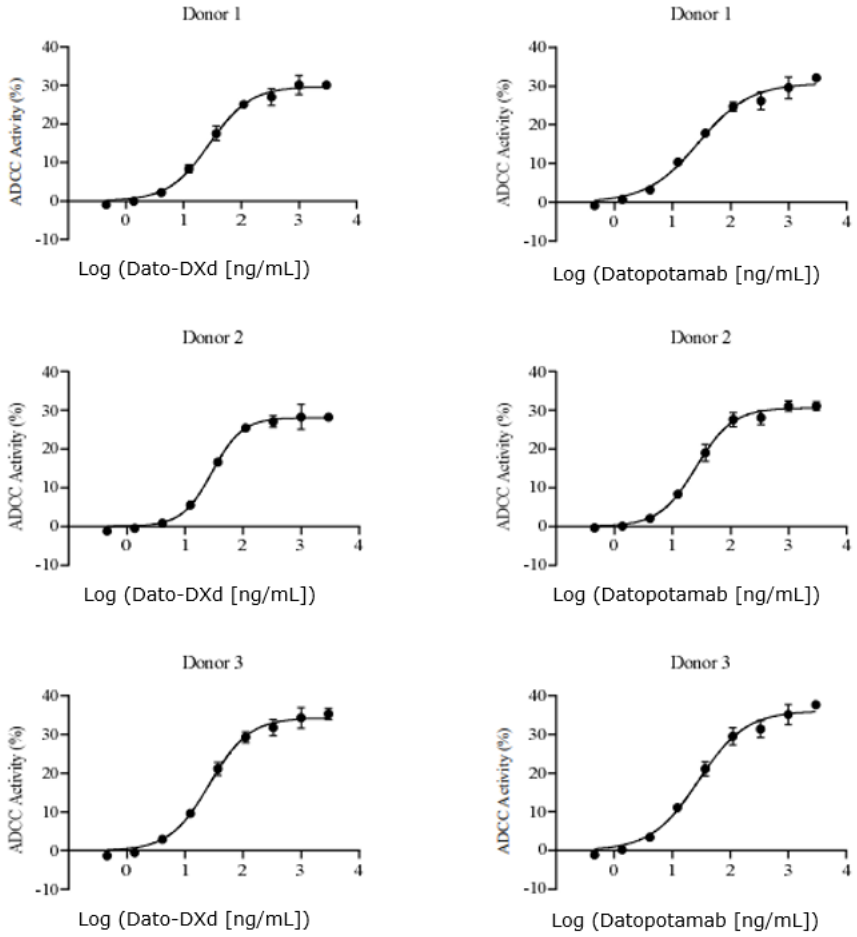
Antibody-dependent cellular cytotoxic activity of datopotamab deruxtecan

Datopotamab deruxtecan (Dato-DXd or DS-1062a) exhibited cytotoxic activity against human lung cancer NCL-H322 cells expressing TROP2 in the presence of human peripheral blood mononuclear cells (hPBMCs), with EC_{50} of 5.27 and 10.8 ng/mL.

Please note, that in the study values from one donor with 206 ng/mL (95% CI: 9.09 to 4660 ng/mL) and 25.1%, was considered unreliable due to the large CI. The percentage of NK cell in the hPBMCs was 11-21.8% in the tree donors.

A new study was conducted showing that datopotamab (MAAP-9001a) and datopotamab deruxtecan (Dato-DXd) exhibited ADCC activity of similar magnitudes against TROP2-exprssing NCI-H322 cells in the presence of human PBMCs within a timeframe of 4 h (Study no. CY19-h0004-R04, included in **Error! Reference source not found.** submitted in the 2. round). The study was conducted following the same principles as the previously conducted study but now including both the conjugated and unconjugated antibody i.e. datopotamab deruxtecan (Dato-DXd or DS-1062a) and datopotamab (MAAP-9001a). No negative control (IgG or IgG-DXd) was included in this new study but results from the previous study showed no cytotoxic effect of IgG-DXd within the 4 h timeframe.

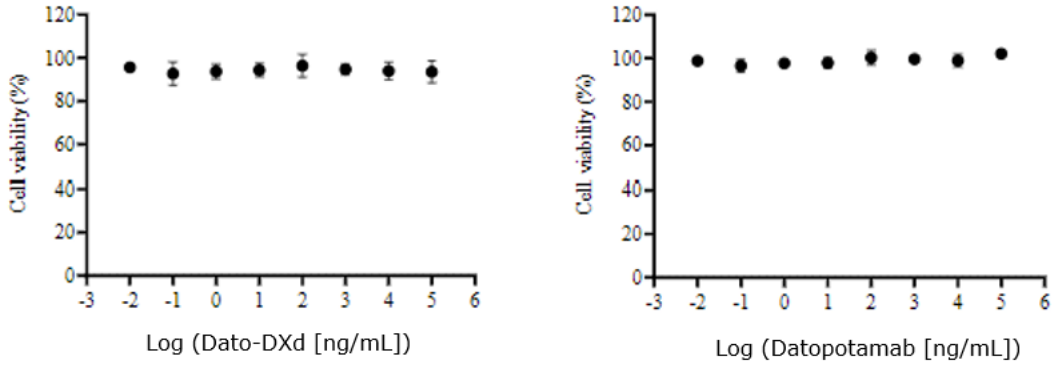
Figure 5 ADCC activity of datopotamab deruxtecan (Dato-DXd) and datopotamab against TROP2-expressing NCI-H322 cells (study no. CY19-h0004-R04). Each point represents the mean and standard deviation of three wells.



Complement-dependent cytotoxic (CDC) activity of datopotamab deruxtecan (Dato-DXd) and datopotamab (CY19-H0004-R06)

The study evaluated complement-dependent cytotoxic (CDC) activity of datopotamab deruxtecan (Dato-DXd or DS-1062a) and datopotamab (MAAP-9001a) in the presence of human complement using a bronchioalveolar carcinoma cell line NCI-H322 expressing human TROP2 on the cell surface. The IC_{50} values of datopotamab deruxtecan (Dato-DXd or DS-1062a) and datopotamab (MAAP-9001a) against NCI-H322 cells in the presence of human complement were both >100000 ng/mL with a mean cell viability of 93.5 and 102.1%, respectively. Rituximab was used as positive control with a the IC_{50} value of 1209 ng/mL against Ramos cells in the presence of human complement. No known negative control was included. The study concluded, that neither datopotamab deruxtecan (Dato-DXd or DS-1062a) nor datopotamab (MAAP-9001a) showed CDC activity against NCI-H322 cells at concentrations up to 100,000 ng/mL.

Figure 6 Cell viability of NCI-H322 cells treated with datopotamab deruxtecan (Dato-DXd) and datopotamab (MAAP-9001a) with human complement

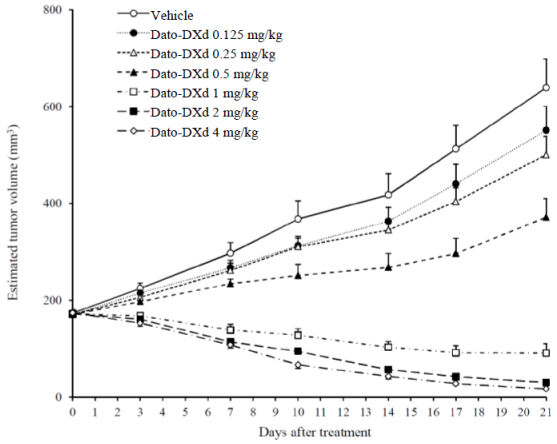


In vivo pharmacodynamic studies

Four in vivo studies were performed with datopotamab deruxtecan (Dato-DXd) administered intravenously to nude mouse xenograft models of human pancreatic cancer, non-small cell lung cancer (NSCLC) and breast cancer, with the two latter being in line with the sought indications. All xenograft models were constructed using TROP2 expressing tumour cell lines. It was noted that all in vivo studies were conducted in only female mice (n = 6/group). This is considered acceptable, as no gender difference in exposure is expected (please see the Pharmacokinetic section).

In the mouse xenograft model of human pancreatic cancer (CFPAC-1), the primary focus was to determined dose-dependency of the anti-tumour activity by testing several doses of datopotamab deruxtecan (Dato-DXd) from 0.125 to 4 mg/kg and using vehicle as control. A significant effect on tumour growth inhibition of 41.9, 85.7, 95.3 and 97.3% was noted at dose of 0.5, 1, 2 and 4 mg/kg, respectively. Hence, datopotamab deruxtecan (Dato-DXd) showed a dose-dependent antitumor activity with the most marked effect from doses ≥ 1 mg/kg. However, no exposure measurements were reported for the different doses.

Figure 7 Antitumor activity of Dato-DXd against human pancreatic cancer cell line CFPAC-1 xenografted nude mice (dose-dependency).

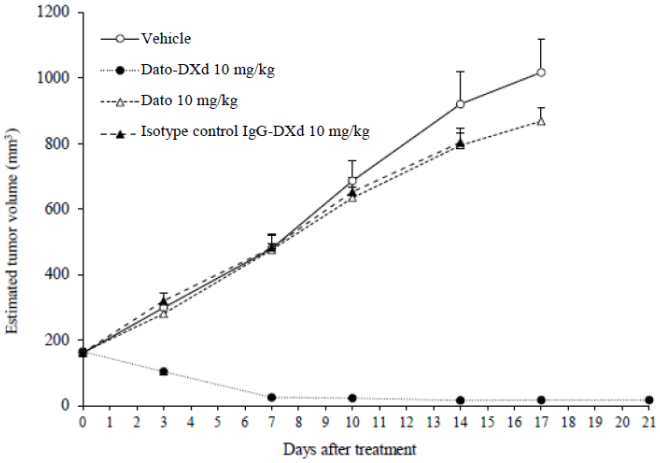


The mean estimated tumor volume and standard error (n = 6) are represented on the graph.

In two mouse xenograft models of non-small cell lung cancer (NSCLC) using the TROP2 expressing cell lines NCI-H292 and HCC827 without and with actionable genomic alterations (AGAs), respectively,

datopotamab deruxtecan (Dato-DXd) at doses of 10 mg/kg significantly inhibited tumour growth compared to vehicle by 98.3% and 82.8%, respectively. No significant inhibitory effect of datopotamab (Dato) or isotype control IgG-DXd were seen. Similar results, with a tumour growth inhibition of 96.1% were demonstrated in the breast cancer (BC) xenograft model of the TROP2 expressing HCC1806 cell line at doses of 10 mg/kg datopotamab deruxtecan (Dato-DXd).

Figure 8 Antitumor activity of Dato-DXd against human Non-Small Cell Lung Cancer cell line NCI-H292 xenografted nude mice.



The mean estimated tumor volume and standard error (n = 6) are represented on the graph.

3.2.2.2. Secondary pharmacodynamic studies

In a secondary pharmacodynamic study, testing DXd against an off-target panel of 86 receptors, channels, transporters or enzymes, no significant response (≥ 50% inhibition) was demonstrated at concentrations of 10 µmol/L (approximately 5000 ng/mL). The tested concentration provided > 1500-fold to the reported highest human C_{max} of 3.13 ng/mL (cycle 1).

It should be noted that this study was conducted for the DXd alone and not for the full antibody drug conjugate (ADC), which is acceptable. The study has previously been submitted and assessed as part of the market authorisation application for Enhertu® (EMA/CHMP/636117/2022). In the screening report, the test substance is referred to as MAAA-1181d, whereas the active drug is named MAAA-1181a. It appears that MAAA-1181d is the monohydrate of MAAA-1181a.

3.2.2.3. Safety pharmacology programme

Two dedicated safety pharmacology studies were performed. A hERG study (study no. SBL315-029) and an in vivo study (study no. IP16220) with telemetered male cynomolgus monkeys assessing cardiovascular, respiratory and CNS endpoints. Both studies were GLP-compliant in accordance to guideline requirement (ICH S7A).

The cardiovascular safety of the DXd was evaluated in a GLP-compliant in vitro hERG study in transfected CHO-cells at concentrations of 1, 3 and 10 µmol/L (SBL315-029), showing no effect of DXd on hERG current at any of the tested concentrations. The tested maximum concentration provided > 1500-fold to the clinically relevant exposure of DXd, concluding that no effect of DXd on hERG K+ channels were expected at clinically relevant doses of datopotamab deruxtecan (Dato-DXd).

In the hERG study report (SBL315-029), the test substance is referred to as MAAA-1181d, whereas the active drug is named MAAA-1181a. It appears that MAAA-1181d is the monohydrate of MAAA-1181a.

Furthermore, it should be noted that the hERG study has previously been submitted and assessed as part of the market authorisation application for Enhertu® (EMA/CHMP/636117/2022).

Cardiovascular, respiratory and CNS endpoints were evaluated in a dedicated safety pharmacology study in telemetered male cynomolgus monkeys (n= 5) after intravenous administration of a single dose of 10 or 80 mg/kg datopotamab deruxtecan (Dato-DXd) (IP16220). Heart rate, blood pressure (systolic, diastolic, and mean), ECG parameters (PR interval, QRS duration, QT interval, and QTc interval), frequency of arrhythmia, physical condition, respiratory rate, blood gas parameters (partial pressure of oxygen and carbon dioxide, pH, and oxygen saturation), body temperature, functional observational battery (FOB) method parameters, body weight and food consumption were monitored and no changes were seen at either dose level. Hence, concluding that datopotamab deruxtecan (Dato-DXd) had no effect on the cardiovascular, respiratory and central nervous systems at single doses up to 80 mg/kg.

It was noted that only male monkeys were used in the safety pharmacology study but this was sufficiently justified due to the availability of better background data in male animals. More importantly, no significant gender differences were noted in exposure or target organs of toxicity, as addressed in the provided justification and confirmed in the pharmacokinetic and toxicology sections.

3.2.2.4. Pharmacodynamic drug interactions

The omission of pharmacodynamic drug interaction studies is accepted, as no drugs with a likely pharmacodynamic interaction are anticipated to be co-administered with datopotamab deruxtecan (Dato-DXd).

3.2.3. Pharmacokinetics

3.2.3.1. Analytical methods

The Dato-DXd and total anti-TROP2 antibody concentrations in rat and cynomolgus monkey plasma were determined with validated LBA methods. ADA in rat and monkey plasma were detected with validated ECL methods. The DXd concentrations in the samples were determined with validated LC-MS/MS methods. Table 4 outlines these validated analytical methods.

Table 4 Validation of Analytical Methods

Analyte	Assay Method	Matrix	Calibration Curve Range (ng/mL)	LLOQ (ng/mL)	Validation Report No.
Dato-DXd[a] and total anti-TROP2 antibody[b]	LBA	Rat and monkey plasma	10.0 to 7500	10.0	
Anti-Dato-DXd antibody	ECL	Rat and monkey plasma	NA	NA	
DXd	LC-MS/MS	Human and mouse plasma, and buffer	0.100 to 20.0	0.100	
	LC-MS/MS	Plasma supernatant (mouse, rat, monkey, human)	0.100 to 20.0	0.100	
	LC-MS/MS	Rat plasma	0.100 to 20.0	0.100	
	LC-MS/MS	Monkey plasma	0.100 to 20.0	0.100	
	LC-MS/MS	Rat and monkey plasma	0.100 to 20.0	0.100	

ECL = electro-chemiluminescence; LBA = ligand binding assay; LC-MS/MS = liquid chromatography-tandem mass spectrometry; LLOQ = lower limit of quantification; NA = not applicable

[a] Dato-DXd was referred to MAAP-9002a in the report.
[b] Total anti-TROP2 antibody was referred to total antibody in the report.

The validation of the analytical methods for determination of DXd in animal plasma using LC-MS/MS has already been assessed as part of the Enhertu® procedure and were considered robust for the purpose of the studies (trastuzumab deruxtecan; publicly available EPAR: EMA/CHMP/636117 /2022). Validation data was also provided for the ligand binding assay, determining datopotamab deruxtecan (Dato-DXd) and total anti TROP2 antibody in rat and monkey plasma. Overall, the methods are considered robust and adequate for analysing plasma samples that have been stored no more than 3 months (92 days) at -80℃ or after 5 freeze/thaw cycles. Incurred sample reanalysis was found to comply with guidelines in the assessed pivotal studies. The presence of ADAs against datopotamab deruxtecan in serum samples from rats and monkeys was furthermore determined using an electrochemiluminescent (ECL) assay. Overall, the methods appear adequate.

3.2.3.2. Absorption

Following single IV dosing in male cynomolgus monkeys of doses between 0.2-6 mg/kg, datopotamab deruxtecan (Dato-DXd) exposure increased dose-dependently and a terminal elimination half-life (t½) of ~1.5-2 days was observed. The volume of distribution was low (38-43 ml/kg), as expected for an antibody and indicative of plasma only distribution. In addition, TK parameters of DXd (MAAA-1181a) dosing were evaluated upon weekly (QW) administration in a rat and monkey 4-week study. TK investigations showed that datopotamab deruxtecan exposure also increases dose-proportionally following repeat dosing of 20-200 mg/kg in rats and 10-80 mg/kg in monkeys, respectively. Linear PK has also been established in humans in the dosing range 4-10 mg/kg. DXd t½ was found to be much lower (0.6 – 4 hrs) after DXd dosing in animals than when dosing with Dato-DXd in humans. No significant sex differences were observed and datopotamab deruxtecan exposure did not accumulate over time. No significant differences in PK parameters were observed between datopotamab deruxtecan and the total anti-TROP2 antibody either following single or repeated dosing. The 3-months intermittent IV dosing study in monkeys confirmed that remaining levels of datopotamab deruxtecan, total anti-TROP2 antibody and DXd were almost completely eliminated at day 57 of the recovery period. Anti-Dato-DXd antibodies (ADAs) were detected in several animals in both the rat and monkey multiple dose studies. ADA-positive animals showed declined levels (or BLQ) of Dato-DXd combined with increased (up to 60-fold) plasma DXd levels at the 4th dosing period. ADA formation was observed in the low dose groups (10 mg/kg) in monkeys after the last dosing and significantly decreased the exposure values for datopotamab deruxtecan. In all other dose groups, ADA formation was however generally limited and it is considered to not affect the overall PK profile in monkeys. Only 1 incidence of ADA formation was observed in rats in treated animals (1 male at 20 mg/kg). However, 4 incidences of ADA-formation were observed in control- and treated groups prior to treatment with the compound, which may suggest an unspecific assay for detecting ADAs. When rats and monkeys were repeatedly dosed with DXd alone, exposure increased dose-proportionally and no sex differences or accumulation was observed.

3.2.3.3. Distribution

Studies on distribution to tissues and blood cells and plasma protein binding have been carried out for DXd. The tissue distribution studies are novel, but the dedicated studies on plasma protein binding and blood cell distribution have previously been assessed as a part of the marketing authorisation application for Enhertu®. The study descriptions and results are harmonised with the publicly available EPAR of Enhertu® (EMA/CHMP/636117/2022).

Tissue distribution was measured in vivo after single intravenous administration of 1 mg/kg ^{14}C-labeled DXd to non-fasted male Sprague Dawley rats (Table 5) and to non-fasted male cynomolgus monkeys

(Table 6). Radioactivity was quickly and widely distributed and cleared quickly as ^{14}C-DXd levels peaked in the majority of tissues within 0.25 or 1 h post-dose, except for the gastrointestinal and excretory organs. In the rat the radioactivity in brain, lens, and spinal cord were below limit of quantification (BLQ) at all time points, and in the monkey the anterior chamber, brain, cornea, lens, pituitary gland, spinal cord, and vitreous humor.

Table 5 Radioactivity Concentrations in Plasma and Tissues after Single Intravenous Administration of 14C-labeled DXd to Non-fasted Male Sprague Dawley Rats

Tissues/Organs	^{14}C-DXd (ng equiv/g) Hours post-dose						
	0.25	2	4	8	24	48	96
Plasma (LSC)	142	13.3	8.52	6.37	3.90	BQL	BQL
Blood (LSC)	94.8	8.82	5.41	4.21	2.53	BQL	BQL
Blood (cardiac)	114	BQL	BQL	BQL	BQL	BQL	BQL
Adrenal cortex	251	10.5	6.19	BQL	14.2	BQL	BQL
Adrenal gland	248	10.6	6.60	BQL	12.4	BQL	BQL
Adrenal medulla	250	10.4	6.98	BQL	6.18	BQL	BQL
Aorta	347	9.60	9.39	BQL	BQL	BQL	BQL
Bile (in duct)	43302	918	56.5	54.4	48.8	BQL	BQL
Bone (femur)	103	7.91	5.18	6.99	8.07	BQL	BQL
Bone marrow (femur)	216	23.1	6.09	BQL	BQL	BQL	BQL
Brown fat	182	8.88	5.75	BQL	BQL	BQL	BQL
Cecum contents	37.0	488	886	12728	933	77.9	7.66
Cecum mucosa	168	26.9	94.8	1100	45.5	5.17	BQL
Epididymis	139	BQL	BQL	BQL	BQL	BQL	BQL
Esophagus wall	215	15.8	BQL	BQL	BQL	BQL	BQL
Ex-orbital lachrymal gland	296	12.4	BQL	BQL	BQL	BQL	BQL
Eye	50.2	BQL	BQL	BQL	BQL	BQL	BQL
Harderian gland	402	79.3	35.5	BQL	BQL	BQL	BQL
Heart	176	6.01	6.07	BQL	BQL	BQL	BQL
Intra-orbital lachrymal gland	295	11.0	BQL	BQL	BQL	BQL	BQL
Kidney	737	32.3	21.0	11.3	13.7	8.60	10.1
Kidney cortex	538	32.5	29.5	13.1	16.9	11.3	11.3
Kidney medulla	915	31.4	8.52	9.39	9.25	BQL	7.43
Large intestine contents	335	51546	54887	57973	2464	77.2	BQL
Large intestine wall	127	4931	8490	20420	104	26.3	BQL
Liver	656	46.1	23.9	18.6	11.7	BQL	BQL
Lung	253	18.1	BQL	BQL	BQL	BQL	BQL
Lymph node (cervical)	270	29.0	BQL	BQL	BQL	BQL	BQL
Meninges	36.6	5.27	BQL	BQL	BQL	BQL	BQL
Muscle (femoral)	264	18.4	BQL	BQL	BQL	BQL	BQL
Nasal turbinates	42.8	BQL	BQL	BQL	BQL	BQL	BQL
Non-pigmented skin	206	99.7	104	87.8	72.6	5.72	5.22
Oral mucosa	157	6.08	5.73	BQL	BQL	BQL	BQL
Pancreas	361	32.6	14.0	8.62	6.65	BQL	BQL
Pituitary gland	413	17.1	BQL	BQL	BQL	BQL	BQL
Prostate	249	98.9	22.3	19.3	7.86	BQL	BQL
Salivary gland	178	15.0	8.93	BQL	BQL	BQL	BQL
Seminal vesicle	91.3	13.4	31.5	BQL	BQL	BQL	BQL
Small intestine contents	44946	9328	316	148	1097	BQL	BQL
Small intestine wall	14489	618	83.3	117	61.4	BQL	BQL
Spleen	207	21.7	45.6	BQL	BQL	BQL	BQL
Stomach contents	BQL	16.5	19.9	9.46	1935	BQL	BQL

Tissues/Organs	^{14}C-DXd (ng equiv/g) Hours post-dose						
	0.25	2	4	8	24	48	96
Stomach wall (glandular)	164	29.0	13.2	7.61	24.4	BQL	BQL
Stomach wall (non-glandular)	85.1	12.7	BQL	11.1	7.19	5.45	BQL
Testis	28.8	BQL	BQL	BQL	BQL	BQL	BQL
Thymus	161	48.3	7.20	BQL	BQL	BQL	BQL
Thyroid gland	177	18.9	11.6	BQL	BQL	BQL	BQL
Trachea	60.5	BQL	BQL	BQL	BQL	BQL	BQL
Urinary bladder contents	39983	832	58.2	75.8	8.56	BQL	BQL
Urinary bladder wall	3372	855	21.4	117	59.2	BQL	BQL
Uveal tract	67.5	BQL	BQL	BQL	BQL	BQL	BQL
White fat (inguinal)	77.3	5.90	BQL	BQL	BQL	BQL	BQL

BQL: below the quantifiable limit; NC: not calculated: LLC: liquid scintillation counting; LLOQ: lower limit of quantification. BQL = <LLOQ for QWBA = <5.11 ng equiv/g; BQL = <LLOQ for LSC = <1.31 ng equiv/g (plasma) or <2.31 ng equiv/g (blood).

N=7M; one animal per timepoint for QWBA; blood collected from all by cardiac puncture under anesthesia.

Table 6 Radioactivity Concentrations in Plasma and Tissues after Single Intravenous Administration of 14C-labeled DXd to Non-fasted Male Cynomolgus Monkeys

Tissues/Organs	^{14}C-DXd (ng equiv/g) Hours post-dose				
	1	8	24	48	96
Plasma (LSC)	65.7	12.2	10.4	6.00	3.23
Blood (LSC)	39.6	7.30	5.23	4.01	3.14
Blood (cardiac)	74.8	11.7	BQL	BQL	BQL
Adrenal cortex	101	18.4	BQL	BQL	BQL
Adrenal gland	102	18.3	BQL	BQL	BQL
Adrenal medulla	98.7	18.0	BQL	BQL	BQL
Aorta	146	7.72	BQL	BQL	BQL
Bile (in gall bladder)	86485	22405	1138	545	BQL
Bone (femur)	15.3	BQL	BQL	BQL	BQL
Bone marrow (femur)	33.2	14.8	11.9	9.53	BQL
Brown fat	346	11.6	BQL	BQL	BQL
Cecum contents	59.4	91853	42171	684	46.2
Cecum mucosa	91.7	329	11441	763	BQL
Epididymis	98.1	112	9.37	BQL	BQL
Esophagus wall	85.2	42.0	28.4	18.4	7.85
Ex-orbital lachrymal gland	86.0	28.3	26.7	9.83	BQL
Eye - Choroid	130	BQL	BQL	BQL	BQL
Eye - Ciliary body	227	BQL	BQL	BQL	BQL
Eye - Iris	15.9	BQL	NS	BQL	NS
Eye - Retina	75.5	BQL	BQL	BQL	BQL
Eye - Sclera	179	BQL	BQL	BQL	BQL
Eye - Uveal tract	132	BQL	BQL	BQL	BQL
Eye - Whole	26.0	BQL	BQL	BQL	BQL
Gallbladder	4714	189	174	20.2	BQL
Heart	50.6	BQL	BQL	BQL	BQL
Intra-orbital lachrymal gland	16.7	BQL	BQL	BQL	BQL
Kidney	799	142	202	96.4	74.8
Kidney cortex	875	193	242	133	104
Kidney medulla	471	52.1	128	13.9	11.9
Large intestine wall	96.7	1682	42357	BQL	BQL

Tissues/Organs	^{14}C-DXd (ng equiv/g) Hours post-dose				
	1	8	24	48	96
Liver	497	69.5	43.5	17.5	20.2
Lung	84.0	13.4	BQL	BQL	BQL
Lymph node (cervical)	57.1	BQL	BQL	BQL	BQL
Meninges	41.7	13.4	BQL	BQL	BQL
Muscle (femoral)	30.1	14.7	BQL	BQL	BQL
Nasal turbinates	71.0	11.4	BQL	BQL	BQL
Oral mucosa	91.3	93.8	25.6	17.1	BQL
Orbital area	72.4	BQL	BQL	BQL	BQL
Pancreas	103	29.6	61.6	10.7	BQL
Pigmented skin	296	36.1	BQL	BQL	BQL
Prostate	73.2	24.4	BQL	BQL	BQL
Salivary gland	95.7	14.1	11.2	BQL	BQL
Seminal vesicle	80.3	201	BQL	BQL	BQL
Small intestine wall	31436	1418	46.2	14.4	10.4
Spleen	53.4	19.9	11.3	10.9	7.49
Stomach wall (glandular)	120	20.8	49.1	19.2	7.60
Stomach wall (non-glandular)	64.7	6.99	7.37	BQL	BQL
Testis	44.2	53.5	20.3	6.72	BQL
Thymus	64.9	14.1	BQL	BQL	BQL
Thyroid gland	41.8	23.9	BQL	BQL	BQL
Trachea	69.2	BQL	BQL	BQL	BQL
Urinary bladder wall	1247	1054	22.4	20.0	BQL
White fat (inguinal)	235	113	106	BQL	BQL

BQL: below the quantifiable limit; NC: not calculated: LLC: liquid scintillation counting; LLOQ: lower limit of quantification. BQL = <LLOQ for QWBA = <6.64 ng equiv/g; BQL = <LLOQ for LSC = <1.26 ng equiv/g (plasma) or <0.577 ng equiv/g (blood).
N=5; one animal per timepoint for QWBA; blood collected from all animals just prior to euthanasia.

The radioactivity was located mainly to the large and small intestine walls, the cecum mucosa, gallbladder, kidney, urinary bladder wall and liver in both species. By the end of sampling, the radioactivity in most tissues had declined in proportion to that in blood, or the count rate had decreased by half between sampling intervals, indicating that there was no obvious retention in these tissues. One notable exception was the renal retention observed in rats between sample intervals 24h-48h-96h with no change in measured radioactivity. Similar observation was made in monkeys between 48h and 96h. There was no noteworthy distribution to pigmented tissue and thus no indications of relevant melanin binding. Limited amounts of radioactivity were distributed to male reproductive organs, which was cleared over time. As the study was only conducted in male rats, no data has been generated to investigate distribution to female reproductive organs. In general, limited correlation was observed between tissue site of distribution and the identified target organs for toxicities. Rather, data indicates that organ toxicities correlate with pharmacological inhibition of TROP family proteins, specifically targeting mucosal tissue and excretory organs such as gastrointestinal tract, liver, eye, skin and oesophagus, kidneys, reproductive organs and bone marrow.

The in vitro plasma protein binding of DXd was determined in mice, rats, monkeys, and humans. DXd exhibited high plasma protein binding in the mouse (90.3 - 92.5%), rat (94.2 - 96.7%), monkey (86.5 - 89.1%) and human (96.8 - 98.0%). Unbound DXd plasma concentration appeared app. 2- and 5-fold lower in human plasma as compared to plasma in animals. The plasma protein binding ratios of DXd tended to decrease with the increasing concentration over the tested concentration range in all species tested, but plasma binding remained high.

The in vitro distribution to blood cells and the blood/plasma (B/P) ratios of DXd was examined in mouse, rat, monkey, and human blood. Distribution to blood cells ranged from 13.0% and 17.7% in

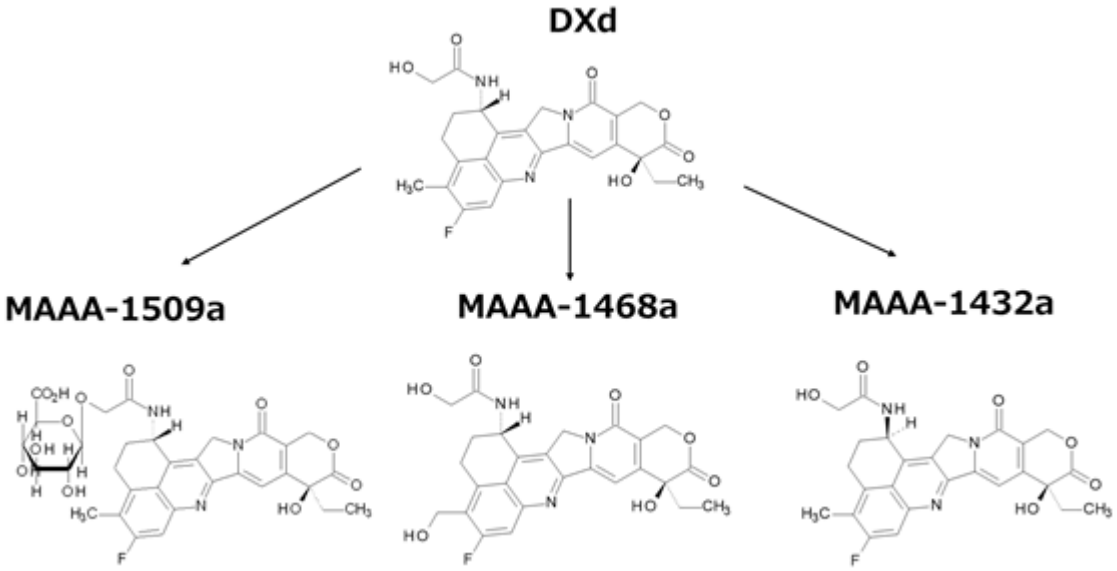
humans and was about 2-fold lower as compared to animals. B/P ratios were below 1 and indicated that DXd primarily was found in the plasma fraction. In summary, data in humans and animals showed limited distribution to blood cells.

No dedicated tissue distribution studies in pregnant animals were conducted and the extend of placental transfer of DXd into foetal tissues is unknown.

3.2.3.4. Metabolism

Release rates of DXd from datopotamab deruxtecan (Dato-DXd) appear to be stable, though a gradual increase in release rate was observed through the 21-days incubation period in mouse, rat, monkey, and human plasma, where release was highest in human and monkey plasma. In vitro tests demonstrate that DXd is stable against UGT enzymes in rat, monkey, and human liver microsomes. Using human CYP-expressing microsomes and human liver microsomes, it was demonstrated CYP3A4 is the primary CYP isoform involved in the metabolism of DXd, while CYP2C8 may play a minor role. DXd was the major radioactive component in urine, feces, and bile in rats and monkeys following single IV administration. Only a minor unidentified metabolite (1.1 %) was observed in feces in rats while nothing was observed in urine or bile. In monkeys, 3 minor metabolites were identified, primarily in feces (1.1% MAAA-1432a, an epimer of DXd) or bile (1.8% MAAA-1468a, a monoxide of DXd and 1.1% MAAA-1509a, a glucuronide of DXd). The proposed metabolic pathway of DXd is shown in Figure 9. The metabolism profile has not been determined in plasma in animals nor in humans.

Figure 9 Proposed metabolic pathway of DXd



3.2.3.5. Excretion

Excretion of ^{14}C-DXd was determined in four mass balance studies in non-fasted male Sprague Dawley rats and male Cynomolgus monkeys both non-cannulated and cannulated using 1 mg/kg. The rat studies have previously been assessed as a part of the marketing authorisation application for Enhertu®. The study descriptions and results related to the rat studies are harmonised with the publicly available EPAR of Enhertu® (EMA/CHMP/636117/2022).

Following a single intravenous administration of 1 mg/kg ^{14}C-DXd in rats, more than 90% of the administered radioactivity was excreted from the body within 48 h. The results indicate that the major excretion route is through the faeces, accounting for 70% of the observed excreted radioactivity. Upon further assessment in cannulated rats, the majority of ^{14}C-DXd (72%) was found excreted through the

bile and supports the presence of enterohepatic recycling. Up to 27% was excreted in urine while negligible amounts were recovered in the expired air, gastro-intestinal contents and carcass. Biliary excretion of DXd in rats was fast, reaching maximal levels within the 0 – 4 h collection interval.

In monkeys, a single intravenous administration (1 mg/kg) of ^{14}C-DXd confirmed faeces as the major excretion route, accounting for 62% of the observed excreted radioactivity. The presence of enterohepatic recycling of ^{14}C-DXd seen in rats was also supported in cannulated monkeys, and biliary excretion was found to be similarly fast to that in rats, reaching maximal levels of 71% within the 0 – 6 h collection interval. Minor amounts of radioactivity were recovered in urine and through cage remains, amounting to 12% or less.

Table 7 Excretion data of 14C-DXd: Cumulative excretion of radioactivity (% of dose)

Species	Study/Anal.	N/ sex	Dose (mg/ kg)	Rou te	Urine (% dose)	Faeces (% dose)	Bile (% dose)	Other sources (% dose)	Recovery (% dose)	Time (h)
Rat	^{14}C-MAAA-1181a	3M	1	*IV*	27.2 ±2.7	**70.4** ±3.1		0.1[a]	**97.7** ±0.5	168
Rat BDC	^{14}C-MAAA-1181a	3M	1	*IV*	21.9 ±3.1	2.7 ±0.7	**71.6** ±3.4	0.4[b]	**96.6** ±1.0	48
Monkey	^{14}C-MAAA-1181a	3M	1	*IV*	5.41 ±5.62	**61.8** ±3.8		10.0[c, e]	**77.2** ±9.4	96
Monkey BDC	^{14}C-MAAA-1181a	4M	1	*IV*	4.78 ±3.41	0.1 ±0.1	**70.7** ±8.1	6.9[d, e]	**82.5** ±9.3	72-96

[a]expired air: 0.1 ±0.0; carcass: 0.0, [b]gastro-intestinal contents (0.2 ± 0.2); carcass (0.2 ± 0.3), [c]cage rinse: 5.51 (4.74); cage debris: 4.32 (0.56); cage wash: 0.18 (0.10), [d]cage rinse: 6.43 (1.19); cage wipe: 0.46 (0.14); bile wipe: 0.01 (-); [e] results from other sources in monkeys were considered part of the urine results. BDC=Bile duct-cannulated. Data is expressed as the mean ± standard deviation.

Unchanged DXd was the predominant radioactive component excreted, accounting for more than 80% in the analysis samples collected from excreta up to 6 h and 24 h post-dose. Possible gender related differences in biliary excretion were not assessed, as only male animals were included in the mass balance studies. However, no differences in pharmacokinetics nor in systemic exposures were noted between sexes in relevant studies. Overall the excretion profile in rats and monkeys is considered translatable to humans. Excretion into milk in lactating animals was not assessed.

3.2.3.6. Pharmacokinetic drug interactions

A rat PK study was conducted to support the transition from the early drug development batch, DS Process-1 used in non-clinical and early clinical studies, to DS Process-2 which has been used in Phase 2/3 studies. No apparent differences in PK parameters were observed between batches.

3.2.4. Toxicology

A comprehensive toxicology programme for datopotamab deruxtecan was conducted in line with ICH guidelines S9, S6(R1) and other relevant ICH guidelines, and in member countries of the OECD Mutual Acceptance Data program in accordance with the OECD Test Guidelines and Principles of Good Laboratory Practice.

For safety assessment of datopotamab deruxtecan, cynomolgus monkeys were chosen as the cross-reactive species, and rats were chosen to evaluate the target-independent effects. To assess the general toxicity profile, 3-month intermittent intravenous dose toxicity studies (every 3 weeks (Q3W),

five times in total) in rats and monkeys were conducted. The reversibility of toxic changes was also evaluated following a 2-month recovery period in the intermittent dose toxicity studies.

In vitro genotoxicity studies of DXd included a bacterial reverse mutation study and a chromosome aberration study with mammalian cultured cells. For the in vivo assessment, a micronucleus study of DXd was performed in rats.

Tissue cross-reactivity studies were conducted to determine the potential cross-reactivity of datopotamab deruxtecan in normal human and cynomolgus monkey tissues. The general toxicity profile of DXd was assessed in 4-week intermittent intravenous dose toxicity studies (every week (QW), 5 times in total) with a 4-week recovery period in rats and cynomolgus monkeys. For DXd, the potential phototoxicity was evaluated in an in vitro 3T3 neutral red uptake phototoxicity study and an in vivo rat phototoxicity study.

To assess the potential for datopotamab deruxtecan to induce cytokine release and immune cell activation, in vitro CRA of datopotamab deruxtecan and datopotamab were performed in a plate-bound format using human peripheral blood mononuclear cells and in a soluble format using human whole blood. The toxicity profile of MAAP-9002b (an antibody-drug conjugate comprised of same antibody, linker, and drug as those of datopotamab deruxtecan; the average drug-to-antibody ratio was approximately seven) was evaluated in a 2-week intermittent intravenous dose toxicity study (QW, two times in total) in cynomolgus monkeys.

Table 8 Summary of Toxicology Program for Datopotamab deruxtecan

Report No	Study Type	Test article	Route	Species/Strain	Regulatory compliance
Repeat–Dose Toxicity					
AN15-H0083-R01	3 months	Datopotamab deruxtecan	I.v.	Rats/Crl:CD(SD)	GLP
AN17-H0001-R01	6 weeks	Datopotamab deruxtecan	I.v.	Cynomolgus monkeys	Non-GLP
SBL315-405	3 months	Datopotamab deruxtecan	I.v.	Cynomolgus monkeys	GLP
SBL315-026	4 weeks	DXd monohydrate	I.v.	Rats/Crl:CD(SD)	GLP
SBL315-032	4 weeks	DXd monohydrate	I.v.	Cynomolgus monkeys	GLP
SBL314-884	2 weeks	MAAP-9002b[c]	I.v.	Cynomolgus monkeys	Non-GLP
Genotoxicity					
SBL315-617	Bacterial reverse mutation	DXd monohydrate[a]	In vitro	*Salmonella typhimurium, Escherichia coli*	GLP
SBL315-618	Chromosomal aberration	DXd monohydrate	In vitro	Chinese hamster lung cells	GLP
SBL315-756	Bone marrow micronucleus (single)	DXd monohydrate	I.v.	Rats/Crl:CD(SD)	GLP
Other toxicity					
20095172	Tissue cross reactivity	Datopotamab deruxtecan	In vitro	Human tissues	GLP
20095173	Tissue cross-reactivity	Datopotamab deruxtecan	In vitro	Cynomolgus monkey tissues	GLP
SBL315-101	Phototoxicity	DXd monohydrate	In vitro	Balb/c mouse 3T3 fibroblasts	GLP
SBL315-450	Phototoxicity	DXd monohydrate[a]	I.v.	Rats/Iar:Long-Evans	GLP
0730-177-R03	In vitro CRA	Datopotamab deruxtecan, Dato[b]	In vitro	Human PBMCs	Non-GLP
0730-177-R04	In vitro CRA	Datopotamab deruxtecan, Dato[b]	In vitro	Human whole blood	Non-GLP

cytokine release assays = CRA; PBMCs = peripheral blood mononuclear cells.
[a] DXd monohydrate was referred to MAAA-1181d in the reports.
[b] Dato was referred to MAAP-9001a in the reports.
[c] MAAP-9002b was an ADC comprised the same antibody, linker, and drug as those of Dato-DXd. The average DAR of MAAP-9002b was approximately 7 and different from that of Datopotamab deruxtecan.

3.2.4.1. Single dose toxicity

No single-dose studies with datopotamab deruxtecan were conducted. Acute toxicity information was available at the first dosing in the intermittent pivotal 3-month i.v. dose toxicity studies in rats and cynomolgus monkeys. Neither deaths nor moribundity were noted up to 200 mg/kg in rats (study No AN15-H0083-R01) or 80 mg/kg in monkeys (study No SBL315-405) in the 1st cycle following datopotamab deruxtecan dosing. Loss of fur was observed in rats at 200 mg/kg from eight days after the 1st dosing and abnormal skin colour was observed in monkeys given ≥30 mg/kg from approximately fourteen days after the 1st dosing. Decreases in body weight were also noted in rats given 200 mg/kg and monkeys given 30 and 80 mg/kg, respectively, after the 1st dosing.

3.2.4.2. Repeat dose toxicity

The general toxicity profile of datopotamab deruxtecan and DXd were assessed in repeat-dose studies in rats and cynomolgus monkeys.

Datopotamab deruxtecan

Table 9 Pivotal repeat-dose toxicity studies with datopotamab deruxtecan

Study details	No:Group	Dose (mg/kg)	Exposure		Major findings & NOAEL
			C0 µg/mL	AUC µg×d/mL	
Sprague-Dawley rats 12 + 8 w Q3W for 3 months i.v. GLP (AN15-H0083-R01)	Main: 10M+10F Recovery: 5M+5F (group 0 and 200 mg/kg)	0	-	-	**20 mg/kg** *Histopathology*: M: Thymus (increased number of tingible body macrophage). **60 mg/kg** *Clinical observations*: M+F: Overgrown teeth. M: Crushing and whitening of teeth. F: ↓*BW.* F: ↓*Food consumption*. *Macroscopic examination*: M+F: Incisor (crushing of teeth, whitening and overgrowth of teeth). *Histopathology*: M: Kidney (hyaline cast and regeneration of tubular epithelium), M+F: Thymus (increased number of tingible body macrophage). rectum (single cell necrosis in crypt), incisor (necrosis of ameloblast), M: Duodenum (single cell necrosis in crypt), incisor (gingivitis), F: Jejunum (single cell necrosis in crypt). **200 mg/kg** *Clinical observations*: M+F: Loss of fur, overgrown teeth, whitening of teeth. F: Crushing of teeth. F: ↓*BW.* M+F: ↓*Food consumption*. *Haematology*: M+F: ↓RBC and WBC. *Clinical chemistry*: M: ↓ALB and A/G. M+F: ↑UN. *Urinalysis*: M+F: ↑Protein. *Organ weight*: M: ↓Epididymides (absolute and relative). *Macroscopic examination*: M+F: Incisor (crushing, whitening, and overgrowth of teeth), skin (alopecia), thymus (small size), M: Lung (coloured focus) and F: Caecum (black contents). *Histopathology*: M+F: Kidney (degeneration of podocyte, hyaline cast, regeneration of tubular epithelium), lung (haemorrhage, infiltration of neutrophil in alveolus, regeneration of alveolar epithelium and infiltration of foamy alveolar macrophage), duodenum, jejunum, ileum, caecum
		20	658	2580	
		60	2270	8740	
		200	6170	25100	

					(single cell necrosis in crypt), bone marrow (decreased erythropoiesis and decreased granulopoiesis), thymus (increased number of tingible body macrophage, atrophy of cortex), incisor (abnormal dentin formation and single cell necrosis in enamel organ), F: Spleen (atrophy of PALS), skin (single cell necrosis in hair follicle), ovary (increased number of atretic follicle), vagina (single cell necrosis of mucosal epithelium), M: Skin (necrosis of epidermis), mammary gland (atrophy of gland epithelium), testis (degeneration of germinal epithelium, atrophy of seminiferous tubule), epididymis (cell debris in duct, decreased number of spermatozoa in duct, single cell necrosis of ductal epithelium), incisor (haemorrhage in root and necrosis in root). Recovery **200 mg/kg** *Clinical observations*: M+F: Whitening and overgrown of teeth and F: crushing of teeth. F: ↓*BW.* *Urinalysis*: M+F: ↑Protein. *Organ weight*: M: ↓Testes and epididymides (absolute and relative). *Macroscopic examination*: M+F: Incisor (crushing of teeth, whitening and overgrowth of teeth), M: Testis (small size). *Histopathology*: M+F: Incisor (gingivitis), M: Kidney (hyaline cast and regeneration of tubular epithelium), lung (haemorrhage and regeneration of alveolar epithelium), mammary gland (increased lipid droplet in glandular epithelium), testis (degeneration of germinal epithelium and atrophy of seminiferous tubule), epididymis (cell debris in duct, decreased number of spermatozoa in duct), F: Incisor (necrosis of ameloblast). **NOAEL: Not determined.**
Cynomolgus monkey 12 + 8 w Q3W for 3 months i.v. GLP (SBL315-405)	Main: 3M+3F Recovery: 2M+2F (group 30 and 80 mg/kg	0	-	-	**10 mg/kg** M: ↓*BW.* *Haematology*: M: ↑Neutro and Mono. M+F: ↓Plat. *Histopathology*: M+F: Small intestine (single cell necrosis in the crypt epithelium). **30 mg/kg** *Clinical observations*: M+F: Abnormal skin color (black; nose, cervix, shoulder, forelegs, chest, lower abdomen, and/or hindlegs). M+F: ↓*BW.* *Ophthalmoscopy*: F: Corneal pigmentation. *Haematology:* M+F: ↑Mono, F: ↑Neutro and Fibrin. M: ↑Luc. *Urinalysis*: M: ↓pH. *Organ weight*: M: ↑Lung weight (absolute and relative). *Macroscopic examination*: M: Red and brown focus in the lung. F: Black discoloration of the skin. *Histopathology*: M+F: Small intestine (single cell necrosis in the crypt epithelium), F: Skin (brown pigmentation in the epidermis), F: Eyeball (brown pigmentation and single cell necrosis in the corneal epithelium), M: Lung (oedema and haemorrhage in the alveolus, aggregation of foamy alveolar macrophage, mononuclear cell infiltration and fibrosis in the interstitium, inflammatory cell infiltration in the alveolus and interstitium and karyomegaly/cytomegaly in the alveolar and bronchiolar epithelium), M+F: Thymus (atrophy), M: Liver (single cell necrosis). **80 mg/kg**
		10	125	217	
		30	645	2520	
		80	1710	8610	

					Clinical observations: M+F: Abnormal skin color (black and red; cervix, forelegs, chest, axilla, lower abdomen, knee, inguinal, and/or hindlegs). F: Incomplete eyelid opening, abnormal gait and excoriation and erosion. M+F: ↓*BW.* *Ophthalmoscopy*: M+F: Corneal pigmentation. *Haematology*: F: ↓RBC, Hb, Ht and ↑Ret, M+F: ↑ Neutro. F: ↑ Fibrin. *Clinical chemistry:* M+F: ↑T-Bil, D-Bil and GLB. ↓ALB and A/G ratio. *Urinalysis*: M+F: ↓pH. *Macroscopic examination*: M+F: Skin (black discoloration), M: Lung (brown focus). F: Skin (red discoloration), hip joint (thickening of articular capsule) and lymph node (enlargement of the right axillary lymph node). *Histopathology*: M+F: Small intestine (single cell necrosis in the crypt epithelium), M+F: Skin (brown pigmentation in the epidermis, F: inflammatory cell infiltration in the epidermis), M+F: Eyeball (single cell necrosis and brown pigmentation and atrophy in and of the corneal epithelium and M: vacuolation in the corneal epithelium), M: Lung (oedema in alveolus, aggregation of foamy alveolar macrophage, mononuclear cell infiltration and fibrosis in the interstitium and karyomegaly/cytomegaly in the alveolar and bronchiolar epithelium), M: Thymus (atrophy), M: Kidney (karyomegaly in the proximal tubules) and F: Hip joint (fibrocartilage formation in the articular surface, erosion in the articular cartilage, hyperplasia of the synovial cell and fibrous thickening of articular capsule in the right hip joint). Recovery **30 mg/kg** *Clinical observations*: M+F: Abnormal skin color (black; nose, cervix, shoulder, forelegs, chest, lower abdomen, and/or hindlegs). F: ↓*BW.* *Ophthalmoscopy*: M+F: Corneal pigmentation. *Macroscopic examination*: M+F: Black discoloration of the skin. *Histopathology*: M+F: Skin (brown pigmentation in the epidermis). **80 mg/kg** *Clinical observations*: M+F: Abnormal skin color (black; nose, cervix, shoulder, forelegs, chest, lower abdomen, hindlegs). F: ↓*BW* *Ophthalmoscopy*: M+F: Corneal pigmentation. *Macroscopic examination*: M+F: Skin (black discoloration). *Histopathology*: M+F: Skin (brown pigmentation in the epidermis), M+F: Eyeball (brown pigmentation in the corneal epithelium), M: Lung (aggregation of foamy alveolar macrophage, fibrosis in the interstitium, haemorrhage in the alveolus, inflammatory cell infiltration in the alveolus and interstitium, and karyomegaly/cytomegaly in the alveolar epithelium) and M: Liver (diffuse vacuolation). **NOAEL: Not determined.**

In a 3-month GLP repeat-dose study with a 2-month week recovery period datopotamab deruxtecan was administered i.v. at doses of 20, 60 or 200 mg/kg every three weeks on five occasions to rats. The

major toxicities were observed in the thymus at ≥20 mg/kg; in the kidney, intestines, and incisor teeth at ≥60 mg/kg; and in the lung, skin, reproductive tract, and lymphatic or haematopoietic organs at 200 mg/kg. All of these changes observed were non-severe and showed recovery or a tendency towards recovery after the 2-month recovery period, except for the male reproductive toxicity. Anti-drug antibodies (ADA) were detected in one male given 20 mg/kg but mainly in pre-dose and control samples (study No AN15-H0083-R01).

In a preliminary 6-week non-GLP study, datopotamab deruxtecan was administered i.v. at doses of 10 and 30 mg/kg every three weeks on three occasions to cynomolgus monkeys. Neither death nor moribundity was observed during the dosing period. The major toxicities were limited to the lung (aggregation of foamy alveolar macrophage and cell infiltration in the interstitium), thymus (increased number of tingible body macrophage) and duodenum (single cell necrosis in crypt) at 30 mg/kg. Total antibody and free DXd were generally increased with dose. Anti-drug antibody formation was not determined in this study (study No AN17-H0001-R01).

Datopotamab deruxtecan was administered i.v. to cynomolgus monkeys at doses of 10, 30 or 80 mg/kg every three weeks on five occasions in a GLP-compliant 3-month toxicity study with a 2-month recovery period, no deaths or moribundity were noted up to 80 mg/kg. Severe lung toxicity was noted in one monkey at each 30 mg/kg and 80 mg/kg, respectively. The other major toxicities were observed in the intestine at ≥10 mg/kg; in the cornea, skin, thymus, and liver at ≥30 mg/kg; and kidney and hip joint cartilage accompanied by abnormal gait at 80 mg/kg. Almost all findings tended to recover, except for some findings in the lung as well as pigmentation in the cornea and skin. Decreased exposure levels of datopotamab deruxtecan were noted at 10 mg/kg in 5/6 monkeys after the 4th dose compared to the 1st dose. After the 4th and 5th the animals exhibited thrombocytopenia and showed lower datopotamab deruxtecan and higher DXd exposures after repeated dosing. Although ADAs were formed exposure was sufficiently maintained during the treatment period in this group (study No SBL315-405).

DXd

A GLP-compliant repeat-dose study in rats with once weekly i.v. injection of 3, 10 and 30 mg/kg DXd monohydrate for 4 weeks with a 4-week recovery period led to toxicity findings in the lymphatic/haematopoietic system, the intestinal tract, and the cornea of the eye observed at ≥3 mg/kg. The changes observed during the dosing period showed reversibility by the end of the recovery period (study No SBL315-026).

In a GLP-compliant 4-week repeat-dose study in cynomolgus monkeys with a 4-week recovery period administration of DXd monohydrate i.v. once weekly on five occasions at doses of 1, 3, and 12 mg/kg resulted in findings similar to those in rats (i.e. toxicity in the lymphatic/haematopoietic system, the intestinal tract, and the cornea) already at dose levels of ≥1 mg/kg. In addition, one female monkey died and one male monkey became moribund in the high dose group at 12 mg/kg. Cardio- and hepatotoxicity were found in the moribund male monkey. Both monkeys exhibited deteriorated physical conditions associated with sustained decreases in food consumption, bone marrow toxicity and intestinal toxicity. The test article-related changes noted during the dosing period showed recovery by the end of the recovery period (study Nos SBL315-026 and SBL315-032).

MAAP-9002b

In a preliminary 2-week toxicity study, a former trophoblast cell surface antigen 2 antibody-drug conjugate, MAAP-9002b (with a drug-to-antibody ratio of approximately seven) was given i.v. at doses of 10, 30, and 80 mg/kg once weekly on two occasions to monkeys. At 80 mg/kg one male monkey died and one female monkey was euthanized due to moribundity. The major findings of toxicity were observed in the skin, oesophagus, vagina and mammary glands at ≥10 mg/kg, in the cornea and

prostate at ≥30 mg/kg and in the liver, intestine, bone marrow, heart, kidney and ovary at 80 mg/kg (study No SBL314-884).

The exposure levels (based on C_0 and AUC_{21d}) of datopotamab deruxtecan in rats were higher than those in humans at the clinically relevant dose of 6 mg/kg. In monkeys, the exposure level at the severely toxic dose of ≥30 mg/kg was 3-fold higher than those in humans at 6 mg/kg.

3.2.4.3. Genotoxicity

Table 10 Overview of genotoxicity studies of DXd

Type of test/study ID/GLP	Test system	Concentrations/Concentration range/metabolising system	Results positive/negative/equivocal
Gene mutations in bacteria/SBL315 617/GLP	Salmonella typhimurium (TA100, TA1535, TA98, TA1537) and Escherichia coli (WP2uvrA) Negative control: DMSO Positive controls: 4 nitroquinoline 1-oxide, sodium azide, 9 aminoacridine hydrochloride monohydrate, or 2 aminoanthracene.	313, 625, 1250, 2500, and 5000 µg/plate +/- S9 Solvent: DXd monohydrate in DMSO	**Negative**
Chromosome aberrations in mammalian cells/SBL315-618/GLP	CHL/IU cell line from the lungs of newborn female Chinese hamsters, sensitive to chemicals that induce chromosome aberrations Negative control: DMSO Positive controls: mitomycin C and cyclophosphamide monohydrate	0.05, 0.1, 0.2, and 0.4 µg/mL (short term treatment, - S9) 0.05, 0.1, 0.2, 0.4, and 1 µg/mL (short term treatment, + S9) 0.0125, 0.025, 0.05, 0.1, and 0.2 µg/mL (continuous treatment, - S9) Solvent: DXd monohydrate in DMSO	**Positive**: DXd increased the number of cells with structural chromosome aberrations in a dose-dependent manner in all treatment conditions. **Negative**: DXd did not cause a statistically significant increase in the number of cells with numerical chromosome aberrations in any treatment condition.
Chromosomal aberrations in-vivo/SBL315-756/GLP	Rats, micronuclei in bone marrow (n = 5 male Sprague-Dawley rats, 8 w old/group) Negative control: physiological saline i.v. Positive control: preserved positive control specimens	0.025, 0.05, 0.1, and 0.2 mg/kg (single dose, i.v.) Solvent: DXd monohydrate in physiological saline	**Positive**: A statistically significant increase in the number of micronucleated immature RBCs was observed at ≥0.05 mg/kg when compared with the negative control group. **Negative**: No statistically signi-ficant change in the proportion of immature RBCs observed when compared with the negative control group.

Genotoxicity studies evaluated the topoisomerase I inhibitor drug component, DXd, of the antibody-drug conjugate datopotamab deruxtecan. DXd was in the form of DXd monohydrate. The genotoxic potential was sufficiently studied in a standard test battery comprising of GLP-compliant in vitro bacterial and mammalian cell assays (study Nos SBL315-617 and SBL315-618) and an in vivo rat bone marrow micronucleus assay (study No SBL315-756). These studies have previously been assessed as a part of the marketing authorisation application for Enhertu® (EMA/CHMP/636117/2022).

DXd showed no potential to induce gene mutation in five standard strains of Salmonella and E. coli in the in vitro bacterial reverse mutation assay (no DXd-related increase in the number of revertant bacterial colonies in any group was observed). However, DXd was positive for the potential to cause chromosomal aberrations when assessed in the in vitro chromosome aberration study and at ≥0.05

mg/kg in the in vivo rat bone marrow micronucleus study. DXd induced structural chromosome aberrations in vitro and increased the number of micronucleated immature red blood cells in vivo, respectively. No statistically significant change in the proportion of immature red blood cells was observed in the in vivo study indicating that bone marrow cell proliferation was not inhibited. The positive findings in the in vitro chromosome aberration study in mammalian cells and in the in vivo rat bone marrow micronucleus study are considered to be clinically relevant.

3.2.4.4. Carcinogenicity

No carcinogenicity studies have been performed.

3.2.4.5. Reproductive and developmental toxicity

Fertility and early embryonic development

Fertility and early embryonic development were not conducted. However, male or female reproductive toxicity of datopotamab deruxtecan (study Nos AN15-H0083-R01, AN17-H0001-R01 and SBL315-405) and DXd (study Nos SBL315-026 and SBL315-032) were evaluated in rat and monkey repeat-dose studies.

Embryo-foetal development

No dedicated embryo-foetal studies were conducted.

Prenatal and postnatal development, including maternal function

Prenatal and postnatal development studies were not conducted.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

No juvenile studies were submitted.

3.2.4.6. Interspecies comparison and exposure margins to clinical exposure

Interspecies comparison data after the 1st and 4th dosing of datopotamab deruxtecan were presented as a comparison of exposures (C_0/C_{max} and AUC_{21d}) of datopotamab deruxtecan and DXd from the pivotal 3-month repeat-dose rat (study No AN15-H0083-R01) and cynomolgus monkey (study No SBL315-405) studies with predicted adult human exposure (single and multiple doses) at the clinical dose of 6.0 mg/kg administered once every three weeks (clinical study No Study TP01).

The exposure levels (based on C_0 and AUC_{21d}) of datopotamab deruxtecan in rats were higher than those in human at 6 mg/kg. Those of DXd (based on C_{max} and AUC_{21d}) in rats ranged between 0.51 to 1.4 compared to the predicted adult human exposure following single and multiple dosing with datopotamab deruxtecan. In monkeys, the exposure level (based on C_0 and AUC_{21d}) of datopotamab deruxtecan at the severely toxic dose of ≥30 mg/kg was 3-fold higher than those in human at 6 mg/kg. In the low dose group (10 mg/kg) margins of exposure ratios between monkey and human ranged from 0.25- to 1.5-fold that in humans. The margin of exposure of DXd (based on C_{max} and AUC_{21d}) at all dose levels in monkeys were comparable with or lower than those in human at 6 mg/kg after the repeated doses and ranged from 0.05 to 2.1.

In addition, a presentation of margin of exposure (based on AUC) of datopotamab deruxtecan at the no observed adverse effect level (NOAEL) of each target organ of toxicity in rats and monkeys compared with the optimal dose of 6 mg/kg (multiple doses) in subjects with non-small cell lung cancer was included. In monkeys, slight intestinal toxicity was observed at ≥10 mg/kg, and no exposure margin was determined (margin of exposure <0.25). The NOAEL for pulmonary, corneal,

dermal, hepatic and lymphoid (thymic) toxicity was concluded to be 10 mg/kg corresponding to a margin of exposure of 0.25. Exposure margin of haematopoietic and renal toxicity (30 mg/kg) was determined to 2.9, whereas reproductive toxicity (up to 80 mg/kg) was 10.

3.2.4.7. Toxicokinetic data

Toxicokinetics of datopotamab deruxtecan and DXd were assessed in section 3.2.3.2 Absorption.

3.2.4.8. Local tolerance

Microscopic evaluation of the injection sites as part of the repeat-dose toxicology studies in both rats (study Nos AN15-H0083-R01 and SBL315-026) and monkeys (study Nos AN17-H0001-R01 and SBL315-405 and SBL315-032) identified no datopotamab deruxtecan- or DXd-related effects.

3.2.4.9. Other toxicity studies

3.2.4.9.1. **Antigenicity**

No stand-alone antigenicity study of datopotamab deruxtecan was conducted. The induction of antibody formation in animals is not predictive of a potential for antibody formation in humans. Nevertheless, formation of anti-drug antibodies (ADA) against datopotamab deruxtecan and its impact on toxicokinetics was assessed based on data from i.v. 3-month repeat-dose toxicity studies in rats (study No AN15-H0083-R01) and cynomolgus monkeys (study No SBL315-405) in accordance with the ICH guideline S6(R1).

In rats, ADA formation was primarily seen in pre-dose and control samples (0 mg/kg: 2/20 animals; 20 mg/kg: 2/20 animals and 200 mg/kg: 1/20 animals) and in 1/8 animals on Day 85 dosed at 20 mg/kg. The applicant did not comment on ADA formation in samples from non-treated animals. In 5/6 monkeys given 10 mg/kg ADA formation was observed at the end of the 3-month dosing period and there was a reduction in datopotamab deruxtecan exposure after the 4th dose compared to the 1st dose. After the 4th and 5th repeated dose the animals exhibited thrombocytopenia and showed lower datopotamab deruxtecan and higher DXd exposures. after repeated dosing. Although ADAs were formed, exposure was still sufficiently maintained during the treatment period in this group. On recovery Day 57, 4/4 monkeys in the 30 mg/kg group had developed ADAs.

3.2.4.9.2. **Immunotoxicity**

Immunotoxicity evaluations were integrated in the repeat-dose toxicity studies. Datopotamab deruxtecan-related lymphatic organ toxicity was noted in rats and monkeys and included an increased number of tingiblebody macrophage in the thymus and thymic atrophy, respectively.

3.2.4.9.3. **Dependence**

No studies were submitted.

3.2.4.9.4. **Studies on metabolites**

No studies on metabolites were presented.

3.2.4.9.5. **Studies on impurities**

No data on impurities were presented in the toxicology part of the dossier.

3.2.4.9.6. **Phototoxicity studies**

Study ID	Test system	Concentrations/concentration range of DXd	UVA exposure/source	Major findings
SBL315-101/GLP	Balb/c mouse 3T3 fibroblasts Positive control: Chlorpromazine hydrochloride	0.195 to 25 µg/mL	5J/cm^2 (single exposure) Sunlamps (1.70 mW/cm^2 for 50 min.)	- IC50 cell viability = 2.356 µg/mL in the presence of UV-A irradiation - MPE = 0.432 →phototoxic
SBL315-450/GLP	Rat (Iar:Long-Evans, 5 animals per dose group) Positive control: 8-methoxyp-soralen (orally)	Single i.v. dose 1 or 3 mg/kg	10J/cm^2 (single exposure)	None

The conducted phototoxicity studies evaluated the topoisomerase I inhibitor drug component, DXd, of the antibody-drug conjugate datopotamab deruxtecan. DXd was in the form of DXd monohydrate.

The phototoxic potential was sufficiently studied in a standard test battery comprising of GLP-compliant studies; an in vitro 3T3 Neutral Red Uptake Phototoxicity Test (3T3 NRU-PT) (study No SBL315-101) and an in vivo i.v. single dose phototoxicity study in male Iar:Long-Evans pigmented rats (study No SBL315-450). These studies have previously been assessed as a part of the marketing authorisation application for Enhertu® (EMA/CHMP/636117/2022).

DXd showed phototoxic potential in vitro however, no concern was identified in a follow-up in vivo i.v. single dose phototoxicity study in male pigmented rats. The negative result in the in vivo phototoxicity study supersedes the positive in vitro result and no further phototoxicity testing is warranted. Based on the non-clinical data, no direct phototoxicity is anticipated in humans following administration of datopotamab deruxtecan.

3.2.4.9.7. **Excipients studies**

No data on excipients were presented in the toxicology part of the dossier.

3.2.4.9.8. **Other (toxicity) studies (including mechanistic studies)**

In two GLP-compliant studies datopotamab deruxtecan tissue cross-reactivity were further assessed in a panel of cynomolgus monkey (study No 20095173) and human tissues (study No 20095172). Plasma membranous staining in the epithelium of the urinary bladder, eye (conjunctiva), fallopian tube, oesophagus, stomach, liver, lung, pancreas, salivary gland, skin, thyroid, tonsil, ureter, and uterus was commonly observed in monkeys and humans. Test article membrane stained tissue elements that were seen in the cynomolgus monkey but not in the human tissues included the small intestine and testis. In addition, membranous staining in the eye (cornea), breast, kidney, thymus and placenta was noted in humans.

The potential risk of datopotamab deruxtecan and datopotamab to induce infusion-related reactions (IRRs) via drug-induced cytokine release and immune cell activation was evaluated in two non-GLP in vitro cytokine release assays in Human Peripheral Blood Mononuclear Cells (hPBMC) (Plate-Bound Format) (study No 0730-177-R03) and Human Whole Blood (Soluble Format) (study No 0730-177-R04), respectively. Datopotamab deruxtecan and datopotamab were analysed at four concentrations (0.15-150 µg/mL) in each assay. Incubation with Datopotamab deruxtecan and Datopotamab

increased the levels of multiple cytokines compared to vehicle in the hPBMC assay. However, these changes were either lower or comparable to what was seen for bevacizumab (IRR incidence in clinic: <3%). No signal of cytokine release activity was found in the human whole blood assay. These findings suggest that the risk of IRRs associated with datopotamab deruxtecan is comparable to that of other monoclonal antibodies, and likely falls within the lower range of risk.

3.2.5. Ecotoxicity/environmental risk assessment

Rapporteur's comments:

The active pharmaceutical ingredient of datopotamab deruxtecan is DXd, a topoisomerase I inhibitor. DXd is released from the mAb and linker portion upon binding to the target cell. Therefore, the environmental risk assessment considers this molecule in isolation. This is accepted, since the rest of the molecule can be considered of protein nature, which is susceptible to rapid degradation in the environment.

The maximum daily dose of DXd for a European adult with an average weight of 70.8 kg (Walpole et al. 2012) is estimated to be 5.5 mg per inhabitant per day. The calculation assumes the maximum daily dose is taken every day by all patients. This conservative approach is accepted.

Partition coefficient

The partition coefficient of DXd in n-octanol/water was determined using the shake flask method (OECD 107) at the test facility Scymaris Ltd., Brixham, UK. The test was performed according to the protocol of OECD 107 and in compliance with GLP. Thus, the results of log Dow of 1.280, 1.799 and 1.924 at pH 9, 7 and 5, respectively, are considered acceptable and below the trigger limit of 4.5.

Prevalence-based Fpen refinement and PECsw calculation for Non-small cell lung cancer (NSCLC):

The Globocan database was accessed in 2023, where data from 2020 was used to estimate Hungary to be the European Member State with the highest single year prevalence of lung cancer; 1-year prevalence is 59.2 per 100,000. NSCLC comprises over 80% of total incidence of lung cancer (Howlader 2014) and data from population-based studies have reported approximately 80% to 90% of all lung cancers are NSCLC (Howlader 2014; Yang 2005; Janssen-Hejinen 2001; Cataldo 2011). In the calculation of the PECsw, the highest reported incidence rates of NSCLC (90%) are applied to the overall prevalence rate of lung cancer for Hungary, in order to calculate the market penetration factor (Fpen = 0.000533). Stage of disease was not included in this calculation, therefore, the Fpen is considered to provide a worst-case assumption resulting in a PECsw of 0.00147 µg/L.

Of note, the evaluation of the 1-year prevalence data provided by the IARC has given rise to the conclusion of being insufficient since it does not illustrate the total number of patients, that may be eligible for treatment of breast cancer and non-small cell lung cancer with datopotamab deruxtecan. Therefore, the applicant is asked to provide 5-year prevalence data, which is considered a more accurate measure for the potential patient populations, or to otherwise justify the use of 1-year prevalence data. The applicant may also further refine Fpen based on treatment regimen (**OC**).

In general, the applicant submitted a well-structured environmental risk assessment (ERA), which comprised of Phase I studies and selected ERA studies of Phase II, i.e. respiration inhibition test of activated sludge microorganisms (OECD 209), determination of toxicity to the green alga *Pseudokirchneriella subcapitata* and blue-green alga *Anabaena flos-aquae* (OECD 201), reproduction test in *Daphnia magna* (OECD 211). According to the applicant, the ERA stops after Phase I, and Phase II studies were submitted for completeness.

The applicant's proposal for Section 6.6 of the SmPC is considered adequate. In addition, the following labelling for the package leaflet is proposed and considered acceptable: "*Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.*"

Table 11 Summary of main study results

Substance (INN/Invented Name): Deruxtecan/DXd/MAAA-1181d (drug part of datopotamab deruxtecan)			
CAS-number (if available): 1599440-13-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}/D_{ow}	OECD107	1.924 @ pH 5 1.799 @ pH 7 1.280 @ pH 9	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}/D_{ow}	1.924 @ pH 5 1.799 @ pH 7 1.280 @ pH 9	not B
PBT-statement:	Deruxtecan is considered to be not PBT, nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC_{sw}, refined (based on 1-year prevalence)	0.0263	µg/L	$\geqslant$ 0.01 threshold: N

3.2.6. Discussion on non-clinical aspects

3.2.6.1. Pharmacology

Primary pharmacodynamics

Mechanism of action – direct cytotoxicity

The following mechanism of action for datopotamab deruxtecan (Dato-DXd) was suggested by the applicant: After binding of datopotamab deruxtecan to TROP2, it undergoes internalisation and intracellular linker cleavage in the lysosomes to release DXd (MAAA-1181a), that induces DNA damage and apoptotic cell death. The applicant has striven to demonstrate the different steps of the mechanism of action in the conducted in vitro studies, as addressed below.

Datopotamab deruxtecan, as a TROP2 targeting antibody-drug-conjugate, was demonstrated by specific binding to TROP2. Target binding with relative similar binding affinity were seen between human and cynomolgus TROP2 (EC_{50} of 110.42 ng/mL and 97.65 ng/mL, respectively). No target cross-reactivity were observed in other species (i.e. mouse or rat), confirming the cynomolgus monkey as the appropriate species for the non-clinical pharmacokinetic and toxicology program. It should be noted, that binding affinity was tested at 4°C and not at body temperature of 37°C, which would have been more optimal to reflect the condition at which the antibody binds in the body.

Lysosomal transport of datopotamab deruxtecan (Dato-DXd) was illustrated by showing co-localisation of Alexa 488-labeled datopotamab deruxtecan (Dato-DXd) (green) with the lysosomal marker anti-LAMP2 antibody (red) in BxPC-3 cells. Results were reported based on a publication by Okajima et al. from 2021. Hence, it is unclear which study report supports the intracellular trafficking lysosomal study and for the completeness of the dossier the study report must be identified or re-submitted (**OC**).

A TROP2-mediated effect of datopotamab deruxtecan on growth inhibition in human TROP2-positive pancreas adenocarcinoma cell lines were seen. No inhibition was seen in the TROP2-negative Calu-6 anaplastic carcinoma cell line. Furthermore, a tendency toward a correlation between high TROP2 expression levels and low IC_{50} values existed. Conjugation of DXd to the antibody datopotamab appeared to limit the cytotoxic effect to TROP2 expressing cells, as cytotoxicity was seen in all three cell lines (TROP2 positive or negative) exposed to DXd alone.

The mechanisms of cytotoxicity were further examined in vitro by showing dose-dependent topoisomerase I inhibitory activity of the DXd with an IC_{50} value of 3581.19 nmol/L. Results were confirmed in a study (CR16-H0009-R04) showing the ability of datopotamab deruxtecan and DXd to induce double-strand DNA breaks and apoptosis using phosphorylation of Chk1 and cleaved PARP as markers, respectively. However, a positive response for phosphorylated Chk1 for the isotype control antibody IgG-DXd was noted in study CR16-H0009-R04, exhibiting a band intensity slightly weaker than for datopotamab deruxtecan (Dato-DXd). It was suggested that the positive pChk1 signal for the isotype control antibody IgG-DXd could be caused by target-independent uptake of ADC (e.g., macropinocytosis) or penetration of free DXd deconjugated from ADC outside the CFPAC-1 cells. However, most importantly it was stressed that cleaved PARP was not detected for the isotype control IgG-DXd, suggesting that the Chk1 phosphorylation was not enough to induce apoptosis. Of note, datopotamab deruxtecan (Dato-DXd) and the DXd induced clear signal of cleaved PARP in addition to Chk1 phosphorylation.

Other cytotoxic mechanisms of action

It was stated that: *"DXd is cell membrane-permeable, giving it the ability to penetrate and act in surrounding cancer cells. It has been reported that ADCs with CDx can exhibit a bystander killing effect, where the DXd can diffuse out of a targeted cell into adjacent cells"* (Ogitani et al., 2016). This was shown in the cell growth inhibition study (CR16-H0009-R03) where the DXd exhibited cytotoxic effect against cancer cells most likely as a result of deconjugated DXd penetrating into adjacent cells regardless of TROP2 expression. This furthermore correlated with positive findings of bystander cytotoxicity from other DXd-ADCs including trastuzumab deruxtecan (T-DXd) and patritumab deruxtecan (HER3-DXd). The potential of inducing bystander cytotoxicity should be included in the SmPC section 5.1.

In order to examine the pharmacological activity of the antibody part (i.e. datopotamab), an antibody-dependent cellular cytotoxicity (ADCC) study was conducted. However, the rapporteur disagrees with the conclusion made based on this study. It is unclear how conclusions on ADCC can be made based on results using only the conjugated antibody datopotamab deruxtecan, as the observed cytotoxicity could be mediated by the DXd moiety. Hence, a new ADCC study was conducted (study no. CY19-h0004-R04) including both the conjugated and unconjugated antibody i.e. datopotamab deruxtecan (Dato-DXd or DS-1062a) and datopotamab (MAAP-9001a). The new study showed that datopotamab (MAAP-9001a) and datopotamab deruxtecan (Dato-DXd) exhibited ADCC activity of similar magnitudes against TROP2-exprssing NCI-H322 cells in the presence of human PBMCs within a timeframe of 4 h. Hence, confirming that the antibody Fc part of datopotamab deruxtecan (Dato-DXd) and datopotamab has ADCC activity. This information should be included in section 5.1 of the SmPC.

In a new study (study no. CY19-H0004-R06) evaluating complement-dependent cytotoxic (CDC) activity of datopotamab deruxtecan (Dato-DXd or DS-1062a) and datopotamab (MAAP-9001a) in the presence of human complement using a bronchioalveolar carcinoma cell line NCI-H322 expressing human TROP2 on the cell surface, it was concluded that neither datopotamab deruxtecan nor datopotamab showed CDC activity at concentrations up to 100,000 ng/mL.

No studies on antibody-dependent cellular phagocytosis (ADCP) activity were conducted for datopotamab deruxtecan (Dato-DXd) or datopotamab. As Fc receptor-mediated ADCC activity was

identified, this emphasizes the need for information on ADCP activity. Hence, unless otherwise justified, the ADCP potential of datopotamab deruxtecan (Dato-DXd) should be evaluated (**OC**).

Furthermore, indirect cytotoxicity caused by e.g. bystander cytotoxicity, ADCC, ADCP or CDC was not mentioned in the SmPC section 5.1. Please, include information on bystander cytotoxicity, CDC, ADCC and ADCP in the mode of action description in section 5.1 of the SmPC (**OC**).

In vivo studies

Four in vivo pharmacology studies in xenograft mouse models of human pancreatic cancer (CFPAC-1 cell line), non-small cell lung cancer (NCI-H292 and HCC827 cell lines) and breast cancer (HCC1806 cell line) confirmed the efficacy of datopotamab deruxtecan (Dato-DXd) at doses of 10 mg/kg on tumour growth inhibition of 82.8 to 96.1% and revealed a tendency towards a dose-dependent effect (from doses ≥ 1 mg/kg). However, as no exposure measurements were reported, only limited information could be subtracted from the in vivo studies. Especially for the dose-dependency study, a comparison of effective exposure levels to the clinically relevant situation would have added more value to the study.

Secondary pharmacodynamics

In a secondary pharmacodynamic study testing DXd against an off-target panel of 86 receptors, channels, transporters or enzymes, no significant response (≥ 50% inhibition) was demonstrated at concentrations of 10 µmol/L (approximately 5000 ng/mL). The tested concentration provided > 1500-fold to the reported human C_{max} of 3.13 ng/mL (cycle 1).

Safety pharmacology

Two dedicated GLP-compliant safety pharmacology studies were performed. In the in vitro hERG study, DXd had no effect on hERG current at concentrations of 1, 3 and 10 µmol/L in hERG transfected CHO-cells. The maximum concentration tested provided a sufficient margin of exposure to the human clinically relevant C_{max} (> 1500-fold). Additionally, no cardiovascular, respiratory or central nervous effects were noted at single doses up to 80 mg/kg of datopotamab deruxtecan (Dato-DXd) in male cynomolgus monkeys using telemetric measurements, blood gas analysis, and a functional observational battery method for the assessment of traditional safety endpoints. Only male monkeys were used in the safety pharmacology study; however, this was sufficiently justified and supported by a lack of significant gender differences in exposure or target organs of toxicity.

Please note that in the repeat-dose toxicity studies, marked pulmonary toxicity identified the lungs as a target organ of toxicity and events of interstitial lung disease/pneumonitis have been observed in the clinical studies. This is further addressed in the toxicology and clinical parts of the assessment.

3.2.6.2. Pharmacokinetics

Analytical methods

The analytical methods in support of the pivotal toxicology studies were GLP-compliant and fully validated, and appear robust and adequate for the purpose of the studies.

Absorption

Single and repeated dosing resulted in dose-proportional increases in exposure of datopotamab deruxtecan (Dato-DXd), total anti-TROP2 antibody and DXd in both rats and monkeys, with slightly shorter terminal half-lives in rats and monkeys (~1.5-2 days) compared to humans (~5-5.5 days). No sex differences or accumulation over time were observed. Positive ADA-responses were observed in untreated rats prior to dosing with datopotamab deruxtecan as well as in 5/6 monkeys given 10 mg/kg

at the end of the 3-month dosing period with a corresponding reduction in datopotamab deruxtecan exposure and higher DXd exposures. Moreover, on recovery Day 57, 4/4 monkeys in the 30 mg/kg group had developed ADAs. Sufficient exposure was still maintained during the treatment period and reduction in exposure could be correlated to formation of ADAs. As ADA formation is not considered to affect the pharmacokinetic/ pharmacodynamic parameters or the incidence/severity of adverse events, this is considered acceptable.

Distribution

In tissue distribution studies using male rats and monkeys, ^{14}C-DXd was shown to quickly and widely distribute throughout the body and rapidly clear from tissues, mostly without any relevant retention. However, some retention was observed in several kidney substructures and appeared more pronounced in monkeys compared to rats. Kidney retention may be an event unique to DXd, possibly mediated through renal drug transporters leading to reabsorption, which would also explain the delay in urinary excretion observed in the monkey mass balance study, where urinary excretion was continued beyond 96 hors post administration, albeit at low levels. Nonetheless, seeing that DXd is only to be administered conjugated with datopotamab in a clinical setting and that the total Dato-DXd has shown to be very stable, the clinical relevance of renal retention of free DXd appears negligible. However, it should be noted that distribution studies have not been performed for total Dato-DXd and that kidney was identified as a target organ for total Dato-DXd in the general toxicity studies. Apart from the retainment in kidneys in the distribution studies, ^{14}C-DXd was mainly distributed to the large and small intestine walls but also to the cecum mucosa, gallbladder, kidney, urinary bladder wall and liver. There was no noteworthy distribution to pigmented tissue and thus no indications of relevant melanin binding, which supports the negative results from the phototoxicity as presented in the Toxicology section. Limited amounts of radioactivity were distributed to male reproductive organs, which was cleared over time. As the study was only conducted in male rats, no data has been generated to investigate distribution to female reproductive organs. The general toxicology studies report some degree of toxicity in both male and female reproductive organs. The general toxicology studies report some degree of toxicity in both male and female reproductive organs. The in vitro plasma protein binding of DXd was high (~ 98% in humans vs. ≥87% in animals tested) and blood cell uptake of DXd was limited. No dedicated tissue distribution studies in pregnant animals were conducted and the extend of placental transfer of DXd into foetal tissues is unknown.

Metabolism

It was demonstrated in vitro that datopotamab deruxtecan appears to be stable in mouse, rat, monkey, and human plasma during a 21-day incubation period. Metabolism via UGT seems to be minimal, however, one of the identified minor metabolites were the glucuronide of DXd (MAAA-1509a). The main metabolizing enzyme was determined as CYP3A4 in vitro in human CYP-expressing microsomes and human liver microsomes, however, no characterization of the in vivo metabolism profile in humans has been performed. Apart from MAAA-1509a, only two other minor metabolites were identified, MAAA-1432a, an epimer of DXd and MAAA-1468a, a monoxide of DXd. The metabolism profile in animals was only established in excreta over the course of 6 or 24 hours and was not investigated in plasma.

Excretion

The major excretion pathway after intravenous administration of ^{14}C-DXd in rat and monkey was the faeces via the biliary route, accounting for ~71% of total excretion. Minor to minimal excretion was observed via the urine (~24% and ~12% in rat and monkey). Urinary excretion was continued in monkey (not in rat) beyond 96 hors post administration, albeit at low levels. Biliary excretion was fast and almost complete at 6 hours post administration. Excretion into milk in lactating animals was not

studied. This is reflected in the SmPC and considered acceptable given the sought indication. Overall, identified excretions routes are considered translatable to humans.

Pharmacokinetic drug interactions

In vitro pharmacokinetic drug interactions have been studied using human biomaterials and are described in the clinical part of this MAA only. A rat PK bridging study demonstrated comparability in PK profile between the non-clinical/early clinical batch DS Process-1 and batch DS Process-2 which has been used in Phase 2/3 studies.

3.2.6.3. Toxicology

The binding profile of datopotamab deruxtecan showed that the antibody-drug conjugate (ADC) bound to trophoblast cell surface antigen (TROP) 2 in cynomolgus monkeys and humans, but not to TROP2 in mice or rats. Therefore, cynomolgus monkeys were used for the toxicity evaluations of datopotamab deruxtecan and rats were used to evaluate the target-independent effects. For supportive evaluations of DXd toxicity rat and cynomolgus monkey were selected as relevant species. In addition, no disproportionate drug metabolites of DXd were identified and the metabolism of DXd was similar in rat, cynomolgus monkey and human hepatocytes.

Single dose toxicity

In accordance with the ICH guideline M3(R2) no single-dose studies with datopotamab deruxtecan were conducted. Acute toxicity information was available at the first dosing in the intermittent pivotal 3-month i.v. dose toxicity studies in rats and cynomolgus monkeys which is acceptable. Acute toxicity in rats and cynomolgus monkeys comprised of loss of fur in rats (at 200 mg/kg) and abnormal skin colour in monkeys (≥30 mg/kg) eight to fourteen days after the 1st dosing. Decreases in body weight were also noted in rats and monkeys given 30 and 80 mg/kg, respectively.

Repeat-dose toxicity

The common target organs/tissues of datopotamab deruxtecan in rats and monkeys were the lung, skin, intestine, thymus and kidney. In monkeys the target organs/tissues of toxicity also included cornea, liver and hip joint cartilage, whereas, lymphatic/haematopoietic organs (spleen and bone marrow), male and female reproductive tracts and incisor tooth were identified as target organs/tissues of toxicity in rats.

The most significant change related to datopotamab deruxtecan was severe lung toxicity in monkeys at ≥30 mg/kg characterised as interstitial pneumonitis without reversibility after the recovery period. Non-severe pulmonary findings such as haemorrhage, infiltration of neutrophils in the alveolus, regeneration of the alveolar epithelium, and infiltration of foamy alveolar macrophages were also observed in rats at 200 mg/kg. However, no pulmonary toxicity was induced by DXd monohydrate in rats up to 30 mg/kg or in monkeys up to 12 mg/kg. Trophoblast cell surface antigen 2 expression in the human lungs has been reported but the comprehensive mechanisms of pulmonary toxicity related to datopotamab deruxtecan still remain unclear. Events of interstital lung disease/pneumonitis have been observed in clinical studies and is considered to be an important identified risk.

Non-severe skin toxicity was observed in rats at 200 mg/kg and in monkeys at ≥30 mg/kg of datopotamab deruxtecan. Epidermal necrosis and alopecia were observed in rats and pigmentation, erosion and inflammation in monkeys. These changes, showed reversibility after the recovery period in rats and monkeys with the exception of histopathological findings of brown pigmentation in the epidermis of monkeys at ≥30 mg/kg. Trophoblast cell surface antigen 2 is expressed in the human epidermis, however, the involvement of datopotamab deruxtecan via TROP2 in skin toxicity was undetermined, as rats, the non-cross-reactive species of datopotamab deruxtecan, also showed similar

lesions. No apparent finding after DXd monohydrate administration was seen in rats or in monkeys given up to 30 or 12 mg/kg, respectively. Several skin adverse events (e.g. rash, pruritus, dry skin and skin hyperpigmentation) are considered identified risks for datopotamab deruxtecan based on the evaluation of clinical study data.

Gastrointestinal toxicity was observed in the 3-month pivotal repeat-dose studies, characterised by single cell necrosis of the crypt epithelium in the intestines in rats at ≥60 mg/kg and in monkeys at ≥10 mg/kg of datopotamab deruxtecan. These changes showed reversibility after the recovery period in both species. The intestinal toxicity noted in relation to datopotamab deruxtecan also occurred in the toxicity studies of DXd monohydrate in rats and monkeys. Gastrointestinal toxicity is a typical dose-limiting toxicity of topoisomerase I inhibitors in humans. Therefore, gastrointestinal toxicity is attributable to the cytotoxic mechanism of action of DXd and datopotamab deruxtecan-related intestinal toxicity might be caused, at least in part, by DXd released into plasma. Several gastrointestinal adverse events (e.g. nausea, vomiting, diarrhoea and constipation) are considered identified risks for datopotamab deruxtecan based on the evaluation of clinical study data.

Renal changes in rats included hyaline casts and regeneration of tubular epithelium at ≥60 mg/kg and degeneration of podocytes at 200 mg/kg of datopotamab deruxtecan. In addition, a slight tubular change of anisokaryosis in the proximal tubule was observed in monkeys at 80 mg/kg of datopotamab deruxtecan. In this connection, changes in urinary and clinical chemistry parameters were also observed. These changes showed reversibility after the recovery period in rats and monkeys. In repeat-dose dose toxicity studies with DXd monohydrate, no renal changes were noted in rats and monkeys up to 30 and 12 mg/kg, respectively. The renal tubular findings related with datopotamab deruxtecan in monkeys may be due to an off-target effect by datopotamab deruxtecan since no TROP2 expression in the proximal tubule has been reported in immunohistochemistry, but the clinical relevance of the renal toxicity in monkeys and rats was not understood and the applicant was asked to include it as a safety concern in the Risk Management Plan (RMP) or provide an adequate justification, which could also be based on clinical experience with deruxtecan, why it should not be included. Moreover, a discussion was requested on why renal toxicity was still observed upon treatment with datopotamab deruxtecan despite renal clearance being a minor elimination pathway. The applicant argued that adverse renal changes observed in the non-clinical rat and monkey studies occurred at exposures exceeding that predicted in humans at the proposed therapeutic dose which is not entirely agreed. As the effects also occurred in rats, it is most likely due to off-target deruxtecan effects since the rat is not responsive to datopotamab. Therefore, using the margin of exposure based on the Dxd AUC is considered more appropriate. Consequently, at the NOAEL in rats (20 mg/kg) and monkeys (30 mg/kg), DXd exposures are below the clinically anticipated exposure (0.084 in rats and 0.24 for monkeys). Nevertheless, renal toxicity at exposure levels of the topoisomerase I inhibitor below clinical plasma exposure is adequately reflected in SmPC section 5.3. Although the mechanism behind renal toxicity remains unknown, especially in rats pronounced renal retention may have contributed (see also Pharmacokinetics section. The applicant provided a clear overview on the absence of clinical renal toxicity findings although the occurrence of renal adverse effects in the pivotal clinical studies (Study Nos TL01 and TB01) may be influenced by a number of confounding factors, including malignant disease, underlying renal disease at baseline and concomitant medication use. For Enhertu® renal toxicity was also included in the RMP as a potential risk based on non-clinical data. Therefore, the applicant is requested, besides inclusion as a potential risk in the updated non-clinical section of the RMP, to include renal toxicity in Part II Module SVII of the RMP, under the heading "SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP". It is considered that there is no harm in including adverse effects on renal toxicity as a potential risk in the RMP section SVII.1.1, requiring no further characterisations but only follow up via routine pharmacovigilance and risk minimisation information in the product information (**OC**).

Single cell necrosis and brown pigmentation in the corneal epithelium, which was accompanied by corneal pigmentation in ophthalmological examination, were observed in monkeys at ≥30 mg/kg of datopotamab deruxtecan. In addition, atrophy of the corneal epithelium was observed in monkeys at 80 mg/kg of datopotamab deruxtecan. The corneal findings showed reversibility after the 2-month recovery period, except for the pigmentation findings. It suggested that the corneal atrophy related to datopotamab deruxtecan in monkeys was due to the transient disruption of turnover during the treatment period. Single cell necrosis in the corneal epithelium also occurred in rats at ≥3 mg/kg and in monkeys at 12 mg/kg of DXd monohydrate. Therefore, corneal toxicity in the animals given datopotamab deruxtecan as well as DXd monohydrate would be attributable to the cytotoxic mechanism of action of DXd. Trophoblast cell surface antigen 2 is expressed in the corneal epithelium of cynomolgus monkeys. It is unclear whether target-mediate drug disposition via TROP2 is involved in the corneal toxicity in monkeys given datopotamab deruxtecan because of the ocular barrier (i.e. blood-aqueous barrier) that generally inhibits distribution of drugs to the eye, including antibody-drug conjugates. Based on data from clinical studies, eye disorders are considered identified risks for datopotamab deruxtecan. Lung, skin and ocular changes from the repeat-dose studies occurred at clinically relevant doses and should be adequately reflected in section 5.3 of the SmPC (**OC**).

Single cell necrosis in hepatocytes were observed in a monkey at 30 mg/kg of datopotamab deruxtecan. Single cell necrosis, focal necrosis, and increased mitosis in hepatocytes, dilatation and bile thrombus of the bile canaliculus, and brown pigment deposition in Kupffer cells in the liver were noted in monkeys at 12 mg/kg of DXd monohydrate, and were accompanied by increases in hepatic enzyme parameters. Involvement of TROP2 in the hepatocellular findings in the monkey is unlikely since no TROP2 expression in hepatocyte has been reported in immunohistochemistry. No evidence of liver toxicity has been identified from clinical studies.

As lymphatic toxicity, an increased number of tingible body macrophages in the thymus was observed in rats at ≥20 mg/kg of datopotamab deruxtecan. Atrophy of the cortex in the thymus and of periarteriolar lymphoid sheaths in the spleen was seen in rats at 200 mg/kg. Thymic atrophy was also observed in monkeys at ≥30 mg/kg of datopotamab deruxtecan. As haematopoietic toxicity, decreases in reticulocyte, white blood cell, neutrophil, and lymphocyte counts were noted in rats at 200 mg/kg of datopotamab deruxtecan. In monkeys, decreases in platelets count were observed at 10 mg/kg of datopotamab deruxtecan. In addition, decreases in red blood cell count, haemoglobin concentration, and haematocrit value, and increases in reticulocyte ratio were observed in monkeys at 80 mg/kg of datopotamab deruxtecan. The lymphatic/haematopoietic organ toxicity in rats and monkeys showed reversibility after the recovery period. Lymphatic/haematopoietic toxicity also occurred following the administration of DXd monohydrate in rats and monkeys, suggesting that these effects of datopotamab deruxtecan are attributable to the cytotoxic mechanism of action of DXd, and that the datopotamab deruxtecan-related lymphatic/haematopoietic organ toxicity could be caused, at least in part, by DXd released into plasma. In fact, bone marrow toxicity is a typical dose-limiting factor of topoisomerase I inhibitors as well as cytotoxic anti-cancer drugs in humans. Based on the evaluation of clinical study data and biological plausibility, anaemia is considered an adverse drug reaction for datopotamab deruxtecan.

Reproductive tract toxicity comprised degeneration of the germinal epithelium and atrophy of seminiferous tubules in the testis and cell debris, decreased number of spermatozoa in ducts, and single cell necrosis of the ductal epithelium in the epididymis in rats given 200 mg/kg of datopotamab deruxtecan. The seminiferous tubular atrophy in rats at 200 mg/kg remained after the recovery period and no clear tendency toward recovery was suggested. An increased number of atretic follicles in the ovary and single cell necrosis of mucosal epithelium in the vagina were observed in rats at 200 mg/kg of datopotamab deruxtecan. These changes in female rats showed reversibility. Hence, the applicant was requested to include impairment of both male and female fertility and reproductive function as

well as clinical relevance in section 4.6 and 5.3 of the SmPC. The applicant was also asked to include adverse effects on fertility as a potential safety concern in the RMP, or justify why it should not be included. The applicant only agreed to include male fertility and reproductive function in section 4.6 and 5.3 of the SmPC. However, the margin of exposure based on unbound DXd, the NOAEL for these female fertility effects corresponded to exposures below clinical exposures (<1). Although the effects were slight, they were treatment related and the reasoning that only "few animals" (two to three out of ten animals are not considered "few animals") were affected and that reversibility was observed in the recovery period is not accepted to refute the findings. Reversibility within two months of recovery does not mean that the risk, especially if higher exposure margins would be achieved, can be excluded, especially since treatment may be chronic and the rats were only dosed for three months. Hence, section 4.6 and 5.3 of the SmPC should be updated accordingly (please refer to the SmPC for further details) (**OC**). The statements from the applicant that women of childbearing potential will not be expected to conceive, that adverse effects on fertility would not impact the benefit-risk balance of datopotamab deruxtecan in the target patient population and that conducting a clinical study to evaluate adverse effects on fertility is not feasible are agreed. However, this does not mean that the risk for effects on both male and female fertility can be excluded. In addition, the potential for embryo-foetal harm does not exclude the risk for adverse effects on fertility. It is also considered that there is no harm in including adverse effects on fertility as a potential risk in the RMP section SVII.1.1, requiring no further characterisations but only follow up via routine pharmacovigilance and risk minimisation information in the product information. Considering the proposed anticonception measures, inclusion in SVII.1.2 (Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP) is not required. The applicant is requested to include adverse effects on fertility as a potential risk in the updated non-clinical section of the RMP and in Part II Module SVII of the RMP, under the heading "SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP" (**OC**).

Following once weekly dosing for two weeks with MAAP-9002b, a former trophoblast cell surface antigen 2 antibody-drug conjugate (drug-to-antibody ratio (DAR) of approximately seven), mucosal necrosis and cell infiltration in the oesophagus were observed in monkeys at ≥10 mg/kg. No similar finding was noted in repeat-dose studies with rats or monkeys given datopotamab deruxtecan or DXd monohydrate. As the stratified squamous epithelium in the human oesophagus expresses TROP2, the findings in the oesophagus from monkeys given MAAP-9002b may be TROP2-mediated. The differences in DAR and dose regimen between datopotamab deruxtecan and MAAP-9002b might explain why datopotamab deruxtecan was not involved in mucosal injuries in monkeys. Based on the evaluation of clinical study data, stomatitis is considered an identified risk for datopotamab deruxtecan.

Following dosing at 80 mg/kg datopotamab deruxtecan to monkeys, abnormal gait was associated with fibrocartilage formation in the articular surface, erosion in the articular cartilage, hyperplasia of synovial cells, and fibrous thickening of the articular capsule in the right hip joint of one female animal. Based on the lack of information on the expression of TROP2 in the bones and joints in humans and cynomolgus monkeys, the focal finding only in one animal in the 80 mg/kg group, and the clinical relevance of these findings in cynomolgus monkey to humans, the applicant concluded that it is unlikely that the hip joint finding was a direct effect of datopotamab deruxtecan. This conclusion is supported. Hence, section 5.3 of the SmPC should be revised accordingly by deleting hip joint cartilage from the text (**OC**).

An effect on incisor teeth were noted in rats at ≥60 mg/kg. The tooth toxicity would be a rodent-specific change considering species differences (i.e. continuous growth of incisors in adult rats). Hence, the possibility of tooth toxicity in humans is limited.

DXd caused myocardial degeneration/necrosis in one moribund monkey at 12 mg/kg but not in rat up to 30 mg/kg. No toxicity finding in the heart was noted in rats up to 200 mg/kg and in monkeys up to

80 mg/kg of datopotamab deruxtecan. Based on exposure data, the monkeys given 80 mg/kg datopotamab deruxtecan were exposed to DXd 25,000 (C_{max}) and 31 (AUC) times lower than those in the monkey showing cardiotoxicity. Furthermore, the safety pharmacology studies demonstrated that datopotamab deruxtecan did not affect the cardiovascular system. Hence, cardiotoxicity in humans is considered unlikely.

An effect on incisor teeth were noted in rats at ≥60 mg/kg. The tooth toxicity would be a rodent-specific change considering species differences (i.e. continuous growth of incisors in adult rats). Hence, the possibility of tooth toxicity in humans is limited.

Differences in toxicity between DXd and datopotamab deruxtecan can most likely be explained by the longer exposure to DXd following slow release from the antibody-drug conjugate compared to a higher, but shorter exposure to DXd when administered as monohydrate due to the differences in half-life, which is dependent on whether DXd is linked to datopotamab. The applicant was requested to discuss the margin of exposure for rats and monkeys dosed with DXd monohydrate compared to human exposure to DXd. Margin of exposures at each dose level in rats and cynomolgus monkeys given DXd monohydrate to pharmacokinetic data from 50 subjects with non-small cell lung cancer was provided by the applicant. When based on C_{max}/C_0, the margins of exposure ratios were very high and of limited relevance given the slower DXd release when administered together with datopotamab in patients. The only additional toxicity observed with administration of DXd monohydrate compared to Dato-DXd was cardiac toxicity in the monkey which occurred at a margin of exposure 23-fold fold the clinical exposure.

ADA formation was observed in 5/6 animals in the low dose group at 10 mg/kg leading to a reduction in datopotamab deruxtecan exposure followed by an increase in DXd exposure. However, exposure was sufficiently maintained during the treatment period in this group. In rats, except for one animal, ADA formation was primarily detected in non-treated animals questioning the validity of the ADA assay.

The exposure levels (based on C_0 and AUC_{21d}) of datopotamab deruxtecan in rats were higher than those in humans at 6 mg/kg. Margin of exposure (based on AUC) of datopotamab deruxtecan at the no-observed-adverse-effect level (NOAEL) of each target organ of toxicity in monkeys compared with the optimal dose of 6 mg/kg (multiple doses) in subjects with non-small cell lung cancer was:

- Slight intestinal toxicity was observed at ≥10 mg/kg: No exposure margin was determined (margin of exposure <0.25).
- The NOAEL for pulmonary, corneal, dermal, hepatic and lymphoid (thymic) toxicity was concluded to be 10 mg/kg corresponding to a margin of exposure of 0.25.
- Exposure margin of haematopoietic and renal toxicity (NOAEL was 30 mg/kg) was determined to 2.9 whereas reproductive toxicity (no change up to 80 mg/kg) was 10.

It was noted that there was an approximately 2- and 5.5-fold higher free fraction of DXd in rat and monkey plasma respectively, compared to DXd in human plasma. Hence, the applicant was asked to discuss whether margin of exposure corrected for free fraction would be more relevant and if necessary to provide an updated table in the Nonclinical Overview. The applicant did not discuss whether margin of exposure corrected for free fraction would be more relevant but provided updated tables in the Nonclinical Overview and Toxicological Written Summary, respectively, that also included the margins of exposure corrected for the free fraction. It is the Assessors belief that the margin of exposure corrected for free fraction would have been more accurate and relevant.

Nevertheless, considering the sought indication low margins of exposure are acceptable and within the scope of the ICH guideline S9 but need to be adequately addressed in the SmPC.

Genotoxicity

DXd was clastogenic in both an in vivo rat bone marrow micronucleus assay and an in vitro Chinese hamster lung chromosome aberration assay. The results demonstrate that free DXd may pose a hazard by inducing genotoxic effects, potentially leading to off-target DNA alterations and changes in both somatic and germ cellular functions. This could result in an increased risk of cancer development and increased risk of spontaneous abortions, infertility or heritable damage to the offspring, possibly extending to subsequent generations. The plasma exposure of DXd in the rats was significantly below clinical plasma exposure levels. Dosing of 3 mg/kg DXd in another GLP-compliant repeat-dose toxicology study in rats showed a mean $AUC_{0\text{-}24h}$ of 27.8 ng·day/mL which increased with dose. Assuming linear toxicokinetics, dosing of 0.05 mg/kg DXd, the lowest dose level at which increases in the number of micronucleated immature red blood cells was observed, would result in a mean $AUC_{0\text{-}24h}$ of 0.5 ng·day/mL. This exposure level is ~38 times lower than the clinical exposure level of DXd after administration of the clinically recommended dose (6 mg/kg) of the antibody-drug conjugate datopotamab deruxtecan where the AUC_{tau} for DXd was reported to be 19.2 ng·day/mL.

The positive findings in the in vitro chromosome aberration study in mammalian cells and in the in vivo rat bone marrow micronucleus study are considered to be clinically relevant.

The genotoxicity of DXd with regards to fertility and pregnancy is adequately reflected in section 4.6 of the SmPC, including adequate recommendations for the duration of use of effective contraception following the last dose of datopotamab deruxtecan. Genotoxicity in section 5.3 of the SmPC should be revised as previously requested (**OC**) (see SmPC for details). The potential genotoxicity of the linker molecule was addressed following an Other Concern. Herein, the applicant provided more information on the potential genotoxicity of the linker molecule which consists of a maleimide tetrapeptide. The peptide moiety is a naturally occurring structure and is not considered a genotoxic risk. In datopotamab deruxtecan, maleimide binds to the antibody in the succinimide state. Based on two newly submitted non-GLP studies, the maleimide part (SuMH) and linker (MFAH) were deemed negative in the Ames test. Hence, it is agreed with the applicant that no genotoxic risk of the linker is expected.

Carcinogenicity

The lack of carcinogenicity studies was acceptable based on the proposed indication being in scope of ICH guideline S9.

Developmental and reproductive toxicology (DART)

In accordance with ICH guideline S9 dedicated fertility and early embryonic development studies were not conducted. However, male and female reproductive toxicity of datopotamab deruxtecan and DXd was evaluated in the pivotal repeat-dose studies.

According to ICH guideline S9, embryo-foetal toxicity studies were not considered essential for anticancer pharmaceuticals that are genotoxic and target rapidly dividing cells in general toxicity studies or belong to a class that has been well characterized as causing developmental toxicity. Toxicity studies in rats and monkeys with datopotamab deruxtecan and DXd indicated toxic effects on rapidly dividing cells (lymphatic/haematopoietic organs, intestines or testes). DXd was genotoxic in an in vitro chromosome aberration study with mammalian cultured cells and an in vivo micronucleus study in rats. Taken together, the characteristics of DXd indicate that datopotamab deruxtecan could cause foetal harm when administered to a pregnant woman which is adequately reflected in the SmPC.

In accordance with ICH guideline S9 no prenatal and postnatal development, including maternal function studies were conducted.

No juvenile studies were submitted which is accepted, as the proposed marketing authorisation application of datopotamab deruxtecan is for treatment of adult patients.

Interspecies comparison and exposure margins to clinical exposure

The exposure levels (based on C_0 and AUC_{21d}) of datopotamab deruxtecan in rats were higher than those in humans at 6 mg/kg. In monkeys, the exposure level at the severely toxic dose of ≥30 mg/kg was 3-fold higher than those in humans at 6 mg/kg. Slight intestinal toxicity was observed at ≥10 mg/kg, thus, no exposure margin could be determined. However, the NOAEL for pulmonary, corneal, dermal, hepatic and lymphoid (thymic) toxicity was concluded to be 10 mg/kg corresponding to a margin of exposure of 0.25. Exposure margin of haematopoietic and renal toxicity (30 mg/kg) was determined to 2.9, whereas reproductive toxicity (up to 80 mg/kg) was 10. Considering the sought indication low margins of exposure are acceptable and within the scope of the ICH guideline S9.

Toxicokinetics

Toxicokinetics of datopotamab deruxtecan and DXd were assessed in section 3.2.3.2 Absorption.

Local tolerance

Microscopic evaluation of the injection sites as part of the repeat-dose toxicology studies in both rats and monkeys identified no datopotamab deruxtecan or DXd-related effects at the injection sites.

Other toxicity studies

Anti-drug antibody formation was observed in 5/6 animals in the low dose group at 10 mg/kg and there was a reduction in datopotamab deruxtecan exposure after the 4th dose compared to the 1st dose followed by an increase in DXd exposure. Although ADAs were formed exposure was sufficiently maintained during the treatment period in this group. On recovery Day 57, it was noted that 4/4 monkeys in the 30 mg/kg group had developed ADAs. In rats, except for one animal, ADA formation was primarily detected in non-treated animals questioning the validity of the ADA assay. One OC was raised with regard to the sensitivity and drug tolerance for ADAs in method validation report No PRD15-449.

Immunotoxicity evaluations were incorporated in the repeat-dose toxicity studies consistent with the ICH guideline S9. Datopotamab deruxtecan-related lymphatic organ toxicity was noted in rats and monkeys.

The dependence potential of datopotamab deruxtecan is unlikely as target is not expressed in the CNS and no effect was observed in CNS safety pharmacology parameters.

No disproportionate drug metabolites of DXd were identified. Overall, the metabolism of datopotamab deruxtecan was sufficiently explored.

The pivotal non-clinical GLP-compliant studies used test material that was comparable or identical to the material used in clinical studies and to the intended marketed product. No concern regarding impurities was identified in the Quality Assessment Report. Hence, additional studies on impurities are not warranted.

According to information stated in the toxicology introduction of the Nonclinical Overview, the phototoxicity potential of DXd was evaluated because it demonstrated photoabsorption in the ultraviolet-visible light range. These data are however not presented in the dossier. It would have been preferred to have these data and the relevant Molar Extinction Coefficients presented. Additionally, it would have been appreciated if the applicant had included a discussion on the phototoxicity potential based on photochemical properties, drug class and on tissue distribution in relation to phototoxicity. However, this will not be pursued further and the omit is accepted. DXd showed phototoxic potential in the in vitro 3T3 NRU-PT study. The Mean Photo Effect (MPE) was calculated and above the cut-off value of 0.15 (MPE = 0.432). However, due to the low specificity of this test, a positive result is not regarded as indicative of a likely clinical phototoxic risk, but rather as a signal to perform follow-up

studies to assess whether the potential phototoxicity identified in vitro correlates with a response in vivo. No phototoxicity was noted in a follow-up in vivo single dose (i.v.) phototoxicity study in male pigmented rats. The plasma concentration of DXd in the high-dose 3 mg/kg group (90.5 ng/mL) provided a 29-fold safety margin of exposure to the C_{max} in humans given clinically relevant doses (6 mg/kg) of datopotamab deruxtecan (3.13 ng/mL, single dose) in a clinical trial (study No TP01). The negative result in the in vivo phototoxicity study supersedes the positive in vitro result. Based on the non-clinical data, no direct phototoxicity is anticipated in humans following administration of datopotamab deruxtecan.

Excipients in datopotamab deruxtecan drug product are well known and of compendial grade quality.

Good Laboratory Practice-compliant tissue cross-reactivity studies of datopotamab deruxtecan were evaluated in a panel of cynomolgus monkey and human tissues. Plasma membranous staining in the epithelium of the urinary bladder, eye, fallopian tube, oesophagus, stomach, liver, lung, pancreas, salivary gland, skin, thyroid, tonsil, ureter and uterus was commonly observed in both species. In addition, membranous staining in the breast, kidney, thymus and placenta in humans and that in the small intestine and testis in monkeys were also noted.

Intravenous administration of monoclonal antibodies is commonly associated with infusion-related reactions (IRR), and in vitro cytokine release assays may serve as a valuable tool for assessing the immunomodulatory effects and potential risks associated with cytokine-mediated adverse events of such agents. TNF-α, IFN-γ, IL-2, IL-6, IL-10, MIP-1β, and IP-10 were measured in two non-GLP in vitro cytokine release assays (hPBMC and human whole blood). Cell viability was assessed by a water-soluble tetrazolium salts assay. Bevacizumab (IRR incidence in clinic: <3%) and alemtuzumab (IRR incidence in clinic: 89%) were used as reference antibodies. Incubation with Datopotamab deruxtecan and Datopotamab increased the levels of multiple cytokines compared to vehicle in the hPBMC assay. However, these changes were either lower or comparable to what was seen for bevacizumab. No signal of cytokine release activity was found in the human whole blood assay. These findings suggest that the risk of IRRs associated with datopotamab deruxtecan is comparable to that of other monoclonal antibodies, and likely falls within the lower range of risk. Mild to moderate IRRs have been reported in clinical trials (study No TB-01 and TL-01), and IRRs are listed as very common (≥1/10) in section 4.8 of the SmPC. Recommendations regarding premedication, infusion times, and post-infusion observation periods are provided in section 4.2 of the SmPC. The risk of IRRs is also addressed in the Risk Management Plan.

3.2.6.4. Environmental Risk Assessment

Deruxtecan (DXd) as part of datopotamab deruxtecan is not considered a PBT substance as log Kow does not exceed 4.5. The applicant provided 1-year prevalence data from the IARC (Globocan) webside to refine the market penetration factor (Fpen). The evaluation of these 1-year prevalence data has given rise to the conclusion of being insufficient since the data do not illustrate the total number of patients, that may be eligible for treatment with datopotamab deruxtecan. Therefore, the applicant is asked (1) to provide 5-year prevalence data, which is considered a more accurate measure for the potential patient population, or (2) to otherwise justify the use of 1-year prevalence data. The applicant may also further refine Fpen based on treatment regimen.

3.2.7. Conclusion on non-clinical aspects

Overall, the primary pharmacodynamic studies provided adequate evidence that datopotamab deruxtecan showed anti-tumour activity against TROP2 positive cancer models in vitro and in vivo. The suggested mechanism of action was largely verified; however further elaboration of some subphases were needed. No particular concern to the cardiovascular, respiratory or central nervous systems was

seen in a hERG study and an in vivo safety pharmacology study in cynomolgus monkeys at single doses of datopotamab deruxtecan up to 80 mg/kg. Nevertheless, marked pulmonary toxicity was noted at repeated administrations of datopotamab deruxtecan in the conducted toxicology studies.

In conclusion, the PK profile in rats and monkeys appears generally to be well described, and the rat and monkey as relevant non-clinical species for testing toxicity are supported by human PK data. Renal retention and an alignment between DXd half-life and excretion rates in monkeys should be discussed. The sensitivity of the ADA assay in rats should be addressed. Datopotamab deruxtecan is considered approvable from a non-clinical point of view, provided that the raised concerns have been properly addressed.

Overall, the toxicology programme of datopotamab deruxtecan revealed no major concerns. The binding profile of datopotamab deruxtecan showed that the ADC bound to TROP 2 in cynomolgus monkeys and humans. Therefore, cynomolgus monkeys were used for the toxicity evaluations of datopotamab deruxtecan, and rats were chosen to evaluate the target-independent effects. The toxicity studies supporting the marketing authorisation of datopotamab deruxtecan for the treatment of adult patients with locally advanced or metastatic non-squamous non-small cell lung cancer were performed according to appropriate ICH guidelines. The primary target organs identified with datopotamab deruxtecan in cynomolgus monkeys and rats were the lung, skin, gastrointestinal tract, kidneys, cornea, liver, lymphatic/haematopoietic system and male and female reproductive tract. Sparse ADA formation was seen rats and monkeys following repeated doses of datopotamab deruxtecan. Margin of exposure in rats and monkeys ranged between 0.25 and 29 and was acceptable considering the sought indication. The toxic DXd was clastogenic in both an in vitro lung chromosome aberration assay and an in vivo rat bone marrow micronucleus assay. Male and female reproductive and embryo-foetal toxicity were seen after treatment with DXd. No concerns were identified regarding antigenicity, immunotoxicity, dependence, metabolites, impurities or phototoxicity.

In conclusion, no major objections were identified in the non-clinical dossier, however, a number of other concerns have been raised (please refer to the list of questions) which still need to be sufficiently addressed before approval of datopotamab deruxtecan can be supported from a non-clinical view.

The environmental risk assessment (ERA) led to the conclusion that deruxtecan (DXd) as part of datopotamab deruxtecan is not considered a persistant, bioaccumulative or toxic substance. Data for the evaluation of the predicted environmental concentration in surface water (PECsw) have been requested to draw conclusions on the PECsw of DXd and the need for further ERA studies.

3.3. Clinical aspects

- **Tabular overview of clinical studies**

Table 12 Summary of Clinical Pharmacology Studies with Dato-DXd as Monotherapy

Study Number DCO	Study Title (N=Number Enrolled)	Objectives of the Studies	Dosage and Regimen[a]	Pharmacokinetic Assessments Immunogenicity
TL01 (TROPION-Lung01; DS1062-A-U301) 18 Nov 2023 See Module 5.3.5.1 TL01 CSR (DCO 29 Mar 2023)	Phase 3 randomized study of DS-1062a vs. docetaxel in previously treated advanced or metastatic NSCLC with or without actionable genomic alterations (N=604; N=299 for Dato-DXd; N=305 for docetaxel)	**Primary** • To compare the efficacy of Dato-DXd with that of docetaxel, as measured by PFS and OS, for subjects with NSCLC with or without actionable genomic alterations **Secondary** • To further evaluate the efficacy of Dato-DXd compared with docetaxel • To further evaluate the safety of Dato-DXd compared with docetaxel • To assess the PK of Dato-DXd • To assess the immunogenicity of Dato-DXd **Exploratory** • To evaluate PFS2 for Dato-DXd compared with that of docetaxel • To evaluate biomarkers that may associate with the clinical benefit from Dato-DXd used to treat NSCLC • To explore how changes in biomarkers may relate to exposure and clinical outcomes • To evaluate ER relationships for efficacy and safety endpoints • To evaluate PRO endpoints for Dato-DXd compared with that of docetaxel	*Dato-DXd*: 6 mg/kg IV on Day 1 of each 21-day cycle *Docetaxel*: 75 mg/m^2 IV on Day 1 of each 21-day cycle	*PK*: Plasma concentrations and PK parameters for Dato-DXd, total anti–TROP2 antibody, and DXd *Immunogenicity*: ADA
TL05 (TROPION-Lung05; DS1062-A-U202) 28 July 2023 See Module 5.3.5.2 TL05 CSR (DCO 14 Dec 2022)	Phase 2, single-arm, open-label study of DS-1062a in advanced or metastatic NSCLC with actionable genomic alterations and progressed on or after applicable targeted therapy and platinum-based chemotherapy (N=137)	**Primary** • To assess the efficacy of Dato-DXd, as measured by ORR by BICR, as a treatment for subjects with NSCLC with actionable genomic alterations who have progressed on or after 1 platinum-containing therapy and 1 or more lines of targeted therapy to the applicable genomic alterations in the study **Secondary** • To further evaluate the efficacy of Dato-DXd • To further evaluate the safety of Dato-DXd • To assess the PK of Dato-DXd • To assess the immunogenicity of Dato-DXd **Exploratory** • To evaluate biomarkers that may associate with the clinical benefit from Dato-DXd used to treat NSCLC • To explore how changes in biomarkers may relate to exposure and clinical outcomes • To evaluate pretreatment tumor biopsy samples and archival tumor samples for key biomarkers that correlate with the clinical benefit from Dato-DXd • To evaluate ER relationships for efficacy and safety endpoints	*Dato-DXd*: 6 mg/kg IV on Day 1 of each 21-day cycle	*PK*: Plasma concentrations and PK parameters for Dato-DXd, total anti–TROP2 antibody, and DXd *Immunogenicity*: ADA

TP01 (TROPION-PanTumor-01; DS1062-A-J101) See Module 5.3.3.2 TP01 NSCLC CSR (DCO 30 Jul 2021) and Module 5.3.3.2 TP01 BC CSR (DCO 22 Jul 2022)	Phase 1, 2-part, multicenter, open-label, multiple-dose, first-in-human study of Dato-DXd in subjects with advanced solid tumors (N=210 for NSCLC and N=85 for BC)	**Primary** *Dose Escalation* • To investigate the safety and tolerability and to determine the MTD and the RDE of Dato-DXd *Dose Expansion* • To investigate the safety and tolerability of Dato-DXd **Secondary** *Dose Escalation*: • To characterize the PK properties of Dato-DXd, total anti–TROP2 antibody, and DXd • To investigate the antitumor activity of Dato-DXd • To assess the incidence of ADA against Dato-DXd *Dose Expansion*: • To investigate the antitumor activity of Dato-DXd • To characterize the PK properties of Dato-DXd total anti–TROP2 antibody, and DXd • To assess the incidence of ADA against Dato-DXd **Exploratory** *Dose Escalation* and *Dose Expansion*: • To explore biomarkers which correlate with response to Dato-DXd	*Dose Escalation*: Dose levels from Dato-DXd 0.27 to 10 mg/kg IV on Day 1 of each 21-day cycle *Dose Expansion*: Dato-DXd 4 mg/kg IV 6 mg/kg IV 8 mg/kg IV On Day 1 of each 21-day cycle	*PK profiles*: Plasma concentrations and PK parameters for Dato-DXd, total anti–TROP2 antibody, and DXd *Immunogenicity*: ADA

ADA = anti-drug antibody; BC = breast cancer; BICR = blinded independent central review; CSR = clinical study report; DCO = data cutoff; ER = exposure-response; FL-DP = frozen liquid drug product; IV = intravenous; Lyo-DP = lyophilized powder drug product; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); PRO = patient reported outcome; RDE = recommended dose for expansion; TROP2 = trophoblast cell surface antigen 2; vs. = versus.
[a] Formulation used in Study TL05 was clinical Lyo-DP; in Study TL01, it was clinical Lyo-DP and to be-marketed Lyo-DP; in Study TP01, it was FL-DP (Module 2.7.1).

3.3.1. Clinical pharmacology

3.3.1.1. Pharmacokinetics

Bioanalytical methods

In the conducted clinical studies of Dato-DXd (datopotamab deruxtecan or DS-1062a) the following three moiety were quantified by PPD in plasma: Dato-DXd (conjugated antibody), total anti TROP2 antibody (conjugated and unconjugated antibody) and the "free" ADC payload DXd.

The main drug, Dato-DXd, was quantified in plasma with two validated ligand binding assay based on the Gyrolab platform using fluorescent detection. A mouse monoclonal antibody, anti-XAFG-5737/1A3, that specifically binds to conjugated DXd was utilized in the method. The two assays, one for each drug product, Fl-DP and Lyo-DP, were cross-validated and able to quantify Dato-Dxd in the nominal concentration range of 20 to 5000 ng/ml and 100 to 5000 ng/ml, respectively.

The total anti TROP2 antibody (conjugated and unconjugated antibody) was also quantified in plasma with two validated ligand binding assay based on the Gyrolab platform using fluorescent detection. A mouse monoclonal antibody that specifically binds to the MAb of Dato-DXd was utilized in the method. The two assays, one for each drug product, Fl-DP and Lyo-DP, were cross-validated and able to quantify Dato-Dxd in the nominal concentration range of 20 to 5000 ng/ml and 100 to 5000 ng/ml, respectively.

The "free" payload DXd (MAAA-1181a) in plasma was quantified with a validated LC-MS/MS method using a stable labelled internal standard. Samples were analyzed over the nominal concentration range of 10 to 2000 pg/mL.

The bioanalytical methods for the three analytes were also transferred to LabCorp in China, for analysing clinical samples collected from China subjects. The China methods were cross-validated with the original methods.

PD biomarker method

The TROP2 immunohistochemistry was performed on Formalin-Fixed Paraffin-Embedded (FFPE) tissue samples collected in the TB01 study. The validated biomarker method, was based on an antibody against TROP2, the rabbit monoclonal EPR20043, that recognises an epitope in the intracellular domain of TROP2 protein, and utilized the OptiView detection kit on a Benchmark ULTRA staining platform.

Immunogenicity methods

Immunogenicity was evaluated in a tiered fashion: Plasma samples were first evaluated using a Anti Dato-DXd antibody method (ADA assay) and of the ADA confirmed positives, the ADA titter was determined and for NAbs against Dato-DXd was determined (NAb assay).

Anti Dato-DXd antibody in plasma was measured at PPD using a Meso Scale Discovery platform-based LBA with electrochemiluminescent detection. In this assay, clinical samples, positive controls, and negative controls were diluted in acetic acid to disrupt any antibody-antigen complexes. Two assays were validated for each of the two drug products, FL-DP and Lyo-DP. The drug tolerance to Dato-DXd in the FL-DP ADA assay was determined to 75 µg/mL of Dato-DXd in the presence of a 100 ng/mL positive control antibody. The drug tolerance to Dato-DXd in the Lyo-DP ADA assay was determined to 25 µg/mL of Dato-DXd for a 250 ng/mL PC antibody and estimated to 10 µg/mL in the presence of 130 to 144 ng/mL PC antibody.

Nab against Dato-DXd was measured at PPD using a validated cell-based neutralizing antibody (NAb) bioassay. A Bead Extraction with Acid Dissociation (BEAD) sample pre-treatment was done to overcome high concentrations of Dato-DXd in samples, followed by a functional cell-based neutralizing antibody (NAb) bioassay. Cell proliferation of Bx-PC-3 cells expressing TROP2 was measured using the CellTiter-Glo® Luminescent Cell Viability Assay. In the presence of neutralizing antibodies to Dato-DXd, cell proliferation is not inhibited. Drug tolerance toward Dato-DXd in the assay was determined; 0.978 µg/mL neutralizing antibodies can be detected in the presence of up to 2.50 µg/mL excess Dato-DXd.

The ADA and Nab assay were also transferred to LabCorp in China, for analysing clinical samples collected from China subjects. The LabCorp methods were cross validated with the PPD methods.

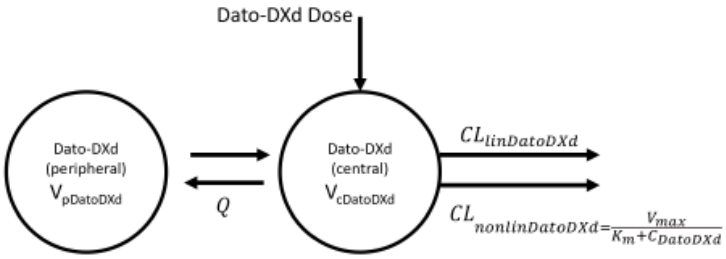
Evaluation and qualification of models

Pop PK modelling

The Pop PK model dataset for Dato-DXd and DXd originated from three studies DS1062-A-J101, DS1062-A-U202 and DS1062-A-U301. The Pop PK population consisted mainly of patients with NSCLC (n=642). Study J101 also included data from 86 patients with breast cancer.

Dato-DXd PK was described by a 2-compartment model with parallel linear clearance and nonlinear Michaelis-Menten clearance from the central compartment. Body weight effect on CLlinDatoDXd was allometrically scaled with a fixed exponent of 0.75 while weight effects on VcDatoDXd and VpDatoDXd were estimated. The structure of the final Dato-DXd model is shown in Figure 10.

Figure 10 Illustration of the final Dato-DXd model.



$$CL_{linDatoDXd} = 0.386 \times \left(\frac{WT}{66}\right)^{0.750} \times \left(\frac{ALB}{38}\right)^{-0.788} \times \left(\frac{AGE}{62}\right)^{-0.306} \times \begin{cases} 1 \; if \; male \\ 1 - 0.263 \; if \; female \end{cases} \times \begin{cases} 1 \; if \; not \; Japan \; country \\ 1 - 0.219 \; if \; Japan \; country \end{cases}$$

$$V_{cDatoDXd} = 3.06 \times \left(\frac{WT}{66}\right)^{0.415} \times \begin{cases} 1 \; if \; male \\ 1 - 0.160 \; if \; female \end{cases}$$

$$V_{pDatoDXd} = 2.88 \times \left(\frac{WT}{66}\right)^{0.311}$$

$$V_{max} = 8410 \times \left(\frac{Tumor \; size}{66}\right)^{0.125}$$

Parameters of the final Dato-DXd model is shown in Table 13.

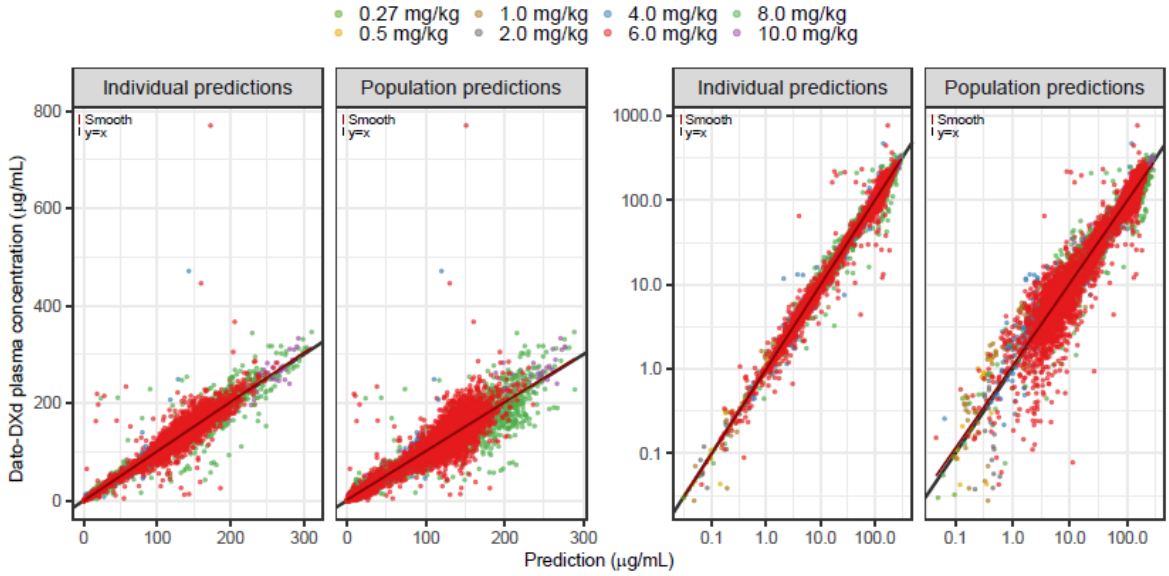
Table 13 Parameter estimates of the final Dato-DXd model

	Final model			
Run		3013		
OFV		–19208.82		
Condition number		38.31		
	Unit	**Value**	**RSE (%)**	**SHR (%)**
WT on $CL_{linDatoDXd}$		0.750		
WT on $V_{cDatoDXd}$		0.415	7.12	
$CL_{linDatoDXd}$	(L/d)	0.386	2.34	
$V_{cDatoDXd}$	(L)	3.06	0.959	
$Q_{DatoDXd}$	(L/d)	0.422	1.92	
$V_{pDatoDXd}$	(L)	2.88	1.62	
V_{max}	(µg/d)	8410	3.07	
K_m	(ng/mL)	4490	4.06	
WT on $V_{pDatoDXd}$		0.311	20.4	
Age on $CL_{linDatoDXd}$		-0.306	20.9	
ALB on $CL_{linDatoDXd}$		-0.788	9.41	
Japanese on $CL_{linDatoDXd}$		-0.219	10.8	
Female sex on $CL_{linDatoDXd}$		-0.263	7.24	
Tumor size on V_{max}		0.125	12.4	
Female sex on $V_{cDatoDXd}$		-0.160	7.06	
IIV RUV	(CV)	0.458	2.39	0
IIV $CL_{linDatoDXd}$	(CV)	0.272	3.69	9.87
IIV $V_{cDatoDXd}$	(CV)	0.145	2.85	2.89
IIV $Q_{DatoDXd}$	(CV)	0.311	3.45	20.7
IIV $V_{pDatoDXd}$	(CV)	0.312	3.42	11.1
IIV V_{max}	(CV)	0.192	5.78	32.7
RUV	(CV)	0.121	2.19	3.44

The RSE for IIV and RUV parameters are reported on the approximate SD scale.

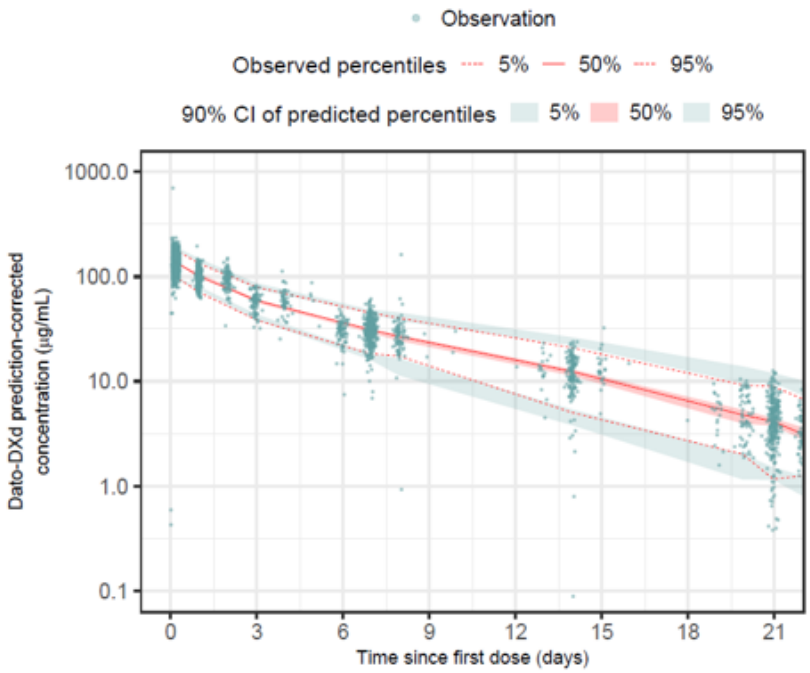
The final Dato-DXd model was evaluated by bootstrap, goodness-of-fit plots and VPCs. A GoF plot for Dato-DXd of the full pop PK population is shown in Figure A3-6.

Figure 11 Observed versus predicted concentrations for the final Dato-DXd model, colored by treatment group. Data are presented on linear scale (left) and logarithmic scale (right).



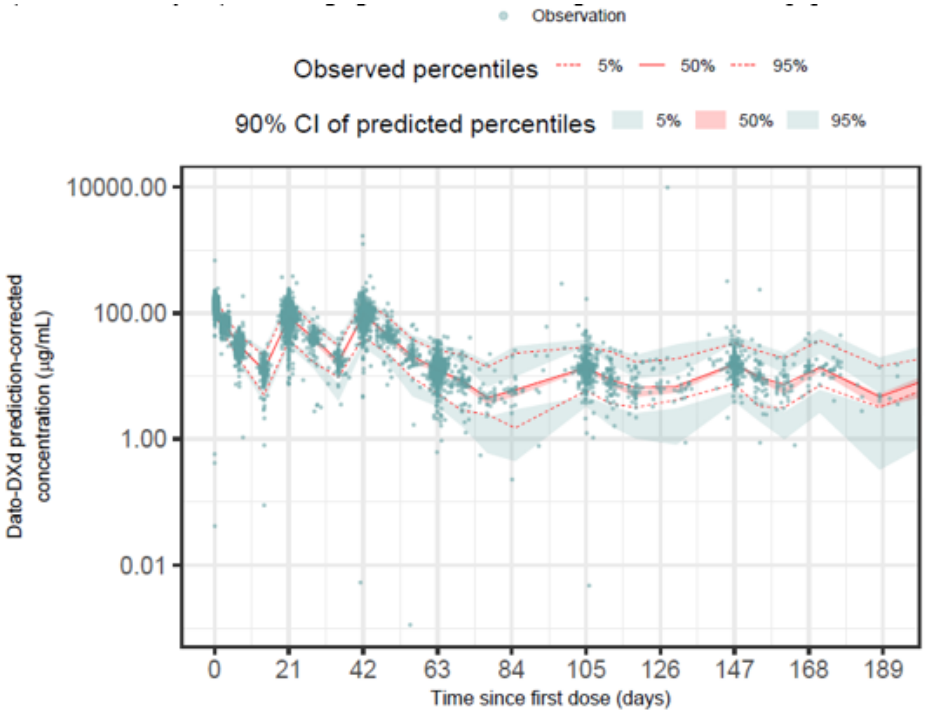
The pcVPCs of Dato-DXd concentrations versus time since first dose for Cycle 1 and for all cycles in subjects with NSCLC who received 6.0 mg/kg Q3W are shown in Figure 1 and 2.

Figure 12 Prediction-corrected visual predictive check of Dato-DXd concentrations versus time since first dose at Cycle 1 (truncated to 21 days) after 6 mg/kg administration using the final Dato-DXd population PK model



CI=confidence interval; Dato-DXd=datopotamab deruxtecan
Data are presented on a semi-logarithmic scale. Observations before the first Dato-DXd administration were removed.

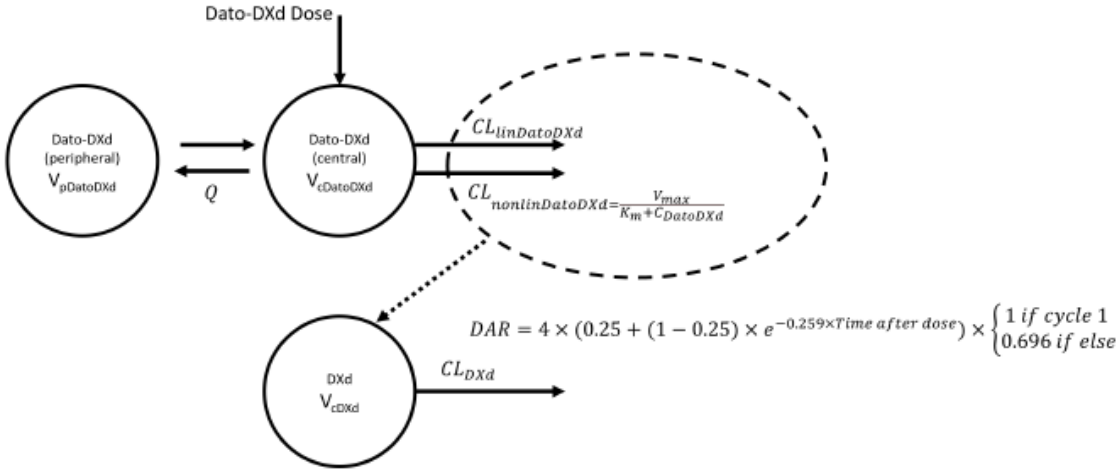
Figure 13 Prediction-corrected visual predictive check of Dato-DXd concentrations versus time since first dose (truncated to 9 cycles) after 6 mg/kg administration, using the final Dato-DXd population PK model



CI=confidence interval; Dato-DXd=datopotamab deruxtecan
Data are presented on a semi-logarithmic scale. Observations before the first Dato-DXd administration were

DXd PK was described by a 1-compartment model with first-order elimination, a release equal to the linear and nonlinear elimination rate of Dato-DXd and a decreasing drug-to-antibody ratio over time within- and between cycles. The effect of body weight on CL and Vc was fixed to estimated values before inclusion of other covariates. The structure of the final DXd model is shown in Figure below.

Figure 14 Illustration of the final DXd model



$$DAR = 4 \times (0.25 + (1 - 0.25) \times e^{-0.259 \times Time\ after\ dose}) \times \begin{cases} 1\ if\ cycle\ 1 \\ 0.696\ if\ else \end{cases}$$

$$CL_{DXd} = 2.66 \times \left(\frac{WT}{66}\right)^{0.298} \times \left(\frac{ALB}{38}\right)^{0.343} \times \left(\frac{AST}{22}\right)^{-0.154} \times \left(\frac{TBIL}{0.4}\right)^{-0.139} \times \begin{cases} 1\ if\ US\ or\ Japan\ country \\ 1 + 0.240\ if\ Europe\ countries \\ 1 + 0.196\ if\ Rest\ of\ the\ World\ countries \end{cases}$$

$$V_{cDXd} = 25.1 \times \left(\frac{WT}{66}\right)^{0.530} \times \begin{cases} 1\ if\ male \\ 1 - 0.185\ if\ female \end{cases}$$

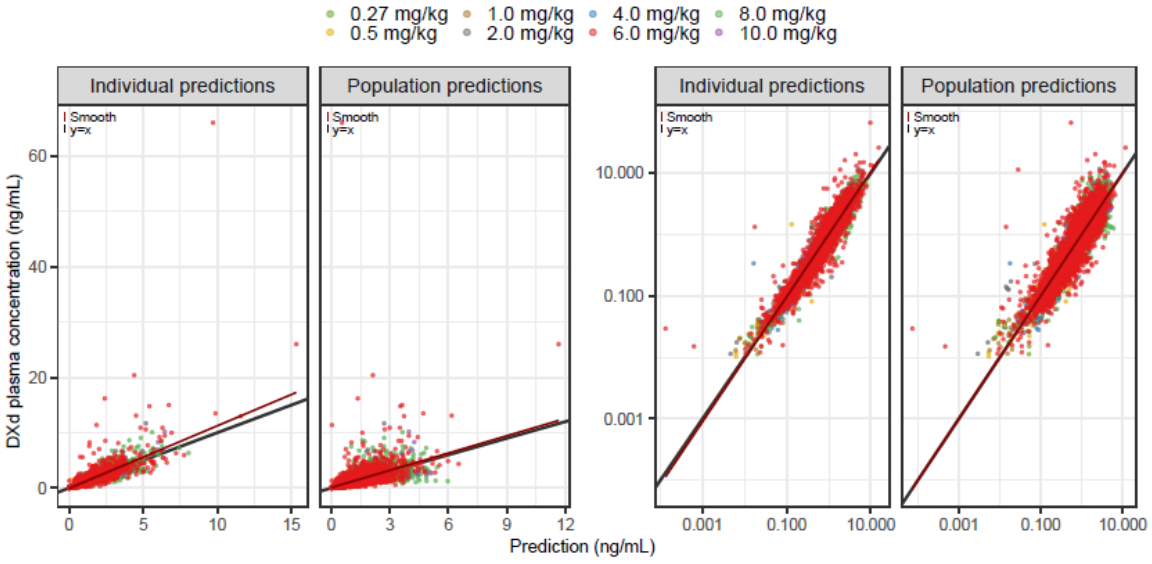
Table 14 Parameter estimates of the final DXd model

	Final model			
Run		319		
OFV		–9340.64		
Condition number		7.93		
	Unit	**Value**	**RSE (%)**	**SHR (%)**
CL_{DXd}	(L/h)	2.66	1.57	
V_{cDXd}	(L)	25.1	2.24	
Factor1		0.696	0.750	
β		0.259	2.85	
WT on CL_{DXd}		0.298		
WT on V_{cDXd}		0.530		
ALB on CL_{DXd}		0.343	13.9	
AST on CL_{DXd}		-0.154	14.7	
Europe on CL_{DXd}		0.240	12.1	
RoW on CL_{DXd}		0.196	15.6	
Tot. bili on CL_{DXd}		-0.139	18.4	
Female sex on V_{cDXd}		-0.185	10.6	
IIV RUV	(CV)	0.292	4.32	11.8
IIV CL_{DXd}	(CV)	0.314	3.41	5.21
IIV V_{cDXd}	(CV)	0.363	3.45	7.74
RUV	(CV)	0.283	1.41	2.86

The RSE for IIV and RUV parameters are reported on the approximate SD scale. See Glossary for explanation of abbreviations.

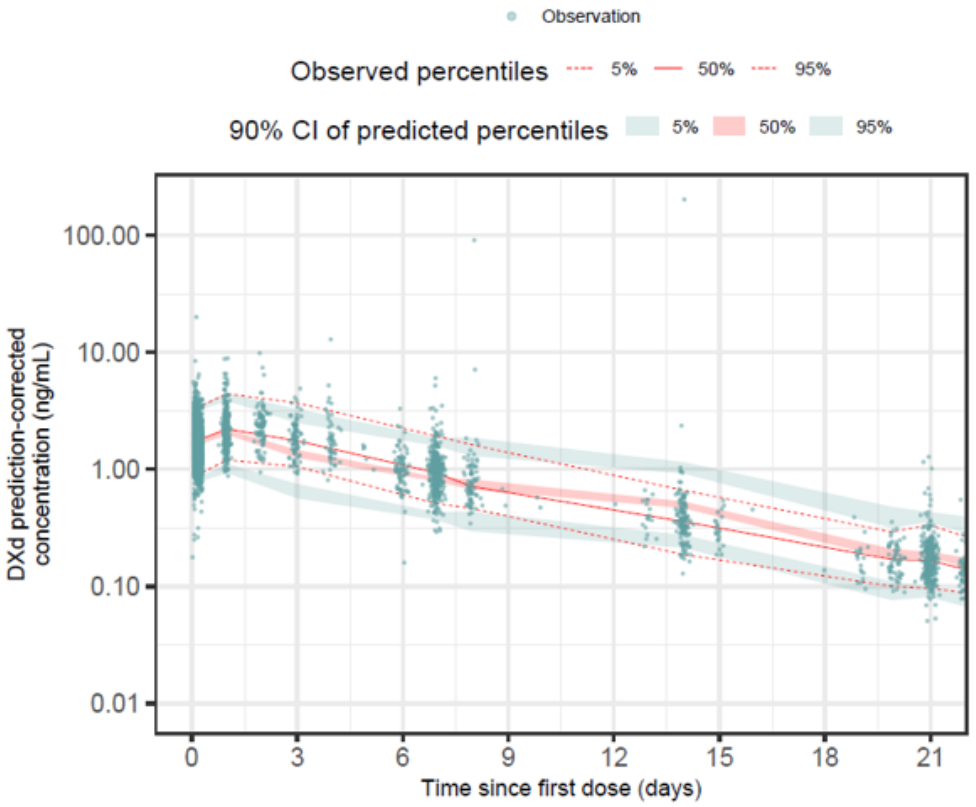
The final DXd model was evaluated by bootstrap, goodness-of-fit plots and VPCs. A GoF plot for DXd of the full pop PK population is shown in Figure below.

Figure 15 Observed versus predicted concentrations for the final DXd model, colored by treatment group. Data are presented on linear scale (left) and logarithmic scale (right).



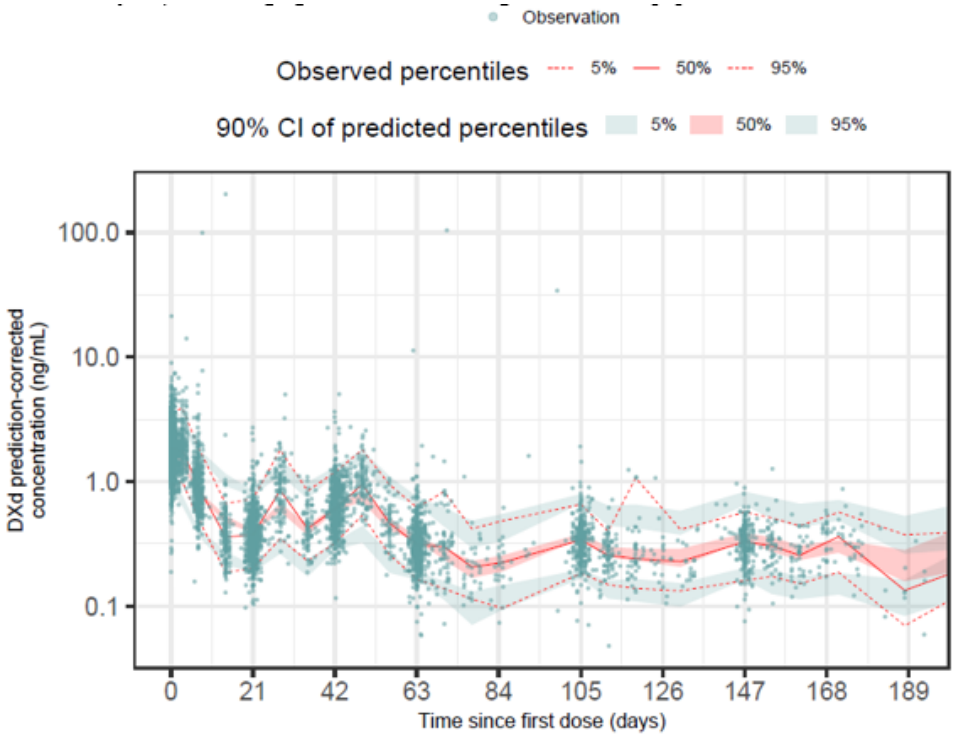
The pcVPCs of DXd concentrations in Cycle 1 and all cycles in subjects with NSCLC who received 6.0 mg/kg Q3W are shown in Figures below.

Figure 16 Prediction-corrected visual predictive check of DXd concentrations versus time since first dose at Cycle 1 (truncated to 21 days) after 6 mg/kg administration using the final DXd population PK model.



CI=confidence interval; Dato-DXd=datopotamab deruxtecan; DXd=released drug component of Dato-DXd; Data are presented on a semi-logarithmic scale. Observations before the first Dato-DXd administration were removed.

Figure 17 Prediction-corrected visual predictive check of DXd concentrations versus time since first dose (truncated to 9 cycles) after 6 mg/kg administration using the final DXd population PK model.



CI=confidence interval; Dato-DXd=datopotamab deruxtecan; DXd=released drug component of Dato-DXd; Data are presented on a semi-logarithmic scale. Observations before the first Dato-DXd administration were removed.

The most impactful covariate on Dato-DXd and DXd exposure was body weight as shown for Cmax in the Forest plots in Figures below.

Figure 18 Forest plots illustrating the effects of covariates on Dato-DXd Cmax3, conditioned on a typical reference subject, based on the final Dato-DXd model. Reference: Male, 62 years, 66 kg, not Japanese,albumin 38 g/L and with a tumor size of 66 mm.

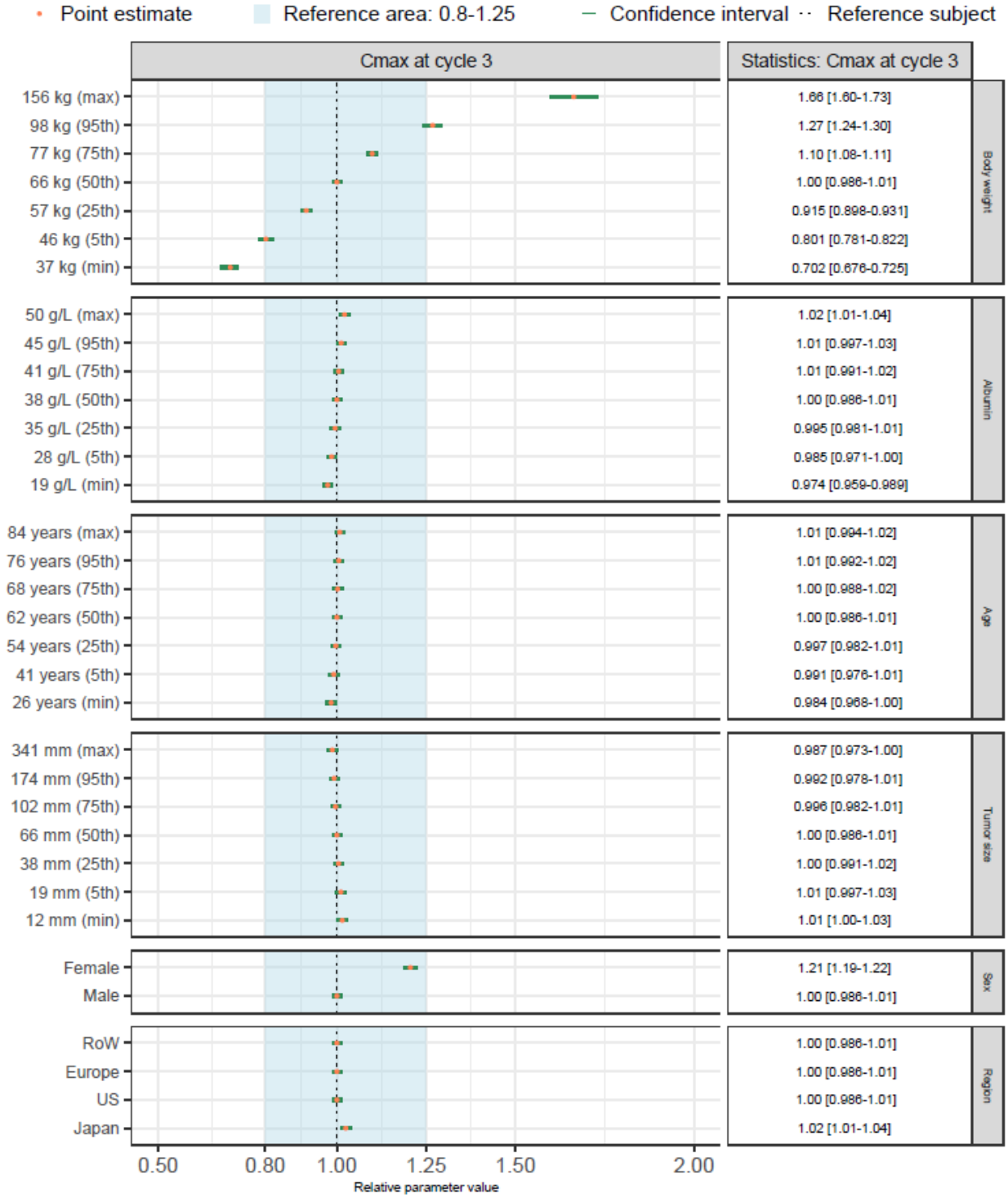
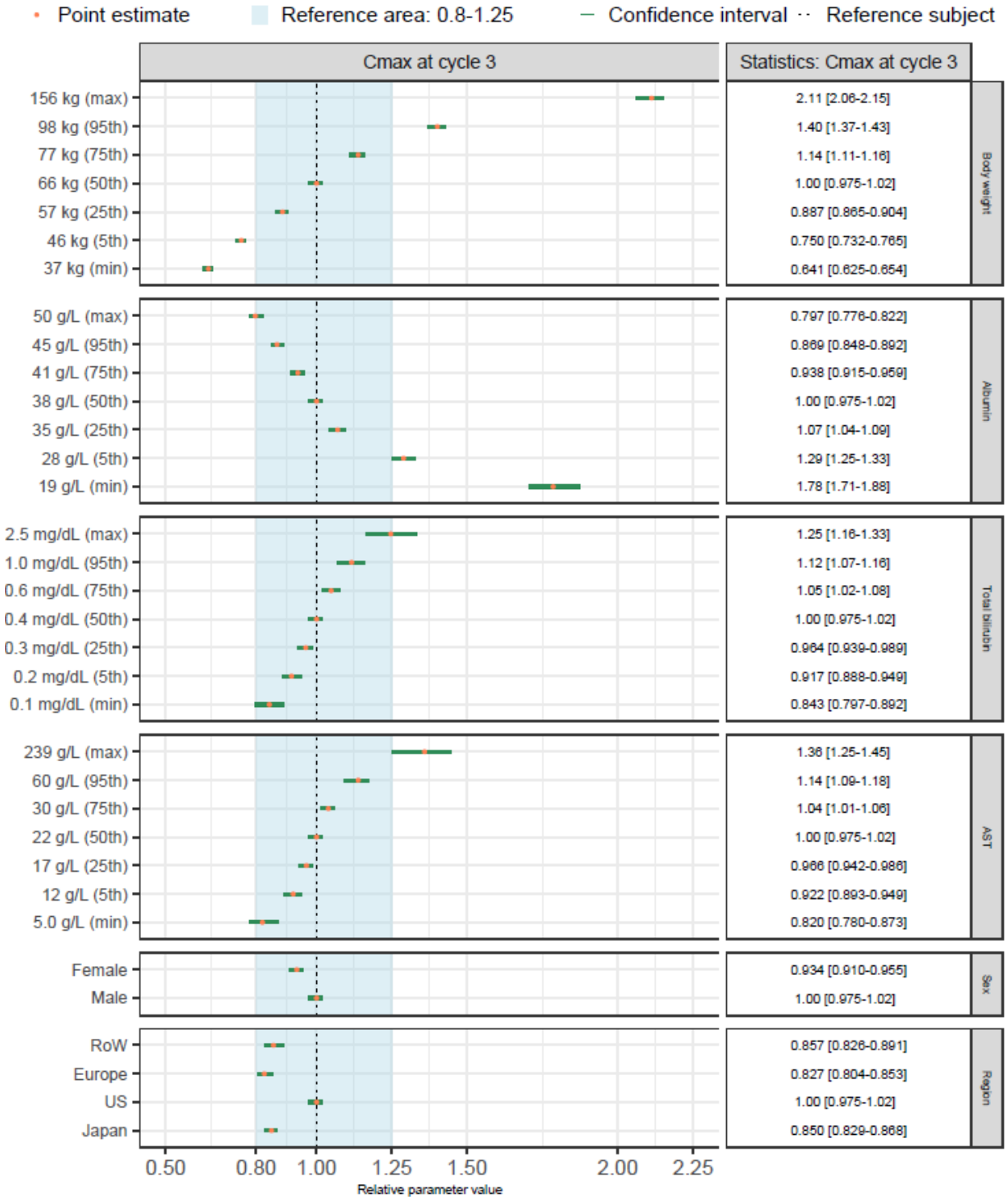


Figure 19 Forest plots illustrating the effects of covariates on DXd parameter Cmax3, conditioned on a typical reference subject, based on the final DXd model. Reference: US Male, 66 kg, albumin 38 g/L, AST 22 g/L and total bilirubin 0.4 mg/dL.



c-QT modelling

The C-QTc analysis used data from study DS1062-A-J101 with a cutoff date of 30 Jul 2021. Dose levels in the escalation part ranged from 0.27 mg/kg to 10 mg/kg Q3W. Time-matched PK sampling and ECG measurement are shown in Table 15.

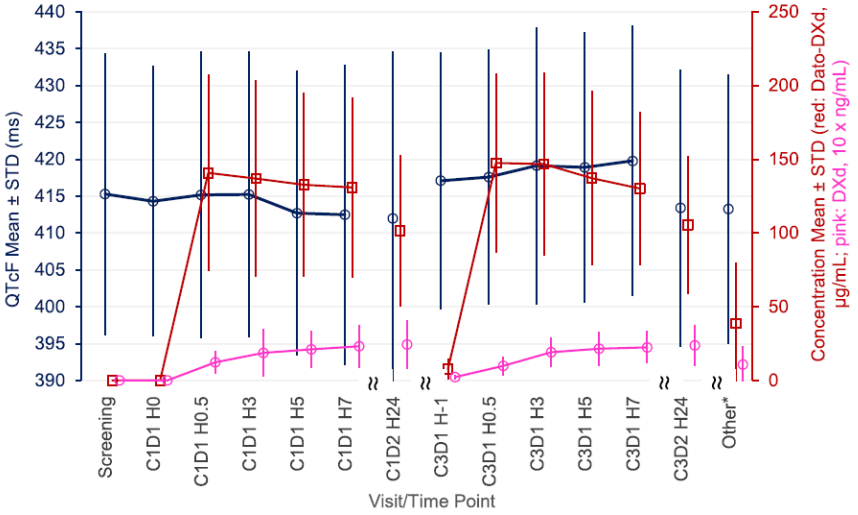
Table 15 Pharmacokinetic Sampling and ECG Measurement Time Points

Cycle	Day	PK Sampling Time Point (Acceptable Range) (Relative to ECG Measurement, if Applicable)
1	1	· Before SOA (-8 h) (within 15 min after end of ECG) · EOA (within 30 min after EOA) (within 15 min after end of ECG) · 3 h after SOA (± 15 min) (within 15 min after end of ECG) · 5 h after SOA (± 15 min) (within 15 min after end of ECG) · 7 h after SOA (± 15 min) (within 15 min after end of ECG)
	2	24 h after SOA (± 2 h) (within 15 min after end of ECG)
	4	3 days after SOA (± 1 day) (within 15 min after end of ECG)
	8	7 days after SOA (± 1 day)
	15	14 days after SOA (± 1 day)
2	1	· Before administration (- 8 h) (within 15 min after end of ECG) · EOA (within 30 min after EOA)
	8	7 days after SOA (± 2 days)
	15	14 days after SOA (± 2 days)
3	1	· Before administration (- 8 h) (within 15 min after end of ECG) · EOA (within 30 min after EOA) (within 15 min after end of ECG) · 3 h after SOA (± 15 min) (within 15 min after end of ECG) · 5 h after SOA (± 15 min) (within 15 min after end of ECG) · 7 h after the SOA (± 15 min) (within 15 min after end of ECG)
	2	24 h after SOA (- 2 to + 4 h) (within 15 min after end of ECG)
	4	3 days after SOA (± 1 day) (within 15 min after end of ECG)
	8	7 days after SOA (± 2 days)
	15	14 days after SOA (± 2 days)
4, 6, 8	1	Before administration (- 8 h) (within 15 min after end of ECG)

ECG: electrocardiogram; EOA: end of administration; h: hours; min: minutes, PK: pharmacokinetic; SOA: start of administration.

Mean PK concentrations of Dato-DXd and DXd across time versus QTcF are depicted in Figure 20.

Figure 20 Concentration and QTcF by Visit/Time Point



* End of treatment or unscheduled.
CxDy Hz: Cycle x Day y Hour z (see time point definitions in Table 4-1); QTcF: heart-rate-corrected QT interval using Fridericia's method; STD: standard deviation.
Source: Table 10-2.

Static linear mixed effects exposure-response models including effects of covariates tested on the intercept term was used to describe the exposure-QTc relation. Correction of the baseline QTc for heart-rate using a population approach gave a better alignment than the Fridericia method, therefore both correction methods were used. The parameters of the final models were estimated with good precision except for Slope. The random effects were large on all parameters as well as the residual

error. All 95% CI on Slope contained the null except in the model of Dato-DXd and ΔQTcP where the p-value for Slope was 0.031 (Table 16).

Table 16 Parameter Estimates for Secondary Final Models (AQTcP)

a. Dato-DXd

Parameter	Estimate	SE	RSE (%)	95% CI	p-value
Fixed Effects					
Intercept (ms)	-0.335	0.505	N/A	(-1.33, 0.656)	0.508
Concentration slope (ms/[µg/mL])	0.00803	0.00371	46.2%	(0.000752, 0.0153)	0.031
Baseline QTcP - mean (ms/ms)	-0.165	0.0277	16.8%	(-0.220, -0.111)	<0.001
Between-Subject Variability (Random Effects)					
Intercept STD (ms)	5.39	0.448	8.31%	(4.59, 6.34)	—
Concentration slope STD (ms/[µg/mL])	0.0253	0.00434	17.2%	(0.0182, 0.0352)	—
Intercept-concentration slope correlation	0.497	—	—	(-0.0109, 0.801)	—
Residual (Unexplained) Variability					
STD σ (ms)	9.14	0.146	1.60%	(8.86, 9.43)	—

2205 observations in 195 subjects. Shrinkages: intercept STD, 11.8%, concentration STD, 30.1%, residual STD, 4.22%.

b. DXd

Parameter	Estimate	SE	RSE (%)	95% CI	p-value
Fixed Effects					
Intercept (ms)	0.0507	0.498	N/A	(-0.925, 1.03)	0.919
Concentration slope (ms/[ng/mL])	0.229	0.237	103%	(-0.237, 0.694)	0.336
Baseline QTcP - mean (ms/ms)	-0.168	0.0274	16.3%	(-0.223, -0.114)	<0.001
Between-Subject Variability (Random Effects)					
Intercept STD (ms)	5.37	0.432	8.04%	(4.59, 6.28)	—
Concentration slope STD (ms/[ng/mL])	1.78	0.318	17.9%	(1.27, 2.51)	—
Intercept-concentration slope correlation	0.428	—	—	(0.0412, 0.704)	—
Residual (Unexplained) Variability					
STD σ (ms)	9.10	0.148	1.63%	(8.81, 9.39)	—

2203 observations in 195 subjects. Shrinkages: intercept STD, 12.3%, concentration STD, 29.3%, residual STD, 4.51%.

CI: confidence interval; N/A: not applicable; QTcP: population-derived heart-rate-corrected QT interval; ΔQTcP: change from baseline QTcP; RSE: relative standard error; STD: standard deviation; SE: standard error; "—": could not be calculated.
Model: ΔQTcP = Intercept + Slope × Concentration + Baseline_coefficient × (Baseline - mean) + ε.
Source: *dato-dxd-c-qtc.r*, *dato-dxd-tables.xlsx*.

Exposure-response modelling

The exposure-response (E-R) data set for NSCLC patients originated from studies DS1062-A-J101, DS1062-A-U202, and DS1062-A-U301. Data from 85 subjects with BC (Study A-J101) were excluded from efficacy evaluations. Time-to-event (TTE) models were applied for OS and PFS while logistic regression was used for ORR. For the investigated 13 safety end-points, logistic regression models were developed and some selected safety end-points were also evaluated using TTE modelling.

Final model parameters for efficacy end-points OS, PFS and ORR are shown in Table 17, Table 18, and Table 19.

Table 17 Parameter estimates of the final TTE model for OS.

		Final model	
Run		20109	
OFV		4851.85	
Condition number		75.62	
	Unit	**Value**	**RSE (%)**
Baseline hazard	$year^{-1}$	0.378	23.1
Shape parameter	$year^{-1}$	0.588	18.6
Slope for linear effect of Dato-DXd AUC_1 on the base hazard	$(mg/mL \cdot h)^{-1}$	-0.0184	53.3
Albumin at baseline on the base hazard	$(g/L)^{-1}$	-0.0668	18.1
ECOG>0 on the base hazard		0.666	20.2
Liver metastasis on the base hazard		0.386	33.7
Region Japan on the base hazard		-0.350	42.0
Female sex on the base hazard		-0.361	32.8
Tumor size at baseline on the base hazard	mm^{-1}	0.00425	26.6
Squamous histology on the base hazard		0.339	46.3

See Glossary for explanation of abbreviations.

Table 18 Parameter estimates of the final TTE model for PFS

		Final model	
Run		20211	
OFV		5310.1	
Condition number		142.3	
	Unit	**Value**	**RSE (%)**
Baseline hazard	$year^{-1}$	5.85	12.8
EC_{50} for AUC_τ on the base hazard	mg·h/mL	17.6	41.9
E_{max} for AUC_τ on the base hazard	-	-3.45	20.4
Age on the base hazard	$year^{-1}$	-0.0156	30.9
Albumin at baseline on the base hazard	$(g/L)^{-1}$	-0.0266	37.1
Squamous histology on the base hazard		0.598	22.6
Last prior line of IO on the base hazard		-0.303	34.3
Liver metastasis on the base hazard		0.537	23.4
Female sex on the base hazard		-0.312	34.0

See Glossary for explanation of abbreviations.

Table 19 Parameter estimates of the final ORR model

		Final model	
Run		20308	
OFV		664.62	
Condition number		34.49	
	Unit	**Value**	**RSE (%)**
Base probability		0.000586	(FIX)
EC_{50} for E_{max} effect of Dato-DXd C_{av} on the base probability[a]	(mg/mL)	0.00404	33.6
E_{max} for E_{max} effect of Dato-DXd C_{av} on the base probability[a]		7.44	4.34
Squamous histology on the base probability[a]		-1.26	29.3
Number of prior line therapy >2 on the base probability[a]		0.602	32.1

[a] Estimated on the logit scale. See Glossary for explanation of abbreviations.

Table 20 and Table 21 show significant exposure metrics for safety events.

Table 20 Overview over significant exposure metrics and covariate effects for the TEAEs and AESIs included in the AEs analysis data set.

TEAE/AESI	Significant exposure metrics	Significant covariate effect	Section
G3+ TEAEs	DXd C_{av}	Asian race, ECOG>0	Section 5.3.1
Serious TEAEs	DXd C_{av}	Asian race, ECOG>0, squamous histology, breast cancer	Section 5.3.2
TEAEs associated with dose interruption	Dato-DXd AUC_1	-	Section 5.3.3
TEAEs associated with dose delay	-	-	Section 5.3.4
TEAEs associated with dose reduction	Dato-DXd AUC_1	Region Europe, mild or worse renal impairment	Section 5.3.5
TEAEs associated with treatment discontinuation	-	-	Section 5.3.6
Mucosal inflammation (any grade)	DXd C_{av}	Regions Europe, Japan, rest of the world[a], breast cancer[a]	Section 5.3.7
Mucosal inflammation (grade≥2)	DXd C_{av}	Regions Europe[a], Japan, rest of the world[a], breast cancer[a], mild or worse renal impairment	Section 5.3.8
Oral mucositis/stomatitis (any grade)	Dato-DXd AUC_1	Squamous histology, breast cancer	Section 5.3.9
Oral mucositis/stomatitis (grade≥2)	Dato-DXd AUC_1	Female sex	Section 5.3.10
Ocular surface toxicity (any grade)	Dato-DXd AUC_1	Regions Europe, rest of the world	Section 5.3.11
Ocular surface toxicity (grade≥2)	Dato-DXd C_{av}	-	Section 5.3.12
Treatment-related adjudicated ILD	-	-	Section 5.3.13

[a] Due to no observed events, the parameter estimate for the covariate effect was fixed to the lower parameter boundary of -20 to avoid influence on other covariate categories.
See Glossary for explanation of abbreviations.

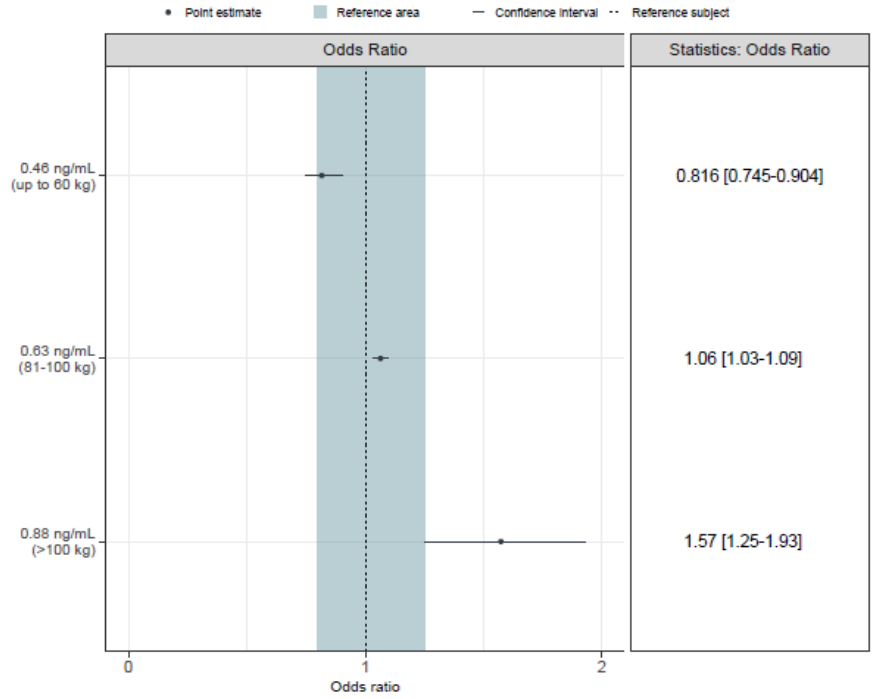
Table 21 Overview over significant exposure metrics and covariate effects for the AESIs included in the TTE AESIs analysis data set.

TEAE/AESI	Significant exposure metrics	Significant covariate effect	Section
Mucosal inflammation (any grade)	DXd C_{av}	Regions Europe, Japan, rest of the world[a], breast cancer[a]	Section 5.4.1
Mucosal inflammation (grade≥2)	DXd C_{av}	Regions Europe[a], Japan, rest of the world[a], breast cancer[a]	Section 5.4.2
Oral mucositis/stomatitis (any grade)	DXd C_{av}	Female sex	Section 5.4.3
Oral mucositis/stomatitis (grade≥2)	Dato-DXd AUC_1	Female sex	Section 5.4.4
Ocular surface toxicity (any grade)	Dato-DXd AUC_1	Regions Europe, Japan, rest of the world	Section 5.4.5
Ocular surface toxicity (grade≥2)	Dato-DXd C_{av}	Regions Japan, rest of the world	Section 5.4.6
Treatment-related adjudicated ILD	-	AGA positive, breast cancer	Section 5.4.7

[a] Due to no observed events, the parameter estimate for the covariate effect was fixed to the lower parameter boundary of -20 to avoid influence on other covariate categories.
See Glossary for explanation of abbreviations.

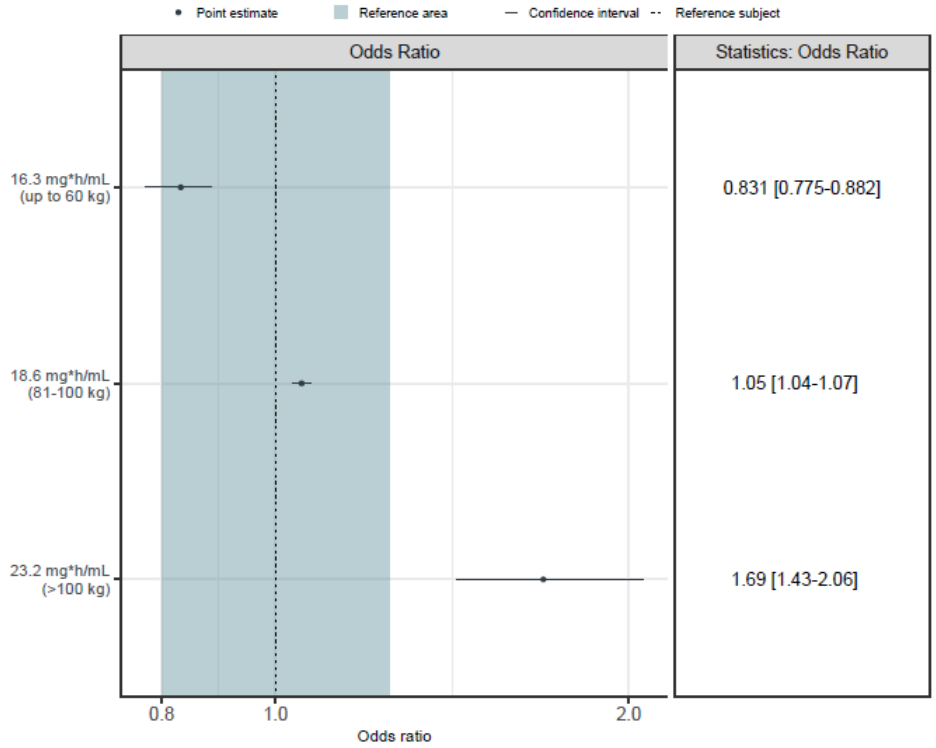
Forest plots for a selection of safety end-points illustrating the impact of body weight on the odds ratio are shown in Figure 21, Figure 22 and Figure 23.

Figure 21 Forest plot showing ORs to experience serious TEAEs for the median DXd Cay in different WT groups in the 6 mg/kg Q3W dose group, based on the final serious TEAEs logistic regression model.



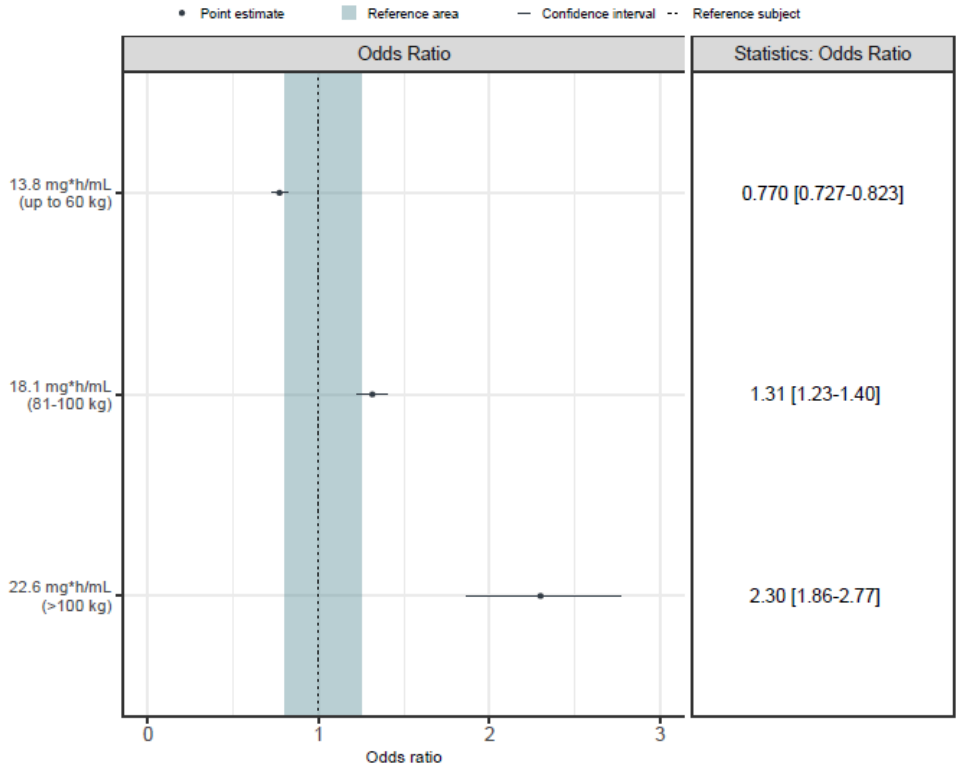
The dots and the whiskers represent the median and the 95% CI of the OR, respectively, displayed numerically as median [95% CI] on the right of each panel. The reference subject (with OR=1) is a non-Asian subject with ECOG 0, non-squamous histology, and the median DXd Cav for the serious TEAEs endpoint in the body weight group 61-80 kg in the 6 mg/kg Q3W dose group in the AEs analysis data set (0.59 ng/mL).

Figure 22 Forest plot showing ORs to experience TEAEs associated with dose interruption for the median Dato-DXd AUC1 in different WT groups in the 6 mg/kg Q3W dose group, based on the final TEAEs associated with dose interruption logistic regression model.



The dots and the whiskers represent the median and the 95% CI of the OR, respectively, displayed numerically as median [95% CI] on the right of each panel. The reference subject (with OR=1) is a subject with the median Dato-DXd AUC1 for the TEAEs associated with dose interruption endpoint in the body weight group 61-80 kg in the 6 mg/kg Q3W dose group in the AEs analysis data set (18.1 mg/mL-h).

Figure 23 Forest plot showing ORs to experience TEAEs associated with dose reduction for the median Dato-DXd AUC1 in different WT groups in the 6 mg/kg Q3W dose group, based on the final TEAEs associated with dose reduction logistic regression model.

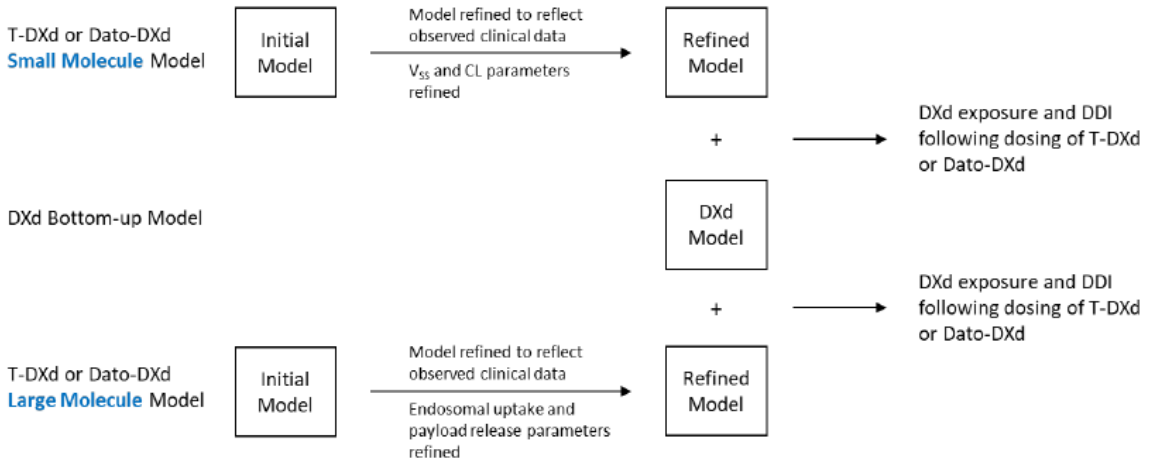


The dots and the whiskers represent the median and the 95% CI of the OR, respectively, displayed numerically as median [95% CI] on the right of each panel. The reference subject (with OR=1) is a subject not from the region Europe with normal renal function and the median Dato-DXd AUC1 for the TEAEs associated with dose reduction endpoint in the body weight group 61-80 kg in the 6 mg/kg Q3W dose group in the AEs analysis data set (15.9 mg/mL-h).

PBPK modelling

Previous PBPK models for T-DXd developed in Simcyp V18 were updated in Simcyp V21 to describe the pharmacokinetics of T-DXd and Dato-DXd which share the same payload molecule DXd (MAAA-1181A). For both ADCs two different modelling approaches were used: the small molecule simulator or a mechanistic minimal ADC PBPK model. PK of the payload DXd was described by a bottom-up PBPK model which was subsequently linked to the final models for Dato-DXd and T-DXd as a metabolite in the small molecule simulator and as a payload in the ADC simulator to give the final models.

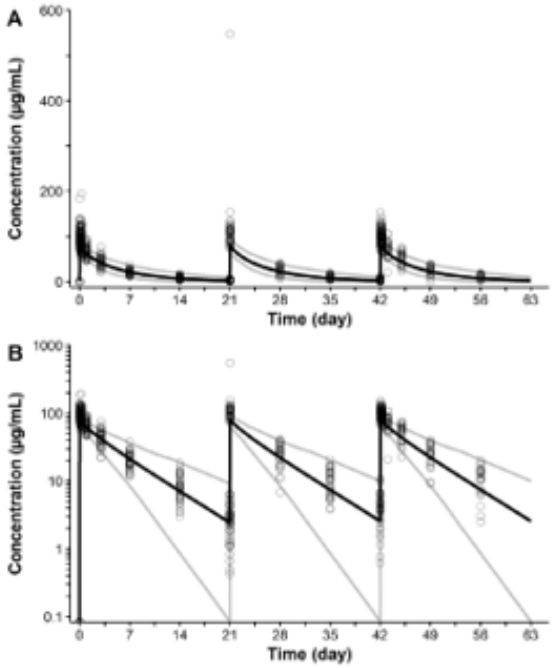
Figure 24 Steps taken in the development of the PBPK models for T-DXd / Dato-DXd and DXd



V_{SS}: volume of distribution at steady state; CL: clearance

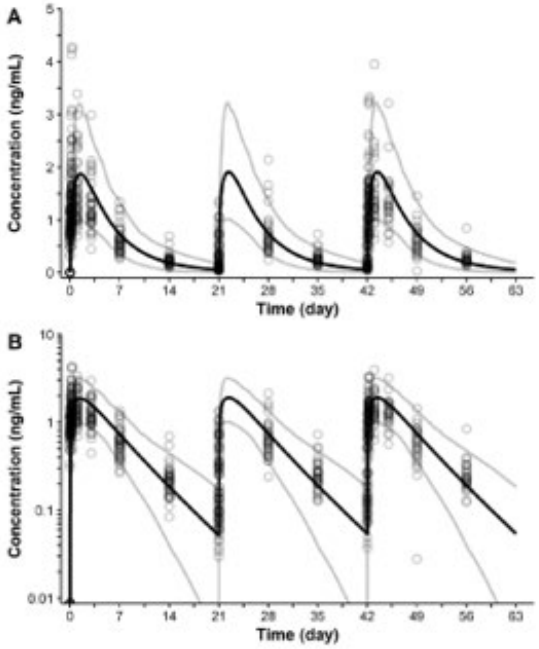
The final PBPK models for T-DXd and Dato-DXd were evaluated against clinical data that was part of model development and verified with clinical data not used in model development. The minimal ADC model for Dato-DXd could fit the observed data of Dato-DXd and DXd well in all data set and therefore this PBPK model seems most suitable for description of Datopotamab deruxtecan Daiichi Sankyo PK. See Figure 25 and Figure 26.

Figure 25 Simulated mean (solid black line) and 5h and 95m percentile (grey lines) plasma concentrations of Dato-DXd following a 4 mg/kg dose every 21 days predicted using the mechanistic minimal ADC model.



The simulated population consisted of 3 trials of 49 Japanese individuals aged 35 – 70 years, with a proportion of females = 0.49. The symbols represent the observed individual data from Clinical Study DS1062-A-J101. In Panel (B) data are shown with the y-axis on a logarithmic scale [Simulated source: 47-dai-9b-ver-lm-ds1062-maaa1181-frel-0pt4-delayed-4-dar1-8].

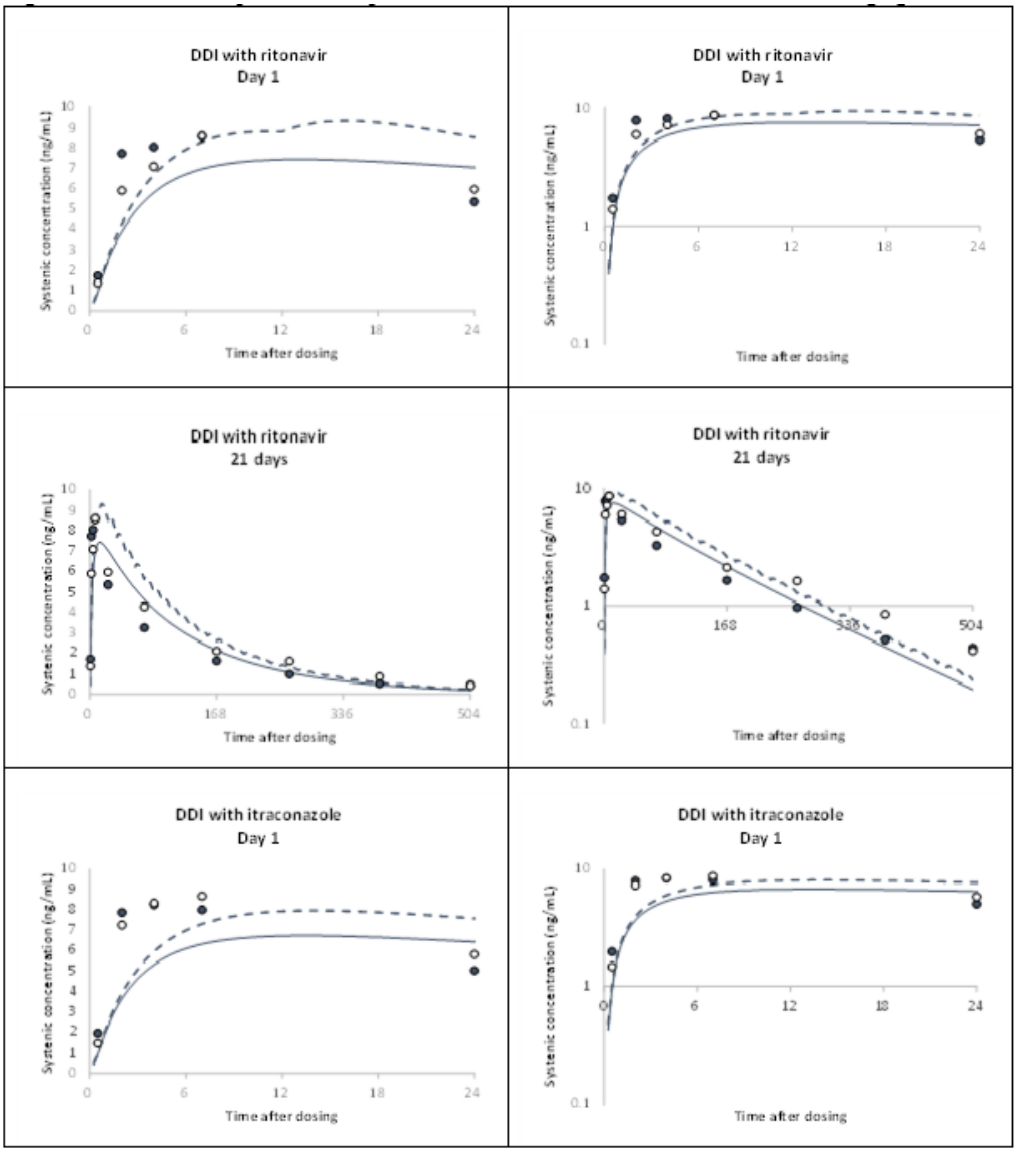
Figure 26 Simulated mean (solid black line) and 5th and 95ª percentile (grey lines) plasma concentrations of DXd following a 4 mg/kg Dato-DXd dose every 21 days predicted using the mechanistic minimal ADC model.

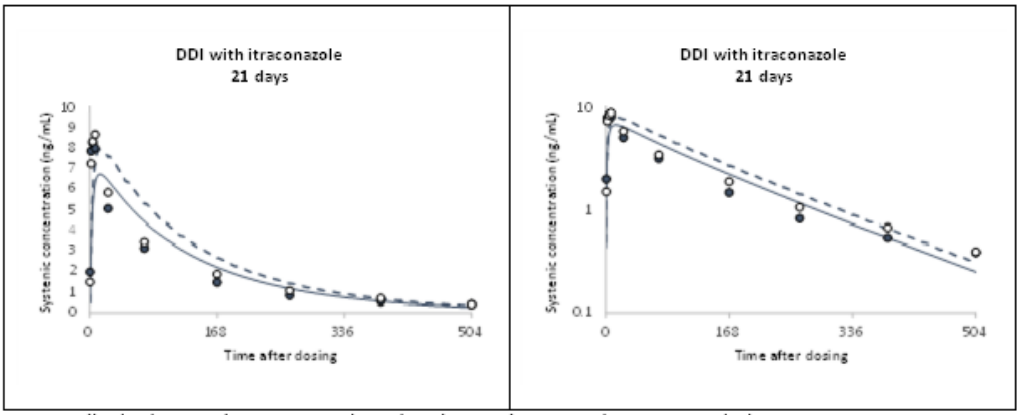


The simulation was performed using the Japanese population with the Simcyp Simulator and uses 3 trials of 49 subjects with an age range of 35 – 70 years and a proportion of females = 0.49. The symbols represent the observed individual data from Clinical Study DS1062-A-J101. Panel B shows the data with the y axis on a logarithmic scale [Simulated source: 47-dai-9b-ver-lm-ds1062-maaa1181-frel-0pt4-delayed-4].

DXd is a substrate of OATP1B and CYP3A. T-DXd DDI in presence of either ritonavir (a strong OATP1B/CYP3A inhibitor) or itraconazole (a strong CYP3A inhibitor) was investigated in clinical study DS8201-A-A104. The observed results were compared to predicted effects on T-DXd PK using the updated V21 T-DXd PBPK models. The DXd PK profiles of Day 1 and 21 days in Cycle 2 and Cycle 3 predicted by the mechanistic minimal ADC model for T-DXd overlaid with the corresponding observed DXd profiles from Study DS8201-A-A104 are shown in Figure 27.

Figure 27 Observed and predicted PK profiles of DXd after T-DXd administration at 5.4 mg/kg





ADC=antibody-drug conjugate; DDI=drug-drug interaction; T-DXd=trastuzumab deruxtecan
The simulations were performed in the mechanistic minimal ADC model of T-DXd with 10 trials of 12 Japanese subjects aged 48 to 70 years (DDI with ritonavir) or 14 Japanese subjects aged 31 to 69 years (DDI with itraconazole) based on Study DS8201-A-A104.
The observed data were referred to Study DS8201-A-A104.
Solid line: Predicted in Cycle 2 without inhibitor; Dashed line: Predicted in Cycle 3 with inhibitor; Closed circle: Observed in Cycle 2 without inhibitor; Open circle: Observed in Cycle 3 with inhibitor

The impact of concomitant ritonavir or itraconazole was simulated using each of the final PBPK models for Dato-DXd. No clinical DDI studies has been performed with Dato-DXd.

Absorption

Dato-DXd was administered by IV infusion in the conducted clinical studies. Therefore, bioavailability studies and food-effect studies were not conducted.

Bioequivalence – comparability of drug products

Different Dato-DXd drug products (DP) have been administered to patients in the conducted clinical studies: FL-DP used in the Phase I TPO study, clinical Lyo-DP in the phase II study TL05 and in the phase 3 studies TL01, in which also the to-be-marketed (tbm) Lyo-DP was administered.

The comparability of the pharmacokinetics of the different drug products was evaluated using integrated non-compartmental analysis of Cycle 1 full PK data from studies TP01 (FL-DP), TL05 (clinical Lyo-DP), and TL01 (to-be-marketed Lyo-DP) at a Dato-DXd dose of 6.0 mg/kg. The NCA analysis was complemented with a Pop-PK analysis, in which DP was included as a covariate.

Comparison FL-DP vs clinical Lyo-DP

A comparison of the PK for the FL-DP and the clinical Lyo-DP at 6.0 mg/kg using NCA of observed Cycle 1 full PK data from studies TP01 (FL-DP, n = 133) and TL05 (clinical Lyo-DP, n = 45) is presented in Table 22. The geometric mean ratios (GMR) of the Cmax, AUCtau and AUCinf for all three analytes, of the clinical Lyo-DP and the FL-DP were determined. The GMRs were found to be within the range of 0.8 to 1.25, indicating the similarity of the two drug products.

Table 22 Comparison of Pharmacokinetic Parameters of Dato-DXd, Total Anti-TROP2 Antibody, and DXd Between FL-DP and Clinical Lyo-DP at Dato-DXd 6.0 mg/kg in Cycle 1

Analyte	PK Parameter	Geometric Mean (%CV) [N]		Geometric Mean Ratio of Clinical Lyo-DP/FL-DP	90% CI for Geometric Mean Ratio
		FL-DP [a]	Clinical Lyo-DP		
Dato-DXd	Cmax (µg/mL)	158 (20.04) [132]	147.1 (19.33) [45]	0.93	0.88 to 0.98
	AUCtau (µg·d/mL)	709.6 (30.59) [130]	613.8 (29.07) [44]	0.87	0.79 to 0.94
	AUCinf (µg·d/mL)	743.6 (29.71) [127]	641.3 (30.63) [43]	0.86	0.79 to 0.94
Total anti-TROP2 antibody	Cmax (µg/mL)	159.4 (19.93) [132]	145.9 (19.81) [45]	0.91	0.86 to 0.97
	AUCtau (µg·d/mL)	728.2 (32.47) [131]	666.9 (29.06) [45]	0.92	0.84 to 1.00
	AUCinf (µg·d/mL)	775.4 (30.54) [126]	708.4 (31.46) [43]	0.91	0.84 to 1.00
DXd	Cmax (ng/mL)	2.8 (60.25) [133]	3.1 (54.93) [45]	1.12	0.96 to 1.31
	AUCtau (ng·d/mL)	18.9 (41.35) [122]	18.6 (46.75) [43]	0.98	0.87 to 1.11
	AUCinf (ng·d/mL)	20.7 (40.83) [119]	19.9 (46.51) [43]	0.96	0.86 to 1.09

AUCinf = area under the plasma concentration-time curve from time 0 to infinity; AUCtau = area under the plasma concentration-time curve during the dosing interval (0 to 21 days); CI = confidence interval; Cmax = maximum plasma concentration; CV = coefficient of variation; Dato-DXd = datopotamab deruxtecan; DXd = deruxtecan; FL-DP = frozen-liquid drug product; Lyo-DP = lyophilized drug product; PK = pharmacokinetic; TROP2 = trophoblast cell surface antigen 2.

[a] Reference group for geometric mean ratios (and 90% CI).

Note: Data combined across drug products. Subjects who received more than one drug product in cycle 1 are not included.

Source: Dato-DXd Integrated PK Summary Table 5.4.4.

Comparison clinical Lyo-DP with to-be-marketed Lyo-DP

A comparison of the PK for the clinical Lyo-DP and the to-be-marketed Lyo-DP at 6.0 mg/kg using non-compartmental analysis of observed Cycle 1 full PK data from studies TL05 (Clinical Lyo-DP, n = 45) and TL01 (to-be-marketed Lyo-DP, n = 20) is presented in Table 3.3.

The geometric mean ratios (GMR) of the Cmax, AUCtau and AUCinf for all three analytes, of the two drug products clinical Lyo-DP and the to-be-marketed Lyo-DP were determined. The GMRs were found to be within the range of 0.8 to 1.25, indicating the similarity of the two drug products, see Table 23.

The median time to reach maximum plasma concentration (Tmax) of Dato-DXd and total anti-TROP2 antibody were around 2 hours for drug products, which largely reflected the sampling time at the end of the infusion. The median Tmax of DXd was slightly lower for to-be-marketed Lyo-DP, 5.9 hr, compared to the clinical Lyo-DP, 7.0 hr. Furthemore, the median Tmax of DXd for FL-DP was higher, 22.4 hr.

Table 23 Comparison of Pharmacokinetic Parameters of Dato-DXd, Total Anti-TROP2 Antibody, and DXd Between Clinical Lyo-DP and to-be-marketed Lyo-DP at Dato-DXd 6.0 mg/kg in Cycle 1

Analyte	PK Parameter	Geometric Means (%CV) [N]		Geometric Mean Ratio of To-be-marketed Lyo-DP/ Clinical Lyo-DP/	90% CI for Geometric Mean Ratio
		Clinical Lyo-DP [a]	To-be-marketed Lyo-DP		
Dato-DXd	Cmax (µg/mL)	147.1 (19.33) [45]	141.4 (20.96) [20]	0.96	0.88 to 1.05
	AUCtau (µg·d/mL)	613.8 (29.07) [44]	559.7 (30.70) [19]	0.91	0.80 to 1.04
	AUCinf (µg·d/mL)	641.3 (30.63) [43]	581.2 (32.39) [19]	0.91	0.79 to 1.04
Total anti-TROP2 antibody	Cmax (µg/mL)	145.9 (19.81) [45]	133.8 (20.83) [20]	0.92	0.84 to 1.00
	AUCtau (µg·d/mL)	666.9 (29.06) [45]	624.2 (33.34) [19]	0.94	0.82 to 1.07
	AUCinf (µg·d/mL)	708.4 (31.46) [43]	655.7 (35.61) [19]	0.93	0.80 to 1.07
DXd	Cmax (ng/mL)	3.1 (54.93) [45]	2.5 (48.29) [20]	0.81	0.64 to 1.01
	AUCtau (µg·d/mL)	18.6 (46.75) [43]	15.4 (37.23) [18]	0.82	0.68 to 1.01
	AUCinf (µg·d/mL)	19.9 (46.51) [43]	16.3 (37.23) [16]	0.82	0.66 to 1.01

AUCinf = area under the plasma concentration-time curve from time 0 to infinity; AUCtau = area under the plasma concentration-time curve the dosing interval (0 to 21 days); CI = confidence interval; Cmax = maximum plasma concentration; CV = coefficient of variation; Dato-DXd = datopotamab deruxtecan; DXd = deruxtecan; Lyo-DP = lyophilized drug product; PK = pharmacokinetic; TROP2 = trophoblast cell surface antigen 2.
[a] Reference group for geometric mean ratios (and 90% CI).
Note: Data combined across drug products. Subjects who received more than one drug product on cycle 1 are not included.

Population PK analysis of comparability

The influence of drug product (FL-DP, clinical Lyo-DP, and the to-be-marketed Lyo-DP) on the PK of Dato-DXd and DXd was evaluated in Dato-DXd and DXd population PK models. Using clinical Lyo-DP as a reference drug product, comparable Dato-DXd and DXd exposures (Cmax and AUCtau in Cycle 3) were observed for the to-be-marketed Lyo-DP and clinical Lyo-DP. A slight increase in the exposure of FL-DP was observed, manifested by an 8% increase in Dato-DXd AUC and a 17% increase in DXd AUC. These results indicate that the clinical PK of all three drug products are comparable. In conclusion, no statistically significant influence of drug product on Dato-DXd and DXd PK was identified in the population PK analysis, consistent with the NCA.

Justification for not performing a dedicated comparative BA and bioequivalence (BE) study

No dedicated comparative BA/BE studies have been performed. The clinical PK comparability of different Dato-DXd drug products used across the clinical development program (FL-DP, clinical Lyo-

DP, and to-be-marketed Lyo-DP) was established using integrated PK and population PK analyses using data from the clinical studies TP01, TL05 and TL01.

Distribution

The Cycle 1 PK data were integrated across TL01, TL05, and TP01 (NSCLC and BC), and Cycle 1 PK parameters using noncompartmental analysis of observed full PK data for Dato DXd, total anti–TROP2 antibody, and DXd are presented in Table 24.

For a typical subject with a body weight of 66 kg, the geometric mean (geoCV%) of Vss is calculated to be 3.52 L (22.9%). Similarly, the geometric mean (geoCV%) of clearance for a subject weighing 66 kg is calculated to be 565.6 mL/day (31.5%), or equivalently, 0.566 L/day, approximately 0.024 L/hr. Based on Population PK analysis, the central volume of distribution of Dato-DXd (VcDatoDXd) was estimated to be 3.02 L

Table 24 Summary of PK Parameters on Cycle 1 at 6 mg/kg Dato-DXd

PK Parameter	**Statistic**	**Dato-DXd**	**Total Anti-TROP2 Antibody**	**DXd**
Cmax[a] (µg/mL)	N Median (min, max) Mean (standard deviation) GeoMean (CV%)	197 155 (91.0, 262) 157 (31.8) 154 (20.3)	197 155 (96.4, 254) 157 (32.2) 153 (20.5)	198 2.61 (0.953, 66.0) 3.53 (5.05) 2.82 (58.1)
Tmax (h)	N Median (min, max)	197 2.02 (1.50, 192.45)	197 2.00 (1.50, 192.45)	198 21.29 (2.78, 192.82)
Ctrough (µg/mL)	N Median (min, max) Mean (standard deviation) GeoMean (CV%)	184 4.43 (0, 17.7) 4.89 (2.99) NC (NC)	184 5.94 (0, 21.4) 6.13 (3.66) NC (NC)	185 0.16 (0, 0.698) 0.179 (0.0974) NC (NC)
AUCtau (µg·d/mL)[b]	N Median (min, max) Mean (standard deviation) GeoMean (CV%)	193 694 (241, 2210) 702 (222) 671 (31.4)	195 730 (230, 2190) 737 (229) 703 (32.1)	183 17.9 (7.50, 131) 20.5 (13.4) 18.5 (42.6)
AUCinf (µg d/mL)[b]	N Median (min, max) Mean (standard deviation) GeoMean (CV%)	189 729 (239, 1480) 733 (215) 701 (31.4)	188 785 (242, 1620) 781 (227) 747 (31.7)	178 19.4 (8.25, 136) 22.2 (14.0) 20.0 (42.3)
t1/2 (d)	N Median (min, max) Mean (standard	192 4.82 (1.04, 8.23)	194 5.23 (1.05, 10.91)	179 5.50 (3.16, 8.75)

PK Parameter	Statistic	Dato-DXd	Total Anti-TROP2 Antibody	DXd
	deviation) GeoMean (CV%)	4.86 (1.07) 4.72 (26.1)	5.25 (1.29) 5.07 (28.5)	5.57 (1.04) 5.48 (19.0)
CL (mL/d/kg)	N Median (min, max) Mean (standard deviation) GeoMean (CV%)	189 8.25 (4.06, 25.1) 9 (3.09) 8.57 (31.5)	NR	NR
Vss (mL/kg)	N Median (min, max) Mean (standard deviation) GeoMean (CV%)	189 53.5 (29.3, 93.7) 54.6 (12.5) 53.3 (22.9)	NR	NR

AUCinf = area under the plasma concentration-time curve from time 0 to infinity; AUCtau = area under the plasma concentration-time curve during dosing interval; CL = total body clearance; Cmax = maximum plasma concentration; Ctrough = trough plasma concentration; CV = coefficient of variation; d = day; max = maximum; min = minimum; NC = not calculated; NR = not reported; PK = pharmacokinetic(s); t1/2 = terminal elimination half-life; Tmax = time to Cmax; TROP2 = trophoblast cell surface antigen 2; Vss = volume of distribution at steady state.

[a] ng/mL for DXd.

[b] ng•d/mL for DXd.

Notes: Means are arithmetic means.

NR noted when parameter was not analyzed.

Plasma protein binding and blood to plasma ratio of DXd

The mean human plasma protein binding of DXd was determined using ultracentifugation to 96.8% and 98.0% across the concentration range of 10 to 100 ng/ml. The ratio of the concentration of radioactivity in blood to that in plasma was 0.59 to 0.62 across the concentration range of 10 to 100 ng/ml.

Elimination

In the integrated PK analysis at 6 mg/kg, the geometric mean (geoCV%) of clearance for Dato-DXd in Cycle 1 was 565.6 mL/day (31.5%), or equivalently, 0.566 L/day, approximately 0.024 L/hr for a typical subject with a body weight of 66 kg. The median elimination half-life (t1/2) was 4.82 days for Dato DXd, 5.23 days for total anti–TROP2 antibody, and 5.50 days for DXd.

Excretion

The routes of excretion was not investigated in humans for the relevant payload part DXd of Dato-DXd. After IV administration of 14C-labeled DXd (14C-DXd) to rats and monkeys, urine, and faeces (from non-cannulated animals) and bile (from bile-duct–cannulated animals) were collected and indicated

that the major excretion pathway of radioactivity was faeces via the biliary route and that DXd was the most abundant component of radioactivity in urine, faeces, and bile, see also non-clinical part.

Metabolism

The humanized TROP2 IgG1 MAb is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. Dato-DXd stability and relase of DXd was investigated in vitro using human plasma. In vitro DatoDXd was stablein human plasma.

The metabolism of DXd in humans has only been investigated with in vitro methods. In vitro clearance studies of DXd with CYP-expressing microsomes showed that CYP1A2, CYP2D6, CYP3A4, and CYP3A5 were involved in the metabolism of DXd. Additional experiments in human liver microsomes with specific inhibitors of CYP enzymes indicated that CYP3A4 is the primary CYP isoform involved in the metabolism of DXd. In additional in vitro studies it was shown that DXd is not metabolized by UGT enzymes.

Dose proportionality and time dependencies

Dose proportionality

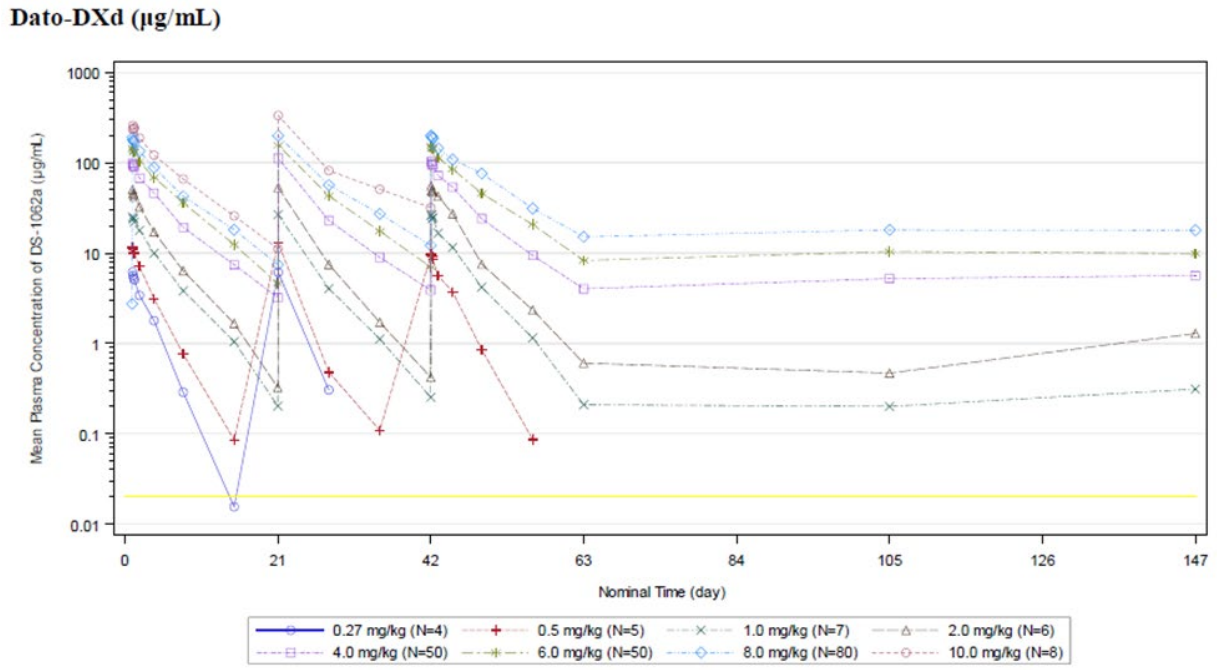
Dose-proportionality was evaluated using a PK-data set of cycle 1 which was combined over all 3 clinical studies, TP01 (NSCLC and BC), TL05 (NSCLC) and TL01 (NSCLC) with full PK-sampling, as cycle 1 PK data generated for all or cohort of participants in all 3 studies. Dose proportionalities for Cmax and AUCtau of Dato-DXd were evaluated using a LN transformed power model ($\ln(PK) = \beta 0 + \beta 1 * \ln(Dose) + \varepsilon$). For the dose range of 4.0 to 10 mg/kg, the slope estimates and 90% CIs of the slopes of Cmax and AUCtau were within the pre-specified interval (0.757, 1.24) for dose-proportionality. In an analysis over an extended dose ranges of 0.27 to 10 mg/kg of Dato-DXd, it was found that Cmax was increased in a dose-proportional manner and AUCtau slightly more than dose-proportional.

Time dependency

The PK after a single dose and multiple dosing of Dato-DXd was evaluated in the phase I study TP01, in which intensive PK sampling in both Cycle 1 (D1) and Cycle 3 (D42) was performed in NSCLC patients, see figure 9.1. The PK parameters of Dato-DXd, total anti–TROP2 antibody, and DXd (MAAin Cycle 1 and Cycle 3 from Study TP01 are summarized in Table 25.

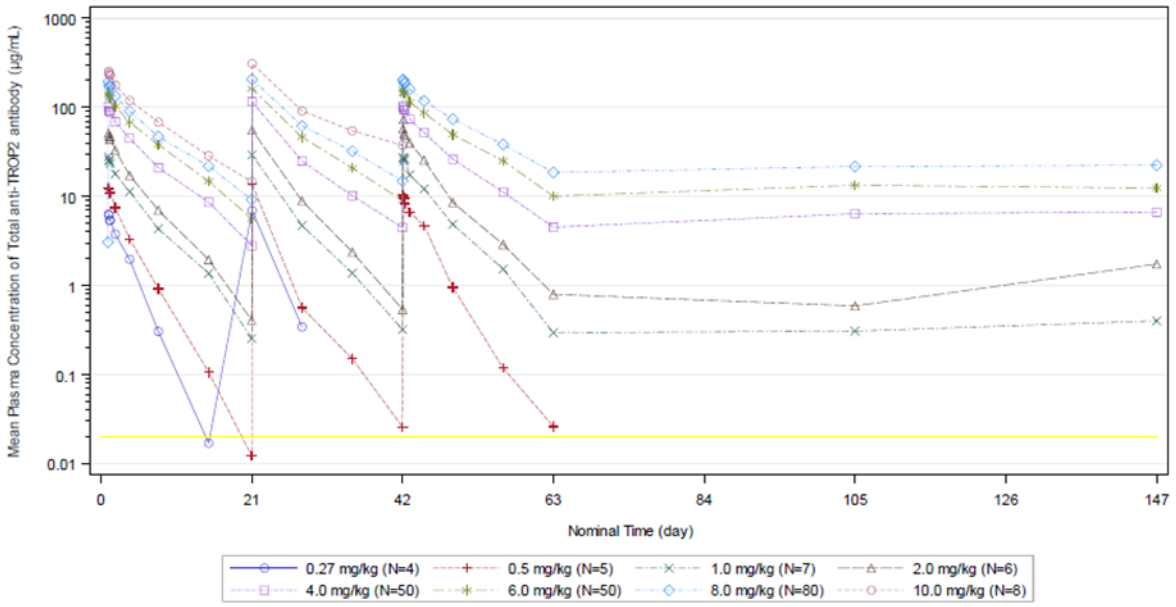
In TP01, after 3 doses of Dato-DXd 6 mg/kg (3 cycles), the geometric mean of the accumulation ratio estimated based on AUC and Cmax was 1.29 and 1.07, respectively. Steady state is expected to be reached by Cycle 3 Day 1 (day 42).

Figure 28 Mean plasma concentration profiles for Dato-DXd by analyte (All Cycles) –Log-Linear Scale – PK Analysis Set in TP01 study



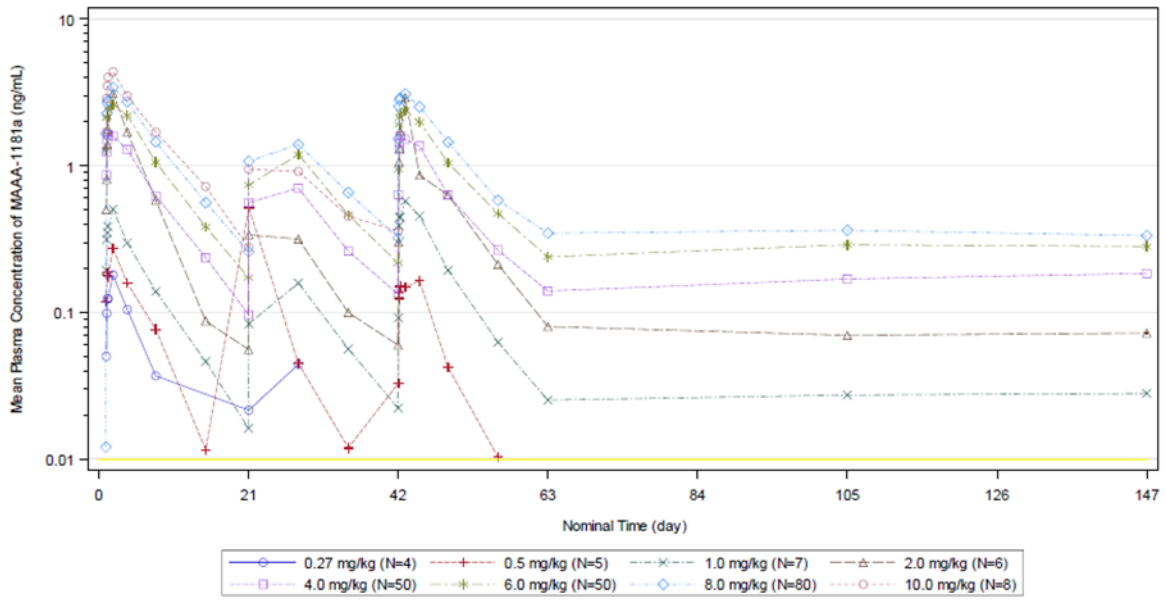
Yellow line indicates lower limit of quantification (Dato-DXd = 0.02 µg/mL).

Total anti-TROP2 antibody (µg/mL)



TROP2 = trophoblast cell-surface antigen 2.
Yellow line indicates lower limit of quantification (total anti-TROP2 antibody = 0.02 µg/mL).

MAAA-1181a (ng/mL)



Yellow line indicates lower limit of quantification (MAAA-1181a = 0.01 ng/mL).

Table 25 Summary of Dato-DXd, Total Anti–Trophoblast Cell Surface Antigen 2 Antibody, and DXd PK in Study TP01

Study TP01 (Module 5.3.3.2 TP01 NSCLC and Module 5.3.3.2 TP01 BC)								
Non-Small Cell Lung Cancer								
PK Parameter, Arithmetic Mean (Standard Deviation)[a] GeoMean (GeoCV%)[a]		Cmax (µg/mL)	Tmax [b] (h)	AUCtau (µg·d/mL)	AUCinf (µg·d/mL)	t1/2 (d)	CL (mL/d/kg)	Vss (mL/kg)
Dato-DXd (Cycle 1)	0.27 mg/kg (N=4)	6.17 (1.52) 6.04 (24.4)	1.83 (1.65, 2.00)	12.6 (4.72) 12.0 (38.9)	12.5 (4.80) 11.8 (40.1)	1.57 (0.330) 1.54 (22.1)	24.1 (8.94) 22.8 (40.1)	51.7 (12.4) 50.6 (24.3)
	0.5 mg/kg (N=5)	11.8 (2.48) 11.6 (21.5)	1.78 (1.77, 6.97)	27.8 (8.24) 26.8 (31.9)	27.7 (8.40) 26.6 (33.1)	1.98 (0.488) 1.93 (27.1)	19.6 (6.74) 18.8 (33.1)	49.8 (7.38) 49.4 (15.2)
	1 mg/kg (N=7)	25.4 (4.14) 25.1 (16.6)	1.87 (1.67, 5.03)	88.4 (26.0) 84.3 (37.8)	89.4 (26.6) 85.1 (38.4)	3.06 (0.758) 2.95 (31.5)	12.5 (5.70) 11.7 (38.4)	48.4 (5.99) 48.1 (12.4)
	2 mg/kg (N=6)	51.6 (10.4) 50.8 (19.6)	1.77 (1.67, 2.12)	155 (49.6) 149 (32.2)	156 (51.5) 150 (33.0)	2.96 (0.777) 2.88 (26.2)	13.9 (4.46) 13.3 (33.0)	51.5 (7.84) 51.0 (15.8)
	4 mg/kg (N=50)	103 (22.4) 101 (19.6)	2.02 (1.55, 7.08)	436 (129) 419 (29.5)	460 (151) 439 (31.4)	4.72 (1.11) 4.59 (24.7)	9.53 (2.90) 9.11 (31.4)	56.9 (10.6) 55.9 (19.0)
	6 mg/kg (N=50)	148 (29.9) 145 (20.4)	2.03 (1.65, 192)	677 (279) 639 (33.4)	681 (177) 658 (27.2)	4.82 (0.975) 4.71 (22.8)	9.45 (2.66) 9.12 (27.2)	59.1 (12.3) 57.9 (21.1)
	8 mg/kg (N=80)	194 (39.7) 190 (20.6)	1.97 (0.800, 7.13)	882 (229) 854 (26.2)	959 (261) 925 (27.6)	5.54 (1.34) 5.38 (24.9)	8.97 (2.47) 8.65 (27.6)	62.6 (15.7) 60.9 (23.9)
	10 mg/kg (N=8)	271 (36.4) 269 (14.0)	3.08 (1.83, 6.92)	1280 (187) 1270 (14.9)	1370 (245) 1350 (18.2)	5.19 (1.35) 5.02 (29.1)	7.53 (1.35) 7.43 (18.2)	52.9 (8.70) 52.3 (16.3)

PK Parameter, Arithmetic Mean (Standard Deviation)[a] GeoMean (GeoCV%)[a]		Cmax (µg/mL)	Tmax [b] (h)	AUCtau (µg·d/mL)	AUCinf (µg·d/mL)	t1/2 (d)	CL (mL/d/kg)	Vss (mL/kg)
Dato-DXd (Cycle 3)	0.27 mg/kg	NR	NR	NR	NR	NR	NR	NR
	0.5 mg/kg (N=5)	9.69 (NC) 9.69 (NC)	0.783 (0.783, 0.783)	24.1 (NC) 24.1 (NC)	NR	2.18 (NC) 2.18 (NC)	20.7 (NC) 20.7 (NC)	61.7 (NC) 61.7 (NC)
	1 mg/kg (N=7)	27.0 (3.35) 26.8 (12.8)	2.98 (0.717, 5.03)	91.8 (36.0) 83.6 (57.7)	NR	2.87 (0.877) 2.73 (39.2)	13.7 (9.26) 12.0 (57.7)	49.7 (13.6) 48.5 (24.4)
	2 mg/kg (N=6)	56.6 (11.0) 55.8 (20.1)	0.875 (0.817, 5.13)	189 (82.7) 177 (44.0)	NR	3.20 (1.00) 3.09 (30.8)	12.1 (4.78) 11.3 (44.0)	47.1 (8.37) 46.5 (18.0)
	4 mg/kg (N=50)	108 (32.9) 105 (25.1)	1.83 (0.667, 7.20)	518 (129) 500 (28.3)	NR	5.37 (1.25) 5.24 (22.6)	8.33 (2.60) 8.00 (28.3)	56.6 (11.2) 55.6 (19.4)
	6 mg/kg (N=50)	160 (34.4) 156 (25.3)	0.900 (0.633, 7.07)	861 (251) 825 (31.2)	NR	5.55 (1.15) 5.43 (21.2)	7.62 (2.46) 7.28 (31.2)	56.8 (15.8) 55.0 (25.2)
	8 mg/kg (N=80)	215 (53.2) 209 (23.1)	1.44 (0.0333, 6.88)	1270 (338) 1230 (25.4)	NR	6.90 (1.71) 6.72 (23.3)	6.71 (1.59) 6.51 (25.4)	60.1 (11.5) 58.9 (21.6)
	10 mg/kg (N=8)	NC	NC	NC	NC	NC	NC	NC

PK Parameter, Arithmetic Mean (Standard Deviation)[a] GeoMean (GeoCV%)[a]		Cmax (µg/mL)	Tmax[b] (h)	AUCtau (µg·d/mL)	AUCinf (µg·d/mL)	t1/2 (d)	CL (mL/d/kg)	Vss (mL/kg)
Total anti–TROP2 antibody (Cycle 1)	0.27 mg/kg (N=4)	6.40 (1.48) 6.29 (21.8)	2.56 (1.75, 3.25)	13.6 (4.71) 13.0 (35.4)	13.5 (4.80) 12.9 (36.5)	1.56 (0.360) 1.53 (24.1)	NR	NR
	0.5 mg/kg (N=5)	12.5 (2.28) 12.4 (18.7)	1.78 (1.77, 6.97)	30.5 (7.51) 29.7 (26.8)	30.5 (7.76) 29.6 (28.2)	2.21 (0.543) 2.15 (29.1)	NR	NR
	1 mg/kg (N=7)	28.9 (2.78) 28.8 (10.0)	1.90 (1.67, 5.02)	98.3 (27.3) 94.0 (36.78)	99.5 (28.1) 95.1 (37.4)	3.16 (0.767) 3.06 (31.2)	NR	NR
	2 mg/kg (N=6)	51.7 (7.51) 51.3 (13.8)	1.78 (1.67, 3.22)	162 (41.7) 158 (26.1)	164 (44.2) 159 (27.1)	3.12 (0.836) 3.03 (26.3)	NR	NR
	4 mg/kg (N=50)	106 (24.7) 104 (21.2)	2.02 (1.55, 7.08)	445 (112) 431 (26.5)	474 (126) 457 (28.2)	4.90 (0.893) 4.82 (17.9)	NR	NR
	6 mg/kg (N=50)	150 (31.3) 147 (21.1)	2.00 (1.65, 192)	699 (289) 655 (36.9)	722 (204) 694 (29.4)	5.06 (1.15) 4.91 (26.7)	NR	NR
	8 mg/kg (N=80)	198 (41.6) 193 (21.7)	1.97 (0.800, 7.03)	948 (237) 919 (25.7)	1040 (285) 999 (28.3)	6.02 (1.56) 5.85 (24.0)	NR	NR
	10 mg/kg (N=8)	268 (41.0) 265 (16.1)	2.01 (1.83, 4.92)	1250 (276) 1280 (17.1)	1440 (306) 1410 (21.1)	5.73 (1.82) 5.48 (33.6)	NR	NR
Total anti–TROP2 antibody (Cycle 3)	0.27 mg/kg	NR	NR	NR	NR	NR	NR	NR
	0.5 mg/kg (N=5)	10.3 (NC) 10.3 (NC)	0.783 (0.783, 0.783)	28.1 (NC) 28.1 (NC)	NR	2.38 (NC) 2.38 (NC)	NR	NR
	1 mg/kg (N=7)	28.2 (3.12) 28.1 (11.4)	0.733 (0.667, 5.03)	103 (35.5) 96.8 (43.5)	NR	3.09 (0.949) 2.94 (39.1)	NR	NR
	2 mg/kg (N=6)	77.3 (38.6) 71.5 (46.1)	1.93 (0.833, 3.17)	199 (81.8) 188 (40.1)	NR	3.38 (1.10) 3.25 (32.1)	NR	NR
	4 mg/kg (N=50)	107 (17.5) 106 (16.2)	1.73 (0.600, 7.00)	539 (144) 518 (30.6)	NR	5.60 (1.22) 5.47 (22.1)	NR	NR
	6 mg/kg (N=50)	165 (36.4) 160 (25.5)	0.900 (0.633, 6.92)	928 (264) 891 (30.0)	NR	5.91 (1.21) 5.78 (21.6)	NR	NR
	8 mg/kg (N=80)	215 (55.0) 209 (23.3)	1.57 (0.650, 6.85)	1380 (409) 1330 (28.9)	NR	7.42 (1.66) 7.24 (22.2)	NR	NR
	10 mg/kg (N=8)	NC	NC	NC	NC	NC	NR	NR

PK Parameter, Arithmetic Mean (Standard Deviation)[a] GeoMean (GeoCV%)[a]		Cmax (ng/mL)	Tmax (h)	AUCtau (ng·d/mL)	AUCinf (ng·d/mL)	t1/2 (d)	CL (mL/d/kg)	Vss (mL/kg)
DXd (Cycle 1)	0.27 mg/kg (N=4)	0.190 (0.0760) 0.178 (43.7)	23.3 (5.00, 23.8)	0.834 (0.364) 0.772 (53.7)	0.441 (NC) 0.441 (NC)	2.54 (NC) 2.54 (NC)	NR	NR
	0.5 mg/kg (N=5)	0.261 (0.127) 0.242 (41.7)	24.3 (23.7, 30.5)	1.90 (1.03) 1.75 (62.3)	1.96 (1.02) 1.82 (59.3)	3.80 (1.27) 3.69 (35.2)	NR	NR
	1 mg/kg (N=7)	0.506 (0.152) 0.487 (31.5)	23.3 (3.08, 24.1)	2.73 (0.835) 2.64 (28.8)	2.86 (0.918) 2.75 (30.2)	4.40 (1.01) 4.28 (27.8)	NR	NR
	2 mg/kg (N=6)	2.77 (4.38) 1.45 (141)	23.0 (4.98, 25.7)	12.6 (17.2) 7.80 (116)	12.9 (17.4) 8.07 (114)	4.22 (0.836) 4.16 (19.1)	NR	NR
	4 mg/kg (N=50)	1.79 (0.770) 1.66 (40.7)	7.17 (2.95, 49.0)	11.6 (4.04) 11.0 (34.1)	12.3 (4.51) 11.6 (35.1)	5.47 (0.817) 5.41 (15.0)	NR	NR
	6 mg/kg (N=50)	3.13 (2.23) 2.73 (51.8)	23.2 (3.05, 94.5)	19.2 (6.74) 18.0 (38.3)	20.6 (7.51) 19.3 (39.1)	5.50 (0.851) 5.44 (15.3)	NR	NR
	8 mg/kg (N=80)	3.62 (1.81) 3.27 (45.8)	23.6 (3.05, 98.7)	25.5 (11.9) 23.6 (39.0)	27.3 (9.62) 25.8 (34.8)	6.25 (1.29) 6.13 (20.9)	NR	NR
	10 mg/kg (N=8)	4.48 (2.66) 3.99 (50.8)	15.5 (4.92, 94.5)	32.6 (10.5) 31.2 (32.1)	33.8 (10.9) 32.5 (30.6)	6.82 (2.46) 6.48 (34.7)	NR	NR
DXd (Cycle 3)	0.27 mg/kg	NR	NR	NR	NR	NR	NR	NR
	0.5 mg/kg (N=5)	0.164 (NC) 0.164 (NC)	47.2 (47.2, 47.2)	NC	NR	NC	NR	NR
	1 mg/kg (N=7)	0.575 (0.176) 0.556 (29.9)	23.5 (22.2, 47.5)	3.70 (1.54) 3.46 (41.6)	NR	4.60 (0.983) 4.49 (25.7)	NR	NR
	2 mg/kg (N=6)	2.37 (2.81) 1.54 (128)	24.3 (23.1, 52.1)	13.1 (12.7) 9.78 (98.3)	NR	5.04 (1.15) 4.94 (23.0)	NR	NR
	4 mg/kg (N=50)	1.69 (0.686) 1.57 (39.7)	7.08 (2.95, 74.9)	12.4 (4.80) 11.7 (34.9)	NR	6.15 (1.01) 6.08 (15.4)	NR	NR
	6 mg/kg (N=50)	2.63 (0.918) 2.49 (34.8)	7.23 (4.83, 51.2)	19.2 (6.51) 18.1 (35.6)	NR	6.88 (1.55) 6.72 (22.6)	NR	NR
	8 mg/kg (N=80)	3.41 (1.49) 3.16 (40.2)	7.08 (2.83, 67.2)	25.9 (10.3) 24.4 (35.7)	NR	7.49 (1.90) 7.29 (23.5)	NR	NR
	10 mg/kg (N=8)	NC	NC	NC	NR	NC	NR	NR

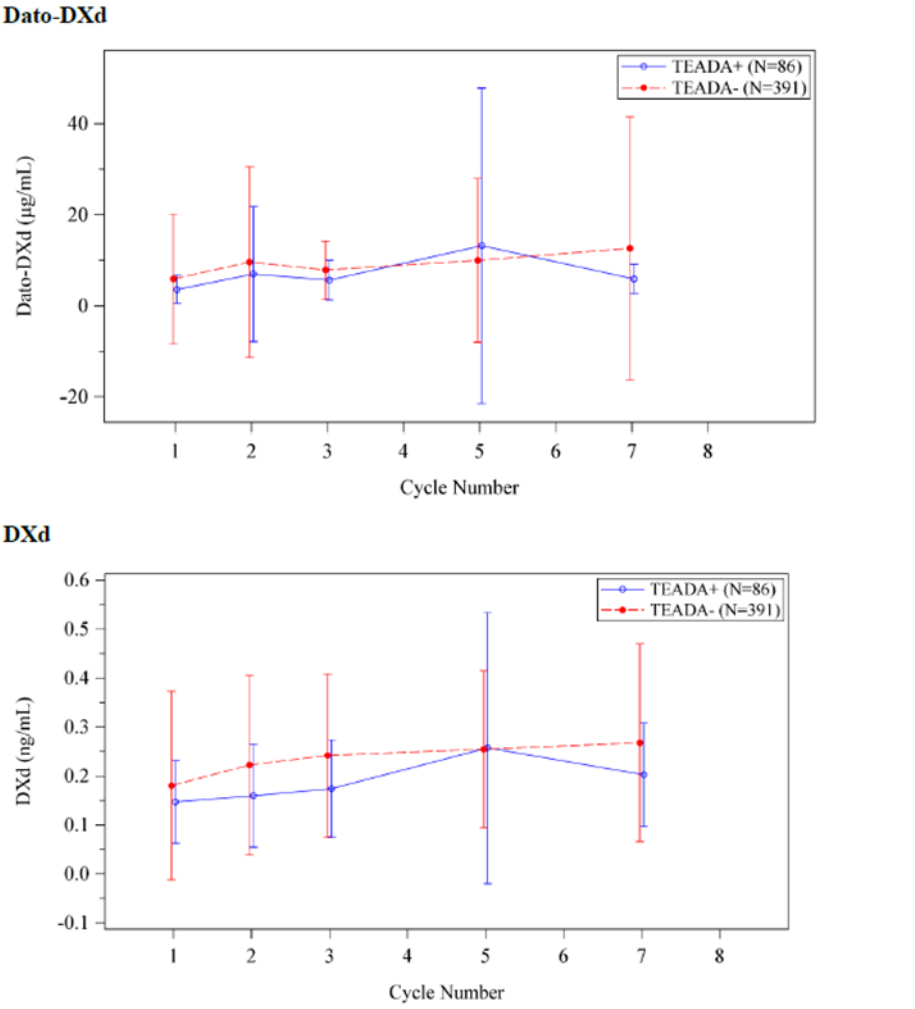
Impact of ADA's on PK of Dato-DXd and DXd

The impact of anti-Dato-DXd antibodies on the PK of Dato-DXd and DXd was assessed in subjects with NSCLC who received the 6 mg/kg dose. The analysis was performed using compiled data from all conducted studies TL01, TL05 and TP01. The effect of ADA was evaluated using both integrated PK analysis and population PK analysis.

The time-course of Dato-DXd and DXd trough concentrations among all subjects who received 6 mg/kg dose were similar between the TEADA-positive and TEADA-negative subgroups, see Figure 29.

In the population PK analysis ADA was not identified as a significant covariate on Dato-DXd or DXd clearance. The final population PK model predicted Dato-DXd and DXd exposure (Cmax and AUC in Cycle 3) were similar between TEADA-positive subjects and TEADA-negative subjects (difference <5%)

Figure 29 Dato-DXd and DXd Trough Concentration (±SD) by Treatment-emergent Anti-drug Antibody Status



N = total number of subjects in subgroup; NSCLC = non-small cell lung cancer; SD = standard deviation; TEADA+ = subjects with treatment-emergent anti-drug antibody; TEADA- = subjects without treatment-emergent anti-drug antibody; TL01 = TROPION-Lung01; TL05 = TROPION-Lung05; TP01 = TROPION-PanTumor01
Notes: Subjects in the immunogenicity analysis set who were in TL05, TL01, and TP01 NSCLC 6 mg/kg cohort are included in this figure. Data summarized for Cycle 1 only.
Plot shows mean ± SD.
Source: Dato-DXd ISI TFLs Figures 2.1.4.1 and 2.1.4.3

Intra- and inter-individual variability

Inter-individual variability of PK-parameters were determined in the phase-1 study TP01, in which intensive PK sampling in both Cycle 1 (D1) and Cycle 3 (D35) was performed in NSCLC subjects, see Table 25.

After single doses of 6 mg/kg Dato-DXd in patients with NSCLC, the inter-individual variability for Dato-DXd (geometric CV%) 20.4% for Cmax, 35.4% AUCtau, 27.4% for AUCinf, see Table 25. After multiple doses of 6 mg/kg Dato-DXd in participants with NSCLC, the inter-individual variability Dato-DXd (geometric CV%) at steady state was 25.3% for Cmax and 31.2% for AUCtau.Intra-individual variability has not been estimated.

Pharmacokinetic in target population

The pharmacokinetics of Dato-DXd and its components has only been established in the target populations i.e. breast cancer (BC) and non-small cell lung cancer (NSCLC). The effect of cancer type (BC vs NSCLC) on the PK of Dato-DXd was evaluated in an integrated PK analysis and in the PopPK analysis. In the integrated PK analysis, the geometric mean ratio for Dato-DXd and DXd Cycle 1 PK parameters (Cmax, AUCtau, and AUCinf) of BC vs NSCLC ranged from 0.99 to 1.25.

In the Pop-PK analysis, tumour type was included as a categorical covariate. The Pop-PK dataset included 643 NSCLC patients and 85 BC patients. In BC patients, the Cmax and the AUC3 (steady-state) of Dato-DXd was 12% and 18% higher, respectively, compared to NSCLC patients. Furthermore, in BC patients, the Cmax and the AUC3 (steady-state) of DXd was 4% and 7% higher, respectively, compared to NSCLC patients.

Overall, in the NCA analysis and in the Pop-PK analysis no clinically meaningful difference in Dato-DXd and DXd PK between lung cancer and breast cancer was observed.

Therapeutic window

In the Study TP01 a dose range of 0.27 to 10 mg/kg Q3W Dato-DXd was investigated in subjects with NSCLC. The clinical efficacy results in TP01 showed that antitumor activity was observed at a dose as low as 2 mg/kg Q3W, corresponding to a Dato-Dxd exposure, AUC3, of 3.76 mg*h/m. In the TP01 study, the MTD of Dato-DXd was determined to be 8 mg/kg Q3W, corresponding to a Dato-Dxd exposure, AUC3, of 23.9 mg*h/mL.

Special populations

Impaired renal function

No dedicated renal impairment (RI) study was conducted for Dato-DXd. The impact of renal impairment was evaluated in the Pop-PK model, in which creatinine clearance, CRCL (ml/min), determined by the Cockroft-Gault formula, was incorporated as a covariate and a measure of renal function, see figure 40 and 48. The Pop-PK dataset included 300 patients with mild RI, 137 with moderate RI, 2 patients with severe RI and 290 patients with normal renal function.

Mild RI (baseline CrCL $\geq$ 60 & baseline CrCL < 90) and moderate RI (baseline CrCL $\geq$ 30 & baseline CrCL < 60) did not influence the steady state exposure, AUC3 (cycle 3), of Dato-DXd and DXd in a clinically meaningful way, as AUC3 within 80-125% criteria of AUC3 in patients with normal renal function. The impact of severe renal impairment has not been fully evaluated due to the limited number of patients. The scatterplot of exposure versus CRCL shows the lack of significant relationship of Dato DXd and DXd exposure and renal functions, see Figure 30 and **Figure 31**. The recommended dosage of Dato-DXd has not been established in patients with severe renal impairment.

Figure 30 Individual Dato-DXd exposure metrics Cmax3 and AUC3, after 6.0 mg/kg Dato-DXd IV infusion Q3W, versus CRCL capped at 150 mL/min, colored by renal function. The blue line is a smooth associated with the 90% CI (grey area).

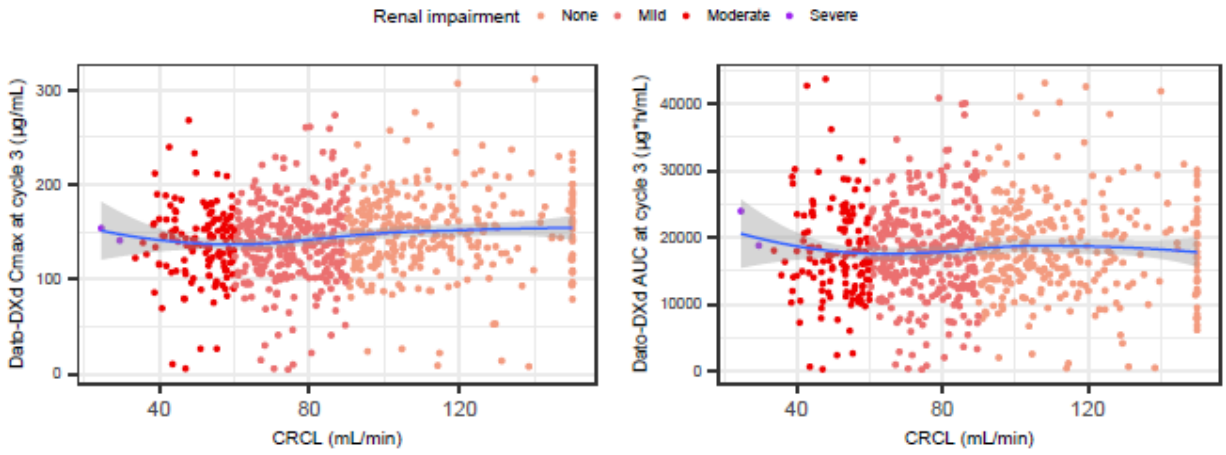
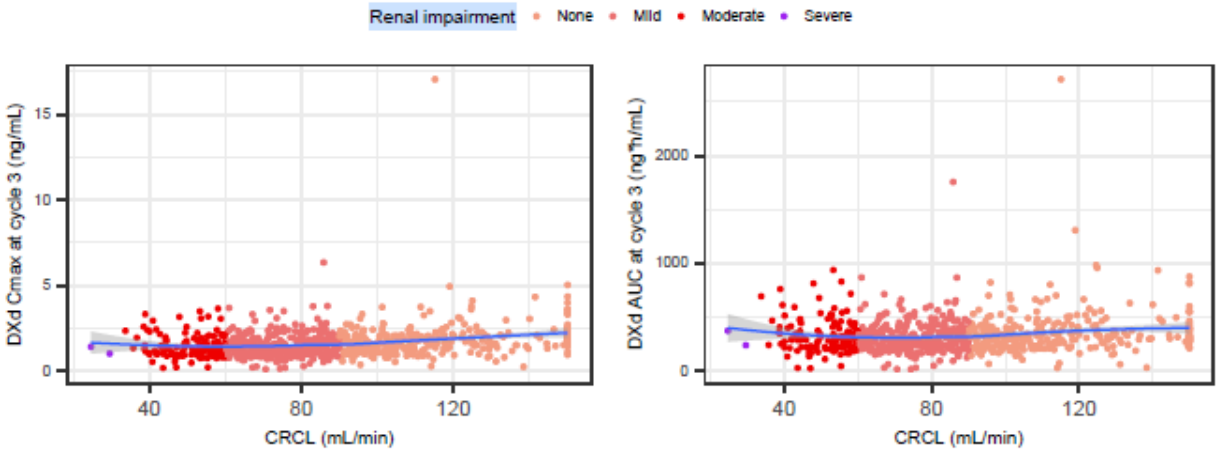


Figure 31 Individual DXd exposure metrics Cmax3 and AUC3, after 6.0 mg/kg Dato-DXd IV infusion Q3W, versus CRCL capped at 150 mL/min, colored by renal function. The blue line is a smooth associated with the 90% CI (grey area).



Impaired hepatic function

No dedicated hepatic impairment (HI) study was conducted for Dato-DXd. The impact of HI on Dato-DXd and DXd PK was evaluated in the Pop-PK analysis, in which HI status was determined using the NCI-ODWG criteria from total bilirubin and alanine aminotransferase (AST) baseline values. The Pop-PK dataset included 129 patients with mild HI (total bilirubin ≤ ULN and any AST > ULN or total bilirubin >1 to 1.5 times ULN and any AST), 1 subject with moderate HI (total bilirubin >1.5 to 3 times ULN and any AST), no subject with severe HI (total bilirubin >3 times ULN and any AST) and 599 patients with normal function.

No clinically meaningful differences in the steady-state exposure, AUC3, of Dato-DXd and DXd in patients with mild HI compared to patients with normal liver function, as the ratio of Dato-DXd AUC3 between these 2 subgroups was 1.03, and the ratio of DXd AUC3 was 1.00, see **Figure 32** and **Figure 33**.

For patients with moderate hepatic impairment, there are limited data to draw conclusions on the impact of moderate hepatic impairment on DXd PK (N=1). Dato-DXd has not been studied in patients with severe hepatic impairment.

Figure 32 Boxplots showing Dato-DXd exposure metrics Cmax3 and AUC3, after 6.0 mg/kg Dato-DXd IV infusion Q3W, versus hepatic function and overlaid by the individual Dato-DXd Cmax3 and AUC3 values.

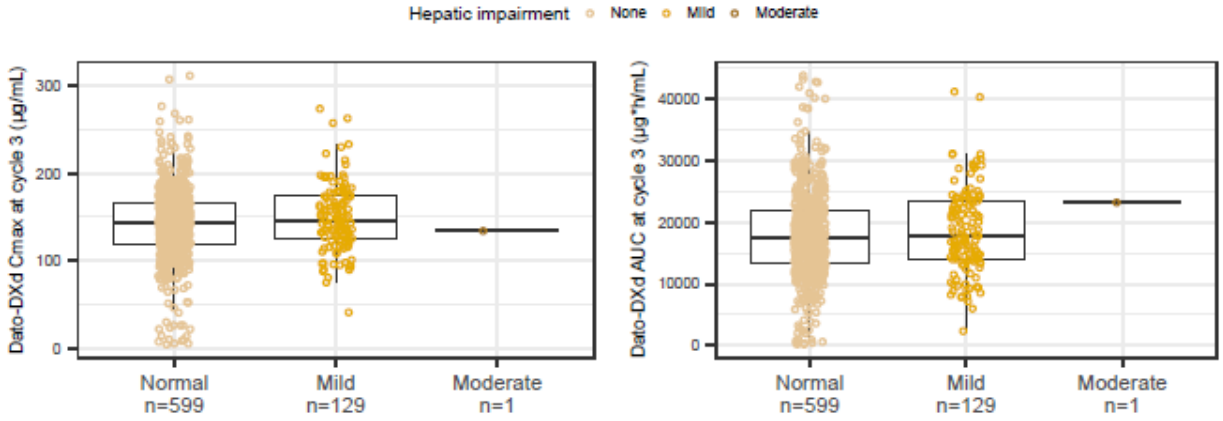
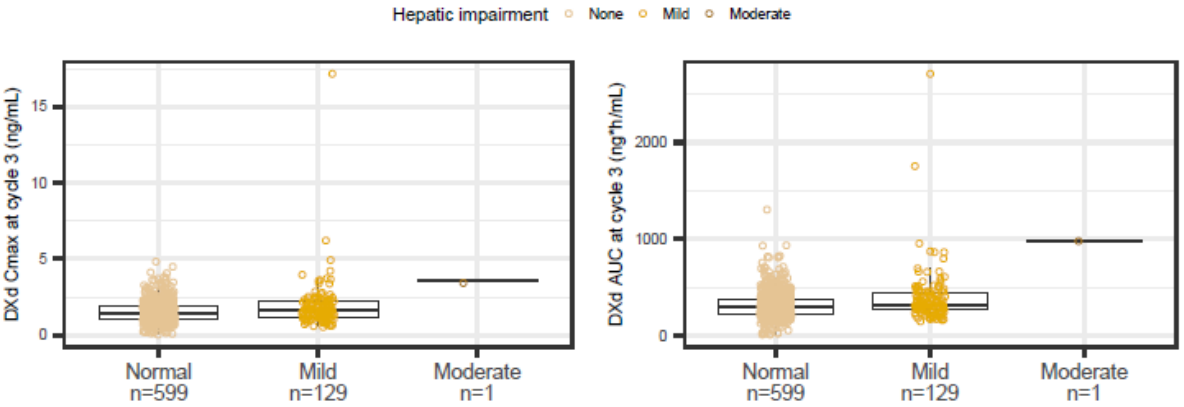


Figure 33 Boxplots showing DXd exposure metrics Cmax3 and AUC3, after 6.0 mg/kg Dato-DXd IV infusion Q3W, versus hepatic function and overlaid by the individual DXd Cmax3 and AUC3 values.



Gender

The effect of gender was evaluated using NCA analysis of cycle 1 PK-data from the three conducted clinical studies (TP01 (NSCLC and BC), TL05 (NSCLC) and TL01 (NSCLC). The exposure, AUCtau, AUCinf and Cmax, of Dato-DXd and DXd, was not impacted by gender in a clinically meaningful manner i.e. GMR of Cmax, AUCtau, AUCinf within 80-125% criteria. The effect of gender on the PK of Dato-DXd and DXd was also evaluated in the Pop-PK model, including data from 379 female (52%) and 350 male (48%) in the model. Sex was determined to have a significant effect on the CLlin and Vc of Dato-DXd and Vc of DXd. The CLlin of Dato DXd in females was estimated to be 26.3% lower than in males. The Vc of Dato-DXd in female was estimated to be 15.9% lower and Vc of DXd in females was 18.8% lower than in males. The statistical significance of sex on PK parameters did not translate to a clinically meaningful effect on the AUCss of Dato-DXd as the AUCss of Dato-DXd was 15% higher in females versus males. The AUCss of DXd in females was 7.6% lower compared to males. No dose adjustment is deemed necessary based on gender.

Ethnic factors

The impact of race on the PK of Dato-DXd and DXd was evaluated in the population PK analysis. The population data set included: Am. Indian/Alaska 1 (0.14%); Asian 293 (40%); Black/Af. American 16 (2.2%); Hawaiian/Pac. Islander 1 (0.14%); White 334 (46%); Other 76 (10%); (Missing) 8 (1.1%). The AUC3 of Dato-DXd in Asian subjects was 0.96-fold when compared to the AUC3 in White subjects, and in Black subjects was 1.04-fold when compared to the AUC3 in White subjects. The AUC3 of DXd in Asian subjects was 0.92-fold when compared to the AUC3 in White subjects. The AUC3 in Black subjects was 1.25-fold when compared to the AUC3 in White subjects. Overall, race had no clinically relevant effects (ratio within 0.8-1.25) on the steady state exposure of Dato-DXd and DXd.

The impact of country/region (Japan, US, Europe, and rest of the world (RoW) was also evaluated as a covariate in the integrated PK analysis and population PK analysis. The population data set included: 162 from japan, 289 from US, 167 from Europe, and 106 from RoW. The estimated steady state exposure of Dato-DXd, AUC3, in subjects from Europe was 9.1% lower in subjects from Europe, compared to a subject from the US. The steady state exposure of DXd, AUC3, was 20.4% lower in subjects from Europe, compared to a subject from the US. Overall, country/region had no clinically relevant effects (ratio within 0.8-1.25) on the steady state exposure of Dato-DXd and DXd. No dose adjustment is deemed necessary based on race or region/country.

Body weight

The impact of body weight (BW) on the PK of Dato-DXd and DXd was investigated in the Pop-PK model. In the Pop-PK set, the BW was distributed from 37 kg to 156 kg, with a mean (SD) BW of 68.3 (16.3) kg. The population PK analysis showed that body weight was a statistically significant covariate affecting both the clearance and the volume of distribution for Dato-DXd and DXd, with an increase of clearance and volume of distribution with increasing body weight. Among all covariates, body weight exhibited the largest effect on the PK of both Dato-DXd and DXd. The 5th and 95th percentile of body weight (46 and 98 kg, respectively) had a 24.4% lower and 28% higher predicted Dato-DXd AUCss (Cycle 3) compared to the reference patient (female, enrolled in USA, and with median body weight of 64.2 kg) at the same cycle, see **Figure 34**. The 5th and 95th percentile of body weight (46 and 98 kg, respectively) had a 22.2% lower and 32% higher predicted DXd AUCss (Cycle 3) compared to the reference patient (female, enrolled in USA, and with median body weight of 64.2 kg) at the same cycle, see **Figure 35**.

Figure 34 Forest plots illustrating the effects of covariates on Dato-DXd AUC3, conditioned on a typical reference subject, based on the final Dato-DXd model. Reference: Male, 62 years, 66 kg, not Japanese, albumin 38 g/L and with a tumor size of 66 mm.

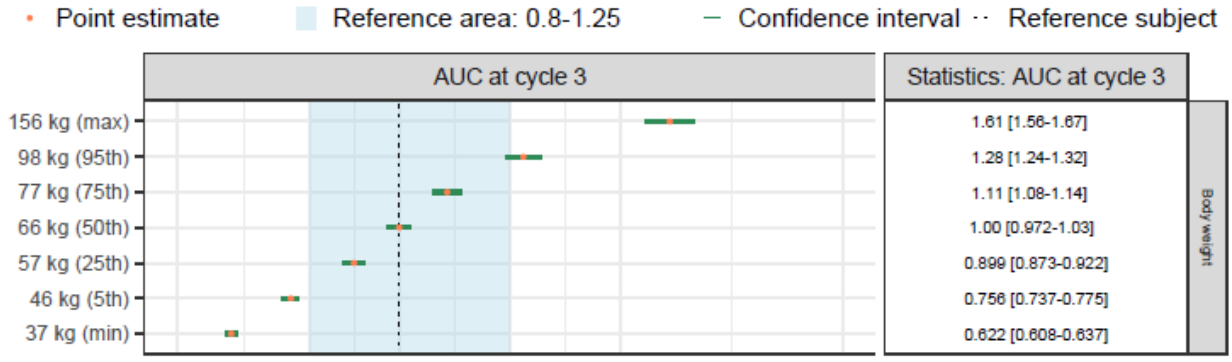
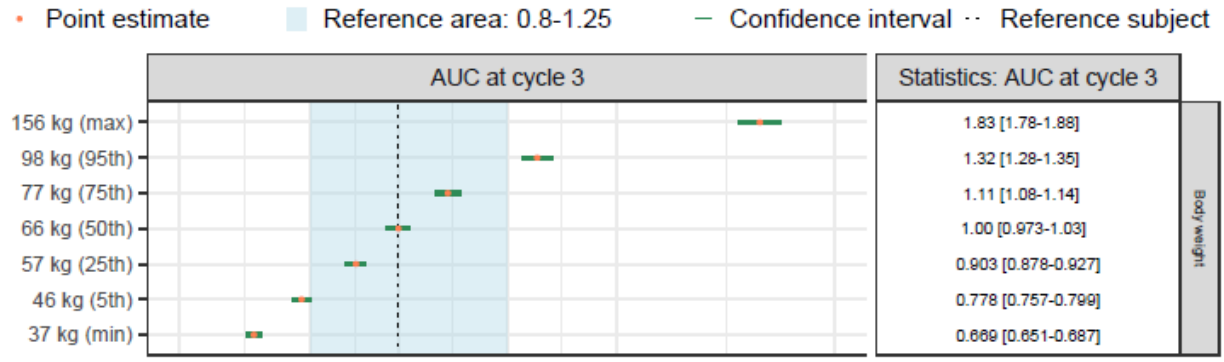


Figure 35 Forest plots illustrating the effects of covariates on DXd parameter AUC3, conditioned on a typical reference subject, based on the final DXd model. Reference: US Male, 66 kg, albumin 38 g/L, AST 22 g/L and total bilirubin 0.4 mg/dL.



Elderly

The effect of age on the PK of Dato-DXd and DXd was assessed across the range of 26 to 84 years in the clinical studies (**Table 26**) and in the population PK analysis. Age was identified as a significant covariate for clearance of Dato DXd. However, age had no clinically meaningful effect on Dato-DXd exposure. At the 5th percentile (41 years), AUC3, decreased by 9.4% and at the 95th percentile (76 years), AUC3 increased by 5% compared to AUC3 at the median age (62 years). The effect of age on DXd exposure was also not clinically meaningful. Compared with AUC3 in subjects between 65 and 75 years, AUC3 in subjects age ≥75 years increased by 4% and AUC3 in subjects < 65 years increased by 4%. Overall, age had no clinically meaningful effect and no dose adjustment based on age is required.

Table 26: Age ranges studied in the elderly population (to be provided by the MAA)

PK study	Age 65 to 74 years (Older subjects number /total number)	Age 75 to 84 years (Older subjects number /total number)	Age 85+ years (Older subjects number /total number)
TP01	77/295	26/295	0/295
TL05	32/137	14/137	0/137
TL01	114/297	21/297	0/297

Pharmacokinetic interaction studies

DDI of the antibody part of Dato-DXd is not expected. DDI of the released payload, as a small molecule, is a possibility. The potential of drug-drug interactions involving the small-molecule payload deruxtecan (DXd) was investigated using in vitro, in silico studies (PBPK) and by leveraging clinical DDI data of the approved DXd ADC trastuzumab deruxtecan (Enhertu). The in vitro DDI studies of DXd have been previously been submitted and assessed as part of the trastuzumab deruxtecan. A brief summary of the in vitro results is provided here.

In vitro

DXd victim DDI

It was shown that DXd was a substrate of CYP3A, see under metabolism. Additionally, it was investigated if DXd was a substrate for the drug transporters, BSEP OAT1, OAT3, OCT1, OCT2,

OATP1B1, OATP1B3, MATE1, MATE2-K, P-gp, BCRP, using different in vitro systems. Overall, based on in vitro human biomaterial studies, DXd is shown to be a substrate for CYP3A4 and the transporters P-gp, MATE2-K, OATP1B1, OATP1B3, BCRP, and MRP1. These data indicated that the hepatic uptake of DXd could be mediated by OATP (1B1 and 1B3) and that P-gp and BCRP could influence the efflux of DXd.

DXd perpetrator DDI

The perpetrator potential of DXd was evaluated in vitro for CYP450 inhibition, CYP induction and Drug transporter inhibition using human liver microsomes, human hepatocytes and different transporter in vitro models, respectively. Based on in vitro data, DXd is not a reversible or time-dependent inhibitor of CYP isoforms and did not show induction potential on messenger ribonucleic acid (mRNA) expression or metabolic activity of CYP isoforms.

In human biomaterial studies of transporters, DXd inhibited organic anion transporter (OAT) 1 and OATP1B1 with 50% inhibitory concentration (IC50) values of 12.7 and 14.4 µmol/L, respectively. No clinically meaningful DDIs are expected with drugs that are substrates of OAT1 or OATP1B1 transporters as IC50 was far over the cut-off value, see **Table 30**.

Table 27: Cut-offs for the evaluation of interaction potential

	50 x Cmax(u)[a] (µM)	25 x Inlet Cmax(u)[a] (µM)	0.1 x dose/250 ml[b] (µM)
DXd	0.0085	NA	NA

a Multiple dose Cmax, 6 mg/kg dose (study TP01)

b Based on a xxx mg dose

NA - Not applicable

Table 28: Summary of in vitro enzyme inhibition (Report AE.7766-G)

Enzyme	Substrate	Competitive inhibition	TDI		Positive signal to evaluate further
		IC50 (µM) no pre-inc./pre-inc.	KI (µM)	Kinact (min-1)	Yes/No
CYP1A2	Phenacetin	> 50 / > 50	-	-	No
CYP2B6	Bupropion hydrochloride	> 50 / > 50	-	-	No
CYP2C8	Amodiaquine dihydrochloride dihydrate	> 50 / > 50	-	-	No
CYP2C9	Diclofenac sodium salt	> 50 / > 50	-	-	No

CYP2C19	*S*-(+)-Mephenytoin	> 50 / > 50	-	-	No
CYP2D6	Testosterone	> 50 / > 50	-	-	No
CYP3A4	Midazolam	> 50 / > 50	-	-	No

Table 29: Summary of in vitro enzyme induction (Report TCRM-DMPK-2020-19)

	Fold induction mRNA											
DXd Conc.	CYP1A2				CYP2B6				CYP3A4			
µM	Lot A	Lot B	Lot C	Lot D	Lot A	Lot B	Lot C	Lot D	Lot A	Lot B	Lot C	Lot D
0.01	0.6	0.9	1.0	1.1	1.0	1.0	0.7	0.9	1.4	1.7	1.3	1.0
0.03	0.6	0.9	0.9	1.1	0.7	0.9	0.8	1.0	1.3	0.6	1.3	0.9
0.1	0.6	0.9	0.9	1.0	0.8	0.8	0.8	1.1	1.5	0.4	1.2	0.8
0.3	0.5	1.0	1.0	1.0	0.8	0.8	0.7	1.2	1.7	1.2	1.3	0.9
1	0.8	0.9	1.2	1.0	0.8	0.8	0.8	1.0	1.1	0.3	1.3	0.8
3	0.6	0.8	1.1	0.9	0.7	0.7	0.8	1.0	0.7	0.2	1.0	0.7
10	0.7	0.9	1.1	1.0	1.0	0.5	0.7	0.9	0.3	0.1	0.7	0.5
30	0.8	0.9	1.1	1.2	0.6	0.3	0.5	0.4	0.1	1.1	0.4	0.3

Table 30: In vitro transporter inhibition (Report GE-1506-G)

Transporter	Substrate	In vitro system	IC50 (µM)	Positive signal (Y/N)
P-gp	Digoxin	Caco-2 Cells	> 30	N
BCRP	Estrone Sulfate	Caco-2 Cells	> 30	N
OATP1B1	Estradiol 17β-D-Glucuronide	Transporter Expressing HEK293 Cells	14.4	N
OATP1B3	Estradiol 17β-D-Glucuronide	Transporter Expressing HEK293 Cells	> 30	N
OAT1	Aminohippuric Acid	Transporter Expressing S2 Cells	12.7	N
OAT3	Estrone Sulfate	Transporter Expressing S2 Cells	> 30	N
OCT2	Metformin	Transporter Expressing HEK293 Cells	> 30	N

OCT1	Metformin	Transporter Expressing HEK293 Cells	> 30	N
MATE1	Metformin	Transporter Expressing HEK293 Cells	> 30	N
MATE2	Metformin	Transporter Expressing HEK293 Cells	> 30	N
BSEP	Taurocholic Acid	Transporter Expressing Vesicles	> 30	N

In Silico

A PBPK model was developed to evaluate the effect of inhibitors of OATP1B and CYP3A, ritonavir, and CYP3A, itraconazole, on the exposures of DXd when they were co-administered with Dato-DXd. The PBPK model predicted when dosed with ritonavir and itraconazole, Dato-DXd at the proposed dose of 6 mg/kg would have the similar size of DDI of DXd as T-DXd at 5.4 mg/kg dosed with ritonavir and itraconazole, see Table 31. The DDI caused by a strong CYP3A inhibitor or an OATP1B/CYP3A inhibitor on DXd PK is therefore by PBPK modelling not expected to be clinically meaningful.

Table 31 Summary of predicted and observed DXd AUC and Cmax GMRs by various models presented in the report

Model	Population	Inhibitor	Predicted AUC GMR	Observed AUC GMR	Predicted C_{max} GMR	Observed C_{max} GMR
T-DXd SM	Japanese	Itraconazole	1.21	1.18	1.20	1.04
T-DXd SM	Cancer	Itraconazole	1.22	1.18	1.21	1.04
T-DXd SM	Japanese	Ritonavir	1.24	1.22	1.24	0.987
T-DXd SM	Cancer	Ritonavir	1.34	1.22	1.34	0.987
T-DXd LM, F_{rel} = 1	Japanese	Itraconazole	1.20	1.18	1.19	1.04
T-DXd LM, F_{rel} = 0.5	Japanese	Itraconazole	1.20	1.18	1.19	1.04
T-DXd LM, F_{rel} = 0.5	Cancer	Itraconazole	1.20	1.18	1.19	1.04
T-DXd LM, F_{rel} = 1	Japanese	Ritonavir	1.24	1.22	1.24	0.987
T-DXd LM, F_{rel} = 0.5	Japanese	Ritonavir	1.24	1.22	1.24	0.987
T-DXd LM, F_{rel} = 0.5	Cancer	Ritonavir	1.32	1.22	1.33	0.987
Dato-DXd SM	Japanese	Itraconazole	1.22	NA	1.21	NA
Dato-DXd SM	Cancer	Itraconazole	1.21	NA	1.20	NA
Dato-DXd SM	Japanese	Ritonavir	1.25	NA	1.25	NA
Dato-DXd SM	Cancer	Ritonavir	1.33	NA	1.32	NA
Dato-DXd LM, F_{rel} = 1.0, immediate	Japanese	Itraconazole	1.20	NA	1.18	NA
Dato-DXd LM, F_{rel} = 0.4, immediate	Japanese	Itraconazole	1.20	NA	1.18	NA
Dato-DXd LM, F_{rel} = 0.4, delayed#	Japanese	Itraconazole	1.20	NA	1.20	NA
Dato-DXd LM, F_{rel} = 0.4, delayed#	Cancer	Itraconazole	1.21	NA	1.21	NA
Dato-DXd LM, F_{rel} = 1.0, immediate	Japanese	Ritonavir	1.24	NA	1.21	NA
Dato-DXd LM, F_{rel} = 0.4, immediate	Japanese	Ritonavir	1.24	NA	1.21	NA
Dato-DXd LM, F_{rel} = 0.4, delayed#	Japanese	Ritonavir	1.24	NA	1.26	NA
Dato-DXd LM, F_{rel} = 0.4, delayed#	Cancer	Ritonavir	1.32	NA	1.34	NA

 # Release of DXd adjusted by a rate constant; SM: small molecule model; LM: mechanistic minimal ADC model; F_{rel}: fraction of DXd released; GMR: Geometric Mean Ratio

In vivo

The conducted DDI study, DS8201-A-A104, of the previously approved deruxtecan ADC, trastuzumab deruxtecan (T-DXd, Enhertu) was resubmitted for Datopotamab deruxtecan Daiichi Sankyo. For T-DXd the systemic exposure of the payload DXd was higher than for Dato-DXdy, ~1.6-fold AUC and ~3.4-fold Cmax, respectively. The victim DDI for DXd of the two ADCs are expected to be comparable. In the Enhertu DDI study it was found that the exposure of DXd was not impacted in a clinically meaningful way by co-administration with either itraconazole, a strong CYP3A inhibitor, or with ritonavir, a CYP3A and OATP1B1 inhibitor, see Table 32. On basis of the trastuzumab deruxtecan DDI

study results, it is highly likely that there are no clinically relevant DDI of Dato-DXd (DXd) with OATP1B1 and CYP3A perpetrators.

Table 32 Drug-drug interactions: effect of ritonavir (200 mb BID) and itraconazole (200 mg BID) on the pharmacokinetics of trastuzumab deruxtecan and MAAA-1181a (DXd) following trastuzumab deruxtecan 5.4 mg/kg Q3W dosing (study DS8201-A-A104, Mean ±SD, median (r

Analyte	PK Parameter (Units)	Trastuzumab Deruxtecan + Inhibitor LSM	Trastuzumab Deruxtecan Alone LSM	Ratio (Test/ Reference)	90% CI
Cohort 1 (ritonavir in Cycle 3; Cycle 2 n = 12, Cycle 3 n = 8)					
Trastuzumab deruxtecan	Cmax (µg/mL)	138	131	1.0490	0.9755, 1.1281
	AUC17d (µg·d/mL)	742	623	1.1921	1.1404, 1.2461
MAAA-1181a	Cmax (ng/mL)	8.38	8.49	0.9865	0.8539, 1.1397
	AUC17d (ng·d/mL)	36.6	30.2	1.2151	1.0780, 1.3696
Cohort 2 (itraconazole in Cycle 3; Cycles 2 and 3 n = 14)					
Trastuzumab deruxtecan	Cmax (µg/mL)	140	137	1.0252	0.9631, 1.0913
	AUC17d (µg·d/mL)	685	617	1.1095	1.0732, 1.1470
MAAA-1181a	Cmax (ng/mL)	8.78	8.43	1.0418	0.9167, 1.1839
	AUC17d (ng·d/mL)	33.9	28.8	1.1778	1.1081, 1.2519

ANOVA = analysis of variance; AUC17d = area under the concentration-time curve from time zero to Day 17; CI = confidence interval; Cmax = maximum observed serum concentration; d = day; LSM = least squares mean; n = number of subjects assessed; PK = pharmacokinetic. Source: DS8201-A-A104 CSR, Table 14.4.3.1, Table 14.4.3.2, Table 14.4.3.3, and Table 14.4.3.4.

Justification provided regarding potential clinical DDI of MATE2-K, BCRP and P-gp for DXd

The efflux transporter MATE2-K is primarily expressed in the kidney and, given the relatively moderate renal elimination of DXd (approximately 15% based on nonclinical absorption distribution metabolism excretion data, the effect of MATE2-K inhibitors would be expected to be minimal. BCRP and P-gp DDIs are more driven through intestinal inhibition and Dato-DXd is giving IV so inhibitors of these transporters are unlikely to have any effect on DXd exposure.

Exposure relevant for safety evaluation

The no-observed-adverse-effect level (NOAEL) of each target organ of toxicity in rats and monkeys was compared at the optimal dose of 6 mg/kg (multiple doses [Cycle 3]) in subjects with NSCLC (Study TP01), see Table 25 under time dependencies.

PK in pivotal phase III clinical study TROPION-LUNG01 (TLO1)

Pharmacokinetic analyses were performed using the PK Analysis Set of 297 patients. Of these 297 patients, 20 patients had full PK sampling performed in cycle 1, whereas others had sparse PK sampling scheme in this study, see tabulated summary of plasma concentrations of Dato-DXd and DXd by visits/timepoints in Table 33 and Table 34.

Table 33 Summary of Plasma Concentrations of Dato-DXd (µg/mL) Pharmacokinetic Analysis Set in the phase 3 study TL01.

	C1D1					C1D2	C1D4	C1D8	C1D15
	BI	EOI	3 h	5 h	7 h	24 h			
Summary Statistics									
n	285	260	17	15	231	16	17	219	12
Number below % BLQ	282	1	0	0	0	0	0	1	0
Mean	0.650	143	132	127	139	96.3	58.5	30.6	7.77
Standard Deviation	9.28	52.0	32.2	34.0	31.1	23.1	17.1	10.8	3.95
CV%	1428.4	36.3	24.4	26.8	22.3	24.0	29.3	35.3	50.8
Geometric Mean	NC	NC	128.6	123.0	135.7	93.8	56.4	NC	6.8
Geometric CV%	NC	NC	21.5	24.8	23.5	23.7	28.3	NC	63.3
Minimum	0.00	0.00	92.7	85.1	55.9	66.1	37.6	0.00	2.48
Median	0.00	139	128	122	136	93.2	53.3	29.7	7.68
Maximum	155	770	233	213	236	149	100	81.8	14.3

	C2D1		C3D1		C4D1		C6D1		C8D1	
	BI	EOI	BI	EOI	BI	EOI	BI	EOI	BI	EOI
Summary Statistics										
n	243	224	179	14	200	182	149	133	109	95
Number below % BLQ	1	1	5	0	3	0	2	0	0	0
Mean	5.16	136	8.38	115	6.49	137	10.9	134	11.4	138
Standard Deviation	11.1	39.7	19.2	29.0	4.67	39.7	26.2	41.1	30.7	55.8
CV%	215.9	29.1	228.8	25.3	71.9	29.1	239.6	30.8	269.0	40.6
Geometric Mean	NC	NC	NC	111.3	NC	126.8	NC	122.6	5.5	123.5
Geometric CV%	NC	NC	NC	25.7	NC	53.0	NC	58.1	124.3	66.3
Minimum	0.00	0.00	0.00	73.4	0.00	5.05	0.00	3.55	0.644	1.87
Median	3.93	136	5.56	106	5.50	140	6.14	134	5.48	127
Maximum	136	245	174	162	26.3	237	197	248	219	446

CV = Coefficient of Variation, CxDy = Cycle x Day y, BI = Before infusion, EOI = End of infusion, NC = Not calculated.
Concentrations below the lower limit of quantitation (BLQ) are set to zero for the calculation of descriptive statistics. If at least one concentration at a timepoint is BLQ then the geometric mean and geometric CV at that time point are not calculated and are presented as NC.

Table 34 Summary of Plasma Concentrations of DXd (ng/mL) Pharmacokinetic Analysis Set in the phase 3 study TL01

	C1D1					C1D2	C1D4	C1D8	C1D15
	BI	EOI	3 h	5 h	7 h	24 h			
Summary Statistics									
n	279	259	17	15	228	15	17	219	12
Number below % BLQ	276	1	0	0	0	0	0	0	0
Mean	0.00442	1.26	1.96	2.44	2.24	2.30	1.71	0.952	0.279
Standard Deviation	0.0707	0.784	0.813	1.01	1.06	0.868	0.793	0.579	0.102
CV%	1597.2	62.1	41.4	41.4	47.2	37.8	46.5	60.8	36.5
Geometric Mean	NC	NC	1.8	2.3	2.1	2.2	1.6	0.8	0.3
Geometric CV%	NC	NC	44.6	42.3	44.0	35.6	44.3	56.2	36.7
Minimum	0.00	0.00	0.779	1.13	0.352	1.36	0.843	0.0272	0.141
Median	0.00	1.09	1.58	2.09	2.05	2.13	1.40	0.862	0.248
Maximum	1.18	8.13	3.61	4.60	10.6	4.27	3.59	6.30	0.481

	C2D1		C3D1		C4D1		C6D1		C8D1	
	BI	EOI	BI	EOI	BI	EOI	BI	EOI	BI	EOI
Summary Statistics										
n	241	223	177	14	199	182	148	132	108	95
Number below % BLQ	0	0	3	0	1	0	2	0	0	0
Mean	0.157	0.743	0.196	1.35	0.213	0.810	0.230	0.745	0.223	0.695
Standard Deviation	0.105	0.423	0.172	1.61	0.172	0.525	0.223	0.436	0.205	0.357
CV%	66.9	56.9	87.5	119.2	80.5	64.9	97.2	58.5	92.1	51.3
Geometric Mean	0.1	0.6	NC	0.8	NC	0.7	NC	0.6	0.2	0.6
Geometric CV%	62.7	66.2	NC	119.6	NC	71.7	NC	61.6	69.5	56.0
Minimum	0.0115	0.0298	0.00	0.275	0.00	0.0775	0.00	0.121	0.0266	0.142
Median	0.133	0.672	0.166	0.806	0.187	0.693	0.184	0.619	0.186	0.629
Maximum	1.18	2.65	1.58	5.63	1.60	3.83	1.67	2.33	1.71	1.79

3.3.1.2. Pharmacodynamics

Mechanism of action

Datopotamab deruxtecan (Dato-DXd, DS-1062a) is an antibody-drug conjugate (ADC). Dato-DXd is a TROP2-targeted antibody and DNA topoisomerase I inhibitor conjugate. The anti-TROP2 component is a humanised IgG1κ monoclonal antibody. The total anti-TROP2 antibody is the sum of all DXd-

conjugated and unconjugated mAb. The payload, DXd, is a DNA topoisomerase I inhibitor derivative of exatecan. The mAb is covalently conjugated to a drug-linker, MAAA-1162a, which is composed of a cleavable maleimide tetrapeptide linker and the payload (DXd). The tetrapeptide linker is designed to be stable in plasma to reduce systemic exposure of the payload. Dato-DXd binds to TROP2, and, after cell internalisation, the payload is released from the drug-linker through enzymatic processing. The released drug inhibits topoisomerase I, which leads to the inhibition of cell replication and promotes apoptosis of the target tumour cells. The released drug is cell membrane-permeable, giving it the ability to penetrate and act in surrounding cancer cells. The average drug-to-antibody ratio of Dato-DXd is 4.

Primary and Secondary pharmacology

No specific PD endpoints or biomarkers were defined and reported.

QTc prolonging effect

The relationship between concentration of Dato-DXd or DXd and change from baseline in QT (ΔQTc) was evaluated in Study TP01 using linear mixed effect modelling. The final models were used to predict means and 90% Cis for ΔQT at the highest observed geometric mean Cmax values across Cycles 1 and 3, for all subjects with valid data at the 6 mg/kg and 8 mg/kg doses. Some subjects were excluded from the Cmax calculation due to dose changes and other reasons, leaving 50 subjects at 6 mg/kg for both Dato-DXd and DXd, and at 8 mg/kg, 74 subjects for Dato-DXd and 76 subjects for DXd.

The dataset contained 2205 ECG assessments with timematched Dato-DXd concentrations (2203 assessments with DXd) from 195 subjects with NSCLC in Dato-DXd dose levels ranging from 0.27 to 10.0 mg/kg. The slopes of ΔQTc (ΔQTc with Fridericia correction as primary analysis [ΔQTcF]; QTc with Population-derived correction [ΔQTcP] as secondary analysis) vs concentration (of Dato-DXd or DXd) were estimated to be near zero at the α = 0.01 (Table 35).

Table 35 Predictions of Mean (90% CI) ΔQTc at the Geometric Means of Cmax Observed at 6 and 8 mg/kg

Model (Analyte, Endpoint)	Cmax at 6 mg/kg	Predicted ΔQTc (ms)		Cmax at 8 mg/kg	Predicted ΔQTc (ms)	
		Mean	90% CI		Mean	90% CI
Dato-DXd, ΔQTcF	153 µg/mL	0.639	(−0.469, 1.75)	201 µg/mL	0.858	(−0.468, 2.18)
DXd, ΔQTcF	2.93 ng/mL	−0.130	(−1.37, 1.11)	3.51 ng/mL	−0.293	(−1.71, 1.12)
Dato-DXd, ΔQTcP	153 µg/mL	0.896	(−0.199, 1.99)	201 µg/mL	1.28	(−0.0300, 2.59)
DXd, ΔQTcP	2.93 ng/mL	0.720	(−0.538, 1.98)	3.51 ng/mL	0.854	(−0.588, 2.30)

CI = confidence interval; Cmax = maximum observed plasma concentration; ΔQTc = change from baseline in QTc.
Source: Module 5.3.4.2 Report DS1062-PMx007 Table A

Immunogenicity

Impact on efficacy

The impact of immunogenicity on efficacy was assessed in the pooled population of TL01 and TL05 who contributed to at least 1 valid ADA result (the "efficacy" pool). There were 427 subjects that were

included in the efficacy evaluation by ADA status, including 360 subjects in the non-squamous population and 67 in the squamous population.

The comparison of efficacy endpoints, including ORR, disease control rate, DoR, time to response, PFS, and OS by histology and ADA status is shown in Table 36.

Table 36 Efficacy Summary by Treatment-emergent Anti-drug Antibody Status

	Non-squamous		Squamous		Overall Population	
	TEADA+ (N = 69)	TEADA- (N = 291)	TEADA + (N = 10)	TEADA- (N = 57)	TEADA+ (N = 79)	TEADA- (N = 348)
Confirmed Objective Response Rate by BICR, n (%)	20 (29.0)	100 (34.4)	1 (10.0)	6 (10.5)	21 (26.6)	106 (30.5)
Confirmed Disease Control Rate by BICR, n (%)	58 (84.1)	232 (79.7)	6 (60.0)	39 (68.4)	64 (81.0)	271 (77.9)
Kaplan-Meier Estimate of Duration of Confirmed Response by BICR (months)[a]						
Number of Subjects	40	200	2	12	21	106
25th Percentile (95% CI)	3.9 (2.6, 8.4)	4.2 (4.2, 4.5)	3.2 (NC)	4.6 (2.9, 5.9)	3.6 (2.6, 8.4)	4.2 (3.9, 5.2)
Median (95% CI)	9.3 (5.5, 10.9)	7.0 (5.6, 8.3)	3.2 (NC)	5.9 (2.9, 7.1)	9.3 (3.3, NC)	6.9 (5.6, 9.0)
75th Percentile (95% CI)	12.9 (9.8, NC)	12.6 (11.1, 14.5)	3.2 (NC)	7.1 (5.9, NC)	12.9 (9.3, NC)	12.6 (10.2, 14.5)
Time to Response for Confirmed Response by BICR (months)						
Number of Subjects	40	200	2	12	21	106
Median	1.5	1.6	1.3	1.4	1.4	1.6
Min, Max	1.1, 11.3	1.2, 9.5	11.3, 1.3	1.2, 9.7	1.1, 11.3	1.2, 9.7
Progression-free Survival by BICR (months)[a]						
Number of Subjects	138	582	20	114	79	348
25th Percentile (95% CI)	2.7 (1.5, 2.9)	2.8 (2.6, 2.9)	1.4 (1.2, 3.3)	1.5 (1.4, 1.7)	2.6 (1.4, 3.0)	2.6 (1.9, 2.8)

	Non-squamous		Squamous		Overall Population	
	TEADA+ (N = 69)	TEADA- (N = 291)	TEADA + (N = 10)	TEADA- (N = 57)	TEADA+ (N = 79)	TEADA- (N = 348)
Median (95% CI)	4.9 (4.2, 5.6)	5.7 (5.4, 6.9)	3.3 (1.4, 4.4)	2.8 (2.6, 4.0)	4.6 (3.9, 5.5)	5.4 (4.3, 5.9)
75th Percentile (95% CI)	10.1 (9.5, 12.3)	11.6 (10.9, 12.5)	4.4 (3.3, NC)	5.8 (4.2, 9.6)	9.6 (5.6, 12.3)	11.2 (9.6, 12.5)
Overall Survival (months)[a]						
Number of Subjects	138	582	20	114	79	348
25th Percentile (95% CI)	5.6 (5.1, 6.6)	7.2 (6.6, 8.2)	3.3 (1.9, 5.4)	3.4 (1.9, 4.3)	5.4 (3.9, 6.6)	6.5 (5.2, 7.5)
Median (95% CI)	12.9 (10.0, 17.3)	14.8 (13.1, 16.5)	6.5 (3.3, 9.9)	6.9 (5.1, 12.1)	12.1 (7.6, 17.3)	13.2 (12.1, 16.0)
75th Percentile (95% CI)	NC (17.3, NC)	20.6 (20.6, NC)	NC (7.6, NC)	15.7 (12.4, NC)	NC (15.0, NC)	20.6 (19.4, NC)

BICR = blinded independent central review; CI = confidence interval; Max = maximum; Min = minimum; n = number of subjects in each category; N = total number of subjects in subgroup; NC = not calculated; TEADA+ = subjects with treatment-emergent anti-drug antibody; TEADA- = subjects without treatment-emergent anti-drug antibody; TL01 = TROPION-Lung01; TL05 = TROPION-Lung05
Notes: Subjects in the immunogenicity analysis set who were in TL05 or TL01 are included in this table.
[a] Median, 25th and 75th Percentile are based on the Kaplan-Meier method. The two-sided 95% CIs for the median and percentiles are computed using the Brookmeyer-Crowley method.
Source: Dato-DXd ISI TFLs Table 3.1.1

Impact on safety

The impact of immunogenicity on safety was assessed by pooling subjects from TL01, TL05, and TP01 NSCLC 6 mg/kg cohort (the "safety" pool). A total of 477 subjects contributed to the ADA safety analyses.

The overall summaries of TEAEs and AESIs by ADA status are presented in Table 37 and Table 38, respectively.

Table 37 Overall Summary of Treatment-emergent Adverse Events by Treatment-emergent Anti-drug Antibody Status

	Non-squamous		Squamous		Overall Population	
	TEADA+ (N = 75)	TEADA- (N = 330)	TEADA+ (N = 11)	TEADA- (N = 61)	TEADA+ (N = 86)	TEADA- (N = 391)
Subjects With Any TEAE, n (%)	75 (100.0)	325 (98.5)	11 (100.0)	57 (93.4)	86 (100.0)	382 (97.7)
Subjects With Any Drug-related TEAE, n (%)	72 (96.0)	290 (87.9)	9 (81.8)	49 (80.3)	81 (94.2)	339 (86.7)
Subjects With Any Grade ≥3 TEAE, n (%)	29 (38.7)	150 (45.5)	7 (63.6)	32 (52.5)	36 (41.9)	182 (46.5)
Subjects With Any Drug-related Grade ≥3 TEAE, n (%)	15 (20.0)	84 (25.5)	5 (45.5)	17 (27.9)	20 (23.3)	101 (25.8)
Subjects With Any TEAE Associated with Dose Reduction, n (%)	18 (24.0)	66 (20.0)	4 (36.4)	10 (16.4)	22 (25.6)	76 (19.4)
Subjects With Any TEAE Associated with Dose Interruption (TP01 only), n/N (%)[a]	1/6 (16.7)	12/39 (30.8)	0/1 (0)	1/4 (25.0)	1/7 (14.3)	13/43 (30.2)
Subjects With Any TEAE Associated with Infusion Interruption (TL01 and TL05), n/N (%)[a]	4/69 (5.8)	6/291 (2.1)	0/10 (0)	2/57 (3.5)	4/79 (5.1)	8/348 (2.3)
Subjects With Any TEAE Associated with Dose Delay (TL01 and TL05), n/N (%)[a]	26/69 (37.7)	106/291 (36.4)	8/10 (80.0)	17/57 (29.8)	34/79 (43.0)	123/348 (35.3)
Subjects With Any TEAE Associated with Drug Withdrawn, n (%)	7 (9.3)	39 (11.8)	1 (9.1)	6 (9.8)	8 (9.3)	45 (11.5)
Subjects With Any Serious TEAE, n (%)	21 (28.0)	92 (27.9)	3 (27.3)	26 (42.6)	24 (27.9)	118 (30.2)
Subjects With Any TEAE Leading to Death, n (%)	1 (1.3)	13 (3.9)	2 (18.2)	7 (11.5)	3 (3.5)	20 (5.1)

AESI = adverse event of special interest; n = number of subjects in each category; N = total number of subjects in subgroup; TEADA+ = subjects with treatment-emergent anti-drug antibody; TEADA- = subjects without treatment-emergent anti-drug antibody; TEAE = treatment-emergent adverse event; TL01 = TROPION-Lung01; TL05 = TROPION-Lung05; TP01 = TROPION PanTumor01

[a] Due to the difference in study case report forms, dose interruption was reported in and summarized for TP01 only; infusion interruption and dose delay were reported in TL01 and TL05 and summarized by pooling these two studies.

Notes: Subjects in the immunogenicity analysis set who received Dato-DXd 6 mg/kg are included in this table.

Source: Dato-DXd ISI TFLs Table 4.1.1

Table 38 Overall Summary of Adverse Events of Special Interest by Treatment-emergent Anti-drug Antibody Status

AESI Category	Non-squamous		Squamous		Overall Population	
	TEADA+ (N = 75)	TEADA- (N = 330)	TEADA+ (N = 11)	TEADA- (N = 61)	TEADA+ (N = 86)	TEADA- (N = 391)
Adjudicated Drug-related ILD, n (%)	7 (9.3)	19 (5.8)	0	6 (9.8)	7 (8.1)	25 (6.4)
CTCAE Grade ≥3	1 (1.3)	6 (1.8)	0	6 (9.8)	1 (1.2)	12 (3.1)
Serious AESI	3 (4.0)	10 (3.0)	0	6 (9.8)	3 (3.5)	16 (4.1)
Associated with Death	0	3 (0.9)	0	1 (1.6)	0	4 (1.0)
IRR, n (%)	13 (17.3)	37 (11.2)	1 (9.1)	7 (11.5)	14 (16.3)	44 (11.3)
CTCAE Grade ≥3	0	1 (0.3)	0	1 (1.6)	0	2 (0.5)
Serious AESI	0	2 (0.6)	0	0	0	2 (0.5)
Study Drug-related AESI	11 (14.7)	32 (9.7)	1 (9.1)	6 (9.8)	12 (14.0)	38 (9.7)
Associated with Death	0	0	0	0	0	0
Oral Mucositis (Stomatitis), n (%)	38 (50.7)	205 (62.1)	4 (36.4)	29 (47.5)	42 (48.8)	234 (59.8)
CTCAE Grade ≥3	4 (5.3)	26 (7.9)	1 (9.1)	2 (3.3)	5 (5.8)	28 (7.2)
Serious AESI	2 (2.7)	5 (1.5)	0	0	2 (2.3)	5 (1.3)
Study Treatment-related AESI	37 (49.3)	188 (57.0)	4 (36.4)	26 (42.6)	41 (47.7)	214 (54.7)
Associated with Death	0	0	0	0	0	0
Ocular Surface Toxicity, n (%)	12 (16.0)	82 (24.8)	2 (18.2)	9 (14.8)	14 (16.3)	91 (23.3)
CTCAE Grade ≥3	1 (1.3)	8 (2.4)	0	0	1 (1.2)	8 (2.0)
Serious AESI	0	2 (0.6)	0	0	0	2 (0.5)
Study Treatment-related AESI	10 (13.3)	68 (20.6)	1 (9.1)	7 (11.5)	11 (12.8)	75 (19.2)
Associated with Death	0	0	0	0	0	0
Mucosal Inflammation, n (%)	2 (2.7)	5 (1.5)	0	2 (3.3)	2 (2.3)	7 (1.8)
CTCAE Grade ≥3	1 (1.3)	0	0	0	1 (1.2)	0
Serious AESI	0	0	0	0	0	0
Study Treatment-related AESI	2 (2.7)	4 (1.2)	0	1 (1.6)	2 (2.3)	5 (1.3)
Associated with Death	0	0	0	0	0	0

AESI = adverse event of special interest; CTCAE = Common Terminology Criteria for Adverse Events; n = number of subjects in each category; N = total number of subjects in subgroup; ILD = interstitial lung disease;
IRR = infusion related reaction; TEADA+ = subjects with treatment-emergent anti-drug antibody;
TEADA- = subjects without treatment-emergent anti-drug antibody
Notes: Subjects in the immunogenicity analysis set who received Dato-DXd 6 mg/kg are included in this table.
Source: Dato-DXd ISI TFLs Table 4.1.2

Relationship between plasma concentration and effect and safety

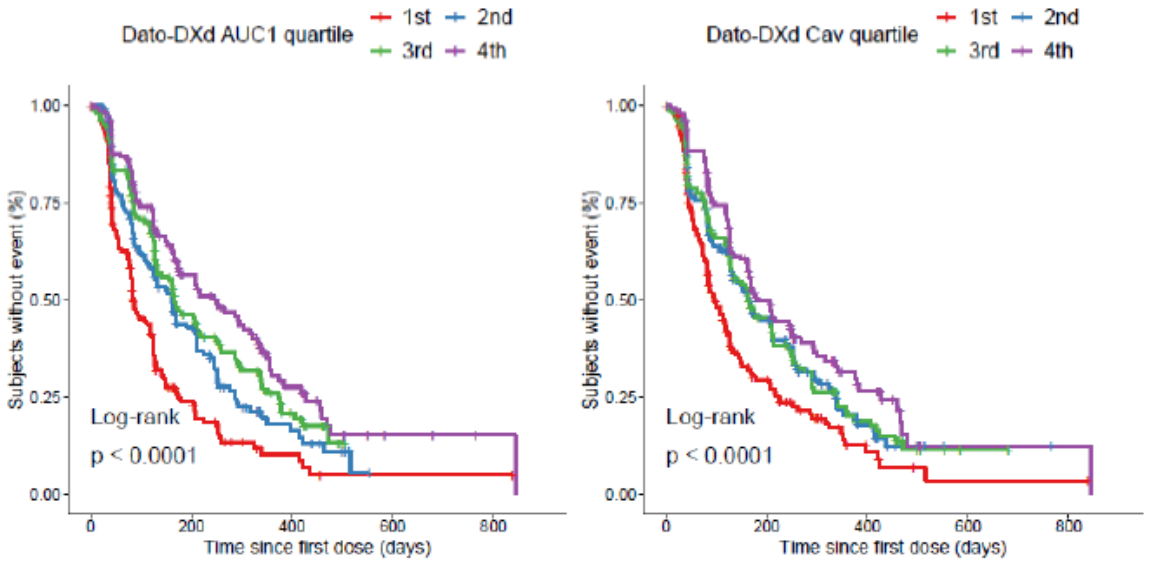
Exposure-efficacy analyses

The ER analyses for efficacy were conducted for the efficacy endpoints of PFS (N=644), OS (N=644), and ORR (N=592) using data from subjects with NSCLC in Studies TL01, TL05, and TP01 who had both PK and efficacy data.

Exposure-efficacy results for PFS

The ER for PFS by BICR analysis included 644 subjects with NSCLC from Studies TL01 (N=297), TL05 (N=137), and TP01 (NSCLC cohort, N=210, Figure 36).

Figure 36 Kaplan-Meier Plot of PFS-BICR Stratified by Dato-DXd AUC-time Curve in Cycle 1 and Cav Quartiles

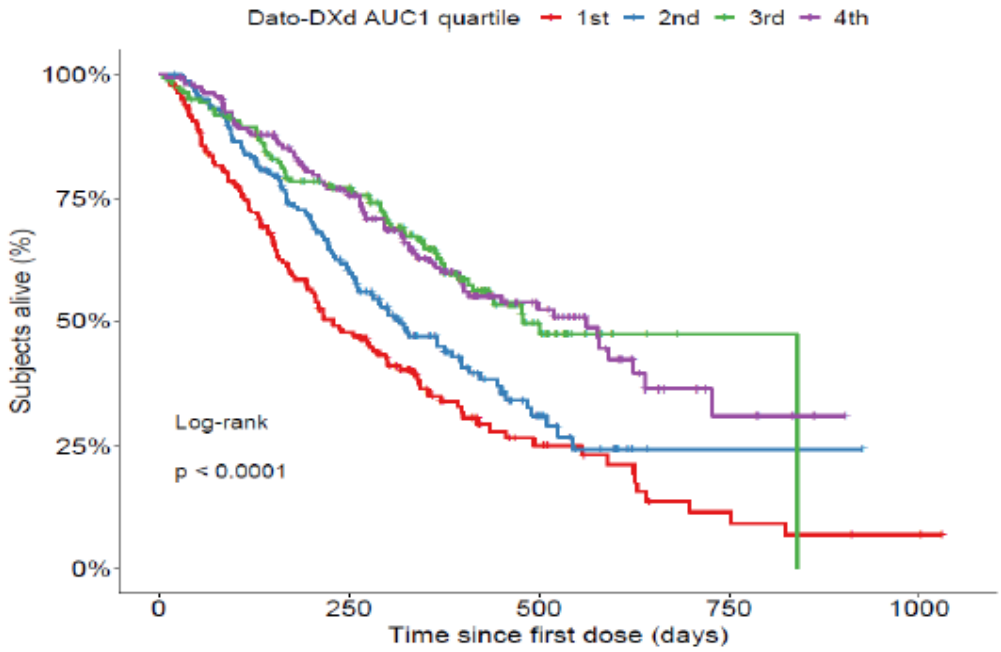


AUC = area under the plasma concentration-time curve; AUC1 = area under the plasma concentration-time curve in Cycle 1; BICR = blinded independent central review; Cav = average concentration to the end of the cycle that included the event; PFS = progression-free survival.
Notes: Percent of subjects without an event, for the PFS endpoint, versus time since first dose, colored by exposure quartiles and stratified by exposure metric.
The solid lines represent the % of subjects without an event. Vertical bars indicate where one or multiple subjects have been censored in time.
Source: ER Analysis Report Figure 13

Exposure-efficacy results for OS

The ER for OS analysis included 644 subjects with NSCLC from Studies TL01 (N=297), TL05 (N=137), and TP01 (NSCLC cohort, N=210, Figure 37).

Figure 37 Kaplan-Meier Plot of OS Stratified by Dato-DXd AUC-Time Curve in Cycle 1 Quartiles

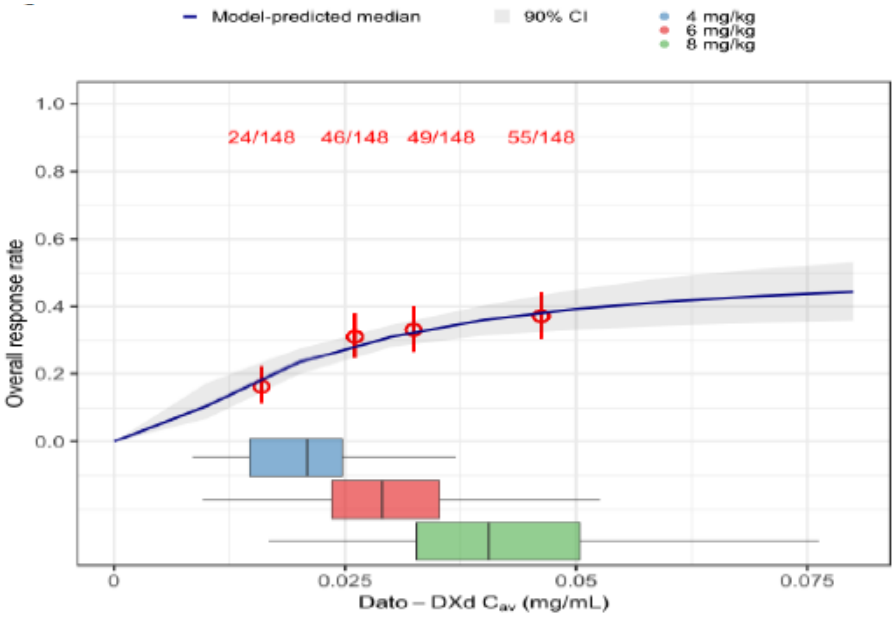


AUC1 = area under the plasma concentration-time curve in Cycle 1; OS = overall survival.
Notes: The solid lines represent the % of subjects alive.
Vertical bars indicate where one or multiple subjects have been censored in time.
Source: ER Analysis Report Figure 4

Exposure-efficacy results for ORR

The ER for ORR by BICR analysis included a total of 592 subjects with NSCLC from Studies TL01 (N=277), TL05 (N=127), and TP01 (NSCLC cohort, N=188). A subset of 52 subjects (TL01 [N=20], TL05 [N=10], and TP01 [N=22]) were not evaluable for the ORR analysis due to reasons of no adequate post-baseline tumor assessment, SD too early, or PD too late (Figure 38).

Figure 38 Observed Logistic Regression Plot for ORR Stratified by Dato-DXd Cav Quartiles



BOR = best overall response; Cav = average concentration to the end of the cycle that included the event; CI = confidence interval; CR= complete response; ORR = objective response rate; PR = partial response; Q3W = every 3 weeks.
Notes: The blue solid line represents the median prediction and the shaded area represents the 90% CI for the predictions obtained from simulations with uncertainty (n=250).
The horizontal boxplots depict the distribution of the observed Dato-DXd C_{av}, colored by dose group, for the dose groups 4 mg/kg, 6 mg/kg, and 8 mg/kg Q3W.
The red circles represent the observed ORR per exposure quartile and the vertical bars represent the respective 90% CIs.
The circles and vertical bars are placed at the respective mean Dato-DXd C_{av} of each exposure quartile.
The red text shows the number of subjects with a BOR of either PR or CR in an exposure quartile divided by the total number of subjects in the exposure quartile.
Source: ER Analysis Report Figure 147

Exposure-safety analyses

The ER analyses for safety were conducted using data from 729 subjects with NSCLC and BC in Studies TL01 (N=297), TL05 (N=137), and TP01 (NSCLC cohort [N=210] and BC cohort [N=85]). Safety endpoints for the exposure-safety analyses are as follows:

Treatment-emergent AEs:

☐ Grade ≥3 TEAEs

☐ Serious TEAEs

☐ TEAEs associated with drug interruption, dose delay, dose reduction, or treatment discontinuation

Adverse events of special interest:

☐ Oral mucositis/stomatitis (any grade and Grade ≥2)

☐ Mucosal inflammation other than oral mucositis/stomatitis (any grade and Grade ≥2)

☐ Adjudicated drug-related ILD/pneumonitis (any grade)

☐ Ocular surface toxicity (any grade and Grade ≥2)

The ER analysis for safety was conducted in 2 segments:

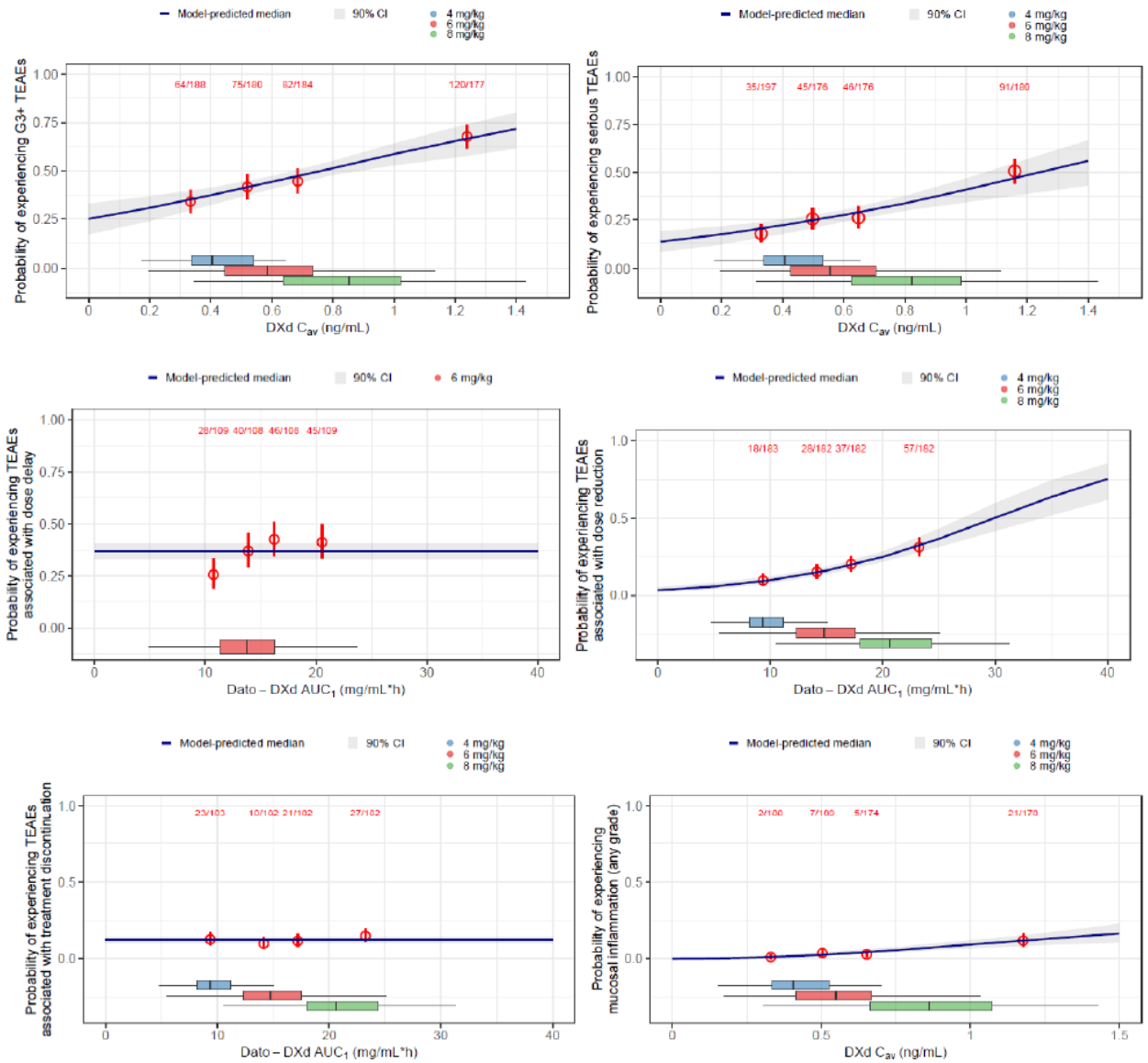
☐ Analysis of the AEs (TEAEs and AESIs) using logistic regression

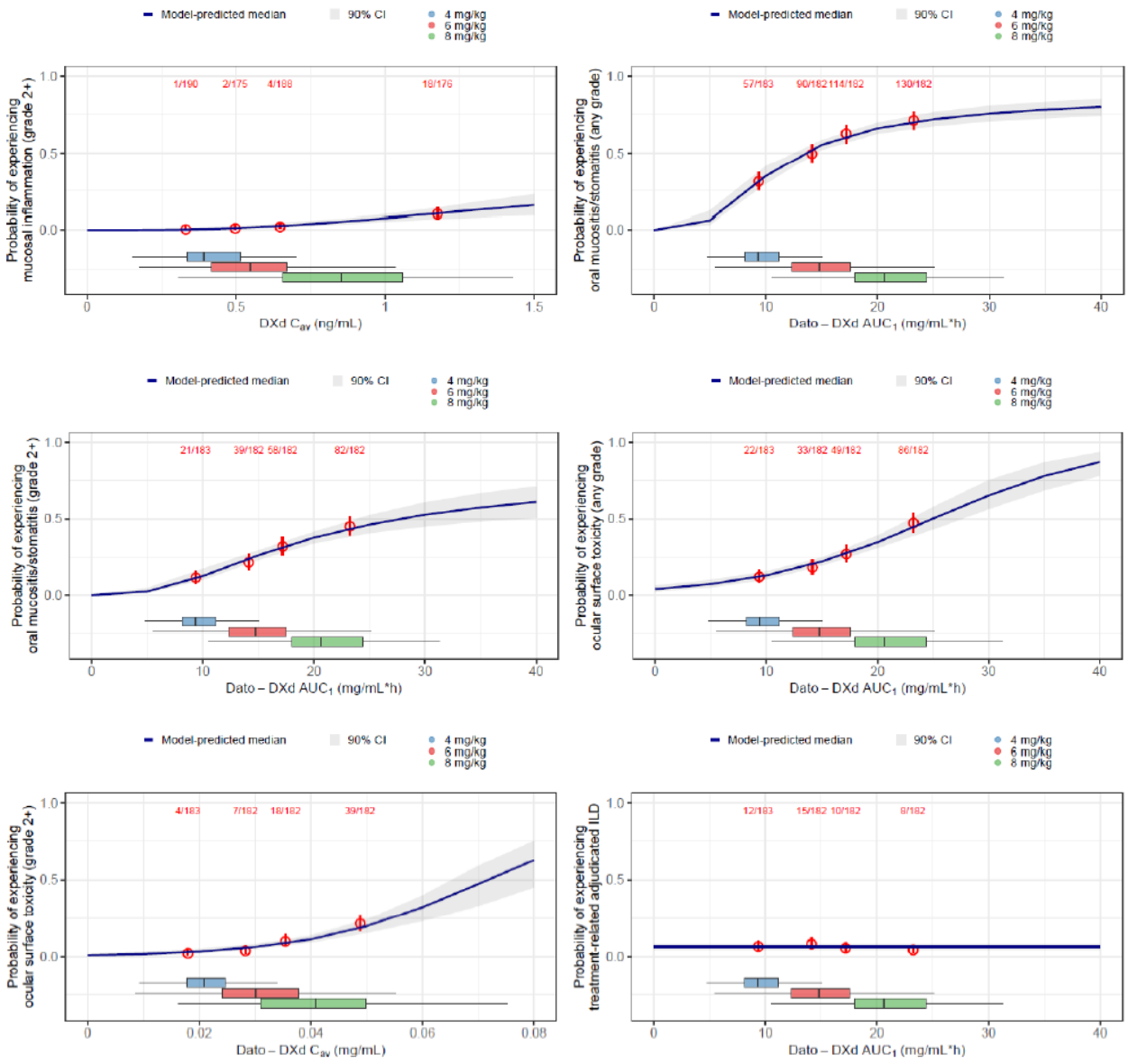
☐ TTE analyses for the AESIs

Logistic regression models were developed to characterize the ER relationships of 13 AEs (6 TEAEs and 7 AESIs), and to identify statistically significant covariate relationships for subjects receiving Dato-DXd. The relationship between exposure and safety was also examined, as depicted in Figure 39. Logistic regression curves highlight the associations between exposure levels and the likelihood of AEs.

Significant ER relationships ($p < 0.01$) were observed for the following AEs: Grade ≥3 TEAEs, serious TEAEs, TEAEs associated with drug interruption, TEAEs associated with dose reduction, oral mucositis/stomatitis (any grade and Grade ≥2), mucosal inflammation (any grade and Grade ≥2), and ocular surface toxicity (any grade and Grade ≥2). No ER relationship was observed for TEAEs associated with dose delay, TEAEs associated with treatment discontinuation, and adjudicated drug-related ILD.

Figure 39 Logistic Regression Analysis of ER-Safety Relationship by Significant Exposure Metrics





AE = adverse event; AUC1 = area under the plasma concentration-time curve in Cycle 1; Cav = average concentration to the end of the cycle that included the event; CI = confidence interval; ER = exposure-response; G = grade; ILD = interstitial lung disease; TEAE = treatment-emergent adverse event
Notes: The shaded area represents the 90% CI for the predictions obtained from simulations with uncertainty (n=250).
The horizontal boxplots depict the distribution of the observed exposure, colored by dose group.
The red circles represent the observed frequency of AEs per exposure quartile and the vertical bars represent the 90% CIs.
The circles and vertical bars are placed at the respective mean exposure of each exposure quartile.
The red text shows the number of subjects experiencing AEs in an exposure quartile divided by the total number of subjects in the exposure quartile.
No significant ER relationships were identified for TEAEs associated with dose delay, TEAEs associated with treatment discontinuation, and adjudicated drug-related ILD.
Source: ER Analysis Report Figure S1

3.3.2. Discussion on clinical pharmacology

Pharmacokinetics

The PK of Datopotamab deruxtecan Daiichi Sankyo was described by NCA and by Pop-PK modelling. The dataset for Pop-PK and for exposure-response analyses for Dato-DXd and DXd originated from three studies: DS1062-A-J101, DS1062-A-U202 and DS1062-A-U301. The Pop PK population consisted mainly of patients with NSCLC (n=642), however, Study J101 also included data from 86 patients with breast cancer. Study J101 was a dose-range finding study with doses ranging from 0.27-10 mg/kg

Q3W, in which 133 subjects received 6.0 mg/kg. In Study 202 and 301, 424 subjects were treated with 6.0 mg/kg Q3W.

Dato-DXd PK was described by a 2-compartment model with parallel linear clearance and nonlinear Michaelis-Menten clearance from the central compartment. DXd PK was described by a 1-compartment model with first-order elimination, a release equal to the linear and nonlinear elimination rate of Dato-DXd and a decreasing drug-to-antibody ratio over time within- and between cycles. The diagnostic plots indicated the models could predict the observed data. Body weight has major impact on Dato-DXd and DXD exposure which increase with dose, despite a weight-based dose regimen.

Previous PBPK models for T-DXd (trastuzumab deruxtecan, Enhertu) developed in Simcyp V18 were updated in Simcyp V21 to describe the pharmacokinetics of T-DXd and Dato-DXd which share the same payload molecule DXd. DDI of T-DXd was investigated in a clinical study with inhibitors of CYP3A4 and OATP1B and showed no clinically relevant impact on Cmax. Cmax of DXd released from Dato-DXd 6 mg/kg was about 1/3 of DXd when released from T-DXd 5.4 mg/kg. Thus, the clinical DDI data may be translatable from T-DXd to Dato-DXd. The T-DXd PBPK model could reproduce the clinical DDI exposure profiles and further verifies the DXd model linked to the updated V21 ADC T-DXd model and thus the V21 ADC Dato-DXd model. Therefore, the Dato-DXd model is accepted to support SmPC recommendations regarding concomitant ritonavir or itraconazole, which are also in line with the outcome of the clinical DDI study with T-DXd.

The relevant analytes for an ADC were quantified in the conducted clinical studies; conjugated drug (Dato-DXd), total AB (total anti-TROP2 antibody) and the payload (DXd). Overall, the bioanalytic performed in support of the Dato-DXd clinical program is found to be in accordance with regulatory requirements. However, the inter-assay precision for the LOQ in study TL05 was not according to guideline criteria. The imprecision was caused by a few samples. The performance of LQCs in each analytical run met the acceptance criteria and the impact on the overall PK is considered as limited. Several BA study reports are interims report, as the clinical studies are still ongoing. The ADA assays were validated according to regulatory guidelines. The drug tolerance of the Lyo-DP ADA assay was reduced and upon request an ADA assay drug tolerance of 10 µg/mL Dato-DXd was interpolated for a PC antibody conc. of 130-144 ng/mL. This interpolation is considered as a reasonable approx. for the low PC antibody (100 ng/ml) drug tolerance level. In nearly all ADA samples the Dato-DXd conc. was above the drug tolerance (10 µg/mL) for a 250 ng/mL PC antibody. Approx. 5-23% of pre-dose ADA samples had Dato-DXd conc. above the 10 µg/mL drug tolerance level. The ADA incidence, mainly for low conc. ADAs of Dato-DXd, in the clinical studies could therefore potentially be slightly underestimated. The clinical relevance of this potential underestimation for low conc. ADAs is considered as limited. The assay for analyzing neutralising antibodies at PPD had an unacceptable selectivity in normal plasma, though it was sufficient in plasma from non-small cell lung cancer patients. An additional assessment of healthy versus disease state matrix was conducted by PPD after the initial submission and the results met the acceptance criteria. The high rate of false negatives using the original method at PPD did not have a clinical consequence, since the false negative percentage was acceptable for plasma samples from patients.

The proposed clinical dose of Dato-DXd is 6 mg/kg in patients on Day 1 of each 21-day cycle. The dose may be decreased to 4 mg/kg and even to 3 mg/kg in case of adverse events. The comparability was evaluated of the Dato-DXd drug products (DP) administered to patients in the conducted clinical studies: FL-DP used in the Phase I TPO study, clinical Lyo-DP in the phase II study TL05 and in the phase 3 study TL01 in which also the to-be-marketed (tbm) Lyo-DP was administered. It was demonstrated using NCA analysis of cycle 1 data and Pop-PK analysis that the different drug products with regards to pharmacokinetics can be considered as comparable. However, clinical data after a single dose across studies TP01, TL01 and TL05 suggest that tmax of DXd is reached earlier for the to-be-marketed lyophilized powder formulation versus the frozen-liquid formulation at the therapeutic

dose of 6 mg/kg. Upon request, the difference in mean Tmax was explained as a result of PK-sampling scheme and the flat PK-profile of DXd. Furthermore, the observed ranges for the t_{max} were similar for the two formulations and the Tmax difference is not expected to affect the efficacy and safety. Overall, the mean Tmax difference is not considered of relevance.

The PK parameters, volume of distribution at steady state Vss and plasma clearance Cl, of Dato-DXd was adequately estimated by NCA using cycle 1 PK data compiled over all 3 conducted clinical studies. The PK dataset contains both BS and NSCLC patients. The compilation of data is acceptable as it was demonstrated that PK of Dato-DXd and DXd is not affected by cancer type or DP. The comparability in plasma exposure of Dato-DXd and total anti-TROP2 AB demonstrates that the amount of unconjugated antibody in systemic circulation is very limited.

A human mass-balance study was not conducted to determine the routes of excretion of DXd. This is reflected in the SmPC and this was also the case for the previously submitted and approved deruxtecan type ADC, trastuzumab deruxtecan T-DXd (Enhertu). This is acceptable and human mass-balance studies has generally not been conducted for nearly all of the approved ADCs. It is assumed from the obtained animal data and in vitro data that DXd is primarily eliminated hepatically by metabolism and biliary excretion in humans, where billiary excretion is presumably the most important pathway of elimination. The analysis of DXd elimination is reasonable in the lack of human mass-balance data and was as previously reported for T-DXd. The in vitro metabolism studies of DXd were resubmitted, previously submitted and reviewed as part of the trastuzumab deruxtecan dossier (Enhertu). The metabolism of DXd in humans has only been investigated using in vitro methods. This is acceptable considering the previous qualification.

It was demonstrated that Dato-DXd exposure, Cmax and AUCtau, were dose proportional across the dose range of 4 to 10 mg/kg. Steady-state of Data-DXD was shown to be reached after 3 cycles and accumulation was limited, consistent with determined terminal half-life. The influence of ADAs on the PK of Dato-DXd and DXd was investigated. The presence of ADA appears not to influence the PK of Dato-DXd or DXd.

The therapeutic window is considered to be a dose range of 2-8 mg/kg. The impact of renal (RI) and hepatic impairment (HI) on the PK of Dato-DXD and DXd has been evaluated in the Pop-PK model. No dedicated RI or HI studies were conducted. This is considered as acceptable due to the toxicity of Dato-DXd, this was also the case for the approved DXd ADC, trastuzumab deruxtecan (T-DXd). As DXd is primarily cleared by the liver (metabolism and biliary excretion), the systemic exposure of the toxic payload DXd could be increased in patients with moderate and severe HI, potentially resulting in an increased systemic toxicity in this Population. It is requested that a warning for use in patients with HI is included in the SmPC, section 4.4, in line with the SmPC for T-DXd or a justification should be provided for not including this warning (**SmPC OC**).

Gender was demonstrated not to impact the PK of Dato-Dxd and Dxd in a clinically relevant manner. The impact of body weight on the PK-parameters and exposure of Dato-DXd and DXd were investigated by Pop-PK modelling. It was demonstrated that the mean AUC3 and Cmax3 of Dato-DXd and DXd in the 5th and 95th BW percentile was outside the 0.8-1.25 range, which is considered as clinically not meaningful. The impact of BW is further discussed below under pharmacodynamics. Overall, the PK of Dato-DXd and DXd in special populations have been acceptably reported in the SmPC.

The in vitro DDI potential of the payload DXd, the DDI relevant small molecule part of Dato-DXd, have been assessed adequately. All of the in vitro studies were previously submitted and reviewed as part of the approved deruxtecan ADC, T-DXd. No perpetrator potential was identified for DXd. The potential victim DDI has not been evaluated in a dedicated clinical DDI study. The previous clinical DDI study of T-DXd is considered to be transferable to Dato-DXd. Therefore, no relevant DDI of Dato-DXd (DXd)

with OATP1B1 and CYP3A perpetrators are expected. This conclusion was also supported by PBPK modelling. The justification provided, that clinical DDI involving the drug transporters MATE-2K, BCRP and P-gp are not likely, is considered as acceptable. Itraconazole has also been reported as a P-gp inhibitor and ritonavir as an OATP1B3, P-gp and a BCRP inhibitor. The hepatic and renal inhibitory effects of itraconazole and ritonavir is according is limited and the study DS8201-A-A104 can thus only to a limited degree be considered as an evaluation of these drug transporters. In a recent perspective paper by the ITC consortium, Taskar et al, Clin. Pharmacol. Ther. 2022, it was concluded that there in general is a limited clinical DDI risk from P-gp or BCRP inhibition in liver. In conclusion, liver DDI of DXd involving P-gp and BCRP are likely not clinically relevant. In conclusion, DDIs of the payload DXd have been adequately evaluated.

The steady state exposure of Dato-DXd applied for estimation of non-clinical safety margin is reasonable. The PK of Dato-DXd in the pivotal phase 3 study was comparable to the phase-I study used for non-clinical safety margin determination.

Pharmacodynamics

Dato-DXd is a TROP2-targeted antibody and DNA topoisomerase I inhibitor conjugate (antibody-drug conjugate). The mechanism of action has been sufficiently characterised and described.

No specific PD endpoints or biomarkers were defined and reported, and no biomarker claims are presented.

Data from study DS1062-A-J101 (cutoff date of 30 Jul 2021), was used for evaluation of a potential c-QTc relation. The parameters of the final models were estimated with good precision except for slope. A large number of ECG records without PK (about 20%) were excluded. In a c-QTc analysis, the highest observed geometric mean Cmax values across Cycles 1 and 3 were used to ensure maximum exposure. At the proposed 6 mg/kg dose, the upper bound of the 90% CIs for ΔQTc(F) at the geometric mean Cmax for DXd was 1.11 ms, indicating that no significant increase in QTc is expected with the proposed dose regimen.

No clinical drug interaction studies with datopotamab deruxtecan have been conducted; this is acceptable. No PD interactions are expected.

Based on the provided data, presence of ADAs does not seem to negatively affect the efficacy or safety associated with the treatment with Dato-DXd. Neutralising Abs (N=14) were only detected in the non-squamous sub-group and this did not seem to affect the efficacy outcome.

For exposure-response analyses, data from subjects with BC were excluded from efficacy evaluations. Individual exposure metrics were derived by Pop PK. E-R was evaluated on Dato-DXd exposure metrics for efficacy end-points and on Dato-DXd or DXd exposure metrics for safety, dependent on the end-point. For evaluation of exposure-efficacy relations, a TTE model was developed for OS with a linear drug effect of Dato-DXd AUC1. The parameter estimate for slope was close to zero. For PFS, time-varying Dato-DXd AUCtau was implemented as a drug effect using an Emax function. A Forest plot indicated that at least 10 mg/mL*h AUCtau required for the PFS hazard ratio to be within 1.25 of reference. A VPC of the KM plot per exposure quartile indicated the model-predicted effect of exposure on PFS was overestimated compared to observed. An Emax function best described the drug effect of Dato-DXd Cav on ORR. A Forest plot indicated at least a Dato-DXd Cav of 0.0225 mg/mL is required to obtain an odds ratio of best objective response within 0.8 of reference.

The Kaplan-Meier analyses indicated a clear trend of increasing PFS and OS with higher exposure quartiles of Dato-DXd AUC1. A positive trend was also observed for ORR.

As for exposure-safety, significant ER relationships were observed for some AEs, including Grade ≥3 TEAEs and serious TEAEs.

In general, the parameter estimates of different safety models were estimated with reasonable-to-low precision. At the 6 mg/kg Q3W dose several safety endpoints showed a positive relation to exposure expressed as DXd Cav or Dato-DXd AUC1. Several safety end-points got worse over time. Overall univariate simulations indicated that a DXd Cav ≤0.7 ng/mL might reduce the odds of several serious safety events to be close to the 1.25 limit and that a Dato-DXd AUC1 ≤18.3 mg/mL*h might reduce the odds of several serious safety events to be close to the 1.25 limit. This was evident for several TEAE categories, for mucosal inflammation, for mucosititis/stomatitis and for ocular toxicity. Forest plots of odds ratio to experience a safety event in the 6 mg/kg Q3W dose group, indicated this may be controlled by dose capping. Model based exposures in weight-categories indicated that subjects with a body weight ≥100 kg would still experience higher exposure with a flat dose of 600 mg, than subjects with a body weight below 100 kg receiving 6 mg/kg. Thus dose-capping at 100 kg is not sufficient. The applicant should discuss whether dose-capping at 90 kg (540 mg) or alternatively at 80 kg (480 mg) would provide better exposure-control and reduce the risk for TEAEs such as ocular surface toxicity and stomatitis **(new OC)**. In order to compare the incidence of AEs to exposure groups, the applicant is asked to provide a table of AE events (by body weight groups: 37-<46 kg; 46-<60 kg; 60-<80 kg; 80-<100 kg and ≥100 kg **(new OC)**.

The applicant has provided a justification, based on non-clinical and clinical PK, efficacy, and safety data, for the selection of the 6 mg/kg dose administered on Day 1 of each 21-day treatment cycle for the pivotal phase 3 study. This justification is considered acceptable. A question regarding the need for a dose cap in heavy weight patients has been raised, though.

3.3.3. Conclusions on clinical pharmacology

The applicant has conducted a sufficient investigation of the clinical pharmacology of Dato-DXd, both with regards to pharmacokinetics and pharmacodynamics, using in vitro studies, clinical pharmacology studies and by modelling and simulation studies. In conclusion, the provided clinical pharmacology package supports approval of Dato-Dxd in non-small cell lung cancer, but a number of other concerns remains to be addressed by the applicant.

3.3.4. Clinical efficacy

3.3.4.1. Dose-response studies

See section 3.3.1.2.

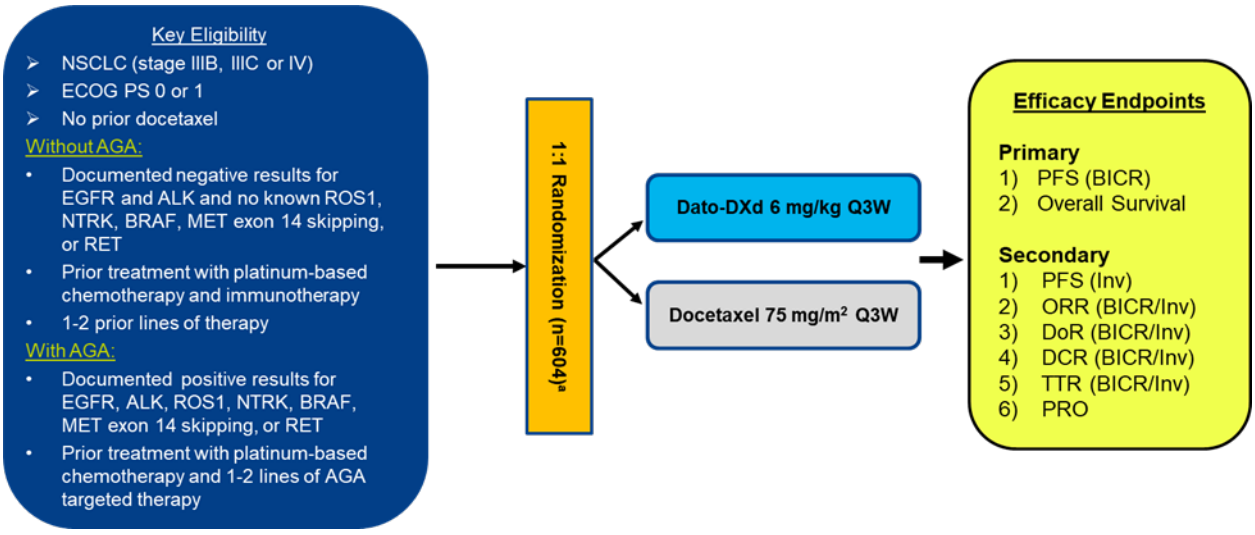
3.3.4.2. Main study

Study TL01 (TROPION-LUNG01)

TL01 (TrOPION-Lung01) is a phase 3, global, multicenter, randomized, active-controlled, open-label study of datopotamab deruxtecan (Dato-DXd) monotherapy vs. docetaxel in previously treated subjects with advanced non-small cell lung cancer (NSCLC) with or without actionable genomic alterations (AGAs). Although the study initially excluded those with AGAs (ie, alterations in genes with approved therapies, such as EGFR, ALK, ROS1, NTRK, BRAF, MET exon 14 skipping, or RET), it was amended during enrollment to include approximately 15% of such subjects.

Figure 40 Study schema

Study Design: TL01 (TROPION-Lung01)



AGA=actionable genomic alterations; ALK=anaplastic lymphoma kinase; BICR=blinded independent central review; BRAF=proto-oncogene B-raf; Dato-DXd=datopotamab deruxtecan; DCR=disease control rate; DoR=duration of response; ECOG PS=Eastern Cooperative Oncology Group performance status; EGFR=epidermal growth factor receptor; MET=mesenchymal-epithelial transition; NSCLC=non-small cell lung cancer; NTRK=neurotrophic tyrosine receptor kinase; ORR=objective response rate; PD-(L)1=programmed cell death (ligand) 1; PFS=progression-free survival; PRO=patient-reported outcome; Q3W=every 3 weeks; RET=rearranged during transfection; ROS1=ROS proto-oncogene 1; TTR=time to response; US=United States

[a] Stratified by documented AGA (present versus absent), histology (squamous versus non-squamous), most immediate prior therapy included anti-PD-(L)1 immunotherapy (yes versus no), and geographical region (US/Japan/Western Europe versus Rest of World).

Methods

Study participants

Key Inclusion Criteria by the latest protocol version (V4.0, 20-JAN-2022):

Subjects eligible for inclusion in the study must meet all inclusion criteria for this study within 28 days before randomization:

1. Subject has pathologically documented Stage IIIB, IIIC or Stage IV NSCLC with or without AGA (note: NSCLC subjects with AGA are eligible under Protocol version 4.0) at the time of randomization (based on the American Joint Committee on Cancer, Eighth Edition) and meets the following criteria for NSCLC:

   Subjects without AGA:

   - Subjects must have documented negative test results for EGFR and ALK genomic alterations. If test results for EGFR and ALK are not available, subjects are required to undergo testing performed locally for these genomic alterations.
   - Subjects have no known genomic alterations in ROS1, NTRK, BRAF, MET exon 14 skipping, or RET.
   - Subjects with known KRAS mutations (testing during screening is not mandatory), in the absence of any driver genomic alterations, are eligible and must meet the prior therapy requirements for subjects without actionable genomic alterations described below. These subjects must be stratified as NSCLC without AGA at the time of randomization.

   Subjects with AGA:

- Subjects must have one or more documented actionable genomic alteration: EGFR, ALK, ROS1, NTRK, BRAF, MET exon 14 skipping, or RET.

2. Subjects with documentation of radiographic disease progression while on or after receiving the most recent treatment regimen for advanced or metastatic NSCLC.

3. Subjects must meet the following prior therapy requirements:

   Subjects without AGA must meet ONE of the following prior therapy requirements for advanced or metastatic NSCLC:

   a) Received platinum-based chemotherapy in combination with α-PD-1/α-PD-L1 monoclonal antibody as the only prior line of therapy.

      - Includes subjects who received prior platinum-based chemotherapy with or without radiotherapy with maintenance α-PD-1/α-PD-L1 monoclonal antibody for Stage III disease and relapsed/progressed within 6 months from the last dose of platinum-based chemotherapy.

      - Includes subjects who received prior platinum-based chemotherapy with or without radiotherapy (with or without maintenance α-PD-1/α-PD-L1 monoclonal antibody) for Stage III disease and subsequently received α-PD-1/α-PD-L1 monoclonal antibody therapy (with or without platinum-based chemotherapy) for recurrent disease.

   OR

   b) Received platinum-based chemotherapy and α-PD-1/α-PD-L1 monoclonal antibody (in either order) sequentially as the only 2 prior lines of therapy.

   NOTE:

   i. Subjects who received α-PD-1/α-PD-L1 monoclonal antibody as frontline therapy may have received the combination of platinum-based chemotherapy and α-PD-1/α-PD-L1 monoclonal antibody in the second line.

   ii. Subjects with known KRAS mutations, in the absence of other AGA, who received KRAS approved target therapy (eg, sotorasib) as a separate line of therapy in addition to the prior therapy requirements described above are not eligible.

   Subjects with AGA must meet the following for advanced or metastatic NSCLC:

   a) Subjects who have been treated with 1 or 2 prior lines of applicable targeted therapy that is locally approved for the subject's genomic alteration at the time of screening; OR one or more of the agents specified in the table below:

      ▪ Subjects who have tumors with EGFR L858R or exon 19 deletion mutations must have received prior Osimertinib.

   ▪ Those who received a targeted agent as adjuvant therapy for early-stage disease must have relapsed or progressed while on the treatment or within 6 months of the last dose OR received at least one additional course of targeted therapy for the same genomic alteration (which may or may not be same agent used in the adjuvant setting) for relapsed/progressive disease.

   ▪ Subjects who have been treated with a prior TKI must receive additional approved targeted therapy, if locally available and clinically appropriate, for the applicable genomic alteration, or the subject will not be allowed in the study.

Genomic Alterations	Applicable Targeted Agents
EGFR	erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib
EGFR exon 20 insertion	amivantamab, mobocertinib
EGFR T790M	osimertinib
ALK fusion	crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib
ROS-1 fusion	entrectinib, lorlatinib, ceritinib, and crizotinib
NTRK fusion	entrectinib and larotrectinib
BRAF V600E	dabrafenib, alone or in combination with trametinib
MET exon 14 skipping	capmatinib and tepotinib
RET rearrangement	selpercatinib and pralsetinib

ALK = anaplastic lymphoma kinase; BRAF = proto-oncogene B-raf; EGFR = epidermal growth factor receptor; MET = mesenchymal-epithelial transition; NTRK = neurotrophic tyrosine receptor kinase; RET = rearranged during transfection; ROS-1 = ROS proto-oncogene 1; TKI = tyrosine kinase inhibitor

b) Subjects who have received platinum-based chemotherapy as the only prior line of cytotoxic therapy:

- One platinum-containing regimen for advanced disease
- Those who received a platinum-containing regimen as adjuvant therapy for early-stage disease must have relapsed or progressed while on the treatment or within 6 months of the last dose OR received at least one additional course of platinum-containing therapy (which may or may not be same as in the adjuvant setting) for relapsed/progressive disease.

c) May have received up to one α-PD-1/α-PD-L1 monoclonal antibody alone or in combination with a cytotoxic agent.

4. Must undergo a pre-treatment tumor biopsy procedure.

   OR

   If available, tumor tissue previously retrieved from a biopsy procedure performed within 2 years prior to the subject signing informed consent and that has a minimum of 10 × 4 micron sections or a tissue block equivalent of 10 × 4 micron sections may be substituted for the pre-treatment biopsy procedure during Screening. If a documented law or regulation prohibits (or does not approve) sample collection, then such samples will not be collected/submitted.

   Note: Results from the TROP2 testing or any other results of the pre-treatment tumor biopsy will not be used to determine eligibility for the study.

5. Has measurable disease based on local imaging assessment using RECIST v1.1.
6. Has an Eastern Cooperative Oncology Group performance status of 0 or 1 at Screening.
7. Has adequate bone marrow, liver, renal, cardiac [left ventricular ejection fraction (LVEF) ≥50% by either echocardiogram (ECHO) or multigated acquisition (MUGA) scan] and blood clotting function.
8. Has an adequate treatment washout period before randomization.

Key Exclusion Criteria by the latest protocol version (V4.0, 20-JAN-2022):

Subjects meeting any exclusion criteria for this study will be disqualified from entering the study:

1. Has 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 may be included in the study.

2. Has leptomeningeal carcinomatosis or metastasis.

- Had prior treatment with any agent, including antibody-drug conjugate (ADC), containing a chemotherapeutic agent targeting topoisomerase I, a TROP2-targeted therapy or docetaxel.

3. Has uncontrolled or significant cardiac disease.
4. Has a history of (non-infectious) interstitial lung disease (ILD)/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.
5. Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (ie, pulmonary emboli within 3 months before randomization, severe asthma, severe chronic obstructive pulmonary disease, restrictive lung disease, pleural effusion, etc.), or any autoimmune, connective tissue, or inflammatory disorders with pulmonary involvement (ie, rheumatoid arthritis, Sjogren's syndrome, sarcoidosis, etc.), or prior pneumonectomy.
6. Clinically significant corneal disease.
7. Has a history of malignancy, other than NSCLC except a) adequately resected non-melanoma skin cancer, b) curatively treated in situ disease, or c) other solid tumors curatively treated, with no evidence of disease for ≥3 years.
8. Has a history of severe hypersensitivity reactions to either the drug substances or inactive ingredients (including but not limited to polysorbate 80) of DS-1062a or docetaxel.

Treatments

Eligible patients were randomized in a 1:1 ratio to Dato-DXd 6 mg/kg or the control treatment, docetaxel 75mg/m2. No crossover between study treatment arms was allowed.

Dato-DXd was administered as a 6 mg/kg IV infusion on Day 1 of each 21-day cycle.
The initial dose of Dato-Dx will be infused over approximately 90 minutes. If there is no IRR, after the initial dose, the next dose of DS-1062a will be infused over approximately 30 minutes. In case of IRR at any time during treatment, all subsequent doses will be infused over
90 minutes. The dose of Dato-DXd could be interrupted for up to 28 days from the planned date of administration. Any interruption longer than 28 days was to result in permanent discontinuation of Dato-DXd. Up to 3 dose reductions were permitted, as shown in Table 39. Once the dose of Dato-DXd was reduced, no dose re-escalation was permitted. After the permitted dose reductions, if further toxicity meeting the requirement for dose reduction occurred, the patient was to be withdrawn from the study drug.

Table 39 Dose Reduction Levels for Dato-DXd

Starting Dose	Dose Reduction 1	Dose Reduction 2	Dose Reduction 3
6 mg/kg	4 mg/kg	3 mg/kg	2 mg/kg

Docetaxel was administered as an IV infusion of 75 mg/m2 over approximately 60 minutes on Day 1 of each 21-day cycle. Docetaxel dosing could be interrupted for up to 28 days from the planned date of administration.
If a patient was assessed as requiring a dose interruption longer than 28 days, the patient was to discontinue treatment with docetaxel. Up to 2 dose reductions were permitted as shown in Table 40.

Table 40 Dose Reduction Levels for Docetaxel

Starting Dose [a]	First Dose Reduction [b]	Second Dose Reduction [b]
75 mg/m^2	55 mg/m^2 or per investigator	Per investigator

[a] The starting dose for all subjects randomized to docetaxel treatment arm was 75 mg/m^2.
[b] All dose reductions were to be made in accordance with the locally approved docetaxel label and/or local clinical practice guidelines for docetaxel.

Once the dose of docetaxel was reduced, no dose reescalation was permitted. After the permitted dose reductions, if further toxicity meeting the requirement for dose reduction occurred, the patient was to be withdrawn from the study drug.

Duration of treatment: Subjects would continue to receive Dato-DXd or docetaxel in the absence of radiographic disease progression as assessed by Investigator, clinical progression, unacceptable toxicity, withdrawal of consent by subject, physician decision, protocol deviation, pregnancy, lost to follow-up, study termination by the Sponsor, death, or other reasons.

Premedication is required prior to any dose of Dato-Dx and must include antihistamines and acetaminophen, with and without glucocorticoids. For prevention of oral mucositis/stomatitis, subjects are advised to initiate a daily oral care protocol (OCP) before study intervention initiation and maintain it throughout the study. An OCP should include daily inert, bland mouth rinses (eg, with a nonalcoholic, bicarbonate-containing mouthwash 4 to 6 times a day), although other prophylaxis regimens (eg, dexamethasone oral solution 0.1 mg/mL 10 mL 3 to 4 times daily swish for 1 minute to 2 minutes then spit out, as well as cryotherapy throughout the infusion) advocated by institutional/local guidelines are permitted.

Patients should be premedicated with oral corticosteroids, such as dexamethasone 16.0 mg per day (for example, 8.0 mg twice a day) for 3 days starting 1 day prior to docetaxel administration, in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. Additional antiemetic premedication may be used at the discretion of the Investigator.

Prohibited therapies/products:

- Other anticancer therapy, including cytotoxic, targeted agents, immunotherapy, antibody, retinoid, transplant, or anticancer hormonal treatment (concurrent use of hormones for noncancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable).
- Other investigational therapeutic agents.
- Radiotherapy (except for palliative radiation to known metastatic sites as long as it does not affect assessment of response or interrupt treatment for more than the maximum time specified in the dose modification section [see Section 6.5]).
- Radiotherapy to the thorax
- Concomitant use of chronic systemic (IV or oral) corticosteroids or other immunosuppressive medications except for managing AEs. (Inhaled steroids or intra-articular steroid injections are permitted in this study.)
- Subjects with bronchopulmonary disorders who require intermittent use of bronchodilators (such as albuterol) will not be excluded from this study.
- Concomitant treatment with chloroquine or hydroxychloroquine is not allowed during the study treatment.

Restricted therapies/products:

- The use of tobacco products, electronic cigarettes and vaping is strongly discouraged.
- The concomitant use of docetaxel with strong cytochrome P450 (CYP) 3A4 inhibitors should be avoided. If the concomitant use of a strong CYP3A4 inhibitor cannot be avoided, a close clinical surveillance is warranted, and a dose-adjustment of docetaxel may be suitable during the treatment with the strong CYP3A4 inhibitor.
- Subjects should be closely monitored when DS-1062a is concomitantly used with drugs that inhibit CYP3A, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, multidrug and toxin extrusion transporter (MATE) 2-K, P-glycoprotein, breast cancer resistance protein (BCRP), and multidrug resistance-associated protein (MRP) 1.
- Live vaccines are not recommended during the study, except for emergency use per Investigator's discretion.

Permitted therapies/products

- Hematopoietic growth factors may be used for prophylaxis or treatment based on the clinical judgment of the Investigator. Subjects receiving docetaxel may receive growth factors (including G-CSF and erythropoietin) at the discretion of the Investigator.
- Concomitant use of dietary supplements, medications not prescribed by the Investigator, and alternative/complementary treatments is discouraged, but not prohibited.
- Prophylactic or supportive treatment of study-drug induced AEs may be used per Investigator's discretion and/or institutional guidelines.
- Based on the currently available clinical safety data, it is recommended that subjects receive prophylactic antiemetic agents prior to infusion of DS-1062a and on subsequent days. Antiemetics such as 5-hydroxytryptamine receptor antagonists or neurokinin-1 receptor antagonists or neurokinin-1 receptor antagonists and/or steroids (eg, dexamethasone) should be considered and administered in accordance with the prescribing information or institutional guidelines.

Study assessments

Radiographic tumor assessments will include all known or suspected sites of disease, as per RECIST v1.1. Imaging must include chest and abdomen CT or MRI scans, and brain CT or MRI scan at baseline (Screening) for all subjects. Subjects with brain metastases at baseline should have brain MRI or CT scan performed every 6 weeks (±7 days) from randomization. Additional brain imaging may be performed as needed clinically.

The CT scans should be performed with contrast agents unless contraindicated for medical reasons. Assessment of response will be made by BICR and the Investigator based on RECIST v1.1. Tumor assessments will continue regardless of study treatment discontinuation or start of new anticancer therapy until radiographic disease progression is assessed by Investigator and by BICR.

Patients who discontinue study treatment for reasons other than radiographic disease progression will continue to undergo tumor assessments every 6 weeks during the Follow-up Period until radiographic disease progression as assessed by Investigator, death, lost to follow-up, or withdrawal of consent. One additional tumor assessment performed at 6 weeks (±7 days) after Investigator-assessed radiographic disease progression will also be required (if BICR has not determined radiographic disease progression).

Ophthalmologic Assessments

Ophthalmologic assessments (OAs) including visual acuity testing, slit lamp examination, intraocular pressure measurement, fundoscopy, and fluorescein staining will be performed at screening, as clinically indicated, and at the end of treatment (EOT) visit by an ophthalmologist, or if unavailable, another licensed eye care provider.

Patient-reported outcomes

PROs will be collected electronically on site at baseline and at home thereafter.

The following PROs will be performed:

- EORTC-QLQ-LC13: 13-item lung cancer-specific questionnaire module except questions 36 and 37
- EORTC-QLQ-C30: assessment of the quality of life of cancer patients
- EQ-5D-5L: standardized instrument for measuring generic health status required for health technology assessments
- PRO-CTCAE: assessment of the impact of AEs on quality of life of cancer patients

Objectives

The primary objective of the study is to compare the efficacy of Dato-DX with that of docetaxel and demonstrate superiority in terms of either PFS or OS for subjects with NSCLC with or without actionable genomic alterations previously treated with platinum-based chemotherapy and at least one prior line of therapy.

This study has 2 independent primary endpoints of OS and PFS as assessed by BICR. The study will be considered positive if the hypothesis test for either one of these primary endpoints is successful.
The following statistical hypotheses will be tested:

- null hypothesis (H01): hazard ratio (HR) of PFS = 1 versus alternative hypothesis (H11): hazard ratio of PFS $\neq$ 1;
- null hypothesis (H02): hazard ratio of OS = 1 versus alternative hypothesis (H12): HR of OS $\neq$ 1

For PFS, if the participant has no evaluable RECIST assessment or does not have baseline data, they will be censored at the date of randomization, unless they die within 2 scheduled scans of baseline (12 weeks + 1 week allowing for a late assessment within the visit window) in which case they are treated as an event with date of death as the event date. Participants who have not progressed or died at the time of analysis are censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if the participant progresses or dies immediately after two or more consecutive missed visits, the participant is censored at the time of the latest evaluable RECIST 1.1 assessment prior to the two missed visits (Note: NE visit is not considered as missed visit).

The secondary objectives are as follows:

1. To further evaluate the efficacy of DS-1062a compared with docetaxel in terms of PFS as assessed by investigator per RECIST v1.1, objective response rate (ORR), duration of response (DoR), time to response (TTR), disease control rate (DCR), as assessed by BICR and by investigator per RECIST v1.1, patient-reported outcomes (PROs) including time to worsening of chest pain, cough, and breathlessness.
2. To further evaluate the safety of DS-1062a compared with docetaxel in terms of treatment-emergent adverse events (TEAE), and other safety parameters during the study.
3. To assess the PK of DS-1062a in terms of plasma concentrations and PK parameters of DS-1062a, total anti-TROP2 antibody, and MAAA-1181a in the full PK sampling cohort.

4. To assess the immunogenicity of DS-1062a in terms of prevalence and incidence of antidrug-antibody (ADA).

The exploratory objectives are as follows:

1. To evaluate PFS2 as assessed by local standard clinical practice for DS-1062a compared with that of docetaxel
2. To evaluate biomarkers that may associate with the clinical benefit from DS-1062a used to treat NSCLC.
3. To explore how changes in biomarkers may relate to exposure and clinical outcomes.
4. To evaluate pre-treatment tumor biopsy samples and archival tumor samples for key biomarkers that correlate with the clinical benefit from DS-1062a.
5. To evaluate exposure-response relationships for efficacy and safety endpoints.
6. To evaluate other PRO endpoints for DS-1062a compared with that of docetaxel.

Outcomes/endpoints

Table 41 Objectives and endpoints

Objectives	Outcome Measure	Endpoints	Category
	Title: Duration of response (DoR) **Description:** DoR as assessed by BICR and investigator per RECIST v1.1. **Time frame:** At the time of the primary analyses of PFS and OS.	DoR is defined as the time from the date of the first documentation of objective response (CR or PR) to the date of the first radiographic disease progression or death due to any cause, whichever occurred first.	Efficacy
	Title: Disease control rate (DCR) **Description:** DCR as assessed by BICR and investigator per RECIST v1.1. **Time frame:** At the time of the primary analyses of PFS and OS.	DCR is defined as the proportion of subjects who achieved a BOR of CR, PR, or stable disease (SD).	Efficacy
	Title: Time to response (TTR) **Description:** TTR as assessed by BICR and investigator per RECIST v1.1. **Time frame:** At the time of the primary analyses of PFS and OS.	TTR is defined as the time from randomization to the date of the first documentation of objective response (CR or PR) in responding subjects.	Efficacy
	Title: Time to deterioration (TTD) **Description:** TTD in any of the 3 symptoms of chest pain, cough, or dyspnea **Time frame:** At the time of the primary analyses of PFS and OS.	**Description:** • European Organisation for Research and Treatment of Cancer Quality of Life Lung Cancer 13 (EORTC QLQ-LC13), except questions 36 and 37 The TTD is defined as the time from randomization to first onset of a ≥10-point increase in cough, chest pain, or dyspnea, confirmed by a second	Efficacy

Objectives	Outcome Measure	Endpoints	Category
		≥10-point increase from randomization in the same symptom at the next scheduled assessment, or confirmed by death within 21 days of the first ≥10-point increase from randomization.	
To further evaluate the safety of Dato-DXd compared with docetaxel.	**Title:** Treatment-emergent adverse events (TEAEs) and other safety parameters during the study **Description:** Descriptive statistics of safety endpoints. **Time frame:** Continuous monitoring and reported at the time of the primary analyses of PFS and OS.	TEAEs, serious adverse events (SAEs), adverse events of special interest (AESIs), Eastern Cooperative Oncology Group performance status (ECOG PS), vital sign measurements, standard clinical laboratory parameters (hematology, serum chemistry, and urinalysis), electrocardiogram (ECG) parameters, echocardiogram (ECHO)/multigated acquisition (MUGA) scan findings, and ophthalmologic findings. Adverse events (AEs) are coded by the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) and both AEs and laboratory test results are graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.	Safety
To assess the pharmacokinetics (PK) of Dato-DXd	**Title:** PK **Description:** Plasma concentrations	Plasma concentrations at each time point and PK parameters (maximum plasma	PK

Objectives	Outcome Measure	Endpoints	Category
	and PK parameters of Dato-DXd, total anti-trophoblast cell surface protein 2 (TROP2) antibody, and DXd (payload) in the full PK sampling cohort. **Time frame**: At the time of the primary analyses of PFS and OS.	concentration [Cmax], time to reach maximum plasma concentration [Tmax], area under the plasma concentration-time curve up to the last quantifiable time [AUClast], area under the plasma concentration-time curve during dosing interval [AUCtau]). If data permit: area under the plasma concentration-time curve up to infinity (AUCinf), terminal half-life (t1/2), total body clearance (CL), volume of distribution at steady-state (Vss), volume of distribution based on the terminal phase (Vz), and elimination rate constant associated with the terminal phase (Kel) of Dato-DXd, total anti-TROP2 antibody, and DXd in the full PK sampling cohort.	
To assess the immunogenicity of Dato-DXd	**Title:** Immunogenicity **Description:** Anti-drug antibody (ADA) prevalence and incidence. **Time frame:** At the time of the primary analyses of PFS and OS.	ADA prevalence: the proportion of subjects who are ADA positive at any point in time (at baseline or post-baseline). ADA incidence: the proportion of subjects having treatment-emergent ADAs. ADA titers and neutralizing antibodies are determined when ADA is positive.	Immunogenicity

Objectives	Outcome Measure	Endpoints	Category
Exploratory			
To evaluate second progression-free survival (PFS2) for Dato-DXd compared with that of docetaxel	**Title:** PFS2 **Description:** PFS2 as assessed by local standard clinical practice **Time frame:** At the time of the primary analyses of PFS and OS.	PFS2 is defined as the time from date of randomization to the first documented progression on next-line therapy or death due to any cause, whichever occurs first.	Efficacy
To evaluate biomarkers that may associate with the clinical benefit from Dato-DXd used to treat NSCLC.	Not applicable.	Tumor TROP2 expression (central laboratory analysis) Other biomarkers including genomic alterations, gene expression, protein expression, and pharmacogenomics may be measured in tumor and blood samples.	Biomarkers and pharmacogenomics
To explore how changes in biomarkers may relate to exposure and clinical outcomes.	Not applicable.	Biomarkers are assessed in cell-free DNA pre- and post-treatment.	Biomarkers
To evaluate exposure-response relationships for efficacy and safety endpoints.	Not applicable.	Characterize population PK and its relationship with efficacy and safety endpoints, and evaluate the effects of covariates (eg, body weight) on PK, efficacy, and safety.	PK
To evaluate patient-reported outcome (PRO) endpoints for Dato-DXd compared with that of docetaxel.	**Title:** PRO • Change from baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) functioning scales. • Change from baseline in global	**Description:** EORTC QLQ-C30 EORTC QLQ-LC13 (except questions 36 and 37) EQ-5D-5L PRO-CTCAE 1-3; 24; 28-29; 51; 74	PRO

Objectives	Outcome Measure	Endpoints	Category
	health (EORTC QLQ-C30 question No. 29). • Change from baseline in quality of life (EORTC QLQ-C30 question No. 30). • Change from baseline in overall health status (EuroQol Questionnaire-5 dimensions-5 levels [EQ-5D-5L] Visual Analog Scale). • Summary statistics (ie, frequency distributions) for each PRO version of the Common Terminology Criteria for Adverse Events (CTCAE). **Time frame:** At the time of the primary analyses of PFS and OS.		

Abbreviations: ADA=anti-drug antibody; AE=adverse event; AESI=adverse event of special interest; AGA=actionable genomic alteration; AUCinf=area under the plasma concentration-time curve up to infinity; AUClast=area under the plasma concentration-time curve up to the last quantifiable time; AUCtau=area under the plasma concentration-time curve during dosing interval; BICR=blinded independent central review; BOR=best overall response; CL=total body clearance; Cmax=maximum plasma concentration; CR=complete response; DCR=disease control rate; DNA=deoxyribonucleic acid; DoR=duration of response; DXd=payload; ECG=electrocardiogram; ECHO=echocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-LC13=European Organisation for Research and Treatment of Cancer Quality of Life Lung Cancer 13; EQ-5D-5L=EuroQol Questionnaire-5 dimensions-5 levels; Kel=elimination rate constant associated with the terminal phase; DXd=payload; MedDRA=Medical Dictionary for Regulatory Activities; MUGA=multigated acquisition; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PFS2=second progression-free survival; PK=pharmacokinetic(s); PR=partial response; PRO=patient-reported outcome; PRO-CTCAE=patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE=serious adverse event; SD=stable disease; t1/2=terminal half-life; TEAE=treatment-emergent adverse event; Tmax=time to reach maximum plasma concentration; TROP2=trophoblast cell surface protein 2; TTD=time to deterioration; TTR=time to response; Vss=volume of distribution at steady-state; Vz=volume of distribution based on the terminal phase.

Sample size

A total of approximately 590 subjects will be randomized to the DS-1062a arm or the docetaxel arm in a 1:1 ratio (295/arm), stratified by documented actionable genomic alteration (present versus absent), histology (squamous versus non-squamous), most immediate prior therapy included anti-PD-1/anti-PD-L1 immunotherapy (yes versus no) and geographical region (US/ Japan/Western Europe versus ROW).

A minimum of 15% of the total study population will comprise subjects with actionable genomic alterations.

For the primary analysis of PFS, approximately 425 PFS events by BICR assessment will be required to have approximately 97% power to detect a hazard ratio of 0.64 at a 2-sided significance level of 0.008, which corresponds to an improvement of 2.1 months in median PFS from 3.8 months in the docetaxel arm to 5.9 months in the DS-1062a arm.

For the primary analysis of OS, approximately 413 OS events will be required to have at least 90% power to detect a hazard ratio of 0.72 at 2-sided significance level of 0.042, which corresponds to an improvement of 3.1 months in median OS from 8 months in the docetaxel arm to 11.1 months in the DS-1062a arm.

Assuming an exponential distribution of OS time, a ramp-up period of 13 months and 48 subjects per month afterwards, the study needs a total of approximately 590 subjects (295 per arm), over an enrollment period of approximately 19 months. The primary analysis for PFS as assessed by

BICR will be performed when approximately 425 PFS events have been reached, and at least 4 months after the last subject has been randomized. The total of approximately 413 OS events would be achieved by approximately 33 months for the primary analysis of OS.

Randomisation and blinding (masking)

Study TL01 (TROPION-Lung01) was a randomized, open-label study.

Patients were randomized at a 1:1 ratio to receive Dato-DXd 6 mg/kg or docetaxel 75 mg/m2, administered IV on Day 1 of each 21-day cycle. Randomization was stratified by the following:

- Histology (squamous versus non-squamous)
- Most immediate prior therapy included anti PD (L)1 immunotherapy (yes versus no)
- Geographical region (United States [US]/Japan/Western Europe versus Rest of World).
- Documented AGA (present versus absent)

Randomization was managed through an IXRS for patients meeting all eligibility criteria. No crossover between study treatment arms was allowed.

This study was designed as an open-label study for the following reasons: 1) differences in pre-treatments for Dato-DXd and for docetaxel, and 2) potentially significant differences in toxicity profiles between the 2 arms. Furthermore, PFS by blinded independent central review (BICR per RECIST v1.1) is used as one of the primary endpoints in the study in order to limit the reader-evaluation bias caused by potential subjective elements influencing the disease progression evaluation in the open-label setting.

Radiographic imaging scans will be sent to a central imaging vendor for BICR assessment. Sites will send subject scans to the central imaging vendor after each tumor assessment visit. If BICR has not determined radiographic disease progression by the time of the 1 additional tumor assessment performed at 6 weeks (±7 days) after Investigator-assessed radiographic disease progression, then sites will retrieve and send subject radiographic scans that are performed as part of local standard clinical practice to the central vendor during the subject's follow-up, or as part of subsequent therapy, including investigational agents, until BICR determines radiographic disease progression. The Sponsor will notify the site to stop sending further scans to the central vendor when BICR determines

radiographic disease progression OR until 7 months after the date of Investigator-assessed radiographic disease progression for the subject, whichever occurs first.

If BICR determines radiographic disease progression before the Investigator, sites will not be notified to stop sending scans until the Investigator determines radiographic disease progression. It is recommended that sites continue to follow a scanning interval frequency of every 6 weeks (±7 days) during the standard of practice follow-up of the subject as long as it is not interfering with the subject's standard of care. The same imaging technique (CT or MRI) used to characterize each identified and reported lesion at baseline should be used in the subsequent tumor assessments. For further instructions, refer to the Imaging Site Manual which will be provided to the site.

The results of BICR assessment of the subject scans will not be shared with the site or Investigator. The Investigator will manage the subject and make treatment decisions based solely or Investigator/local assessment and will be completely independent of BICR.

The results of BICR-assessed tumor response will be used for the primary analysis of PFS in this study.

Assessment of response by BICR and the Investigator will be based on RECIST v1.1. Tumor assessments will continue regardless of study treatment discontinuation or start of new anticancer therapy until radiographic disease progression is assessed by Investigator and by BICR.

Statistical methods

Analysis sets

All Randomized Subjects

All Randomized Subjects will include all subjects who have been randomized into the study. If a subject is randomized more than once into this study, all subject IDs will be retained.

Full Analysis Set (FAS)

The Full Analysis Set (FAS) will include all subjects who have been randomized into the study. If a subject is randomized more than once into this study, only one subject ID will be included in FAS. FAS will be the primary analysis set for all efficacy analysis.

Safety Analysis Set

The safety analysis set will include all subjects from FAS who received at least 1 dose of study treatment. Subjects will be classified according to the study treatment assigned at randomization unless the incorrect treatment(s) are received throughout the dosing period in which case subjects will be classified according to the first treatment received.

Pharmacokinetic (PK) Analysis Set

The PK analysis set will include all subjects from FAS who received at least 1 dose of DS-1062 and had at least 1 PK sample with measurable plasma concentration of DS-1062, total anti- TROP2 antibody or MAAA-1181a. It will be used in the analysis of PK data.

Per-Protocol Analysis Set (PPS)

The PPS includes all subjects of the FAS who complied sufficiently with the protocol with respect to exposure to study treatment, availability of tumor assessments, and absence of major protocol deviations likely to impact efficacy outcome.

Primary endpoints

PFS by BICR

PFS by BICR will be summarized and graphically presented using the Kaplan-Meier method, stratified by the randomization stratification factors. Median event time with 2-sided 95% CI using the Brookmeyer and Crowley method will be presented. In addition, the event-free probability at different time points, e.g. 3, 6, 9 months etc., will be estimated with corresponding 2-sided 95% CIs using the Greenwood's formula. These time points may be adjusted according to actual data observed in the study without amendment to this SAP. Reasons for censoring will also be summarized.

The Cox proportional hazards model, stratified by the randomization stratification factors, will be fitted to estimate the hazard ratio of PFS by BICR between the treatment versus the control arm (docetaxel) and the corresponding 95% CI.

Overall Type I error rate will be maintained at or below 0.05 (2-sided) by allocating alpha=0.008 to the PFS comparison and alpha=0.042 to the OS comparison.

Supportive Analyses for PFS by BICR.

The primary analyses will be repeated using subjects from the Per Protocol Set (PPS) if the difference between the number of subjects in FAS and PPS, calculated by (the number of subjects in FAS the number of subjects in PPS)/(the number of subjects in FAS), is >5%. A stratified Cox proportional hazards model, stratified by the randomization stratification factors, will be fitted to evaluate the effect of other baseline demographic or disease characteristics on the estimated hazard ratio.

Sensitivity Analyses for PFS by BICR

As a sensitivity analysis to assess the impact of stratification on primary efficacy analysis of PFS by BICR, the two treatment arms will be compared using an unstratified log-rank test. The same censoring rules used for the primary efficacy analysis will be applied. The HR for treatment effect with associated 95% CI will also be estimated using unstratified Cox proportional hazards model. The stratified Kaplan-Meier analysis and stratified Cox proportional hazards model will also be repeated for PFS by BICR using strata derived from the clinical database instead of strata from IXRS.

To evaluate the impact of informative censoring on PFS by BICR when a subject immediately discontinued tumor assessments after Investigator-assessed radiographic disease progression (PD) without PD by BICR, a sensitivity analysis will be conducted. This analysis will impute PFS by BICR of subjects with informative censoring by using PFS by BICR from subjects who had PD by Investigator around the same time and had longer follow-up for PFS by BICR (i.e., in such subjects BICR did not verify the PD by Investigator either and tumor assessments continued).

In addition, PFS by BICR will be assessed by 1) censoring subjects due to the initiation of new non-palliative anti-cancer therapy; 2) considering the initiation of new non-palliative anti-cancer therapy as an PFS event, respectively.

A sensitivity analysis will also be performed using all documented events, i.e., without censoring subjects who had 2 consecutive missed tumor assessments.

Sensitivity analyses will be performed to assess possible evaluation-time bias for PFS by BICR that may be introduced if tumor scans are not performed at the protocol-scheduled frequency (every 6 weeks ± 7 days), especially after Investigator PD is claimed without BICR PD. The midpoint between the time of progression and the previous RECIST assessment (either the baseline tumor assessment or the previous adequate post baseline tumor assessment) will be analyzed using a stratified log-rank test, as described for the primary analysis of PFS. For subjects whose death was treated as PFS event, the date of death will be used to derive the PFS time used in the analysis.

OS

The primary analysis of OS will be similar to the primary analysis of PFS by BICR defined for PFS by BICR. Overall Type I error rate will be maintained at or below 0.05 (2-sided) by allocating alpha=0.008 to the PFS comparison and alpha=0.042 to the OS comparison.

Supportive Analyses for OS

The supportive analyses for PFS by BICR will be repeated for OS.

Sensitivity Analyses for OS

The sensitivity analyses for PFS by BICR for 1) unstratified analyses and 2) using strata as derived based on clinical database will be repeated for OS.

Secondary endpoints

PFS by Investigator will be analyzed in a similar manner as PFS by BICR.

The estimate of ORR and its 2-sided 95% exact (Clopper-Pearson) CI will be provided by treatment arm.

DoR will be analyzed in a similar manner as the primary endpoints, except that a hazard ratio will not be generated for DoR.

The estimate of DCR and its 2-sided 95% exact (Clopper-Pearson) CI will be provided by treatment arm.

TTR will be summarized descriptively.

Planned subgroup analyses

Subgroup analyses for PFS by BICR and OS will be performed only if there are at least 20 events in each subgroup, respectively.

Subgroup analyses will be performed on the full analysis set using the following subgroups:

-AGA status (absent, present)

-Histology (squamous, non-squamous)

-Region (USA/Japan/Western Europe, ROW)

-Last prior treatment including -PD- -PD-L1 monoclonal antibody therapy (Yes, No)

-The last ECOG PS before randomization (0, 1)

-Gender (male, female)

-Age (<65, ≥65 years)

-Race (Caucasian/White, Asian, Black/African American, Other)

-Lines of prior systemic therapy (1, 2)

-Smoking status (former/current smoker, never smoked)

-Brain metastases at baseline per BICR (with brain metastases, without brain metastases)

-Protocol version subjects were randomized under (v1.0-3.0, v4.0 and later)

Wherever applicable, the subgroups are based on the last non-missing values before the randomization date. For histology, region, and last prior treatment including -PD- -PD-L1 monoclonal antibody therapy, values collected at randomization in IXRS will be used to determine subgroups.

All the subgroup analyses are intended to explore the consistency (homogeneity) of treatment effect.

No adjustment for multiplicity will be performed. The unstratified HR and its corresponding 95% CI will be computed per subgroup level. The HR and 95% CI for all subgroups will be presented in a forest plot, along with the results of the overall primary analyses.

Subgroup analyses will be conducted for PFS by investigator, OS, ORR, and DoR based on randomization period (before and after protocol version 4.0 to include subjects with actionable genomic alterations) as well as by presence of actionable genomic alterations (present versus absent).

Error probabilities, adjustment for multiplicity and interim analyses

Interim analysis

There is no planned interim analysis for PFS. An interim analysis of OS for superiority is planned at the time of PFS primary analysis. It is projected that approximately 293 deaths will have been observed at the OS interim analysis, i.e., 71% of information fraction (IF, i.e., 293 out of the targeted 413 OS events). The study may be stopped at OS interim analysis if the prespecified superiority boundary is crossed.

A group sequential design utilizing 2-look Lan-DeMets alpha spending -Fleming stop boundary will be used to construct the efficacy stopping boundaries with an overall 2-sided significance level of 0.042. If the OS interim analysis is carried out exactly after 71% of target total of events, the efficacy boundary at the interim analysis is calculated as 0.012 in p-value (2-sided) scale; the observed 2-sided p-value has to be less than these efficacy boundaries to conclude superior efficacy at the interim analysis.

Since the observed number of events at the data cut-off date for OS interim analysis may not be exactly equal to the planned number of events, the efficacy boundaries will need to be recalculated based on the actual number of observed events using the pre-specified alpha spending function.

For PFS primary analysis and OS interim analysis, an independent statistician will perform the analyses for the independent data monitoring committee (DMC). Further details will be described in the DMC Charter.

There will be planned periodic data reviews focusing on safety assessments during the study by the independent DMC.

Multiplicity

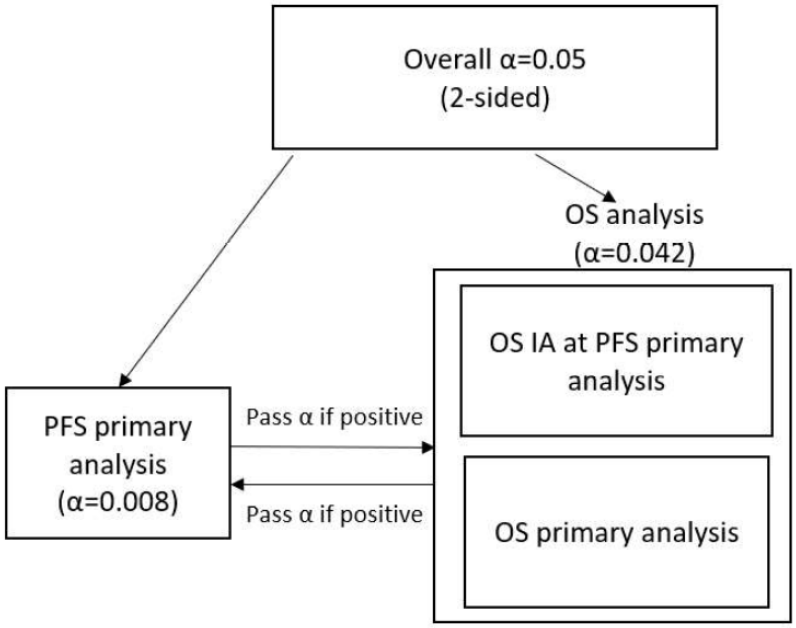
There are 2 potential sources of multiplicity:

Multiplicity arising due to testing two endpoints PFS and OS

Multiplicity arising due to the group sequential design for OS

To address the first multiplicity issue, the overall alpha 0.05 (2-sided) will be split between the two primary efficacy endpoints PFS and OS. PFS will be tested under 2-sided alpha of 0.008, and OS will be tested under 2-sided alpha of 0.042. Alpha is subject to rollover between PFS and OS. The overall alpha for PFS will be 2-sided 0.05 if OS is positive at either IA or primary analysis. If PFS is positive, the overall alpha for OS will be 2-sided 0.05 and the efficacy boundaries for OS IA and primary analysis will be recalculated using Lan-DeMets-Fleming boundary. The testing process and alpha splitting is shown in the schema below.

Figure 41 Testing process and alpha splitting



To address the second issue, a group sequential design utilizing 2-look Lan-DeMets alpha -Fleming boundary, will be used to construct the efficacy stopping boundaries for OS. This guarantees the protection of the overall significance level across the 2 hypotheses and the repeated testing of the OS hypotheses in the interim and the primary analyses.

Table 42 Efficacy analysis timing and boundaries for PFS and OS displays the analyses expected for the two primary endpoints and the associated efficacy boundaries if the analyses are performed at the planned number of events as shown in the table.

Table 42 Efficacy analysis timing and boundaries for PFS and OS

Endpoint	PFS	OS	
Analysis	Primary	Interim	Primary
Analysis cutoff trigger	425 PFS events per BICR	425 PFS events per BICR	413 OS events
Number of events (Information fraction)	425 (100%)	293 (71%)	413 (100%)
p-value boundary			
without alpha rollover	p<0.008	p<0.012	p<0.038
with alpha rollover	p<0.05	p<0.016	p<0.045
Approximate HR boundary [a]			
without alpha rollover	HR < 0.773	HR < 0.746	HR < 0.816
with alpha rollover	HR < 0.827	HR < 0.754	HR < 0.821

Note: The observed number of events at OS interim analysis may not match the planned number of events. The p-value efficacy boundary will be updated based on the actual number of observed events using the pre-specified alpha spending function.
[a] The HR boundaries are estimated based on the same assumptions that are used for sample size calculations. Statistical testing will be based on p-value boundaries and will not be based on approximate HR boundaries.

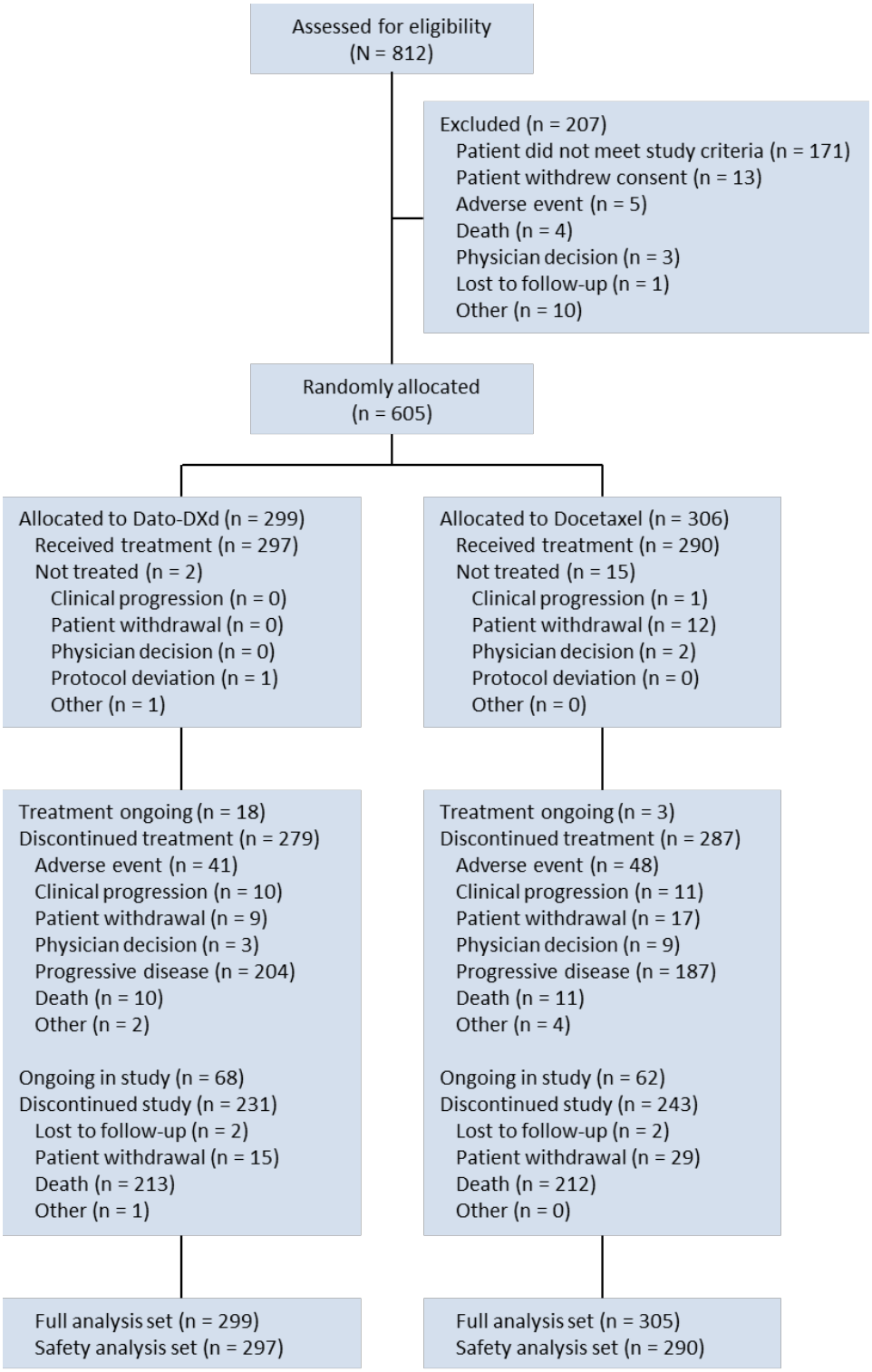
Clarification: AGA was added as a stratification factor in Protocol Version 4.0, with updates made to the randomization system (IXRS) and documentation. Patients enrolled under earlier versions were classified into the non-AGA group. The primary and subgroup analyses were pre-specified to use the IXRS data, with sensitivity analyses planned using CRF data for discrepancies. Due to low event

counts, AGA and another factor were removed from the primary PFS and interim OS analyses. Post hoc analyses were performed using CRF data due to some incorrect randomizations. The response adequately addresses the question, explaining the handling of AGA and justifying analysis plan changes.

Results

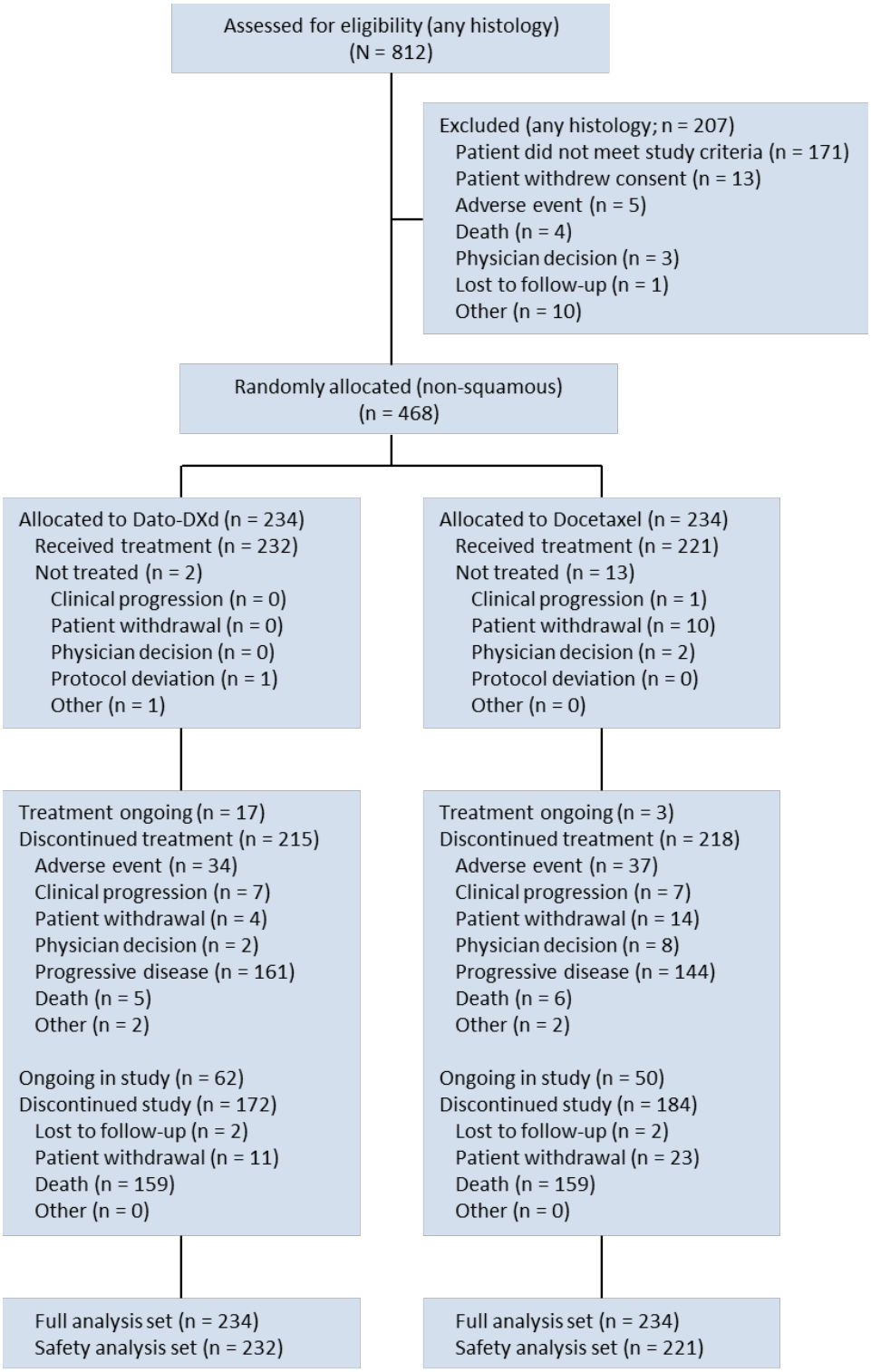
Participant flow

Figure 42 Subject Disposition Flow Diagram (FAS)



Note: One subject was randomized twice, both times in the docetaxel arm; treatment was not initiated under the first subject identifier and only the second subject identifier was included in the analysis.
Source: Module 1, Appendix 7 Table 1

Figure 43 Subject Disposition Flow Diagram (Non-squamous Population per CRF)



Note: Histology was not collected for screening failures; therefore, subjects screened and subjects excluded included any histology.
Source: Module 1, Appendix 7 Table 2

Table 43: Summary of Reasons for Screen Failure (All Screened Subjects)

	Total n (%)
Screened[a]	812
Screen failure[b]	207
Screen failure reason	
Patient did not meet study criteria	171 (82.6)
Did not satisfy inclusion/exclusion criteria	170 (82.1)
The patient doesn't meet inclusion criteria n.11, because he has low platelets count (93000/µL)	1 (0.5)
Patient withdrew consent	13 (6.3)
Withdrawal by subject	12 (5.8)
Withdrawn informed consent	1 (0.5)
Adverse event	5 (2.4)
Death	4 (2.0)
Death	2 (1.0)
Patient died on 08 Apr 2022	1 (0.5)
The patient has died for disease progression	1 (0.5)
Physician decision	3 (1.4)
Lost to follow-up	1 (0.5)
Other	10 (5.0)
28 days passed from the time of ICF signature	1 (0.5)
Cannot perform pulmonary biopsy due to high risk of iatrogenia when presenting constant cough	1 (0.5)
Considering of impact on vitreous hemorrhage due to administration of investigational drug.	1 (0.5)
Screening Period duration (28 days) exceeded	1 (0.5)
Subject was taking concomitant forbidden medication	1 (0.5)
Unexpected event led to a re-screen	1 (0.5)
Duplicated data	1 (0.5)
The patient does not want to rebiopsy	1 (0.5)
The reason was screening period completed and the patient started another treatment.	1 (0.5)
Urgent therapy	1 (0.5)

[a] Subjects who signed ICF and were screened. N=812 includes a subject who was screened and randomized twice (both times in the docetaxel arm); N=811 unique subjects screened.
[b] Percentages are based on the number of screen failure subjects.
Note: The table presents the reasons for screen failures as reported by the sites.
DCO date: 29 Mar 2023
Source: Module 1, Appendix 4 MAA D120 Table Q111; Module 1, Appendix 7 Table 1

Table 44 Subject Disposition (All Screened Subjects)

	Dato-DXd n (%)	Docetaxel n (%)	Total n (%)
Screened [a]			811
Screen Failure			206
Randomized	299	306	605
Full Analysis Set	299	305	604
Treated [b]	297 (99.3)	290 (95.1)	587 (97.2)
Not Treated [b]	2 (0.7)	15 (4.9)	17 (2.8)
Reason Not Treated			
Clinical Progression	0	1 (0.3)	1 (0.2)
Withdrawal by Subject	0	12 (3.9)	12 (2.0)
Physician Decision	0	2 (0.7)	2 (0.3)
Protocol Deviation	1 (0.3)	0	1 (0.2)
Other	1 (0.3)	0	1 (0.2)
Treatment Status [c]			
Treated	297	290	587
Ongoing on Study Drug	52 (17.5)	17 (5.9)	69 (11.8)
Discontinued from Study Drug	245 (82.5)	273 (94.1)	518 (88.2)
Primary Reason for Discontinuation			
Death	10 (3.4)	10 (3.4)	20 (3.4)
Adverse Event	39 (13.1)	46 (15.9)	85 (14.5)
Progressive Disease	173 (58.2)	180 (62.1)	353 (60.1)
Clinical Progression	9 (3.0)	11 (3.8)	20 (3.4)
Withdrawal by Subject	9 (3.0)	14 (4.8)	23 (3.9)
Physician Decision	3 (1.0)	9 (3.1)	12 (2.0)
Other	2 (0.7)	3 (1.0)	5 (0.9)
Study Status [b]			
Ongoing in Study	136 (45.5)	121 (39.7)	257 (42.5)
Discontinued from Study	163 (54.5)	184 (60.3)	347 (57.5)
Primary Reason for Discontinuation			
Lost to Follow-up	1 (0.3)	2 (0.7)	3 (0.5)
Death	145 (48.5)	153 (50.2)	298 (49.3)
Withdrawal by Subject	15 (5.0)	29 (9.5)	44 (7.3)
Other	2 (0.7)	0	2 (0.3)

Abbreviations: DCO=data cut-off; ID=identification number.
If a subject was randomized more than once, only 1 of the subject IDs is included in the Full Analysis Set.
[a] Subjects who signed Inform Consent Form and were screened.
[b] Percentages are based on the number of subjects in the Full Analysis Set.
[c] Percentages are based on the number of treated subjects.
DCO date: 29 Mar 2023
Source: Table 14.1.1.1

Recruitment

The study TL01(TROPION-Lung01) is a global study, which was conducted in 196 sites in 24 countries: **Europe** (**Belgium, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Poland, Spain, Switzerland, United Kingdom**), America (Canada, United States, Mexico, Argentina, Brazil), Australia, Asia (China, Hong Kong, Japan, Republic of Korea, Singapore, Taiwan) and Russia. A total of 131 sites in 23 countries in Europe, Asia, North America, South America, and Australia randomized subjects.

Date first patient signed informed consent form: 04-FEB-2021.

Date first patient randomized: 17-FEB-2021.

Date last patient randomized: 07-NOV-2022.

Date last patient completed: Study ongoing.

Data cut-off (DCO) for primary analysis of PFS: 29-MAR-2023.

The median follow-up time for **PFS** was 10.9 (95% CI 9.8, 12.5) months in the Dato-DXd arm and 9.6 (8.2, 11.9) months in the docetaxel arm.

The median follow-up time of **OS** was 12.4 months (95% CI 11.5, 13.6) for Dato-DXd and 12.4 months (95% CI: 11.3, 13.1) for docetaxel.

Conduct of the study

The original Protocol Version 1.0 dated 05 Oct 2020 was amended 3 times as of the DCO date of 29 Mar 2023.

Table 45 Top-level Protocol Amendment Changes

Document Version, Document Date	Main Purpose for Amendment
Version 4.0, 20 Jan 2022	The main purpose of this amendment was to allow non-small cell lung cancer subjects with known actionable genomic alterations to be included in the DS1062-A-U301 study based on global regulatory feedback.
Version 3.0, 01 Oct 2021	The main purpose of this amendment was to allow for the submission of tumor tissue previously retrieved from a biopsy procedure performed within 2 years prior to the subject signing informed consent, if available, instead of a pre-treatment biopsy procedure performed during screening. Recommendations from global regulatory authorities and updates related to safety were also incorporated.
Version 2.0, 03 Mar 2021	The main purpose of this amendment was to incorporate recommendations from global regulatory authorities including updates to the primary and secondary endpoints of the study based on recent developments in this indication.
Version 1.0, 05 Oct 2020	Original protocol.

Source: CSR DS1062-A-U301 page 68

Clarification: An undetermined number of patients were still randomised under V1-3 of the protocol after adopting V4 (20-JAN-2022), but all 97 AGA+ (according to IXRS) were randomised after 20-JAN-2022.

Table 46 Major Protocol Deviations (Full Analysis Set)

Category Deviation	Dato-DXd (N=299) n (%)	Docetaxel (N=305) n (%)	Total (N=604) n (%)
Subjects with Any Major Protocol Deviation	151 (50.5)	140 (45.9)	291 (48.2)
Inclusion Criteria	18 (6.0)	22 (7.2)	40 (6.6)
Inclusion Criterion 01	0	1 (0.3)	1 (0.2)
Inclusion Criterion 04	0	6 (2.0)	6 (1.0)
Inclusion Criterion 06	11 (3.7)	10 (3.3)	21 (3.5)
Inclusion Criterion 07	3 (1.0)	3 (1.0)	6 (1.0)
Inclusion Criterion 11	1 (0.3)	1 (0.3)	2 (0.3)
Inclusion Criterion 12	1 (0.3)	0	1 (0.2)
Inclusion Criterion 15	1 (0.3)	0	1 (0.2)
Inclusion Criterion 16	4 (1.3)	2 (0.7)	6 (1.0)
Exclusion Criteria	6 (2.0)	0	6 (1.0)
Exclusion Criterion 01	1 (0.3)	0	1 (0.2)
Exclusion Criterion 07	1 (0.3)	0	1 (0.2)
Exclusion Criterion 08	1 (0.3)	0	1 (0.2)
Exclusion Criterion 09	1 (0.3)	0	1 (0.2)
Exclusion Criterion 12	1 (0.3)	0	1 (0.2)
Exclusion Criterion 14	1 (0.3)	0	1 (0.2)
Concomitant and Prohibited Medications or Non-Drug Therapy	10 (3.3)	2 (0.7)	12 (2.0)
Eligibility Criteria	21 (7.0)	23 (7.5)	44 (7.3)
Informed Consent	6 (2.0)	30 (9.8)	36 (6.0)
Investigational Product	15 (5.0)	8 (2.6)	23 (3.8)
Serious Adverse Event Reporting	15 (5.0)	8 (2.6)	23 (3.8)
Study Procedures	123 (41.1)	118 (38.7)	241 (39.9)

Abbreviation: DCO=data cut-off.
A subject may have more than 1 protocol deviation under each category and is counted once in that category.
Percentages are based on the number of subjects in the Full Analysis Set.
DCO date: 29 Mar 2023
Source: Table 14.1.1.2, Listing 16.2.2.3

Source: CSR DS1062-A-U301 page 89

The applicant stated that the study was conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP; CPMP/ICH/135/95), and applicable regulatory requirement(s) including the following:

- European Commission Directive (2001/20/EC Apr 2001) and/or
- European Commission Directive (2005/28/EC Apr 2005) and/or
- United States (US) Food and Drug Administration GCP Regulations: Code of Federal Regulations Title 21, parts 11, 50, 54, 56 and 312 as appropriate and/or
- Japanese Ministry of Health, Labor and Welfare Ordinance No. 28 of 27 March 1997 and/or

- The Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics No. 1 of 25 November 2014
- Other applicable local regulations

Baseline data

Table 47 Demographic and Baseline Characteristics (Full Analysis Set)

	Dato-DXd (N=299)	Docetaxel (N=305)	Total (N=604)
Age (years) [a]			
n	299	305	604
Mean	62.7	62.6	62.6
Standard Deviation	9.09	10.28	9.70
Median	63.0	64.0	64.0
Minimum	26	24	24
Maximum	84	88	88
<65 years, n (%)	162 (54.2)	155 (50.8)	317 (52.5)
≥65 years, n (%)	137 (45.8)	150 (49.2)	287 (47.5)
<75 years, n (%)	278 (93.0)	279 (91.5)	557 (92.2)
≥75 years, n (%)	21 (7.0)	26 (8.5)	47 (7.8)
Sex, n (%)			
Male	183 (61.2)	210 (68.9)	393 (65.1)
Female	116 (38.8)	95 (31.1)	211 (34.9)
Race, n (%)			
American Indian or Alaska Native	1 (0.3)	0	1 (0.2)
Asian	119 (39.8)	120 (39.3)	239 (39.6)
Black or African American	6 (2.0)	4 (1.3)	10 (1.7)
Native Hawaiian or Other Pacific Islander	0	0	0
White	123 (41.1)	126 (41.3)	249 (41.2)
Other	42 (14.0)	47 (15.4)	89 (14.7)
Missing	8 (2.7)	8 (2.6)	16 (2.6)
Ethnicity, n (%)			
Hispanic or Latino	10 (3.3)	8 (2.6)	18 (3.0)
Not Hispanic or Latino	251 (83.9)	253 (83.0)	504 (83.4)
Unknown	30 (10.0)	36 (11.8)	66 (10.9)
Missing	8 (2.7)	8 (2.6)	16 (2.6)
Region/Country Enrollment			
North America	39 (13.0)	26 (8.5)	65 (10.8)
Canada	4 (1.3)	6 (2.0)	10 (1.7)
Mexico	2 (0.7)	3 (1.0)	5 (0.8)
United States	33 (11.0)	17 (5.6)	50 (8.3)
South America	3 (1.0)	1 (0.3)	4 (0.7)
Argentina	3 (1.0)	1 (0.3)	4 (0.7)
Asia	113 (37.8)	118 (38.7)	231 (38.2)
China	5 (1.7)	7 (2.3)	12 (2.0)

	Dato-DXd (N=299)	Docetaxel (N=305)	Total (N=604)
Hong Kong, China	1 (0.3)	0	1 (0.2)
Japan	52 (17.4)	55 (18.0)	107 (17.7)
Republic of Korea	47 (15.7)	45 (14.8)	92 (15.2)
Singapore	1 (0.3)	3 (1.0)	4 (0.7)
Taiwan	7 (2.3)	8 (2.6)	15 (2.5)
Europe	137 (45.8)	152 (49.8)	289 (47.8)
Belgium	6 (2.0)	6 (2.0)	12 (2.0)
Czech Republic	0	4 (1.3)	4 (0.7)
France	47 (15.7)	49 (16.1)	96 (15.9)
Germany	4 (1.3)	4 (1.3)	8 (1.3)
Hungary	0	1 (0.3)	1 (0.2)
Italy	8 (2.7)	13 (4.3)	21 (3.5)
Netherlands	6 (2.0)	13 (4.3)	19 (3.1)
Poland	9 (3.0)	7 (2.3)	16 (2.6)
Russian Federation	8 (2.7)	8 (2.6)	16 (2.6)
Spain	46 (15.4)	42 (13.8)	88 (14.6)
Switzerland	2 (0.7)	3 (1.0)	5 (0.8)
United Kingdom	1 (0.3)	2 (0.7)	3 (0.5)
Australia	7 (2.3)	8 (2.6)	15 (2.5)
Australia	7 (2.3)	8 (2.6)	15 (2.5)
Screening ECOG Performance Status, n (%)			
0	89 (29.8)	94 (30.8)	183 (30.3)
1	210 (70.2)	211 (69.2)	421 (69.7)
Baseline ECOG Performance Status, n (%) [a]			
0	88 (29.4)	99 (32.5)	187 (31.0)
1	210 (70.2)	204 (66.9)	414 (68.5)
2	1 (0.3)	2 (0.7)	3 (0.5)
Height (cm) [a]			
n	299	304	603
Mean	167.02	167.83	167.43
Standard Deviation	8.843	8.966	8.907
Median	168.00	168.00	168.00
Minimum	144.0	138.4	138.4
Maximum	192.0	193.0	193.0
Baseline Weight (kg) [a]			
n	299	304	603
Mean	67.84	70.01	68.94
Standard Deviation	14.157	15.699	14.981

	Dato-DXd (N=299)	Docetaxel (N=305)	Total (N=604)
Median	65.80	68.85	67.10
Minimum	37.0	34.4	34.4
Maximum	127.0	129.0	129.0
Baseline Body Mass Index (kg/m^2) [a]			
n	299	304	603
Mean	24.24	24.72	24.48
Standard Deviation	4.248	4.649	4.458
Median	23.76	24.13	23.94
Minimum	15.3	15.1	15.1
Maximum	40.1	41.9	41.9
Baseline Body Surface Area (m^2) [a]			
n	299	304	603
Mean	1.74	1.78	1.76
Standard Deviation	0.208	0.214	0.212
Median	1.72	1.80	1.80
Minimum	1.0	1.2	1.0
Maximum	2.4	2.6	2.6
Smoking History, n (%)			
Never	61 (20.4)	52 (17.0)	113 (18.7)
Former	199 (66.6)	209 (68.5)	408 (67.5)
Current	39 (13.0)	42 (13.8)	81 (13.4)
Missing	0	2 (0.7)	2 (0.3)
Renal Function at Baseline, n (%) [a]			
Normal Function	106 (35.5)	120 (39.3)	226 (37.4)
Mild Impairment	140 (46.8)	126 (41.3)	266 (44.0)
Moderate Impairment	52 (17.4)	58 (19.0)	110 (18.2)
Severe Impairment	1 (0.3)	0	1 (0.2)
Missing	0	1 (0.3)	1 (0.2)
Hepatic Function at Baseline, n (%) [a]			
Normal Function	247 (82.6)	264 (86.6)	511 (84.6)
Mild Impairment	52 (17.4)	40 (13.1)	92 (15.2)
Moderate Impairment	0	1 (0.3)	1 (0.2)
Severe Impairment	0	0	0

Abbreviations: DCO=data cut-off; ECOG=Eastern Cooperative Oncology Group.
Percentages are based on the number of subjects in the Full Analysis Set.
[a] Baseline is defined as the last available assessment prior to the start of study treatment. If a subject was randomized but never treated, then the last available assessment on or prior to the randomization date was used as the baseline value.
DCO date: 29 Mar 2023
Source: Table 14.1.2.1

Table 48: Demographic and Baseline Characteristics in the Non-squamous Population

	Non-squamous		
	Dato-DXd (N = 234)	**Docetaxel (N = 234)**	**Total (N = 468)**
Age (years)[a]			
n	234	234	468
Mean	62.3	61.3	61.8
Standard deviation	9.29	10.64	9.99
Median	63.0	63.0	63.0
Minimum	26	24	24
Maximum	81	88	88
<65 years, n (%)	126 (53.8)	129 (55.1)	255 (54.5)
≥65 years, n (%)	108 (46.2)	105 (44.9)	213 (45.5)
<75 years, n (%)	220 (94.0)	218 (93.2)	438 (93.6)
≥75 years, n (%)	14 (6.0)	16 (6.8)	30 (6.4)
Sex, n (%)			
Male	134 (57.3)	150 (64.1)	284 (60.7)
Female	100 (42.7)	84 (35.9)	184 (39.3)
Race, n (%)			
American Indian or Alaska Native	1 (0.4)	0	1 (0.2)
Asian	92 (39.3)	96 (41.0)	188 (40.2)
Black or African American	4 (1.7)	3 (1.3)	7 (1.5)
Native Hawaiian or Other Pacific Islander	0	0	0
White	96 (41.0)	90 (38.5)	186 (39.7)
Other	35 (15.0)	39 (16.7)	74 (15.8)
Missing	6 (2.6)	6 (2.6)	12 (2.6)
Ethnicity, n (%)			
Hispanic or Latino	8 (3.4)	7 (3.0)	15 (3.2)
Not Hispanic or Latino	196 (83.8)	194 (82.9)	390 (83.3)
Unknown	23 (9.8)	28 (12.0)	51 (10.9)
Missing	7 (3.0)	5 (2.1)	12 (2.6)
Region/country enrollment, n (%)			
North America	30 (12.8)	21 (9.0)	51 (10.9)
Canada	4 (1.7)	5 (2.1)	9 (1.9)
Mexico	2 (0.9)	2 (0.9)	4 (0.9)
United States	24 (10.3)	14 (6.0)	38 (8.1)
South America	3 (1.3)	1 (0.4)	4 (0.9)
Argentina	3 (1.3)	1 (0.4)	4 (0.9)
Asia	89 (38.0)	93 (39.7)	182 (38.9)
China	4 (1.7)	5 (2.1)	9 (1.9)
Hong Kong, China	1 (0.4)	0	1 (0.2)
Japan	43 (18.4)	44 (18.8)	87 (18.6)

	Non-squamous		
	Dato-DXd (N = 234)	**Docetaxel (N = 234)**	**Total (N = 468)**
Korea, Rep.	34 (14.5)	36 (15.4)	70 (15.0)
Singapore	0	2 (0.9)	2 (0.4)
Taiwan	7 (3.0)	6 (2.6)	13 (2.8)
EU	106 (45.3)	115 (49.1)	221 (47.2)
Belgium	5 (2.1)	4 (1.7)	9 (1.9)
Czechia	0	2 (0.9)	2 (0.4)
France	38 (16.2)	40 (17.1)	78 (16.7)
Germany	4 (1.7)	3 (1.3)	7 (1.5)
Hungary	0	1 (0.4)	1 (0.2)
Italy	7 (3.0)	10 (4.3)	17 (3.6)
Netherlands	4 (1.7)	12 (5.1)	16 (3.4)
Poland	4 (1.7)	5 (2.1)	9 (1.9)
Russian Federation	4 (1.7)	4 (1.7)	8 (1.7)
Spain	38 (16.2)	30 (12.8)	68 (14.5)
Switzerland	1 (0.4)	3 (1.3)	4 (0.9)
United Kingdom	1 (0.4)	1 (0.4)	2 (0.4)
Australia	6 (2.6)	4 (1.7)	10 (2.1)
Australia	6 (2.6)	4 (1.7)	10 (2.1)
Screening ECOG performance status, n (%)			
0	75 (32.1)	74 (31.6)	149 (31.8)
1	159 (67.9)	160 (68.4)	319 (68.2)
Baseline ECOG performance status, n (%)			
0	73 (31.2)	79 (33.8)	152 (32.5)
1	160 (68.4)	154 (65.8)	314 (67.1)
2	1 (0.4)	1 (0.4)	2 (0.4)
Height (cm)			
n	234	233	467
Mean	166.68	167.42	167.05
Standard deviation	9.103	9.191	9.144
Median	168.00	167.30	167.50
Minimum	144.0	138.4	138.4
Maximum	192.0	193.0	193.0
Baseline Weight (kg)			
n	234	233	467
Mean	67.48	68.58	68.03
Standard deviation	13.962	15.770	14.885
Median	65.00	66.00	65.80
Minimum	37.0	37.5	37.0
Maximum	114.0	129.0	129.0
Baseline body mass index (kg/m^2)			
n	234	233	467

	Non-squamous		
	Dato-DXd (N = 234)	**Docetaxel (N = 234)**	**Total (N = 468)**
Mean	24.21	24.35	24.28
Standard deviation	4.174	4.731	4.456
Median	23.67	23.74	23.71
Minimum	16.0	15.1	15.1
Maximum	39.4	41.9	41.9
Baseline body surface area (m^2)			
n	234	233	467
Mean	1.73	1.76	1.75
Standard deviation	0.211	0.214	0.212
Median	1.70	1.77	1.72
Minimum	1.0	1.2	1.0
Maximum	2.2	2.6	2.6
Smoking history, n (%)			
Never	57 (24.4)	48 (20.5)	105 (22.4)
Former	153 (65.4)	151 (64.5)	304 (65.0)
Current	24 (10.3)	33 (14.1)	57 (12.2)
Missing	0	2 (0.9)	2 (0.4)
Renal function at baseline, n (%)			
Normal function	82 (35.0)	93 (39.7)	175 (37.4)
Mild impairment	110 (47.0)	92 (39.3)	202 (43.2)
Moderate impairment	41 (17.5)	48 (20.5)	89 (19.0)
Severe impairment	1 (0.4)	0	1 (0.2)
Missing	0	1 (0.4)	1 (0.2)
Hepatic function at baseline, n (%)			
Normal function	192 (82.1)	200 (85.5)	392 (83.8)
Mild impairment	42 (17.9)	33 (14.1)	75 (16.0)
Moderate impairment	0	1 (0.4)	1 (0.2)
Missing	0	0	0

CRF = case report form; Dato-DXd = datopotamab deruxtecan; DCO = data cutoff; ECOG = Eastern Cooperative Oncology Group; EU = European Union; FAS = Full Analysis Set
[a] Age in years is calculated using the main study informed consent date and the birth date.
Note: Histology subgroup is derived using data collected from CRF.
Percentages are based on the number of subjects in the Full Analysis Set in each subgroup.
Baseline is defined as the last available assessment prior to the start of study treatment.
DCO date: 29 Mar 2023
Source: Module 5.3.5.1, Study TL01 CSR Post Hoc Table 14.7.3.1

Table 49: Baseline Disease Characteristics and AGAs (FAS)

	Dato-DXd (N = 299)	**Docetaxel (N = 305)**	**Total (N = 604)**
Time from diagnosis to randomization (months)			
n	299	305	604
Mean	23.28	21.87	22.57
Standard deviation	22.427	18.850	20.693

	Dato-DXd (N = 299)	Docetaxel (N = 305)	Total (N = 604)
Median	15.34	15.11	15.26
Minimum	2.7	2.0	2.0
Maximum	175.9	104.0	175.9
Histology, n (%)[a]			
Adenocarcinoma	222 (74.2)	223 (73.1)	445 (73.7)
Squamous	65 (21.7)	71 (23.3)	136 (22.5)
Large cell	2 (0.7)	1 (0.3)	3 (0.5)
Small cell	0	0	0
Other	10 (3.3)	10 (3.3)	20 (3.3)
Actionable genomic alterations, n (%)[a]			
Absent	249 (83.3)	254 (83.3)	503 (83.3)
Present	50 (16.7)	51 (16.7)	101 (16.7)
EGFR mutation, n (%)	39 (13.0)	45 (14.8)	84 (13.9)
NTRK fusion, n (%)	2 (0.7)	0	2 (0.3)
BRAF mutation, n(%)	5 (1.7)	2 (0.7)	7 (1.2)
ALK rearrangement	1 (0.3)	2 (0.7)	3 (0.5)
ROS1 rearrangement, n (%)	6 (2.0)	0	6 (1.0)
MET exon 14 skipping, n (%)	1 (0.3)	1 (0.3)	2 (0.3)
RET rearrangement, n (%)	0	2 (0.7)	2 (0.3)
Stage at study entry, n (%)			
IIB	0	1 (0.3)	1 (0.2)
IIIB	6 (2.0)	8 (2.6)	14 (2.3)
IIIC	2 (0.7)	7 (2.3)	9 (1.5)
IV	38 (12.7)	25 (8.2)	63 (10.4)
IVA	94 (31.4)	110 (36.1)	204 (33.8)
IVB	159 (53.2)	154 (50.5)	313 (51.8)
Tumor grade, n (%)			
Well differentiated	16 (5.4)	16 (5.2)	32 (5.3)
Moderately differentiated	24 (8.0)	32 (10.5)	56 (9.3)
Poorly differentiated	48 (16.1)	48 (15.7)	96 (15.9)
Undifferentiated	2 (0.7)	3 (1.0)	5 (0.8)
Unknown	208 (69.6)	206 (67.5)	414 (68.5)
Missing	1 (0.3)	0	1 (0.2)
PD-L1 expression, n (%)			
<1%	104 (34.8)	116 (38.0)	220 (36.4)
≥1%	158 (52.8)	147 (48.2)	305 (50.5)
Unknown	10 (3.3)	6 (2.0)	16 (2.6)

	Dato-DXd (N = 299)	Docetaxel (N = 305)	Total (N = 604)
Not done	26 (8.7)	33 (10.8)	59 (9.8)
Missing	1 (0.3)	3 (1.0)	4 (0.7)
History of brain metastasis, n (%)			
Yes	79 (26.4)	91 (29.8)	170 (28.1)
No	220 (73.6)	214 (70.2)	434 (71.9)
History of other metastasis, n (%)			
Yes	297 (99.3)	298 (97.7)	595 (98.5)
No	2 (0.7)	7 (2.3)	9 (1.5)
Brain metastasis at study entry, n (%)[b]			
Yes	50 (16.7)	47 (15.4)	97 (16.1)
No	249 (83.3)	258 (84.6)	507 (83.9)
Liver metastasis at study entry, n (%)[b]			
Yes	67 (22.4)	47 (15.4)	114 (18.9)
No	232 (77.6)	258 (84.6)	490 (81.1)

[a] Collected on CRF
[b] Brain metastasis and liver metastasis at study entry were identified by BICR.
Note: KRAS mutations were not considered as AGA as there were no approved KRAS G12C inhibitors approved at the time of protocol development.
DCO date: 29 Mar 2023
Source: Module 5.3.5.1, TL01 CSR Table 14.1.3.7, Table 14.1.3.1

Table 50: Disease Characteristics at Baseline in the Non-squamous Population

	Non-squamous		
	Dato-DXd (N = 234)	Docetaxel (N = 234)	Total (N = 468)
Time from diagnosis to randomization (Months)			
n	234	234	468
Mean	24.75	23.73	24.24
Standard deviation	23.978	20.401	22.243
Median	16.53	17.05	17.00
Minimum	3.0	2.0	2.0
Maximum	175.9	104.0	175.9
Histology, n (%)[a]			
Adenocarcinoma	222 (94.9)	223 (95.3)	445 (95.1)
Squamous	0	0	0
Large cell	2 (0.9)	1 (0.4)	3 (0.6)
Small cell	0	0	0
Other	10 (4.3)	10 (4.3)	20 (4.3)
Actionable genomic alterations, n (%)[a]			
Absent	186 (79.5)	184 (78.6)	370 (79.1)
Present	48 (20.5)	50 (21.4)	98 (20.9)

	Non-squamous		
	Dato-DXd (N = 234)	**Docetaxel (N = 234)**	**Total (N = 468)**
EGFR mutation, n (%)	38 (16.2)	44 (18.8)	82 (17.5)
NTRK fusion, n (%)	2 (0.9)	0	2 (0.4)
BRAF mutation, n (%)	4 (1.7)	2 (0.9)	6 (1.3)
ALK rearrangement, n (%)	1 (0.4)	2 (0.9)	3 (0.6)
ROS1 rearrangement, n (%)	6 (2.6)	0	6 (1.3)
MET exon 14 skipping, n (%)	1 (0.4)	1 (0.4)	2 (0.4)
RET rearrangement, n (%)	0	2 (0.9)	2 (0.4)
Stage at study entry, n (%)			
IIB	0	1 (0.4)	1 (0.2)
IIIB	2 (0.9)	3 (1.3)	5 (1.1)
IIIC	0	3 (1.3)	3 (0.6)
IV	31 (13.2)	18 (7.7)	49 (10.5)
IVA	75 (32.1)	80 (34.2)	155 (33.1)
IVB	126 (53.8)	129 (55.1)	255 (54.5)
Tumor grade, n (%)			
Well differentiated	7 (3.0)	11 (4.7)	18 (3.8)
Moderately differentiated	18 (7.7)	20 (8.5)	38 (8.1)
Poorly differentiated	41 (17.5)	37 (15.8)	78 (16.7)
Undifferentiated	1 (0.4)	3 (1.3)	4 (0.9)
Unknown	166 (70.9)	163 (69.7)	329 (70.3)
Missing	1 (0.4)	0	1 (0.2)
PD-L1 expression, n (%)			
<1%	83 (35.5)	96 (41.0)	179 (38.2)
≥1%	127 (54.3)	107 (45.7)	234 (50.0)
Unknown	6 (2.6)	6 (2.6)	12 (2.6)
Not done	17 (7.3)	23 (9.8)	40 (8.5)
Missing	1 (0.4)	2 (0.9)	3 (0.6)
History of brain metastasis, n (%)			
Yes	71 (30.3)	76 (32.5)	147 (31.4)
No	163 (69.7)	158 (67.5)	321 (68.6)
History of other metastasis, n (%)			
Yes	232 (99.1)	229 (97.9)	461 (98.5)
No	2 (0.9)	5 (2.1)	7 (1.5)
Brain metastasis at study entry, n (%)[b]			
Yes	43 (18.4)	41 (17.5)	84 (17.9)
No	191 (81.6)	193 (82.5)	384 (82.1)
Liver metastasis at study entry, n (%)[b]			
Yes	55 (23.5)	35 (15.0)	90 (19.2)

	Non-squamous		
	Dato-DXd (N = 234)	**Docetaxel (N = 234)**	**Total (N = 468)**
No	179 (76.5)	199 (85.0)	378 (80.8)

[a] Collected on CRF.
[b] Brain metastasis and liver metastasis at study entry are identified by BICR.
Note: Histology subgroup is derived using data collected from CRF.
Percentages are based on the number of subjects in the Full Analysis Set in each subgroup.
Tumor grade classification is based on WHO guidance. KRAS mutations were not considered as AGA as there were no approved KRAS G12C inhibitors approved at the time of protocol development.
DCO date: 29 Mar 2023
Source: Module 5.3.5.1, Study TL01 CSR Post Hoc Table 14.7.4.1; Module 1, Appendix 4 MAA D120 Table Q112

Table 51 Prior Cancer Therapy (Full Analysis Set)

	Dato-DXd (N=299)	Docetaxel (N=305)	Total (N=604)
Any Prior Cancer Systemic Therapy, n (%)	299 (100)	305 (100)	604 (100)
Prior Platinum-based Chemotherapy	297 (99.3)	305 (100)	602 (99.7)
Prior Other Chemotherapy	298 (99.7)	304 (99.7)	602 (99.7)
Prior Anti-PD-1/Anti-PD-L1 Immunotherapy	263 (88.0)	268 (87.9)	531 (87.9)
Prior Targeted Therapy for Indicated AGAs [a]	46 (15.4)	50 (16.4)	96 (15.9)
Other Cancer Therapy	59 (19.7)	64 (21.0)	123 (20.4)
Number of Prior Systemic Lines at Locally Advanced or Metastatic Setting, n (%)			
0	2 (0.7)	1 (0.3)	3 (0.5)
1	167 (55.9)	174 (57.0)	341 (56.5)
2	108 (36.1)	102 (33.4)	210 (34.8)
3	17 (5.7)	23 (7.5)	40 (6.6)
4 or more	5 (1.7)	5 (1.6)	10 (1.7)
Intended for, n (%) [b]			
Neo-Adjuvant	5 (1.7)	3 (1.0)	8 (1.3)
Adjuvant	18 (6.0)	16 (5.2)	34 (5.6)
Locally Advanced	44 (14.7)	51 (16.7)	95 (15.7)
Metastatic	264 (88.3)	268 (87.9)	532 (88.1)
Preventive	0	0	0
Maintenance	86 (28.8)	96 (31.5)	182 (30.1)
Other	1 (0.3)	1 (0.3)	2 (0.3)
Best Responses to the Last Prior Anticancer Systemic Therapy, n (%)			

	Dato-DXd (N=299)	Docetaxel (N=305)	Total (N=604)
Complete Response	4 (1.3)	5 (1.6)	9 (1.5)
Partial Response	102 (34.1)	113 (37.0)	215 (35.6)
Stable Disease	107 (35.8)	104 (34.1)	211 (34.9)
Progressive Disease	60 (20.1)	48 (15.7)	108 (17.9)
Unknown	16 (5.4)	22 (7.2)	38 (6.3)
Not Applicable	4 (1.3)	2 (0.7)	6 (1.0)
Missing	6 (2.0)	11 (3.6)	17 (2.8)
Any Prior Cancer Radiation Therapy, n (%)	136 (45.5)	151 (49.5)	287 (47.5)
Intended for, n (%) [b]			
Curative	48 (16.1)	59 (19.3)	107 (17.7)
Palliative	80 (26.8)	88 (28.9)	168 (27.8)
Other	13 (4.3)	14 (4.6)	27 (4.5)
Best Responses to the Last Prior Anticancer Radiation Therapy, n (%)			
Complete Response	5 (1.7)	6 (2.0)	11 (1.8)
Partial Response	21 (7.0)	21 (6.9)	42 (7.0)
Stable Disease	20 (6.7)	27 (8.9)	47 (7.8)
Progressive Disease	11 (3.7)	18 (5.9)	29 (4.8)
Unknown	28 (9.4)	35 (11.5)	63 (10.4)
Not Applicable	51 (17.1)	44 (14.4)	95 (15.7)
Any Prior Cancer Surgery, n (%)	90 (30.1)	55 (18.0)	145 (24.0)

Abbreviations: AGA=actionable genomic alteration; DCO=data cut-off; PD-1=programmed cell death 1; PD-L1=programmed cell death ligand 1.
Percentages are based on the number of subjects in the Full Analysis Set.
[a] Indicated AGAs include epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1), neurotrophic tyrosine receptor kinase (NTRK), proto-oncogene B-raf (BRAF), mesenchymal-epithelial transition (MET) exon 14 skipping, and rearranged during transfection (RET).
[b] A subject can be counted in multiple rows since more than 1 therapy could be taken. Within each row, a subject is counted only once.
DCO date: 29 Mar 2023
Source: Table 14.1.3.4

Table 52: Prior Cancer Therapy, Non-squamous Population (FAS)

	Non-squamous		
	Dato-DXd (N = 234)	Docetaxel (N = 234)	Total (N = 468)
Any prior cancer systemic therapy, n (%)	234 (100)	234 (100)	468 (100)
Prior platinum chemotherapy	232 (99.1)	234 (100)	466 (99.6)
Prior other chemotherapy	233 (99.6)	233 (99.6)	466 (99.6)
Prior anti-PD-1/Anti-PD-L1 immunotherapy	199 (85.0)	200 (85.5)	399 (85.3)
Prior targeted therapy for indicated AGAs[a]	45 (19.2)	49 (20.9)	94 (20.1)
Other cancer therapy	45 (19.2)	50 (21.4)	95 (20.3)
Number of prior systemic lines at locally advanced or metastatic setting, n (%)			
0	1 (0.4)	1 (0.4)	2 (0.4)

	Non-squamous		
	Dato-DXd (N = 234)	**Docetaxel (N = 234)**	**Total (N = 468)**
1	127 (54.3)	131 (56.0)	258 (55.1)
2	86 (36.8)	74 (31.6)	160 (34.2)
3	15 (6.4)	23 (9.8)	38 (8.1)
4 or more	5 (2.1)	5 (2.1)	10 (2.1)
Intended for, n (%)[b]			
Neo-adjuvant	3 (1.3)	1 (0.4)	4 (0.9)
Adjuvant	14 (6.0)	14 (6.0)	28 (6.0)
Locally advanced	26 (11.1)	29 (12.4)	55 (11.8)
Metastatic	215 (91.9)	215 (91.9)	430 (91.9)
Preventive	0	0	0
Maintenance	69 (29.5)	78 (33.3)	147 (31.4)
Other	0	1 (0.4)	1 (0.2)
Best responses to the last prior anticancer systemic therapy, n (%)			
Complete response (CR)	4 (1.7)	4 (1.7)	8 (1.7)
Partial response (PR)	76 (32.5)	87 (37.2)	163 (34.8)
Stable disease (SD)	84 (35.9)	81 (34.6)	165 (35.3)
Progressive disease (PD)	48 (20.5)	34 (14.5)	82 (17.5)
Unknown (UNK)	14 (6.0)	19 (8.1)	33 (7.1)
Not applicable (NA)	2 (0.9)	2 (0.9)	4 (0.9)
Missing	6 (2.6)	7 (3.0)	13 (2.8)
Any prior cancer radiation therapy, n (%)	101 (43.2)	117 (50.0)	218 (46.6)
Intended for, n (%)[b]			
Curative	28 (12.0)	41 (17.5)	69 (14.7)
Palliative	70 (29.9)	73 (31.2)	143 (30.6)
Other	6 (2.6)	10 (4.3)	16 (3.4)
Best responses to the last prior anticancer radiation therapy, n (%)			
Complete response (CR)	5 (2.1)	6 (2.6)	11 (2.4)
Partial response (PR)	9 (3.8)	17 (7.3)	26 (5.6)
Stable disease (SD)	13 (5.6)	18 (7.7)	31 (6.6)
Progressive disease (PD)	7 (3.0)	14 (6.0)	21 (4.5)
Unknown (UNK)	22 (9.4)	25 (10.7)	47 (10.0)
Not applicable (NA)	45 (19.2)	37 (15.8)	82 (17.5)
Any prior cancer surgery, n (%)	76 (32.5)	44 (18.8)	120 (25.6)

[a] Indicated AGAs include EGFR, ALK, ROS1, NTRK, BRAF, or MET exon 14 skipping, and RET.
[b] A subject can be counted in multiple rows since more than one therapies can be taken. Within each row, a subject is counted only once.
Note: Histology subgroup is derived using data collected from CRF.
Percentages are based on the number of subjects in the Full Analysis Set in each subgroup.
DCO date: 29 Mar 2023
Source: Module 5.3.5.3, ISE Outputs Supporting SCE Part 1 Post Hoc Table 14.7.5.1

Table 53 Post Hoc Analysis of Prior Cancer Therapy by Actionable Genomic Alteration Status (Full Analysis Set)

	AGA			Non-AGA		
	Dato-DXd (N=50)	Docetaxel (N=51)	Total (N=101)	Dato-DXd (N=249)	Docetaxel (N=254)	Total (N=503)
Any Prior Cancer Systemic Therapy, n (%)	50 (100)	51 (100)	101 (100)	249 (100)	254 (100)	503 (100)
Prior Platinum-based Chemotherapy	49 (98.0)	51 (100)	100 (99.0)	248 (99.6)	254 (100)	502 (99.8)
Prior Other Chemotherapy	50 (100)	50 (98.0)	100 (99.0)	248 (99.6)	254 (100)	502 (99.8)
Prior Anti-PD-1/Anti-PD-L1 Immunotherapy	16 (32.0)	17 (33.3)	33 (32.7)	247 (99.2)	251 (98.8)	498 (99.0)
Prior Targeted Therapy for Indicated AGAs [a]	45 (90.0)	49 (96.1)	94 (93.1)	1 (0.4)	1 (0.4)	2 (0.4)
Other Cancer Therapy	14 (28.0)	10 (19.6)	24 (23.8)	45 (18.1)	54 (21.3)	99 (19.7)
Number of Prior Systemic Lines at locally advanced or metastatic setting, n (%)						
0	0	0	0	2 (0.8)	1 (0.4)	3 (0.6)
1	5 (10.0)	2 (3.9)	7 (6.9)	162 (65.1)	172 (67.7)	334 (66.4)
2	26 (52.0)	24 (47.1)	50 (49.5)	82 (32.9)	78 (30.7)	160 (31.8)
3	15 (30.0)	21 (41.2)	36 (35.6)	2 (0.8)	2 (0.8)	4 (0.8)
4 or more	4 (8.0)	4 (7.8)	8 (7.9)	1 (0.4)	1 (0.4)	2 (0.4)
Intended for, n (%) [b]						
Neo-Adjuvant	1 (2.0)	0	1 (1.0)	4 (1.6)	3 (1.2)	7 (1.4)
Adjuvant	1 (2.0)	0	1 (1.0)	17 (6.8)	16 (6.3)	33 (6.6)
Locally Advanced	3 (6.0)	4 (7.8)	7 (6.9)	41 (16.5)	47 (18.5)	88 (17.5)
Metastatic	49 (98.0)	50 (98.0)	99 (98.0)	215 (86.3)	218 (85.8)	433 (86.1)
Preventive	0	0	0	0	0	0

	AGA			Non-AGA		
	Dato-DXd (N=50)	Docetaxel (N=51)	Total (N=101)	Dato-DXd (N=249)	Docetaxel (N=254)	Total (N=503)
Maintenance	19 (38.0)	12 (23.5)	31 (30.7)	67 (26.9)	84 (33.1)	151 (30.0)
Other	0	0	0	1 (0.4)	1 (0.4)	2 (0.4)
Best Response to the Last Prior Anticancer Systemic Therapy, n (%)						
Complete Response	1 (2.0)	1 (2.0)	2 (2.0)	3 (1.2)	4 (1.6)	7 (1.4)
Partial Response	22 (44.0)	17 (33.3)	39 (38.6)	80 (32.1)	96 (37.8)	176 (35.0)
Stable Disease	13 (26.0)	22 (43.1)	35 (34.7)	94 (37.8)	82 (32.3)	176 (35.0)
Progressive Disease	10 (20.0)	5 (9.8)	15 (14.9)	50 (20.1)	43 (16.9)	93 (18.5)
Unknown	2 (4.0)	3 (5.9)	5 (5.0)	14 (5.6)	19 (7.5)	33 (6.6)
Not Applicable	1 (2.0)	0	1 (1.0)	3 (1.2)	2 (0.8)	5 (1.0)
Missing	1 (2.0)	3 (5.9)	4 (4.0)	5 (2.0)	8 (3.1)	13 (2.6)
Any Prior Cancer Radiation Therapy, n (%)	22 (44.0)	30 (58.8)	52 (51.5)	114 (45.8)	121 (47.6)	235 (46.7)
Intended for, n (%) [b]						
Curative	6 (12.0)	9 (17.6)	15 (14.9)	42 (16.9)	50 (19.7)	92 (18.3)
Palliative	16 (32.0)	21 (41.2)	37 (36.6)	64 (25.7)	67 (26.4)	131 (26.0)
Other	0	3 (5.9)	3 (3.0)	13 (5.2)	11 (4.3)	24 (4.8)
Best Response to the Last Prior Anticancer Radiation Therapy, n (%)						
Complete Response	0	0	0	5 (2.0)	6 (2.4)	11 (2.2)
Partial Response	3 (6.0)	3 (5.9)	6 (5.9)	18 (7.2)	18 (7.1)	36 (7.2)
Stable Disease	3 (6.0)	4 (7.8)	7 (6.9)	17 (6.8)	23 (9.1)	40 (8.0)
Progressive Disease	2 (4.0)	4 (7.8)	6 (5.9)	9 (3.6)	14 (5.5)	23 (4.6)
Unknown	6 (12.0)	7 (13.7)	13 (12.9)	22 (8.8)	28 (11.0)	50 (9.9)
Not Applicable	8 (16.0)	12 (23.5)	20 (19.8)	43 (17.3)	32 (12.6)	75 (14.9)
Any Prior Cancer Surgery, n (%)	12 (24.0)	8 (15.7)	20 (19.8)	78 (31.3)	47 (18.5)	125 (24.9)

Abbreviations: AGA=actionable genomic alteration; DCO=data cut-off; eCRF=electronic case report form; PD-1=programmed cell death 1; PD-L1=programmed cell death ligand 1.
AGA subgroup is derived using data collected from the eCRF.
Percentages are based on the number of subjects in the Full Analysis Set in each subgroup.
[a] Indicated AGAs include epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1), neurotrophic tyrosine receptor kinase (NTRK), proto-oncogene B-raf (BRAF), mesenchymal-epithelial transition (MET) exon 14 skipping, and rearranged during transfection (RET).
[b] A subject can be counted in multiple rows since more than 1 therapy could be taken. Within each row, a subject is counted only once.
DCO date: 29 Mar 2023
Source: Post Hoc Table 14.7.6.1.1

*For the post-hoc analyses, the eCRF dataset (and not the IXRS dataset) was used to account for mis-stratification. Refer to a clarification note at the beginning of the Ancillary analyses section.

Numbers analysed

Table 54 Data Sets Analyzed

	Dato-DXd n (%)	Docetaxel n (%)	Total n (%)
All Randomized Subjects	299	306	605
Full Analysis Set	299	305	604
Safety Analysis Set	297 (99.3)	290 (95.1)	587 (97.2)
Per Protocol Analysis Set	259 (86.6)	250 (82.0)	509 (84.3)
Pharmacokinetic Analysis Set	297 (99.3)	NA	NA

Abbreviations: DCO=data cut-off; ID=identification number; NA=not applicable; PK=pharmacokinetic.
Percentages are based on the number of subjects in the Full Analysis Set.
All Randomized Subjects includes all subjects who were randomized into this study.
Full Analysis Set includes all randomized subjects. If a subject was randomized more than once, only 1 of the subject IDs is included in the Full Analysis Set.
Safety Analysis Set includes all Full Analysis Set subjects who received at least 1 dose of study drug.
Per Protocol Analysis Set includes all Full Analysis Set subjects who complied sufficiently with the protocol with respect to exposure to study treatment, availability of tumor assessments, and absence of major protocol deviations likely to impact efficacy outcome.
The PK Analysis Set includes all subjects who received at least 1 dose of Dato-DXd and had at least 1 PK sample with measurable plasma concentration of Dato-DXd, total anti-TROP2 antibody, or DXd.
DCO date: 29 Mar 2023
Source: Table 14.1.1.1

One subject in the docetaxel arm was randomized in error prior to meeting all inclusion/exclusion criteria (ie, EGFR/ALK testing), was discontinued from the study, then was rescreened and randomized again after fulfilling all criteria. As a result, the subject was counted twice in the All Randomized Subjects Set, but once in the FAS.

For the post-hoc subgroup analyses, the eCRF dataset (and not the IXRS dataset) was used to account for mis-stratification. Refer to a clarification note at the beginning of the Ancillary analyses section.

Outcomes and estimation

Primary endpoints

- **PFS by BICR**

As of the DCO date for the primary analysis (29 March 2023), the median follow-up time for PFS was 10.9 months (95% CI: 9.8, 12.5) for Dato-DXd and 9.6 months (95% CI: 8.2, 11.9) for docetaxel.

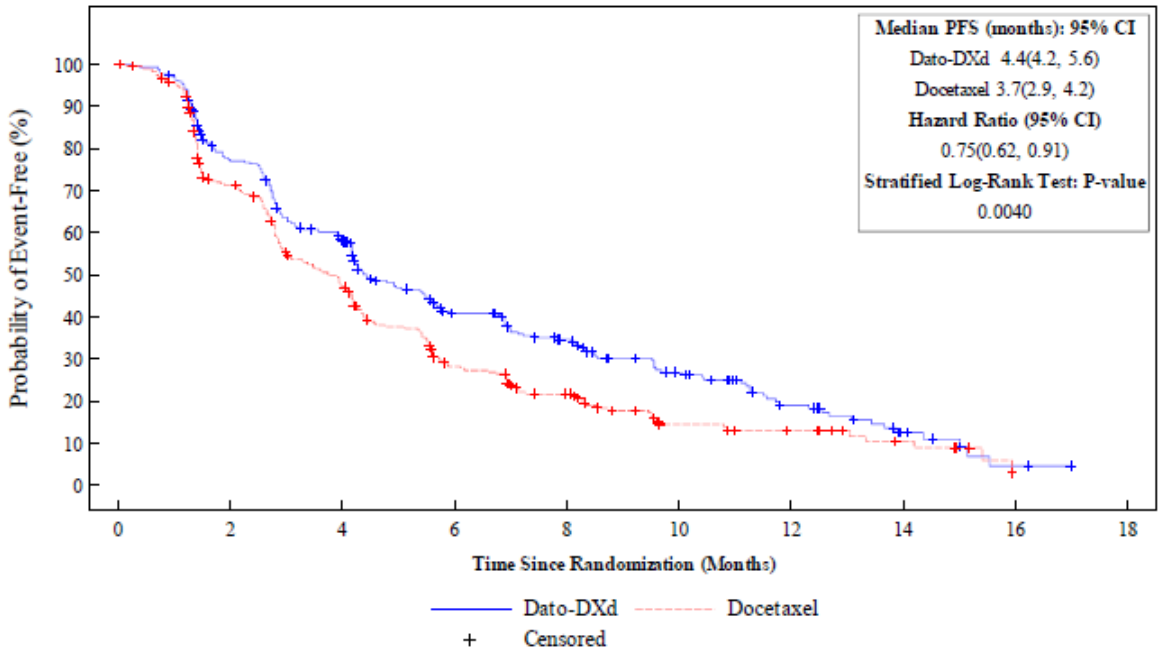
Table 55 Progression-free Survival by Blinded Independent Central Review (Full Analysis Set)

	Dato-DXd (N=299)	Docetaxel (N=305)	*P* value
Subjects with Event, n (%)	213 (71.2)	218 (71.5)	
Progressive Disease	174 (58.2)	187 (61.3)	
Death	39 (13.0)	31 (10.2)	
Subjects Censored, n (%)	86 (28.8)	87 (28.5)	
No Baseline Tumor Assessment	0	0	
No Adequate Post-baseline Assessment	5 (1.7)	26 (8.5)	
Event Occurred after 2 or More Missing Tumor Assessments	14 (4.7)	19 (6.2)	
Withdrawal of Consent	6 (2.0)	6 (2.0)	
Lost to Follow-up	1 (0.3)	0	
Adequate Tumor Assessment No Longer Available	8 (2.7)	6 (2.0)	
Ongoing without Event	52 (17.4)	30 (9.8)	
Progression-free Survival (Months) [a]			
25th Percentile (95% CI)	2.6 (1.7, 2.7)	1.5 (1.4, 2.2)	
Median (95% CI)	4.4 (4.2, 5.6)	3.7 (2.9, 4.2)	
75th Percentile (95% CI)	11.1 (8.5, 11.8)	6.9 (5.6, 8.3)	
Progression-free Survival Probability at (95% CI) [b]			
3 Months	63.7 (57.8, 69.0)	55.3 (49.1, 61.1)	
6 Months	40.8 (34.9, 46.7)	28.2 (22.7, 33.9)	
9 Months	30.1 (24.5, 36.0)	17.8 (13.1, 23.1)	
Stratified Log-Rank Test, as Randomized			0.0040
Stratified Hazard Ratio, as Randomized (95% CI) [c]	0.75 (0.62, 0.91)		

Abbreviations: CI=confidence interval; DCO=data cut-off; PD=progressive disease; PD-1=programmed cell death 1; PD-L1=programmed cell death ligand 1.
Percentages are based on the number of subjects in the Full Analysis Set.
This study has 4 randomization stratification factors: actionable genomic alteration, histology, most immediate prior therapy included anti-PD-1/anti-PD-L1 immunotherapy, and geographic region. Due to the small sample size within some strata, actionable genomic alteration and most immediate prior therapy included anti-PD-1/anti-PD-L1 immunotherapy are removed from stratified analysis.
Progression-free survival is defined as the time (months) from the date of randomization to the earlier of the dates of the first documentation of PD or death due to any cause. Subjects are not censored at the initiation of new anticancer therapy.
[a] Median, 25th and 75th percentile, and progression-free survival probability at specific months are based on the Kaplan-Meier method. The 2-sided 95% CIs for the median and percentiles are computed using the Brookmeyer-Crowley method.
[b] The 2-sided 95% CIs for the progression-free survival at specific months are computed using Greenwood's formula.
[c] Cox proportional hazards model stratified by histology and geographic region (as randomized) is used to estimate the hazard ratio with the option TIES=EXACT to handle ties.
DCO date: 29 Mar 2023
Source: Table 14.2.1.1.1

Source: CSR DS1062-A-U301

Figure 44 Kaplan-Meier Plot of Progression-free Survival by Blinded Independent



No. at Risk

Dato-DXd	299	216	156	96	74	46	24	10	2	0
Docetaxel	305	186	120	63	42	19	14	7	0	0

DCO: 2023-03-29
Source: Figure 14.2.1.1.1

Abbreviations: CI=confidence interval; DCO=data cut-off; PFS=progression-free survival.
DCO date: 29 Mar 2023
Source: Figure 14.2.1.1.1

- **OS**

At the time of the DCO for the primary PFS analysis (29 March 2023), based on the inverse Kaplan-Meier method, the median follow-up time of OS was 12.4 months (95% CI: 11.5, 13.6) for Dato-DXd and 12.4 months (95% CI: 11.3, 13.1) for docetaxel.

Table 56 Overall Survival (Full Analysis Set)

	Dato-DXd (N=299)	Docetaxel (N=305)	*P* value
Number of Subjects Who Died, n (%)	148 (49.5)	157 (51.5)	
Subjects Censored, n (%)	151 (50.5)	148 (48.5)	
Withdrawal of Consent	14 (4.7)	25 (8.2)	
Lost to Follow-up	1 (0.3)	2 (0.7)	
Follow-up No Longer Available	0	0	
Ongoing	136 (45.5)	121 (39.7)	
Overall Survival (Months) [a]			
25th Percentile (95% CI)	5.8 (5.0, 7.2)	5.7 (4.7, 6.5)	
Median (95% CI)	12.4 (10.8, 14.8)	11.0 (9.8, 12.5)	
75th Percentile (95% CI)	20.6 (17.3, NE)	18.9 (16.1, NE)	
Overall Survival Probability at (95% CI) [b]			
3 Months	88.5 (84.3, 91.7)	90.3 (86.2, 93.2)	
6 Months	74.0 (68.5, 78.7)	72.6 (67.0, 77.4)	
9 Months	63.0 (56.9, 68.4)	59.7 (53.6, 65.3)	
12 Months	54.5 (48.0, 60.5)	47.3 (40.8, 53.5)	
15 Months	42.9 (35.8, 49.8)	35.6 (28.5, 42.7)	
18 Months	29.9 (21.5, 38.8)	31.3 (24.1, 38.8)	
Stratified Log-Rank Test, as Randomized			0.3609
Stratified Hazard Ratio, as Randomized (95% CI) [c]	0.90 (0.72, 1.13)		

Abbreviations: CI=confidence interval; DCO=data cut-off; NE=not estimable; PD-1=programmed cell death 1; PD-L1=programmed cell death ligand 1.
Percentages are based on the number of subjects in the Full Analysis Set.
This study has 4 randomization stratification factors: actionable genomic alteration, histology, most immediate prior therapy included anti-PD-1/anti-PD-L1 immunotherapy, and geographic region. Due to the small sample size within some strata, actionable genomic alteration and most immediate prior therapy included anti-PD-1/anti-PD-L1 immunotherapy are removed from stratified analysis.
[a] Median, 25th and 75th percentile, and overall survival probability at specific months are based on the Kaplan-Meier method. The 2-sided 95% CIs for the median and percentiles are computed using the Brookmeyer-Crowley method.
[b] The 2-sided 95% CIs for the overall survival at specific months are computed using Greenwood's formula.
[c] Cox proportional hazards model stratified by histology and geographic region (as randomized) is used to estimate the hazard ratio with the option TIES=EXACT to handle ties.
DCO date: 29 Mar 2023
Source: Table 14.2.1.2.1

Subsequently, the results of the final OS analysis (DCO 01 March 2024) were presented.

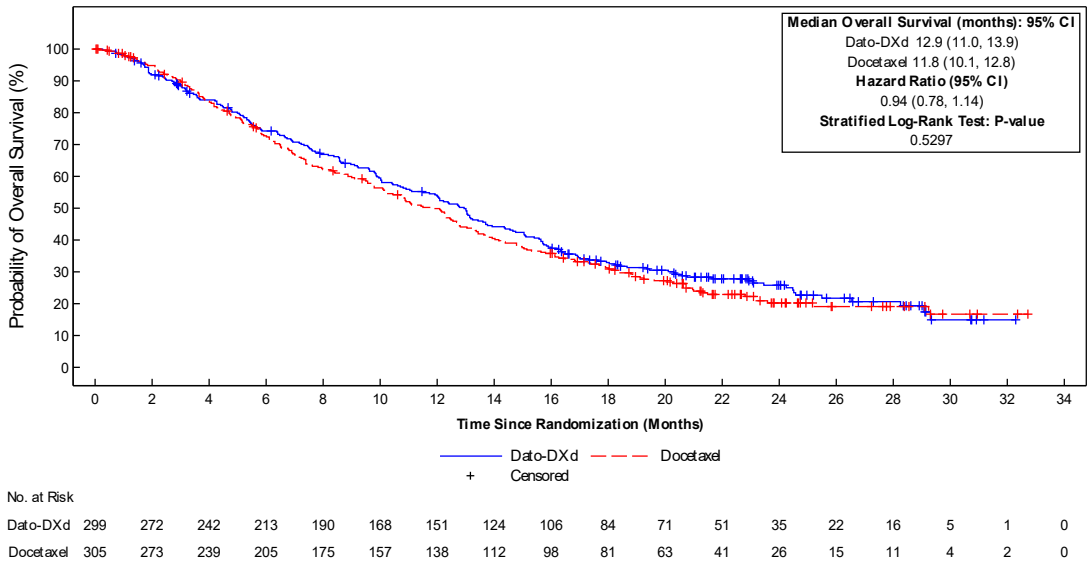
Table 57: Primary Analysis of OS (DCO 01 March 2024)

	FAS		Non-squamous Population	
	Dato-DXd (N = 299)	Docetaxel (N = 305)	Dato-DXd (N = 234)	Docetaxel (N = 234)
Number of subjects who Died, n (%)	215 (71.9)	218 (71.5)	160 (68.4)	163 (69.7)
Subjects censored, n (%)	84 (28.1)	87 (28.5)	74 (31.6)	71 (30.3)
Withdrawal of consent	14 (4.7)	23 (7.5)	10 (4.3)	19 (8.1)
Lost to follow-up	2 (0.7)	2 (0.7)	2 (0.9)	2 (0.9)
Follow-up no longer available	0	0	0	0
Ongoing	68 (22.7)	62 (20.3)	62 (26.5)	50 (21.4)
Overall survival (Months)[a]				

	FAS		Non-squamous Population	
	Dato-DXd (N = 299)	**Docetaxel (N = 305)**	**Dato-DXd (N = 234)**	**Docetaxel (N = 234)**
25th percentile (95% CI)	5.8 (5.0, 7.2)	5.7 (4.7, 6.5)	7.3 (5.8, 8.7)	5.9 (4.9, 6.8)
Median (95% CI)	12.9 (11.0, 13.9)	11.8 (10.1, 12.8)	14.6 (12.4, 16.0)	12.3 (10.7, 14.0)
75th percentile (95% CI)	24.5 (20.1, 29.1)	20.7 (18.3, 25.2)	26.5 (22.9, NE)	21.0 (18.9, NE)
Overall survival probability at (95% CI)[b]				
3 months	88.5 (84.3 ,91.7)	90.0 (85.9 ,92.9)	91.4 (87.0, 94.4)	90.5 (85.8, 93.7)
6 months	74.3 (68.8 ,78.9)	72.8 (67.2 ,77.5)	79.9 (74.1, 84.5)	74.8 (68.5, 80.0)
9 months	63.7 (57.9 ,69.0)	60.0 (54.0 ,65.4)	68.7 (62.2, 74.3)	62.2 (55.4, 68.3)
12 months	53.8 (47.9 ,59.4)	49.9 (43.9 ,55.6)	58.8 (52.0, 64.9)	52.8 (45.9, 59.2)
15 months	42.4 (36.6 ,48.1)	37.6 (31.9 ,43.2)	48.8 (42.1, 55.2)	39.9 (33.3, 46.4)
18 months	32.9 (27.5 ,38.5)	31.3 (25.9 ,36.8)	38.2 (31.8, 44.5)	34.0 (27.7, 40.4)
21 months	28.3 (23.1 ,33.8)	23.9 (18.9 ,29.3)	32.2 (26.0, 38.6)	24.2 (18.4, 30.4)
24 months	25.8 (20.5 ,31.4)	20.2 (15.3 ,25.6)	29.0 (22.8, 35.5)	21.7 (16.0, 28.0)
Follow-up time estimated by inverse Kaplan-Meier (months)[c]				
Median (95% CI)	23.1 (22.0, 24.8)	23.1 (21.7, 24.2)	23.1 (22.0, 24.8)	23.1 (21.7, 24.2)
Unstratified HR (95% CI)[d]	-		0.84 (0.68, 1.05)	
Stratified log-rank test, as randomized	0.5297		-	
Stratified HR, as randomized (95% CI)[e]	0.94 (0.78, 1.14)		-	

[a] Median, 25th and 75th percentiles, and overall survival probability at specific months are based on the Kaplan-Meier method. The 2-sided 95% CIs for the median and percentiles are computed using the Brookmeyer-Crowley method.
[b] The 2-sided 95% CIs for the overall survival at specific months are computed using the Greenwood's formula.
[c] Kaplan-Meier estimates by reversing censoring and event of OS.
[d] A Cox proportional hazards model is used to estimate the HR with the option TIES=EXACT to handle ties.
[e] Cox proportional hazards model stratified by histology and geographic region (as randomized) is used to estimate the HR with the option TIES = EXACT to handle ties.
Note: Histology is derived using data collected from CRF.
DCO date: 01 Mar 2024
Source: Module 1, Appendix 7 Table 3, Table 4

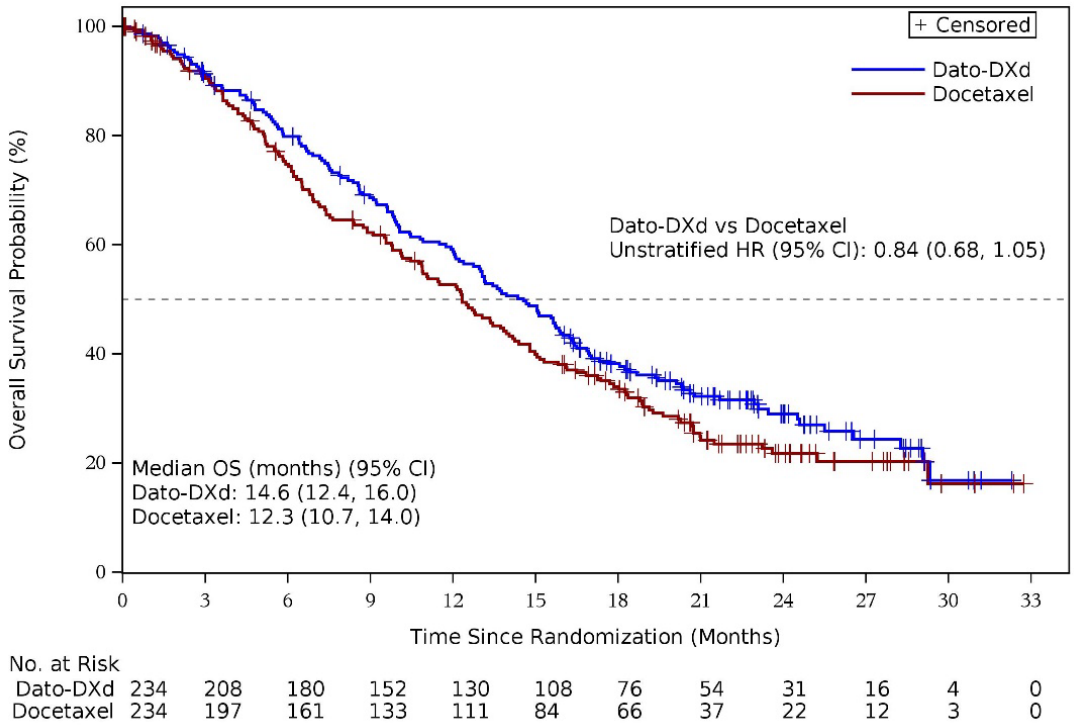
Figure 45: Kaplan-Meier Plots of OS (FAS)



DCO date: 01 Mar 2024

Source: Module 1, Appendix 7 Figure 1

Figure 46: Kaplan-Meier Plots of OS – Non-squamous Population (FAS)



Histology subgroups (squamous, non-squamous) are derived using data collected from the CRF.
DCO date: 01 Mar 2024
Source: Module 1, Appendix 7 Figure 2

Secondary endpoints

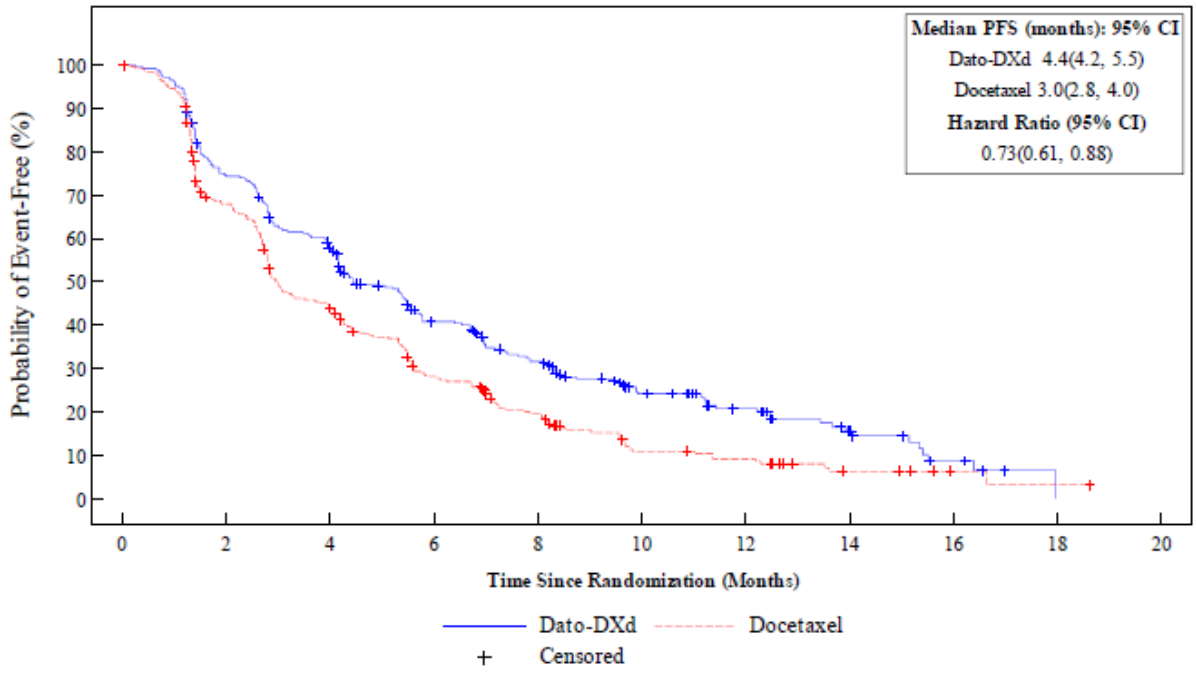
PFS by INV

Table 58 Progression-free Survival by Investigator (Full Analysis Set)

	Dato-DXd (N=299)	Docetaxel (N=305)
Subjects with Events, n (%)	226 (75.6)	237 (77.7)
Progressive Disease	196 (65.6)	215 (70.5)
Death	30 (10.0)	22 (7.2)
Subjects Censored, n (%)	73 (24.4)	68 (22.3)
No Baseline Tumor Assessment	0	0
No Adequate Post-baseline Assessment	5 (1.7)	27 (8.9)
Event Occurred after 2 or more Missing Tumor Assessments	1 (0.3)	10 (3.3)
Withdrawal of Consent	5 (1.7)	1 (0.3)
Lost to Follow-up	0	0
Adequate Tumor Assessment No Longer Available	3 (1.0)	2 (0.7)
Ongoing without Events	59 (19.7)	28 (9.2)
Progression-free Survival (Months) [a]		
25th Percentile (95% CI)	2.0 (1.5, 2.6)	1.4 (1.3, 1.5)
Median (95% CI)	4.4 (4.2, 5.5)	3.0 (2.8, 4.0)
75th Percentile (95% CI)	9.9 (8.2, 12.5)	7.0 (5.6, 7.9)
Progression-free Survival Probability at (95% CI) [b]		
3 Months	63.0 (57.1, 68.2)	50.0 (43.9, 55.8)
6 Months	40.8 (35.0, 46.5)	28.2 (22.9, 33.7)
9 Months	27.6 (22.4, 33.2)	15.7 (11.4, 20.6)
Stratified Hazard Ratio, as Randomized (95% CI) [c]	0.73 (0.61, 0.88)	

Abbreviations: CI=confidence interval; DCO=data cut-off; PD=progressive disease; PD-1=programmed cell death 1; PD-L1=programmed cell death ligand 1.
Percentages are based on the number of subjects in the Full Analysis Set.
This study has 4 randomization stratification factors: actionable genomic alteration, histology, most immediate prior therapy included anti-PD-1/anti-PD-L1 immunotherapy, and geographic region. Due to the small sample size within some strata, actionable genomic alteration and most immediate prior therapy included anti-PD-1/anti-PD-L1 immunotherapy are removed from stratified analysis.
Progression-free survival is defined as the time (months) from the date of randomization to the earlier of the dates of the first documentation of PD or death due to any cause. Subjects are not censored at the initiation of new anticancer therapy.
[a] Median, 25th and 75th percentile, and progression-free survival probability at specific months are based on the Kaplan-Meier method. The 2-sided 95% CIs for the median and percentiles are computed using the Brookmeyer-Crowley method.
[b] The 2-sided 95% CIs for the progression-free survival at specific months are computed using Greenwood's formula.
[c] Cox proportional hazards model stratified by histology and geographic region (as randomized) is used to estimate the hazard ratio with the option TIES=EXACT to handle ties.
DCO date: 29 Mar 2023
Source: Table 14.2.2.1.1

Figure 47 Kaplan-Meier Plot of Progression-free Survival by Investigator (Full Analysis Set)



No. at Risk

Dato-DXd	299	217	164	105	77	46	28	15	5	0	0
Docetaxel	305	182	117	69	43	20	16	6	2	1	0

DCO: 2023-03-29
Source: Figure 14.2.2.1.1

Abbreviations: CI=confidence interval; DCO=data cut-off; PFS=progression-free survival.
DCO date: 29 Mar 2023
Source: Figure 14.2.2.1.1

Table 59 Concordance of Progression-free Survival by Blinded Independent Central

Treatment Group	Investigator PFS Result	BICR PFS Result, n (%)			Total	Discordance Rate (%)
		Death	Progressive Disease	Censored		
Dato-DXd (N=299)	Death	26 (86.7)	4 (13.3)	0	30	
	Progressive Disease	13 (6.6)	154 (78.6)	29 (14.8)	196	
	Censored	0	16 (21.9)	57 (78.1)	73	
	Total	39 (13.0)	174 (58.2)	86 (28.8)	299	15.1
Docetaxel (N=305)	Death	19 (86.4)	3 (13.6)	0	22	
	Progressive Disease	12 (5.6)	171 (79.5)	32 (14.9)	215	
	Censored	0	13 (19.1)	55 (80.9)	68	
	Total	31 (10.2)	187 (61.3)	87 (28.5)	305	14.8
Total (N=604)	Death	45 (86.5)	7 (13.5)	0	52	
	Progressive Disease	25 (6.1)	325 (79.1)	61 (14.8)	411	
	Censored	0	29 (20.6)	112 (79.4)	141	
	Total	70 (11.6)	361 (59.8)	173 (28.6)	604	14.9

Abbreviations: BICR=blinded independent central review; DCO=data cut-off; PFS=progression-free survival.
The discordance rate is the number of subjects with different PFS status (event, including progressive disease and death, versus censored) by BICR and investigator divided by the total number of subjects within the treatment arm.
Percentages are based on the row total.
DCO date: 29 Mar 2023
Source: Table 14.2.1.1.7.1

ORR by BICR

Table 60 Confirmed Best Overall Response, Objective Response Rate, and Disease Control Rate by Blinded Independent Central Review (Full Analysis Set)

	Dato-DXd (N=299) n (%)	Docetaxel (N=305) n (%)
Best Overall Response, n (%)		
Complete Response (CR)	4 (1.3)	0
Partial Response (PR)	75 (25.1)	39 (12.8)
Stable Disease (SD)	149 (49.8)	153 (50.2)
Non-CR/Non-PD	3 (1.0)	6 (2.0)
Progressive Disease (PD)	46 (15.4)	64 (21.0)
Not Evaluable	22 (7.4)	43 (14.1)
Objective Response Rate (ORR; CR+PR), n (%)	79 (26.4)	39 (12.8)
95% Confidence Interval [a]	(21.5, 31.8)	(9.3, 17.1)
Disease Control Rate (DCR; CR+PR+SD [non-CR/non-PD]), n (%)	231 (77.3)	198 (64.9)
95% Confidence Interval [a]	(72.1, 81.9)	(59.3, 70.3)

Abbreviation: DCO=data cut-off.
Percentages are based on the number of subjects in the Full Analysis Set.
Confirmed responses require at least 2 determinations of responses at least 4 weeks apart before progression.
[a] The 2-sided 95% confidence intervals are based on the Clopper-Pearson exact binomial method.
DCO date: 29 Mar 2023
Source: Table 14.2.2.2.1

DOR and TTR by BICR

Table 61 Duration of Response and Time to Response for Confirmed Response by Blinded Independent Central Review (Full Analysis Set)

	Dato-DXd (N=299)	Docetaxel (N=305)
Subjects with Confirmed CR/PR:	79	39
Duration of Response (Months)		
Minimum, Maximum [a]	1.3+, 12.9	1.4+, 11.9+
Duration of Response, n (%)		
≥6 months	33 (41.8)	11 (28.2)
≥9 months	18 (22.8)	5 (12.8)
Subjects with Events, n (%)	44 (55.7)	24 (61.5)
Progressive Disease	38 (48.1)	23 (59.0)
Death	6 (7.6)	1 (2.6)
Subjects without Events (Censored), n (%)	35 (44.3)	15 (38.5)
Event after ≥2 Missing Assessments	3 (3.8)	0
Withdrawal of Consent	1 (1.3)	0
Lost to Follow-up	1 (1.3)	0
Adequate Tumor Assessment No Longer Available	0	0
Ongoing without Events	30 (38.0)	15 (38.5)
Kaplan-Meier Estimate of Duration of Response (Months) [b]		
25th Percentile (95% CI)	4.5 (3.5, 5.5)	4.2 (2.8, 5.4)
Median (95% CI)	7.1 (5.6, 10.9)	5.6 (5.4, 8.1)
75th Percentile (95% CI)	12.0 (10.9, 12.9)	10.4 (5.7, NE)
Kaplan-Meier Estimate Event-free Probability at (95% CI)		
3 months	87.7 (77.7, 93.4)	86.5 (70.5, 94.1)
6 months	53.6 (40.8, 64.8)	39.7 (23.0, 55.9)
9 months	43.8 (31.1, 55.9)	31.5 (15.9, 48.4)
12 months	25.7 (12.4, 41.4)	NE (NE, NE)
Time to Response (Months) [c]		
N	79	39
Mean	2.59	2.75
Standard Deviation	1.929	1.973
Median	1.61	2.60
Minimum, Maximum	1.2, 9.7	1.0, 11.1

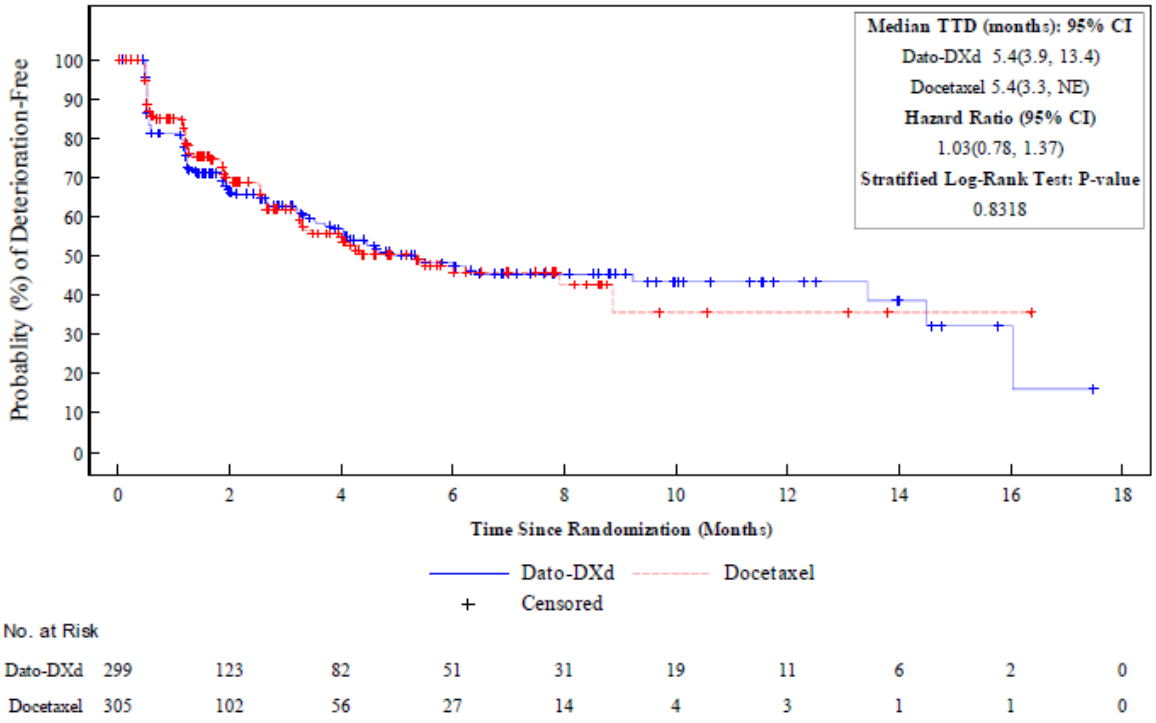
Abbreviations: CI=confidence interval; CR=complete response; DCO=data cut-off; NE=not estimable; PR=partial response.
Percentages are based on the number of subjects in the Full Analysis Set with best overall response of confirmed CR/PR.
Confirmed responses require at least 2 determinations of responses at least 4 weeks apart before progression.
Duration of response is defined as the time (months) from the date of the first documentation of objective response (confirmed CR or confirmed PR) to the date of the first documentation of progressive disease, or death due to any cause, whichever occurs first. Subjects are not censored at the initiation of new anticancer therapy.
[a] + means the value is censored.
[b] Median, 25th and 75th percentile, and point estimates at specific months are based on the Kaplan-Meier method. The 2-sided 95% CIs for the median and percentiles are computed using the Brookmeyer-Crowley method. The 2-sided 95% CIs for the event-free probability at specific months are computed using Greenwood's formula.
[c] Time to response is defined as the time from the date of randomization to the date of the first documentation of objective response (confirmed CR or confirmed PR).
DCO date: 29 Mar 2023
Source: Table 14.2.4.1

Time to Deterioration Based on the EORTC QLQ-LC13
Table 62 Time to First Clinically Meaningful Deterioration Based on EORTC QLQ-LC13 Patient-reported Outcome (Full Analysis Set)

	Dato-DXd (N=299)	Docetaxel (N=305)	*P* value
Number of Subjects with Deterioration, n (%)	110 (36.8)	90 (29.5)	
Subjects Censored, n (%)	189 (63.2)	215 (70.5)	
Withdrawal of Consent	6 (2.0)	5 (1.6)	
Lost to Follow-up	0	0	
Deterioration after 2 or More Consecutive Missed Assessments	5 (1.7)	6 (2.0)	
No Baseline Assessment	28 (9.4)	36 (11.8)	
No Post-baseline Assessment	19 (6.4)	28 (9.2)	
Assessment No Longer Available	59 (19.7)	83 (27.2)	
Ongoing	72 (24.1)	57 (18.7)	
Deterioration-free (Months) [a]			
25th Percentile (95% CI)	1.2 (1.1, 1.9)	1.7 (1.2, 2.1)	
Median (95% CI)	5.4 (3.9, 13.4)	5.4 (3.3, NE)	
75th Percentile (95% CI)	16.0 (14.5, NE)	NE (8.9, NE)	
Deterioration-free Probability at (95% CI) [b]			
3 Months	62.8 (56.0, 68.9)	61.9 (54.2, 68.7)	
6 Months	48.3 (40.6, 55.6)	47.5 (38.5, 56.0)	
9 Months	45.3 (37.4, 52.9)	35.6 (20.8, 50.6)	
12 Months	43.4 (35.0, 51.5)	35.6 (20.8, 50.6)	
Stratified Log-Rank Test, as Randomized			0.8318
Stratified Hazard Ratio, as Randomized (95% CI) [c]	1.03 (0.78, 1.37)		

Abbreviations: CI=confidence interval; DCO=data cut-off; EORTC QLQ-LC13=European Organisation for Research and Treatment of Cancer Quality of Life Lung Cancer 13; NE=not estimable; PD-1=programmed cell death 1; PD-L1=programmed cell death ligand 1.
Percentages are based on the number of subjects in the Full Analysis Set.
Time to deterioration is defined as time from randomization to the first clinically meaningful deterioration in cough, chest pain, or dyspnea. Clinically meaningful deterioration is defined as an increase of ≥10 points in severity in the linearly transformed scale, which is confirmed by a second increase of ≥10 points for the same symptom at the next scheduled assessment or death within 22 days (21 days + 1 day window). Only data collected at or prior to the end of treatment visit (+7 days) are used.
This study has 4 randomization stratification factors: actionable genomic alteration, histology, most immediate prior therapy included anti-PD-1/anti-PD-L1 immunotherapy, and geographic region. Due to the small sample size within some strata, actionable genomic alteration and most immediate prior therapy included anti-PD-1/anti-PD-L1 immunotherapy are removed from stratified analysis.
[a] Median, 25th and 75th percentile, and deterioration-free probability at specific months are based on the Kaplan-Meier method. The 2-sided 95% CIs for the median and percentiles are computed using the Brookmeyer-Crowley method.
[b] The 2-sided 95% CIs for the deterioration-free probability at specific months are computed using Greenwood's formula.
[c] Cox proportional hazards model stratified by histology and geographic region (as randomized) is used to estimate the hazard ratio with the option TIES=EXACT to handle ties.
DCO date: 29 Mar 2023
Source: Table 14.4.5.2

Figure 48 Kaplan-Meier Plot of Time to First Clinically Meaningful Deterioration (Months) Based on EORTC QLQ-LC13 (Full Analysis Set)



TTD = Time to Deterioration
DCO: 2023-03-29
Source: Figure 14.4.5.2

Abbreviations: CI=confidence interval; DCO=data cut-off; EORTC QLQ-LC13=European Organisation for Research and Treatment of Cancer Quality of Life Lung Cancer 13; NE=not estimable; TTD=time to deterioration. Time to deterioration is defined as time from randomization to the first clinically meaningful deterioration in cough, chest pain, or dyspnea. Clinically meaningful deterioration is defined as an increase of ≥10 points in severity in the linearly transformed scale, which is confirmed by a second increase of ≥10 points for the same symptom at the next scheduled assessment or death within 22 days (21 days + 1 day window). Only data collected at or prior to the end of treatment visit (+7 days) are used.
DCO date: 29 Mar 2023
Source: Figure 14.4.5.2

SUBSEQUENT THERAPIES

Table 63 Post-treatment Cancer Therapy (Full Analysis Set)

Class Preferred Term	Dato-DXd (N=299) n (%)	Docetaxel (N=305) n (%)	Total (N=604) n (%)
Subjects with Any Post-treatment Cancer Therapy	118 (39.5)	145 (47.5)	263 (43.5)
Post-Treatment Platinum Chemotherapy	28 (9.4)	38 (12.5)	66 (10.9)
Post-Treatment Other Chemotherapy	104 (34.8)	105 (34.4)	209 (34.6)
Post-Treatment Immunotherapy	15 (5.0)	33 (10.8)	48 (7.9)
Post-Treatment Targeted Therapy	42 (14.0)	46 (15.1)	88 (14.6)
Other Post-Treatment Cancer Therapy	3 (1.0)	3 (1.0)	6 (1.0)
Anaplastic Lymphoma Kinase (ALK) Inhibitors	3 (1.0)	1 (0.3)	4 (0.7)
Alectinib	1 (0.3)	0	1 (0.2)
Crizotinib	1 (0.3)	1 (0.3)	2 (0.3)
Lorlatinib	1 (0.3)	0	1 (0.2)
Anthracyclines and Related Substances	0	3 (1.0)	3 (0.5)
Amrubicin Hydrochloride	0	1 (0.3)	1 (0.2)
Doxorubicin	0	1 (0.3)	1 (0.2)
Doxorubicin Hydrochloride	0	1 (0.3)	1 (0.2)
Anti-Estrogens	1 (0.3)	0	1 (0.2)
Fulvestrant	1 (0.3)	0	1 (0.2)
Cyclin-Dependent Kinase (CDK) Inhibitors	1 (0.3)	0	1 (0.2)
Abemaciclib	1 (0.3)	0	1 (0.2)
Ribociclib	1 (0.3)	0	1 (0.2)
Detoxifying Agents for Antineoplastic Treatment	0	2 (0.7)	2 (0.3)
Calcium Levofolinate	0	1 (0.3)	1 (0.2)
Mesna	0	1 (0.3)	1 (0.2)
Epidermal Growth Factor Receptor (EGFR) Inhibitors	0	1 (0.3)	1 (0.2)
Patritumab Deruxtecan	0	1 (0.3)	1 (0.2)
Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitors	5 (1.7)	13 (4.3)	18 (3.0)
Erlotinib	1 (0.3)	2 (0.7)	3 (0.5)

Class Preferred Term	Dato-DXd (N=299) n (%)	Docetaxel (N=305) n (%)	Total (N=604) n (%)
Furmonertinib	1 (0.3)	0	1 (0.2)
Mobocertinib	1 (0.3)	0	1 (0.2)
Osimertinib	1 (0.3)	6 (2.0)	7 (1.2)
Osimertinib Mesilate	1 (0.3)	3 (1.0)	4 (0.7)
Afatinib	0	3 (1.0)	3 (0.5)
Afatinib Dimaleate	0	1 (0.3)	1 (0.2)
Erlotinib Hydrochloride	0	1 (0.3)	1 (0.2)
Gefitinib	0	1 (0.3)	1 (0.2)
Folic Acid Analogues	4 (1.3)	14 (4.6)	18 (3.0)
Pemetrexed	3 (1.0)	11 (3.6)	14 (2.3)
Pemetrexed Disodium	1 (0.3)	0	1 (0.2)
Pemetrexed Disodium Heptahydrate	0	3 (1.0)	3 (0.5)
Human Epidermal Growth Factor Receptor 2 (HER2) Inhibitors	0	1 (0.3)	1 (0.2)
Trastuzumab Deruxtecan	0	1 (0.3)	1 (0.2)
Interleukins	0	1 (0.3)	1 (0.2)
THOR-707	0	1 (0.3)	1 (0.2)
Nitrogen Mustard Analogues	0	2 (0.7)	2 (0.3)
Cyclophosphamide	0	1 (0.3)	1 (0.2)
Ifosfamide	0	1 (0.3)	1 (0.2)
Other Alkylating Agents	0	1 (0.3)	1 (0.2)
Dacarbazine	0	1 (0.3)	1 (0.2)
Other Antineoplastic Agents	6 (2.0)	6 (2.0)	12 (2.0)
Sotorasib	2 (0.7)	2 (0.7)	4 (0.7)
AVID-200	1 (0.3)	0	1 (0.2)
Endostatin	1 (0.3)	0	1 (0.2)
Lurbinectedin	1 (0.3)	0	1 (0.2)
Other Antineoplastic Agents	1 (0.3)	0	1 (0.2)
Adagrasib	0	1 (0.3)	1 (0.2)
Divarasib	0	2 (0.7)	2 (0.3)
Inupadenant	0	1 (0.3)	1 (0.2)
Other Monoclonal Antibodies and Antibody-Drug Conjugates	7 (2.3)	14 (4.6)	21 (3.5)
GEN1046	2 (0.7)	1 (0.3)	3 (0.5)
Bemarituzumab	1 (0.3)	0	1 (0.2)
BMS-986288	1 (0.3)	3 (1.0)	4 (0.7)
Datopotamab Deruxtecan	1 (0.3)	3 (1.0)	4 (0.7)
Ipilimumab	1 (0.3)	1 (0.3)	2 (0.3)
Zenocutuzumab	1 (0.3)	0	1 (0.2)
ABL501	0	1 (0.3)	1 (0.2)
Amivantamab	0	1 (0.3)	1 (0.2)
FS120	0	1 (0.3)	1 (0.2)
Mirzotamab Clezutoclax	0	1 (0.3)	1 (0.2)

Class Preferred Term	Dato-DXd (N=299) n (%)	Docetaxel (N=305) n (%)	Total (N=604) n (%)
Other Monoclonal Antibodies and Antibody-Drug Conjugates	0	2 (0.7)	2 (0.3)
SGN-B6A	0	1 (0.3)	1 (0.2)
Other Protein Kinase Inhibitors	6 (2.0)	9 (3.0)	15 (2.5)
Catequentinib Hydrochloride	3 (1.0)	0	3 (0.5)
Ceralasertib	1 (0.3)	5 (1.6)	6 (1.0)
Defactinib	1 (0.3)	0	1 (0.2)
Nintedanib	1 (0.3)	0	1 (0.2)
Catequentinib	0	1 (0.3)	1 (0.2)
Immune Checkpoint Inhibitors	0	1 (0.3)	1 (0.2)
Pralsetinib	0	1 (0.3)	1 (0.2)
Regorafenib	0	1 (0.3)	1 (0.2)
PD-1/PD-L1 Inhibitors	14 (4.7)	25 (8.2)	39 (6.5)
Nivolumab	6 (2.0)	8 (2.6)	14 (2.3)
Atezolizumab	4 (1.3)	3 (1.0)	7 (1.2)
Durvalumab	2 (0.7)	5 (1.6)	7 (1.2)
Pembrolizumab	2 (0.7)	6 (2.0)	8 (1.3)
PD-1/PD-L1 Inhibitors	0	2 (0.7)	2 (0.3)
Sintilimab	0	1 (0.3)	1 (0.2)
Platinum Compounds	28 (9.4)	38 (12.5)	66 (10.9)
Carboplatin	23 (7.7)	35 (11.5)	58 (9.6)
Cisplatin	5 (1.7)	5 (1.6)	10 (1.7)
Nedaplatin	1 (0.3)	1 (0.3)	2 (0.3)
Podophyllotoxin Derivatives	2 (0.7)	2 (0.7)	4 (0.7)
Etoposide	2 (0.7)	2 (0.7)	4 (0.7)
Pyrimidine Analogues	36 (12.0)	65 (21.3)	101 (16.7)
Gemcitabine	26 (8.7)	49 (16.1)	75 (12.4)
Gimeracil; Oteracil Potassium; Tegafur	7 (2.3)	11 (3.6)	18 (3.0)
Gemcitabine Hydrochloride	3 (1.0)	6 (2.0)	9 (1.5)
Fluorouracil	0	1 (0.3)	1 (0.2)
Gimeracil; Oteracil; Tegafur	0	1 (0.3)	1 (0.2)
Taxanes	83 (27.8)	34 (11.1)	117 (19.4)
Docetaxel	65 (21.7)	16 (5.2)	81 (13.4)
Paclitaxel	16 (5.4)	14 (4.6)	30 (5.0)
Paclitaxel Nanoparticle Albumin-Bound	5 (1.7)	5 (1.6)	10 (1.7)
Topoisomerase 1 (TOP1) Inhibitors	4 (1.3)	7 (2.3)	11 (1.8)
Irinotecan	3 (1.0)	3 (1.0)	6 (1.0)
Irinotecan Hydrochloride	1 (0.3)	2 (0.7)	3 (0.5)
Irinotecan Sucrosofate Pegylated Liposomal	0	1 (0.3)	1 (0.2)
Topotecan	0	1 (0.3)	1 (0.2)
Tuberculosis Diagnostics	0	1 (0.3)	1 (0.2)
Tuberculin	0	1 (0.3)	1 (0.2)

Class Preferred Term	Dato-DXd (N=299) n (%)	Docetaxel (N=305) n (%)	Total (N=604) n (%)
Vascular Endothelial Growth Factor (VEGF/VEGFR) Inhibitors	25 (8.4)	11 (3.6)	36 (6.0)
Ramucirumab	14 (4.7)	2 (0.7)	16 (2.6)
Bevacizumab	11 (3.7)	10 (3.3)	21 (3.5)
Vinca Alkaloids and Analogues	4 (1.3)	26 (8.5)	30 (5.0)
Vinorelbine	2 (0.7)	17 (5.6)	19 (3.1)
Vinorelbine Tartrate	2 (0.7)	9 (3.0)	11 (1.8)
Vincristine Sulfate	0	1 (0.3)	1 (0.2)
Uncoded	1 (0.3)	10 (3.3)	11 (1.8)
Investigational Antineoplastic Drugs	1 (0.3)	10 (3.3)	11 (1.8)

Abbreviations: DCO=data cut-off; PD-1=programmed cell death 1; PD-L1=programmed cell death ligand 1.
Percentages are based on the number of subjects in the Full Analysis Set.
At each level of summarization, a subject is counted only once.
DCO date: 29 Mar 2023
Source: Table 14.1.5.3

PFS2 by INV

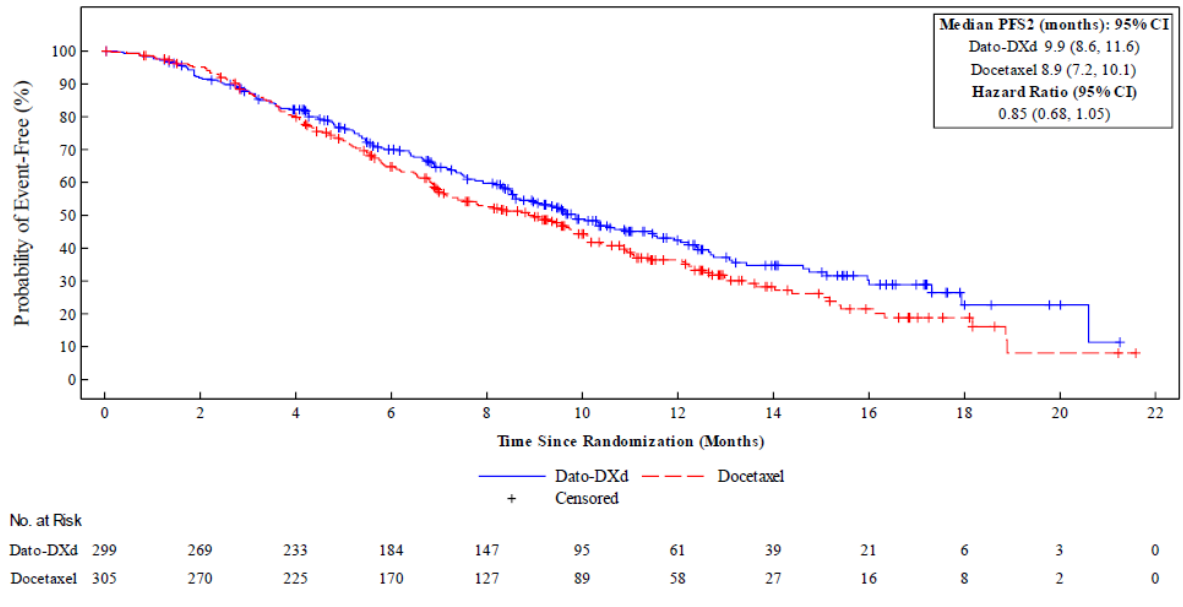
Table 64 Progression Free Survival 2 (PFS2) as Assessed by Investigator

	Dato-DXd (N=299)	Docetaxel (N=305)
Subjects with Events, n (%)	164 (54.8)	184 (60.3)
Progressive Disease on Next Line Therapy	56 (18.7)	62 (20.3)
Death	108 (36.1)	122 (40.0)
Subjects Censored, n (%)	135 (45.2)	121 (39.7)
No RECIST Progression	69 (23.1)	46 (15.1)
No New Anti-Cancer Treatment	35 (11.7)	31 (10.2)
New Anti-Cancer Treatment Started before First RECIST Progression	0	2 (0.7)
Withdrawal of Consent	0	0
Lost to Follow-up	1 (0.3)	1 (0.3)
Follow-up No Longer Available	0	0
Ongoing	30 (10.0)	41 (13.4)
Progression-free Survival 2 (Months) [a]		
25th Percentile (95% CI)	5.2 (4.3, 6.2)	4.7 (4.0, 5.4)
Median (95% CI)	9.9 (8.6, 11.6)	8.9 (7.2, 10.1)
75th Percentile (95% CI)	17.9 (15.1, NE)	15.0 (13.0, 18.2)
Progression-free Survival Probability at (95% CI) [b]		
3 Months	87.7 (83.4, 91.0)	87.7 (83.3, 91.0)
6 Months	70.0 (64.3, 75.0)	64.8 (58.8, 70.1)
9 Months	54.1 (47.9, 59.9)	49.5 (43.3, 55.4)
12 Months	42.4 (35.9, 48.8)	36.4 (30.2, 42.6)
15 Months	32.7 (25.8, 39.7)	26.1 (19.7, 32.9)
18 Months	22.7 (13.7, 33.0)	18.8 (12.4, 26.2)
Stratified Hazard Ratio, as randomized (95% CI) [c]	0.85 (0.68, 1.05)	

NE = Non-estimable. Percentages are based on the number of subjects in the Full Analysis Set.
This study has 4 randomization stratification factors: actionable genomic alteration, histology, most immediate prior therapy included anti-PD-1/anti-PD-L1 Immunotherapy, and geographic region. Due to the small sample size within some strata, actionable genomic alteration and most immediate prior therapy included anti-PD-1/anti-PD-L1 Immunotherapy are removed from stratified analysis.
Progression-free survival 2 is defined as the time (months) from the date of randomization to the earlier of the dates of the first documentation of PD on next line therapy or death due to any cause.
[a] Median, 25th and 75th Percentile, and progression-free survival probability at specific months are based on the Kaplan-Meier method. The two-sided 95% CIs for the median and percentiles are computed using the Brookmeyer-Crowley method.
[b] The two-sided 95% CIs for the progression-free survival at specific months are computed using the Greenwood's formula.
[c] Cox proportional hazards model stratified by histology and geographic region (as randomized) is used to estimate the hazard ratio with the option TIES=EXACT to handle ties.

Source: adam.adtte; Listing 16.2.6.4.2

Figure 49 Kaplan-Meier Plot of Progression Free Survival 2 (PFS2) as Assessed by Investigator Full Analysis Set



Progression-free survival 2 is defined as the time (months) from the date of randomization to the earlier of the dates of the first documentation of PD on next line therapy or death due to any cause.

Source: adam.adtte

Ancillary analyses

Planned and ad hoc subgroup analyses

Clarification on planned vs. ad hoc analyses: In the previous section, the stratification factors collected from the interactive web/voice response system (IXRS) for each subject were used for all the stratified statistical analyses presented. However, the data used for **post hoc** analyses by histology and AGA status were derived from the **eCRF** pages to account for mis-stratification, whereas the **planned** subgroup analyses by histology and AGA status (the 2 stratification factors) used data as captured in the **IXRS**.

Discrepancies: 97 subjects were reported as having AGAs by IXRS, but per eCRF, 4 additional subjects had genomic alterations that currently do not have any treatment approved. The randomization stratification factors for the FAS are summarized as randomized from IXRS in Table 8.2. A comparison of randomization stratification factors collected from the eCRF versus as randomized from IXRS for the FAS is summarized in Table 8.3.

Table 65 Randomization Stratification Factors as Randomized from IXRS (Full Analysis Set)

Stratification Factor	As Randomized from IXRS	Dato-DXd (N=299) n (%)	Docetaxel (N=305) n (%)	Total (N=604) n (%)
Actionable Genomic Alteration	Absent	252 (84.3)	255 (83.6)	507 (83.9)
	Present	47 (15.7)	50 (16.4)	97 (16.1)
Histology	Squamous	70 (23.4)	73 (23.9)	143 (23.7)
	Non-squamous	229 (76.6)	232 (76.1)	461 (76.3)
Most Immediate Prior Therapy Included Anti-PD-1/Anti-PD-L1 Immunotherapy	Yes	238 (79.6)	242 (79.3)	480 (79.5)
	No	61 (20.4)	63 (20.7)	124 (20.5)
Geographic Region	US/Japan/Western Europe	214 (71.6)	216 (70.8)	430 (71.2)
	Rest of World	85 (28.4)	89 (29.2)	174 (28.8)

Abbreviations: DCO=data cut-off; FAS=Full Analysis Set; IXRS=interactive web/voice response system; PD-1=programmed cell death 1; PD-L1=programmed cell death ligand 1; US=United States.
Percentages are based on the number of subjects in the FAS.
DCO date: 29 Mar 2023
Source: Table 14.1.7.2

Table 66 Comparison of Randomization Stratification Factors (Full Analysis Set)

Stratification Factor	As Randomized from IXRS	Per eCRF	Dato-DXd (N=299) n (%)	Docetaxel (N=305) n (%)	Total (N=604) n (%)
Actionable Genomic Alteration	Absent	Absent	249 (83.3)	253 (83.0)	502 (83.1)
		Present	3 (1.0)	2 (0.7)	5 (0.8)
	Present	Absent	0	1 (0.3)	1 (0.2)
		Present	47 (15.7)	49 (16.1)	96 (15.9)
Histology	Squamous	Squamous	64 (21.4)	70 (23.0)	134 (22.2)
		Non-squamous	6 (2.0)	3 (1.0)	9 (1.5)
	Non-squamous	Squamous	1 (0.3)	1 (0.3)	2 (0.3)
		Non-squamous	228 (76.3)	231 (75.7)	459 (76.0)
Most Immediate Prior Therapy Included Anti-PD-1/ Anti-PD-L1 Immunotherapy	Yes	Yes	230 (76.9)	239 (78.4)	469 (77.6)

		No	8 (2.7)	3 (1.0)	11 (1.8)
	No	Yes	4 (1.3)	2 (0.7)	6 (1.0)
		No	57 (19.1)	61 (20.0)	118 (19.5)
Geographic Region	US/Japan/Western Europe	US/Japan/Western Europe	214 (71.6)	216 (70.8)	430 (71.2)
		Rest of World	0	0	0
	Rest of World	US/Japan/Western Europe	0	0	0
		Rest of World	85 (28.4)	89 (29.2)	174 (28.8)
Overall	As randomized is the same as per eCRF	Yes	279 (93.3)	294 (96.4)	573 (94.9)
		No	20 (6.7)	11 (3.6)	31 (5.1)

Abbreviations: DCO=data cut-off; IXRS=interactive web/voice response system; eCRF=electronic case report form; FAS=Full Analysis Set; PD-1=programmed cell death 1; PD-L1=programmed cell death ligand 1; US=United States.
Percentages are based on the number of subjects in the FAS.
DCO date: 29 Mar 2023
Source: Table 14.1.7.1

PFS by BICR, IXRS dataset

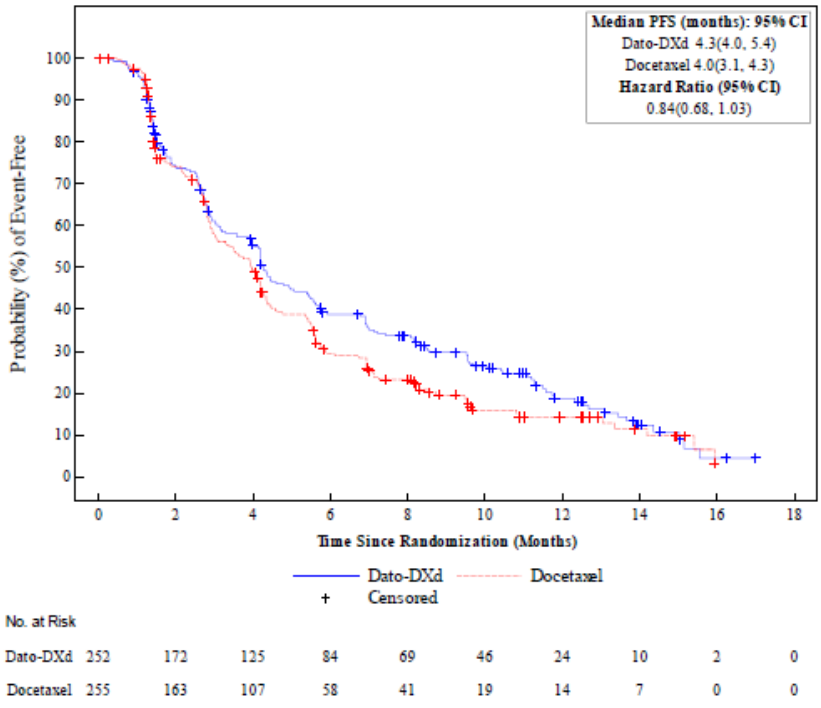
Table 67 Progression-free Survival by Blinded Independent Central Review and by Actionable Genomic Alteration (Full Analysis Set)

	Subjects with Actionable Genomic Alterations		Subjects without Actionable Genomic Alterations	
	Dato-DXd (N=47)	Docetaxel (N=50)	Dato-DXd (N=252)	Docetaxel (N=255)
Subjects with Events, n (%)	24 (51.1)	34 (68.0)	189 (75.0)	184 (72.2)
Progressive Disease	22 (46.8)	26 (52.0)	152 (60.3)	161 (63.1)
Death	2 (4.3)	8 (16.0)	37 (14.7)	23 (9.0)
Subjects Censored, n (%)	23 (48.9)	16 (32.0)	63 (25.0)	71 (27.8)
No Baseline Tumor Assessment	0	0	0	0
No Adequate Post-baseline Assessment	0	5 (10.0)	5 (2.0)	21 (8.2)
Event Occurred after 2 or More Missing Tumor Assessments	1 (2.1)	2 (4.0)	13 (5.2)	17 (6.7)
Withdrawal of Consent	0	2 (4.0)	6 (2.4)	4 (1.6)
Lost to Follow-up	1 (2.1)	0	0	0
Adequate Tumor Assessment No Longer Available	0	1 (2.0)	8 (3.2)	5 (2.0)
Ongoing without Events	21 (44.7)	6 (12.0)	31 (12.3)	24 (9.4)
Progression-free Survival (Months) [a]				
25th Percentile (95% CI)	3.0 (2.7, 4.3)	1.2 (0.8, 1.5)	1.9 (1.5, 2.6)	1.7 (1.4, 2.6)
Median (95% CI)	6.8 (4.2, 8.2)	2.6 (1.4, 4.2)	4.3 (4.0, 5.4)	4.0 (3.1, 4.3)
75th Percentile (95% CI)	8.2 (7.0, NE)	5.6 (3.7, 8.3)	10.4 (8.5, 11.8)	7.1 (5.7, 9.5)
Progression-free Survival Probability at (95% CI) [b]				
3 Months	76.6 (61.7, 86.3)	40.5 (25.6, 54.9)	61.2 (54.6, 67.1)	58.0 (51.3, 64.2)
6 Months	50.7 (33.5, 65.5)	22.3 (10.4, 36.8)	38.8 (32.5, 45.1)	29.5 (23.5, 35.7)
9 Months	NE (NE, NE)	0 (NE, NE)	29.7 (23.8, 35.8)	19.5 (14.3, 25.4)

	Subjects with Actionable Genomic Alterations		Subjects without Actionable Genomic Alterations	
	Dato-DXd (N=47)	Docetaxel (N=50)	Dato-DXd (N=252)	Docetaxel (N=255)
Unstratified Hazard Ratio (95% CI) [c]	0.38 (0.22, 0.65)		0.84 (0.68, 1.03)	

Abbreviations: CI=confidence interval; DCO=data cut-off; IXRS=interactive web/voice response system; NE=not estimable; PD=progressive disease.
Percentages are based on the number of subjects in the Full Analysis Set in each subgroup. Actionable genomic alteration subgroup is determined using data from IXRS.
Progression-free survival is defined as the time (months) from the date of randomization to the earlier of the dates of the first documentation of PD or death due to any cause. Subjects are not censored at the initiation of new anticancer therapy.
[a] Median, 25th and 75th percentile, and progression-free survival probability at specific months are based on the Kaplan-Meier method. The 2-sided 95% CIs for the median and percentiles are computed using the Brookmeyer-Crowley method.
[b] The 2-sided 95% CIs for the progression-free survival at specific months are computed using Greenwood's formula.
[c] Cox proportional hazards model is used to estimate the hazard ratio with the option TIES=EXACT to handle ties.
DCO date: 29 Mar 2023
Source: Table 14.2.1.1.8

Figure 50 Kaplan-Meier Plot of Progression-free Survival by Blinded Independent Central Review for Subjects without Actionable Genomic Alterations (Full Analysis Set)



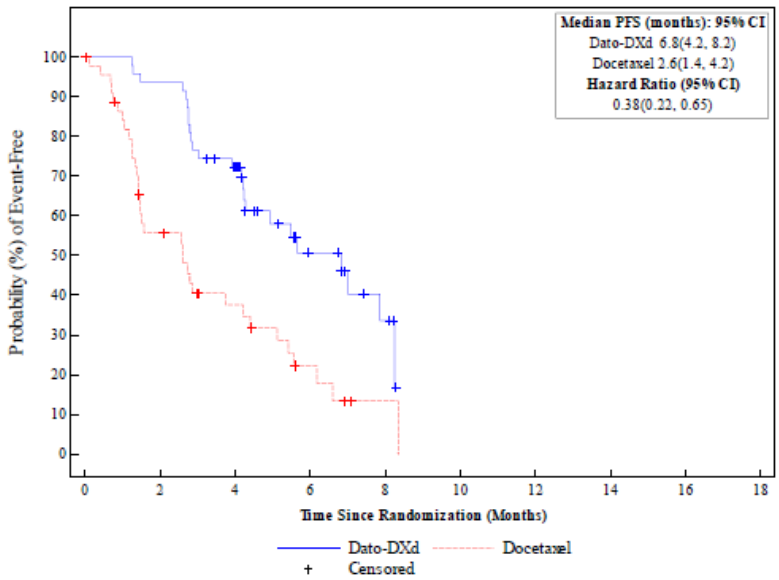
No. at Risk

Dato-DXd	252	172	125	84	69	46	24	10	2	0
Docetaxel	255	163	107	58	41	19	14	7	0	0

Actionable Genomic Alteration subgroup is determined using data from IXRS.
DCO: 2023-03-29
Source: Figure 14.2.1.1.3

Abbreviations: CI=confidence interval; DCO=data cut-off; IXRS=interactive web/voice response system; PFS=progression-free survival.
DCO date: 29 Mar 2023
Source: Figure 14.2.1.1.3

Figure 51 Kaplan-Meier Plot of Progression-free Survival by Blinded Independent Central Review for Subjects with Actionable Genomic Alterations (Full Analysis Set)



No. at Risk										
Dato-DXd	47	44	31	12	5	0	0	0	0	0
Docetaxel	50	23	13	5	1	0	0	0	0	0

Actionable Genomic Alteration subgroup is determined using data from IXRS.
DCO: 2023-03-29
Source: Figure 14.2.1.1.3

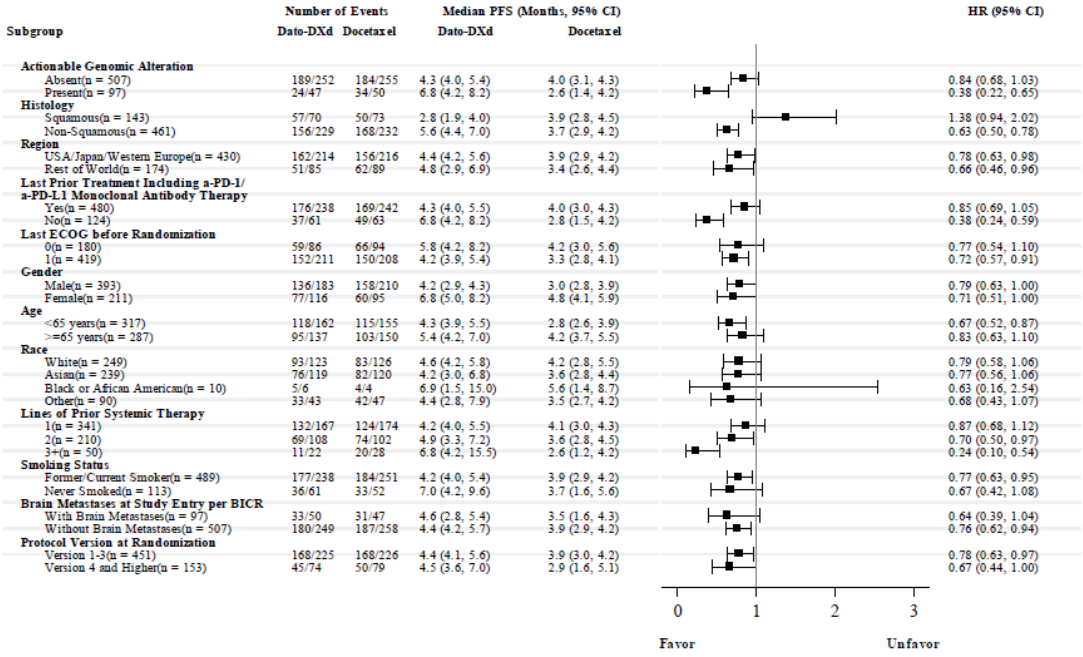
Abbreviations: CI=confidence interval; DCO=data cut-off; IXRS=interactive web/voice response system; PFS=progression-free survival.
DCO date: 29 Mar 2023
Source: Figure 14.2.1.1.3

Table 68 Progression-free Survival by Blinded Independent Central Review and by Protocol Version at Randomization (Full Analysis Set)

	Subjects Randomized under Protocol V1.0-3.0		Subjects Randomized under Protocol V4.0	
	Dato-DXd (N=225)	Docetaxel (N=226)	Dato-DXd (N=74)	Docetaxel (N=79)
Subjects with Events, n (%)	168 (74.7)	168 (74.3)	45 (60.8)	50 (63.3)
Progressive Disease	134 (59.6)	146 (64.6)	40 (54.1)	41 (51.9)
Death	34 (15.1)	22 (9.7)	5 (6.8)	9 (11.4)
Subjects Censored, n (%)	57 (25.3)	58 (25.7)	29 (39.2)	29 (36.7)
No Baseline Tumor Assessment	0	0	0	0
No Adequate Post-baseline Assessment	5 (2.2)	20 (8.8)	0	6 (7.6)
Event Occurred after 2 or More Missing Tumor Assessments	13 (5.8)	14 (6.2)	1 (1.4)	5 (6.3)
Withdrawal of Consent	6 (2.7)	3 (1.3)	0	3 (3.8)
Lost to Follow-up	0	0	1 (1.4)	0
Adequate Tumor Assessment No Longer Available	8 (3.6)	3 (1.3)	0	3 (3.8)
Ongoing without Events	25 (11.1)	18 (8.0)	27 (36.5)	12 (15.2)
Progression-free Survival (Months) [a]				
25th Percentile (95% CI)	2.3 (1.6, 2.7)	1.8 (1.4, 2.7)	2.8 (1.5, 3.0)	1.4 (1.2, 1.5)
Median (95% CI)	4.4 (4.1, 5.6)	3.9 (3.0, 4.2)	4.5 (3.6, 7.0)	2.9 (1.6, 5.1)
75th Percentile (95% CI)	11.1 (8.5, 12.3)	6.9 (5.6, 8.3)	NE (7.0, NE)	6.9 (5.4, NE)
Progression-free Survival Probability at (95% CI) [b]				
3 Months	62.9 (55.9, 69.0)	57.7 (50.5, 64.3)	66.2 (54.2, 75.7)	48.2 (35.8, 59.6)
6 Months	40.5 (33.7, 47.2)	27.5 (21.4, 34.0)	41.6 (29.4, 53.4)	31.5 (20.1, 43.5)
9 Months	30.9 (24.5, 37.4)	18.7 (13.3, 24.7)	25.2 (12.6, 39.9)	12.0 (3.7, 25.6)
Unstratified Hazard Ratio (95% CI) [c]	0.78 (0.63, 0.97)		0.67 (0.44, 1.00)	

Abbreviations: CI=confidence interval; DCO=data cut-off; NE=not estimable; V=version.
Percentages are based on the number of subjects in the Full Analysis Set in each subgroup.
Progression-free survival is defined as the time (months) from the date of randomization to the earlier of the dates of the first documentation of PD or death due to any cause. Subjects are not censored at the initiation of new anticancer therapy.
[a] Median, 25th and 75th percentile, and progression-free survival probability at specific months are based on the Kaplan-Meier method. The 2-sided 95% CIs for the median and percentiles are computed using the Brookmeyer-Crowley method.
[b] The 2-sided 95% CIs for the progression-free survival at specific months are computed using Greenwood's formula.
[c] Cox proportional hazards model is used to estimate the hazard ratio with the option TIES=EXACT to handle ties.
DCO date: 29 Mar 2023
Source: Table 14.2.1.1.19

Figure 52 Forest Plot of Progression-free Survival by Blinded Independent Central Review (Full Analysis Set)



Line of prior therapy included locally advanced or metastatic setting
DCO: 2023-03-29
Source: Figure 14.2.1.1.6

Abbreviations: BICR=blinded independent central review; CI=confidence interval; DCO=data cut-off; ECOG= Eastern Cooperative Oncology Group; HR=hazard ratio; PD-1=programmed cell death 1; PD-L1=programmed cell death ligand 1; PFS=progression-free survival; USA=United States of America.
DCO date: 29 Mar 2023
Source: Figure 14.2.1.1.6

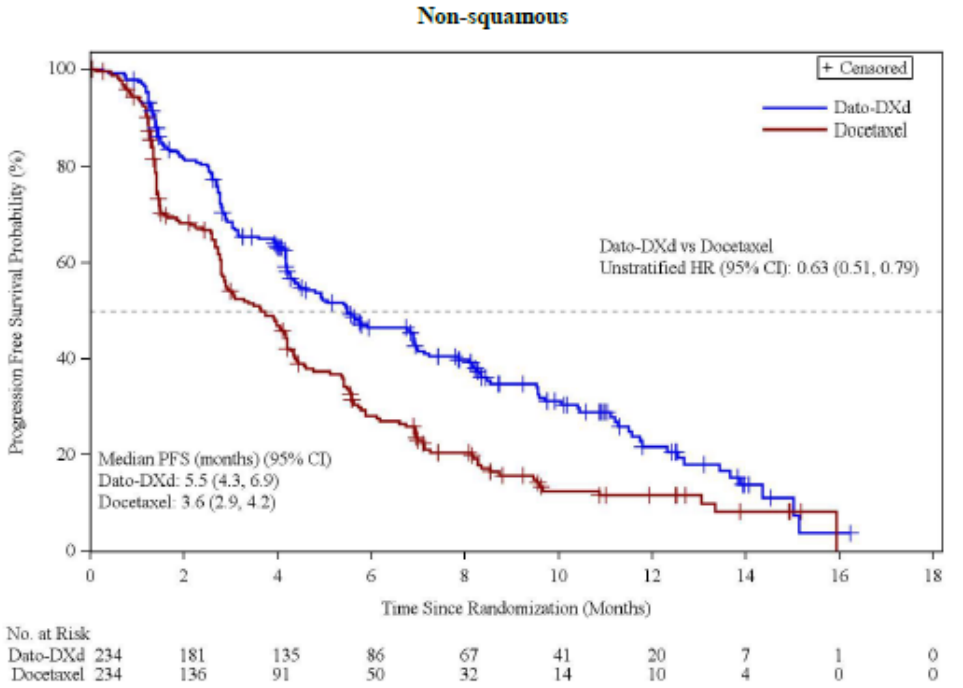
Post-hoc analyses of BICR-PFS (eCRF dataset)

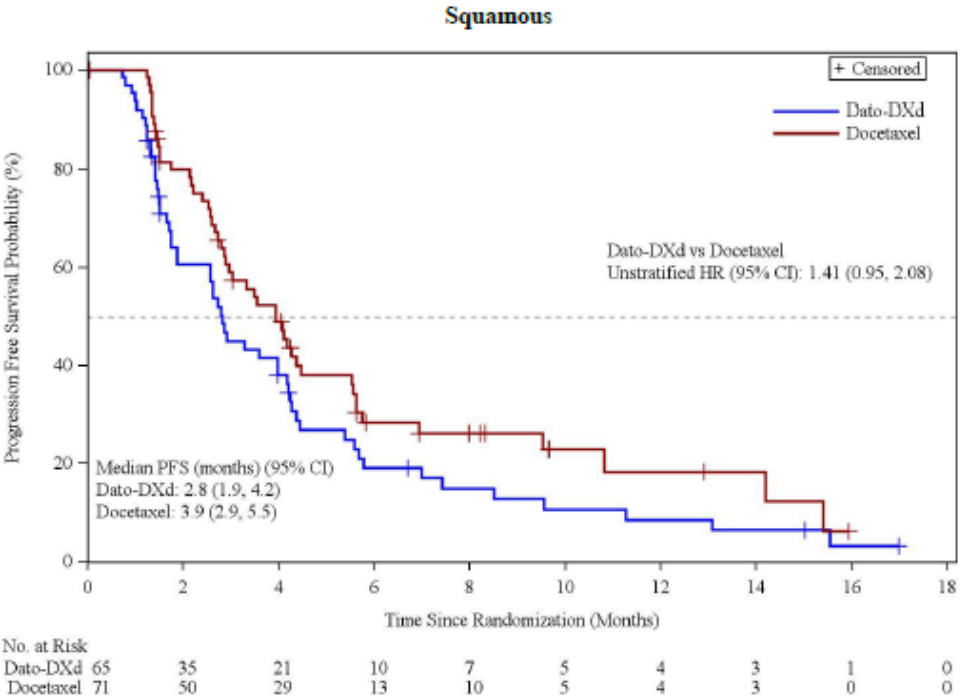
Table 69 Post Hoc Analysis of Progression-free Survival per Blinded Independent Central Review by Histology (Full Analysis Set)

	Non-squamous		Squamous	
	Dato-DXd (N=234)	Docetaxel (N=234)	Dato-DXd (N=65)	Docetaxel (N=71)
Subjects with Events, n (%)	159 (67.9)	170 (72.6)	54 (83.1)	48 (67.6)
Progressive Disease	134 (57.3)	152 (65.0)	40 (61.5)	35 (49.3)
Death	25 (10.7)	18 (7.7)	14 (21.5)	13 (18.3)
Subjects Censored, n (%)	75 (32.1)	64 (27.4)	11 (16.9)	23 (32.4)
No Baseline Tumor Assessment	0	0	0	0
No Adequate Post-baseline Assessment	4 (1.7)	21 (9.0)	1 (1.5)	5 (7.0)
Event Occurred after 2 or More Missing Tumor Assessments	12 (5.1)	13 (5.6)	2 (3.1)	6 (8.5)
Withdrawal of Consent	5 (2.1)	5 (2.1)	1 (1.5)	1 (1.4)
Lost to Follow-up	1 (0.4)	0	0	0
Adequate Tumor Assessment No Longer Available	5 (2.1)	3 (1.3)	3 (4.6)	3 (4.2)
Ongoing without Events	48 (20.5)	22 (9.4)	4 (6.2)	8 (11.3)
Progression-free Survival (Months) [a]				
25th Percentile (95% CI)	2.7 (2.4, 2.9)	1.4 (1.4, 1.8)	1.5 (1.2, 1.7)	2.4 (1.5, 2.8)
Median (95% CI)	5.5 (4.3, 6.9)	3.6 (2.9, 4.2)	2.8 (1.9, 4.2)	3.9 (2.9, 5.5)
75th Percentile (95% CI)	11.5 (9.7, 13.4)	6.9 (5.6, 8.3)	5.4 (4.2, 8.5)	9.5 (5.5, 15.4)
Progression-free Survival Probability at (95% CI) [b]				
3 Months	68.7 (62.2, 74.3)	54.1 (47.0, 60.7)	45.1 (32.1, 57.1)	59.1 (45.9, 70.0)
6 Months	46.6 (39.7, 53.2)	28.2 (22.0, 34.7)	19.2 (10.1, 30.5)	28.4 (17.4, 40.4)
9 Months	34.8 (28.1, 41.6)	15.7 (10.7, 21.6)	12.8 (5.4, 23.4)	26.2 (15.5, 38.2)
Unstratified Hazard Ratio (95% CI) [c]	0.63 (0.51, 0.79)		1.41 (0.95, 2.08)	

Abbreviations: CI=confidence interval; DCO=data cut-off; eCRF=electronic case report form; PD=progressive disease.
Histology subgroups (squamous, non-squamous) are derived using data collected from the eCRF.
Percentages are based on the number of subjects in the Full Analysis Set in each subgroup.
Progression-free survival is defined as the time (months) from the date of randomization to the earlier of the dates of the first documentation of PD or death due to any cause. Subjects are not censored at the initiation of new anticancer therapy.
[a] Median, 25th and 75th percentile, and progression-free survival probability at specific months are based on the Kaplan-Meier method. The 2-sided 95% CIs for the median and percentiles are computed using the Brookmeyer-Crowley method.
[b] The 2-sided 95% CIs for the progression-free survival at specific months are computed using Greenwood's formula.
[c] Cox proportional hazards model is used to estimate the hazard ratio with the option TIES=EXACT to handle ties.
DCO date: 29 Mar 2023
Source: Post Hoc Table 14.8.1.1

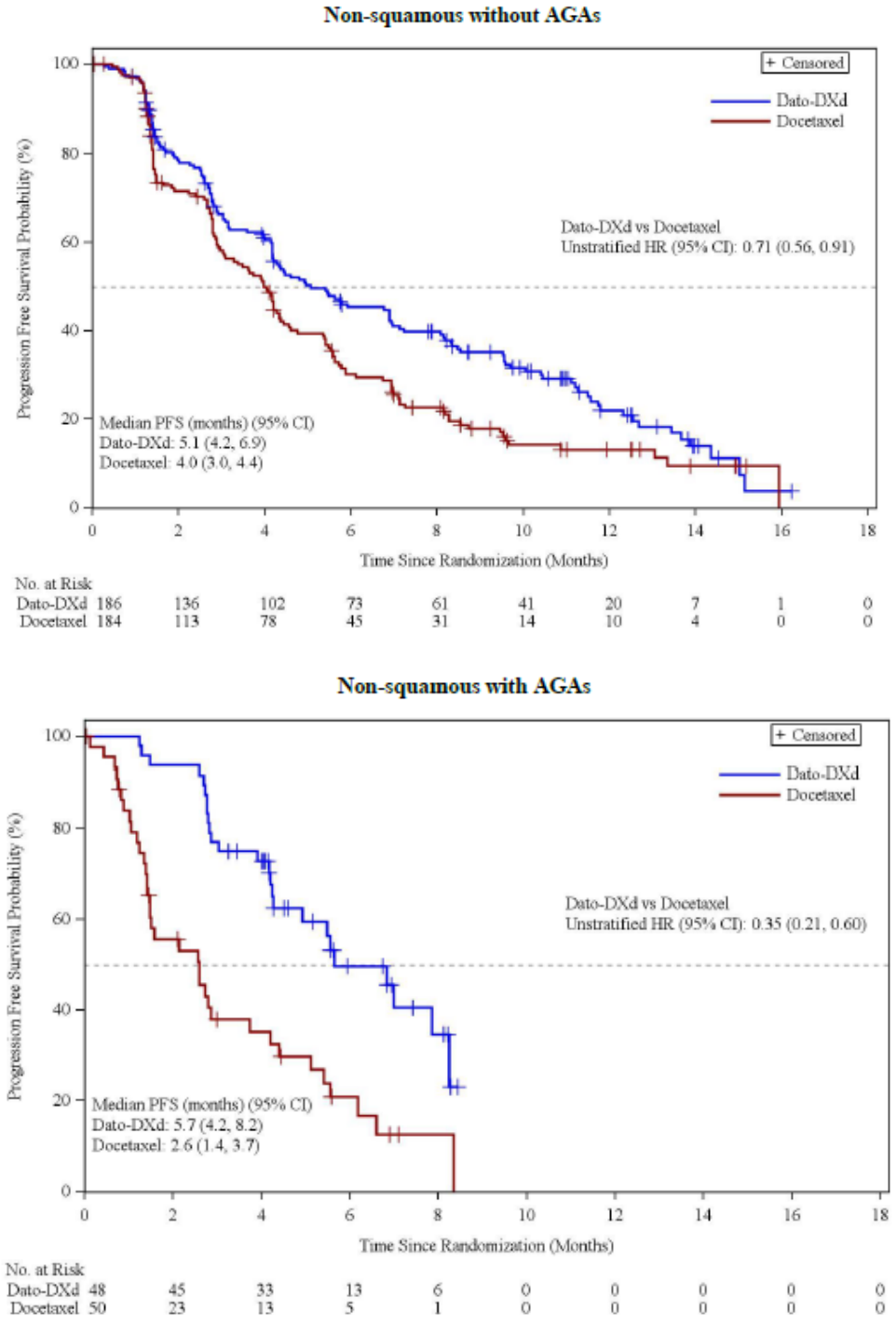
Figure 53 Post Hoc Kaplan-Meier Plots of Progression-free Survival per Blinded Independent Central Review by Histology (Full Analysis Set)





Abbreviations: CI=confidence interval; DCO=data cut-off; eCRF=electronic case report form; HR=hazard ratio; PFS=progression-free survival.
Histology subgroups (squamous, non-squamous) are derived using data collected from the eCRF.
DCO date: 29 Mar 2023
Source: Post Hoc Figure 14.8.1.1

Figure 54 Post Hoc Kaplan-Meier Plots of Progression-free Survival per Blinded Independent Central Review by Non-squamous Actionable Genomic Alteration Status (Full Analysis Set)



Abbreviations: AGA=actionable genomic alteration; CI=confidence interval; DCO=data cut-off; eCRF=electronic case report form; HR=hazard ratio; PFS=progression-free survival.
Non-squamous subgroup and AGA subgroups (absent, present) are derived using data collected from the eCRF.
DCO date: 29 Mar 2023
Source: Post Hoc Figure 14.8.1.1

OS, IXRS dataset (DCO 01 March 2024)

Table 70: OS by Histology Assigned per IXRS - Non-squamous Population (FAS)

	Non-squamous	
	Dato-DXd (N = 229)	**Docetaxel (N = 232)**
Number of subjects who died, n (%)	156 (68.1)	162 (69.8)
Subjects censored, n (%)	73 (31.9)	70 (30.2)
Withdrawal of consent	10 (4.4)	19 (8.2)
Lost to follow-up	2 (0.9)	2 (0.9)
Follow-up no longer available	0	0
Ongoing	61 (26.6)	49 (21.1)
Overall survival (Months)[a]		
25th percentile (95% CI)	7.5 (5.8, 9.1)	5.8 (4.8, 6.8)
Median (95% CI)	14.7 (12.7, 16.2)	12.3 (10.7, 14.0)
75th percentile (95% CI)	26.5 (22.9, NE)	21.0 (18.9, NE)
Overall survival probability at (95% CI)[b]		
3 months	92.1 (87.7, 94.9)	90.4 (85.6, 93.6)
6 months	80.3 (74.5, 85.0)	74.1 (67.7, 79.4)
9 months	69.8 (63.3, 75.4)	61.9 (55.0, 68.0)
12 months	59.6 (52.8, 65.8)	52.8 (45.9, 59.3)
15 months	49.5 (42.7, 55.9)	39.8 (33.2, 46.4)
18 months	38.6 (32.1, 45.0)	33.9 (27.6, 40.4)
21 months	32.5 (26.2, 38.9)	24.1 (18.3, 30.4)
Unstratified hazard ratio (95% CI)	0.83 (0.67, 1.03)	

CI = confidence interval; Dato-DXd = datopotamab deruxtecan; DCO = data cutoff; FAS = Full Analysis Set; IXRS = interactive web/voice response system; NE = not estimable; OS = overall survival

[a] Median, 25th and 75th percentiles, and overall survival probability at specific months are based on the Kaplan-Meier method. The 2-sided 95% CIs for the median and percentiles are computed using the Brookmeyer-Crowley method.

[b] The 2-sided 95% CIs for the overall survival at specific months are computed using Greenwood's formula.

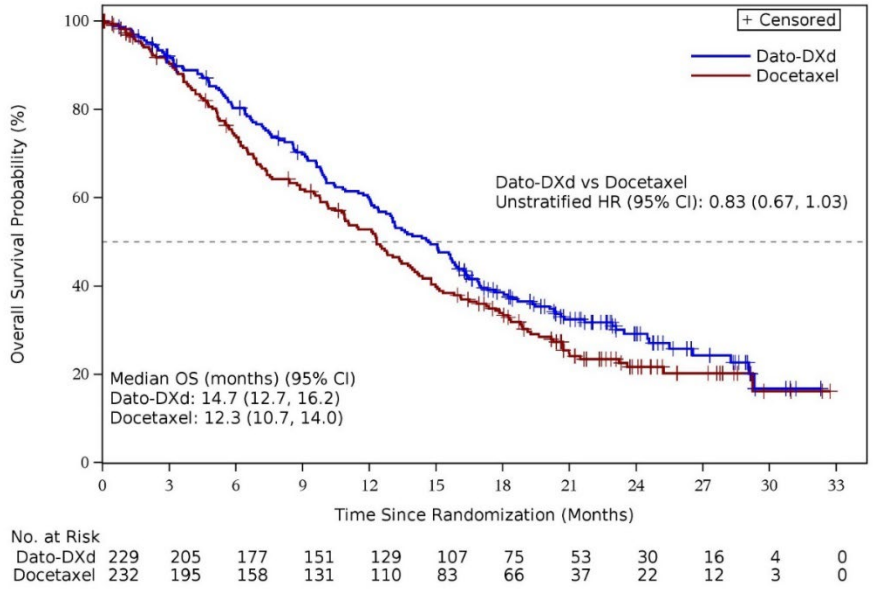
Note: Histology is derived using data collected from IXRS.

Percentages are based on the number of subjects in the FAS in each subgroup column.

DCO date: 01 Mar 2024

Source: Module 1, Appendix 4 MAA D120 Table Q101.1

Figure 55: Kaplan-Meier Plot of OS by Histology Assigned per IXRS - Non-squamous Population (FAS)



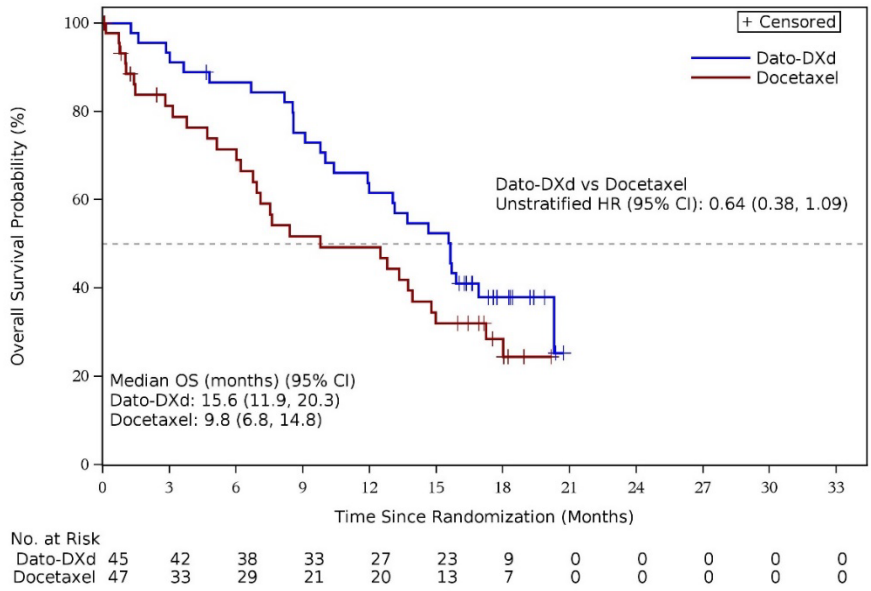
CI = confidence interval; Dato-DXd = datopotamab deruxtecan; DCO = data cutoff; FAS = Full Analysis Set; HR = hazard ratio; IXRS = interactive web/voice response system; OS = overall survival
Note: Histology is derived using data collected from IXRS.
DCO date: 01 Mar 2024
Source: Module 1, Appendix 4 MAA D120 Figure Q101.1

Table 71: OS by Histology and AGA Status Assigned per IXRS - Non-squamous Population (FAS)

	Non-squamous AGA		**Non-squamous Non-AGA**	
	Dato-DXd (N = 45)	**Docetaxel (N = 47)**	**Dato-DXd (N = 184)**	**Docetaxel (N = 185)**
Number of subjects who died, n (%)	28 (62.2)	30 (63.8)	128 (69.6)	132 (71.4)
Subjects censored, n (%)	17 (37.8)	17 (36.2)	56 (30.4)	53 (28.6)
Withdrawal of consent	0	6 (12.8)	10 (5.4)	13 (7.0)
Lost to follow-up	1 (2.2)	0	1 (0.5)	2 (1.1)
Follow-up no longer available	0	0	0	0
Ongoing	16 (35.6)	11 (23.4)	45 (24.5)	38 (20.5)
Overall survival (Months)[a]				
25th percentile (95% CI)	9.1 (4.8, 12.0)	4.7 (1.1, 6.9)	6.9 (5.6, 9.0)	5.9 (5.1, 7.2)
Median (95% CI)	15.6 (11.9, 20.3)	9.8 (6.8, 14.8)	14.4 (12.1, 16.4)	12.3 (10.9, 14.8)
75th percentile (95% CI)	NE (16.9, NE)	18.0 (13.7, NE)	26.5 (22.9, NE)	21.5 (18.9, NE)
Overall survival probability at (95% CI)[b]				
3 months	93.3 (80.7, 97.8)	81.3 (66.0, 90.2)	91.8 (86.7, 95.0)	92.6 (87.6, 95.6)
6 months	86.6 (72.6, 93.8)	71.4 (55.1, 82.7)	78.8 (72.0, 84.1)	74.8 (67.7, 80.6)
9 months	75.2 (59.7, 85.4)	51.7 (35.6, 65.6)	68.5 (61.1, 74.7)	64.3 (56.7, 71.0)
12 months	61.5 (45.6, 74.1)	49.3 (33.4, 63.3)	59.2 (51.5, 66.0)	53.7 (45.9, 60.8)
15 months	52.4 (36.8, 65.9)	32.0 (18.5, 46.3)	48.7 (41.1, 55.9)	41.7 (34.3, 49.0)
18 months	37.9 (23.5, 52.1)	28.5 (15.3, 43.1)	38.9 (31.6, 46.0)	35.2 (28.1, 42.4)
21 months	NE (NE, NE)	NE (NE, NE)	32.9 (26.0, 39.9)	25.2 (18.8, 32.0)
Unstratified hazard ratio (95% CI)	0.64 (0.38, 1.09)		0.87 (0.68, 1.11)	

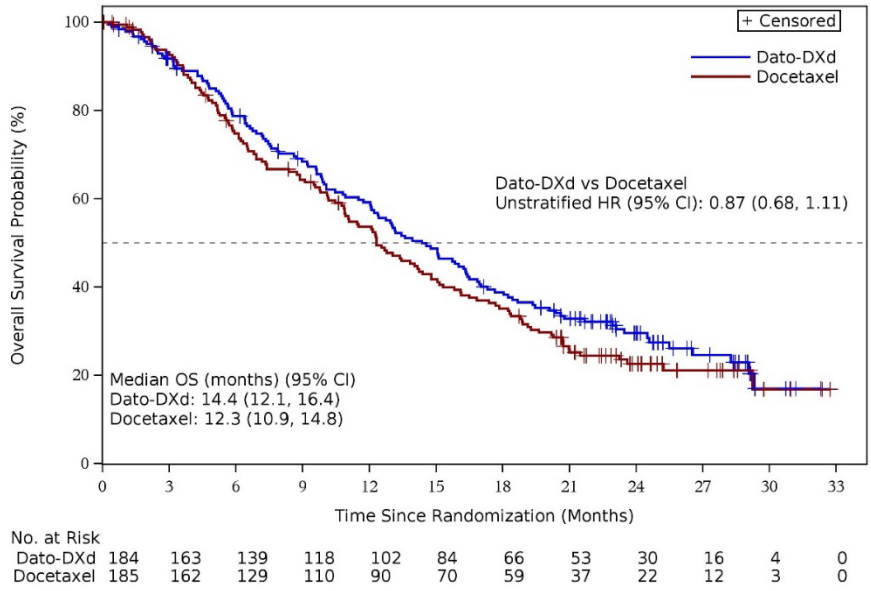
AGA = actionable genomic alteration; CI = confidence interval; Dato-DXd = datopotamab deruxtecan; DCO = data cutoff; FAS = Full Analysis Set; IXRS = interactive web/voice response system; NE = not estimable; OS = overall survival
[a] Median, 25th and 75th percentiles, and overall survival probability at specific months are based on the Kaplan-Meier method. The 2-sided 95% CIs for the median and percentiles are computed using the Brookmeyer-Crowley method.
[b] The 2-sided 95% CIs for the overall survival at specific months are computed using Greenwood's formula.
Note: Histology and AGA subgroups are derived using data collected from IXRS.
Percentages are based on the number of subjects in the FAS in each subgroup column.
DCO date: 01 Mar 2024
Source: Module 1, Appendix 4 MAA D120 Table Q101.1

Figure 56: Kaplan-Meier Plot of OS by Histology and AGA Status Assigned per IXRS - Nonsquamous AGA Population (FAS)



AGA = actionable genomic alteration; CI = confidence interval; Dato-DXd = datopotamab deruxtecan; DCO = data cutoff; FAS = Full Analysis Set; HR = hazard ratio; IXRS = interactive web/voice response system; OS = overall survival
Note: Histology AGA subgroups are derived using data collected from IXRS.
DCO date: 01 Mar 2024
Source: Module 1, Appendix 4 MAA D120 Figure Q101.1

Figure 57: Kaplan-Meier Plot of OS by Histology and AGA Status Assigned per IXRS - Non-squamous Non-AGA Population (FAS)



AGA = actionable genomic alteration; CI = confidence interval; Dato-DXd = datopotamab deruxtecan; DCO = data cutoff; FAS = Full Analysis Set; HR = hazard ratio; IXRS = interactive web/voice response system; OS = overall survival
Note: Histology AGA subgroups are derived using data collected from IXRS.
DCO date: 01 Mar 2024

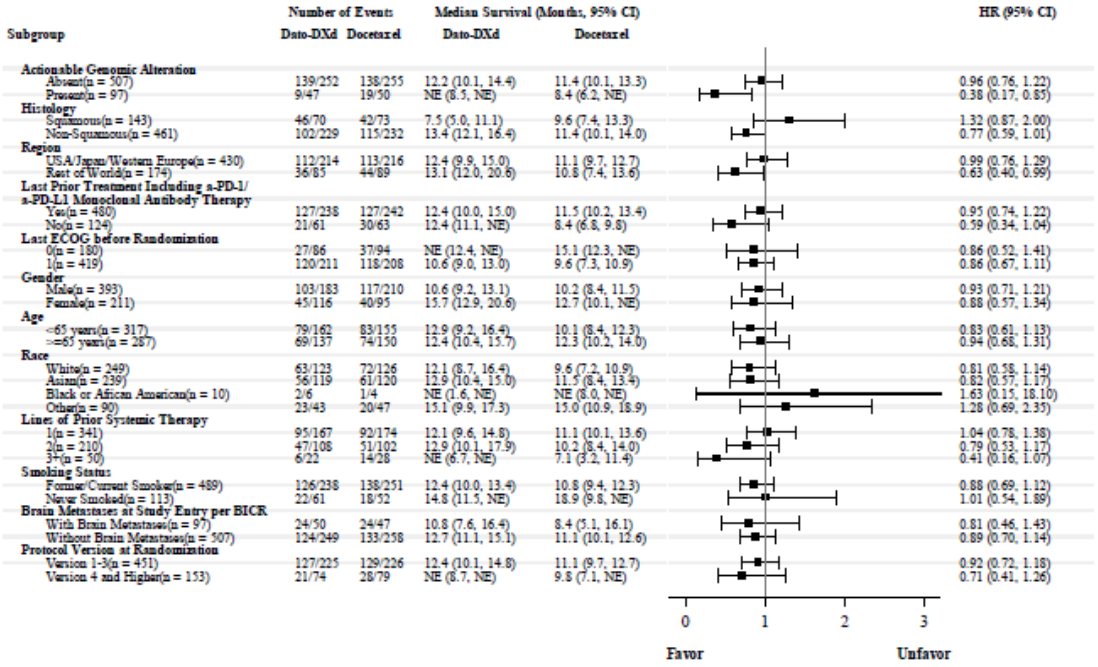
Source: Module 1, Appendix 4 MAA D120 Figure Q101.1

Table 72: OS by Histology (Non-squamous) and AGA Status – per CRF and per IXRS (FAS)

	CRF-based		IXRS-based	
	Dato-DXd	**Docetaxel**	**Dato-DXd**	**Docetaxel**
Non-squamous				
Number of subjects	234	234	229	232
Number of subjects who died, n (%)	160 (68.4)	163 (69.7)	156 (68.1)	162 (69.8)
Median OS, months (95% CI)	14.6 (12.4, 16.0)	12.3 (10.7, 14.0)	14.7 (12.7, 16.2)	12.3 (10.7, 14.0)
Unstratified hazard ratio (95% CI)	0.84 (0.68, 1.05)		0.83 (0.67, 1.03)	
Non-squamous AGA				
Number of subjects	48	50	45	47
Number of subjects who died, n (%)	31 (64.6)	32 (64.0)	28 (62.2)	30 (63.8)
Median OS, months (95% CI)	15.6 (12.0, 16.9)	9.8 (6.2, 14.8)	15.6 (11.9, 20.3)	9.8 (6.8, 14.8)
Unstratified hazard ratio (95% CI)	0.65 (0.40, 1.08)		0.64 (0.38, 1.09)	
Non-squamous Non-AGA				
Number of subjects	186	184	184	185
Number of subjects who died, n (%)	129 (69.4)	131 (71.2)	128 (69.6)	132 (71.4)
Median OS, months (95% CI)	13.6 (11.7, 16.4)	12.3 (10.9, 14.8)	14.4 (12.1, 16.4)	12.3 (10.9, 14.8)
Unstratified hazard ratio (95% CI)	0.89 (0.70, 1.13)		0.87 (0.68, 1.11)	

AGA = actionable genomic alteration; CI = confidence interval; CRF = case report form; Dato-DXd = datopotamab deruxtecan; DCO = data cutoff; FAS = Full Analysis Set; IXRS = interactive web/voice response system; OS = overall survival
DCO date: 01 Mar 2024
Source: Module 1, Appendix 4 MAA D120 Table Q101.1; Module 1, Appendix 7 Table 4, Table 5

Figure 58 Forest Plot of Overall Survival (Full Analysis Set)



Line of prior therapy included locally advanced or metastatic setting
DCO: 2023-03-29
Source: Figure 14.2.1.2.5

Abbreviations: BICR=blinded independent central review; CI=confidence interval; DCO=data cut-off; ECOG= Eastern Cooperative Oncology Group; HR=hazard ratio; NE=not estimable; PD-1=programmed cell death 1; PD-L1=programmed cell death ligand 1; USA=United States of America.
The 95% CI of the HR for Race=Black or African American is out of the plotting area. DCO date: 29 Mar 2023
Source: Figure 14.2.1.2.5

Sensitivity analyses for primary endpoints

Table 73: PFS by BICR – Worst-case Scenario Sensitivity Analysis (FAS)

	Dato-DXd (N = 299)	**Docetaxel (N = 305)**
Subjects with events, n (%)	214 (71.6)	218 (71.5)
Subjects censored, n (%)	85 (28.4)	87 (28.5)
PFS (Months)[a]		
25th percentile (95% CI)	2.5 (1.7, 2.7)	1.5 (1.4, 2.5)
Median (95% CI)	4.4 (4.2, 5.6)	4.1 (3.3, 4.4)
75th percentile (95% CI)	10.4 (8.5, 11.8)	8.3 (6.9, 10.9)
PFS probability at (95% CI)[b]		
3 months	63.5 (57.6, 68.8)	58.0 (52.0, 63.5)
6 months	40.7 (34.7, 46.5)	32.7 (27.2, 38.4)
9 months	30.0 (24.4, 35.9)	23.3 (18.2, 28.7)
Stratified log-rank test P-value	0.2345	
Stratified HR (95% CI)[c]	0.89 (0.74, 1.08)	

[a] Median, 25th and 75th percentiles, and PFS probability at specific months are based on the Kaplan-Meier method. The 2-sided 95% CIs for the median and percentiles are computed using the Brookmeyer-Crowley method.
[b] The 2-sided 95% CIs for the PFS at specific months are computed using the Greenwood's formula.
[c] A Cox proportional hazards model stratified by randomization stratification factors histology (squamous/non-squamous), and geographic region (USA/Japan/Western Europe, Rest of World) (as randomized) is used to estimate the HR with the option TIES = EXACT to handle ties.

Note: Percentages are based on the number of subjects in the FAS.
This study has 4 randomization stratification factors: actionable genomic alteration, histology, most immediate prior therapy included anti-PD-1/anti-PD-L1 immunotherapy, and geographic region. As specified in the SAP, due to the small sample size within some strata, actionable genomic alteration and most immediate prior therapy included anti-PD-1/anti-PD-L1 immunotherapy are removed from stratified analysis.
DCO date: 29 Mar 2023
Source: Module 1, Appendix 4 MAA D120 Table Q78.C.1

Table 74: Tipping Point Analysis of PFS

HR (Informatively vs. Non-informatively Censored)		**Median PFS, months (95% CI)**		**Stratified Log-rank Test**		**Median PFS, months (NSQ/SQ) Informatively Censored Subjects**	
Docetaxel	**Dato-DXd**	**Dato-DXd**	**Docetaxel**	**HR (95% CI)**	**p-value**	**Docetaxel**	**Dato-DXd**
Primary PFS (observed)		**4.4 (4.2, 5.6)**	**3.7 (2.9, 4.2)**	**0.75 (0.62, 0.91)**	**0.0040**	**-**	**-**
0.1	0.1	4.0 (3.1, 4.3)	4.4 (4.2, 5.6)	0.84 (0.69, 1.02)	**0.0715**	15.9 / NA	NA / NA
0.2	0.1	4.0 (3.1, 4.3)	4.4 (4.2, 5.6)	0.82 (0.67, 0.99)	**0.0437**	15.9 / NA	NA / NA
0.3	0.1	3.9 (3.0, 4.3)	4.4 (4.2, 5.6)	0.80 (0.66, 0.98)	**0.0270**	13.0 / 15.4	NA / NA
0.4	0.1	3.9 (3.0, 4.2)	4.4 (4.2, 5.6)	0.79 (0.65, 0.96)	**0.0170**	8.3 / 14.2	NA / NA
0.5	0.1	3.9 (3.0, 4.2)	4.4 (4.2, 5.6)	0.78 (0.64, 0.95)	**0.0115**	6.9 / 9.5	NA / NA
0.6	0.1	3.9 (3.0, 4.2)	4.4 (4.2, 5.6)	0.77 (0.63, 0.93)	0.0080	-	-
0.7	0.1	3.9 (3.0, 4.2)	4.4 (4.2, 5.6)	0.76 (0.63, 0.92)	0.0057	-	-
0.8	0.1	3.7 (2.9, 4.2)	4.4 (4.2, 5.6)	0.75 (0.62, 0.92)	0.0043	-	-
0.9	0.1	3.7 (2.9, 4.2)	4.4 (4.2, 5.6)	0.75 (0.62, 0.91)	0.0032	-	-
1.0	0.1	3.7 (2.9, 4.2)	4.4 (4.2, 5.6)	0.74 (0.61, 0.90)	0.0027	-	-
0.1	1.0	4.0 (3.1, 4.3)	4.4 (4.2, 5.6)	0.84 (0.69, 1.02)	**0.0817**	15.9 / NA	5.5 / 2.8
0.2	1.0	4.0 (3.1, 4.3)	4.4 (4.2, 5.6)	0.82 (0.68, 1.00)	**0.0501**	15.9 / NA	5.5 / 2.8
0.3	1.0	3.9 (3.0, 4.3)	4.4 (4.2, 5.6)	0.81 (0.66, 0.98)	**0.0310**	13.0 / 15.4	5.5 / 2.8
0.4	1.0	3.9 (3.0, 4.2)	4.4 (4.2, 5.6)	0.79 (0.65, 0.96)	**0.0196**	8.3 / 14.2	5.5 / 2.8
0.5	1.0	3.9 (3.0, 4.2)	4.4 (4.2, 5.6)	0.78 (0.64, 0.95)	**0.0134**	6.9 / 9.5	5.5 / 2.8
0.6	1.0	3.9 (3.0, 4.2)	4.4 (4.2, 5.6)	0.77 (0.64, 0.94)	**0.0094**	5.6 / 5.6	5.5 / 2.8
0.7	1.0	3.9 (3.0, 4.2)	4.4 (4.2, 5.6)	0.76 (0.63, 0.93)	0.0067	-	-
0.8	1.0	3.7 (2.9, 4.2)	4.4 (4.2, 5.6)	0.76 (0.62, 0.92)	0.0051	-	-
0.9	1.0	3.7 (2.9, 4.2)	4.4 (4.2, 5.6)	0.75 (0.62, 0.91)	0.0038	-	-

Note: The p-value threshold for statistical significance is 0.008 for PFS. Scenarios where the observed p-values after imputation exceed 0.008 are highlighted in bold.
The median PFS for informatively censored subjects is presented separately for those with non-squamous and squamous histology, as the imputation was conducted independently for each subgroup.
DCO date: 29 Mar 2023
Source: Module 5.3.5.1, Study TL01 CSR Table 14.2.1.1.1; Module 1, Appendix 9, Appendix 10

Table 75: Summary of Sensitivity Analyses of PFS as Assessed by BICR per RECIST v1.1 (Non-squamous Population)

	Hazard Ratio (95% CI)
BICR PFS (primary)[a]	**0.63 (0.51, 0.79)**
BICR PFS (primary)[b]	**0.63 (0.50, 0.78)**
Sensitivity Analysis[b]	
BICR PFS, censored at new anticancer therapy	0.64 (0.51, 0.80)
BICR PFS, new anticancer therapy treated as a PFS event	0.66 (0.54, 0.82)
BICR PFS, without censoring at ≥2 consecutive missed tumor assessments	0.65 (0.53, 0.80)
BICR PFS, using midpoint between time of progression and previous RECIST assessment	0.63 (0.51, 0.79)
BICR PFS, using imputation for informatively censored subjects	0.63 (0.51, 0.78)

[a] Histology determined using data from CRF.
[b] Histology determined using data from IXRS.
DCO date: 29 Mar 2023
Source: Module 1, Appendix 4 MAA D120 Table Q102.2, MAA D120 Table Q102.5, MAA D120 Table Q102.6.1; Module 5.3.5.1, Study TL01 CSR Post Hoc Table 14.8.1.1

Table 76: Summary of Sensitivity Analyses of PFS as Assessed by BICR per RECIST v1.1 (Non-squamous AGA Population)

	Hazard Ratio (95% CI)
BICR PFS (primary)[a]	**0.35 (0.21, 0.60)**
BICR PFS (primary)[b]	**0.40 (0.23, 0.69)**
Sensitivity Analysis[b]	
BICR PFS, censored at new anticancer therapy	0.38 (0.22, 0.67)
BICR PFS, new anticancer therapy treated as a PFS event	0.38 (0.23, 0.64)
BICR PFS, without censoring at ≥2 consecutive missed tumor assessments	0.41 (0.24, 0.70)
BICR PFS, using midpoint between time of progression and previous RECIST assessment	0.38 (0.22, 0.65)
BICR PFS, using imputation for informatively censored subjects	0.34 (0.20, 0.57)

[a] Histology determined using data from CRF.
[b] Histology determined using data from IXRS.
DCO date: 29 Mar 2023
Source: Module 1, Appendix 4 MAA D120 Table Q102.3, MAA D120 Table Q102.5, MAA D120 Table Q102.6.2; Module 5.3.5.1, Study TL01 CSR Post Hoc Table 14.8.1.1

Table 77: IPCW Analysis of OS to Remove the Effect of Initiating Subsequent Docetaxel Therapy in the Dato-DXd Arm by IXRS-based Histology (Non-squamous Population) and AGA Status (FAS)

OS (95% CI)	**Non-squamous**	**Non-squamous AGA**	**Non-squamous Non-AGA**
Primary Analysis			
Dato-DXd – median, months	14.7 (12.7, 16.2)	15.6 (11.9, 20.3)	14.4 (12.1, 16.4)
Docetaxel – median, months	12.3 (10.7, 14.0)	9.8 (6.8, 14.8)	12.3 (10.9, 14.8)
Unstratified hazard ratio	0.83 (0.67, 1.03)	0.64 (0.38, 1.09)	0.87 (0.68, 1.11)
IPCW Analysis – Remove the Effect of Subsequent Docetaxel usage in Dato-DXd Arm			
Dato-DXd – median, months	15.1 (12.7, 16.9)	15.6 (10.4, NE)	14.8 (12.2, 18.0)
Docetaxel – median, months	12.3 (10.7, 14.0)	9.8 (6.8, 14.8)	12.3 (10.9, 14.8)
Unstratified hazard ratio	0.81 (0.64, 1.04)	0.64 (0.38, 1.08)	0.86 (0.65, 1.13)

Note: Histology and AGA subgroups are derived using data collected from IXRS.

DCO date: 01 Mar 2024
Source: Module 1, Appendix 4 MAA Table Q102.1.2, MAA D120 Table Q101.1

Table 78: IPCW Analysis of OS to Remove the Effect of Initiating Subsequent Systemic Anticancer Therapy by IXRS-based Histology (Non-squamous Population) and AGA Status (FAS)

OS (95% CI)	Non-squamous	Non-squamous AGA	Non-squamous Non-AGA
Primary Analysis			
Dato-DXd – median, months	14.7 (12.7, 16.2)	15.6 (11.9, 20.3)	14.4 (12.1, 16.4)
Docetaxel – median, months	12.3 (10.7, 14.0)	9.8 (6.8, 14.8)	12.3 (10.9, 14.8)
Unstratified hazard ratio	0.83 (0.67, 1.03)	0.64 (0.38, 1.09)	0.87 (0.68, 1.11)
IPCW Analysis – Remove the Effect of Subsequent Systemic Therapy from Both Arms			
Dato-DXd – median, months	13.1 (8.6, 18.4)	NE (9.1, NE)	13.1 (7.5, 18.4)
Docetaxel – median, months	9.8 (7.5, 13.0)	7.5 (4.7, NE)	10.9 (7.2, 13.4)
Unstratified hazard ratio	0.75 (0.51, 1.11)	0.41 (0.18, 0.90)	0.91 (0.60, 1.38)

Note: Histology and AGA subgroups are derived using data collected from IXRS.
DCO date: 01 Mar 2024
Source: Module 1, Appendix 4 MAA Table Q102.1.1, MAA D120 Table Q101.1

Table 79: RMST of PFS by BICR

Population	Analysis	PFS by BICR, months (95% CI)			OS, months (95% CI)		
		Dato-DXd	Docetaxel	Difference	Dato-DXd	Docetaxel	Difference
All subjects	RMST[a]	6.5 (5.9, 7.1)	5.2 (4.6, 5.8)	1.3 (0.4, 2.1)	15.0 (13.7, 16.2)	14.2 (13.0, 15.5)	0.7 (-1.0, 2.5)
	KM[b]	4.4 (4.2, 5.6)	3.7 (2.9, 4.2)	NA	12.9 (11.0, 13.9)	11.8 (10.1, 12.8)	NA
Non-squamous	RMST[a]	7.0 (6.3, 7.7)	5.0 (4.4, 5.7)	2.0 (1.0, 2.9)	16.3 (14.9, 17.7)	14.7 (13.3, 16.1)	1.6 (-0.4, 3.6)
	KM[b]	5.5 (4.3, 6.9)	3.6 (2.9, 4.2)	NA	14.6 (12.4, 16.0)	12.3 (10.7, 14.0)	NA
Non-squamous AGA	RMST[a]	5.8 (5.1, 6.5)	3.3 (2.5, 4.1)	2.5 (1.4, 3.5)	14.0 (12.3, 15.7)	10.7 (8.6, 12.9)	3.3 (0.6, 6.1)
	KM[b]	5.7 (4.2, 8.2)	2.6 (1.4, 3.7)	NA	15.6 (12.0, 16.9)	9.8 (6.2, 14.8)	NA
Non-squamous Non-AGA	RMST[a]	6.9 (6.1, 7.7)	5.4 (4.6, 6.1)	1.5 (0.4, 2.6)	16.2 (14.6, 17.8)	15.2 (13.6, 16.8)	1.0 (-1.3, 3.2)
	KM[b]	5.1 (4.2, 6.9)	4.0 (3.0, 4.4)	NA	13.6 (11.7, 16.4)	12.3 (10.9, 14.8)	NA

Note: Histology and AGA subgroups are derived using data collected from CRF.
[a] RMST is the area under the KM curve up to a specific time point, τ. In the above analyses, τ is the minimum of the maximum event time across both KM curves.
[b] Median is based on the KM method. The 2-sided 95% CIs for the median are computed using the Brookmeyer Crowley method.
DCO date: 29 Mar 2023 (PFS); 01 Mar 2024 (OS)
Source: Module 5.3.5.1, Study TL01 CSR Table 14.2.1.1.1, Post Hoc Table 14.8.1.1; Module 1, Appendix 7 Table 3, Table 4, Table 5; Module 1, Appendix 4 MAA D120 Table Q108.1, MAA D120 Table Q108.2, MAA D120 Table Q108.3, MAA D120 Table Q108.4

3.3.4.3. Summary of main efficacy results

Table 80 Summary of efficacy for trial DS1062-A-U301 (TROPION-Lung01 [TL01])

Title: Phase 3 Randomized Study of DS-1062a Versus Docetaxel in Previously Treated Advanced or Metastatic Non-Small Cell Lung Cancer With or Without Actionable Genomic Alterations (DS1062-A-U301 [TROPION-Lung01])			
Study identifier	Sponsor's Protocol Number: DS1062-A-U301 (TROPION-Lung01 [TL01]) ClinicalTrials.gov Identifier: NCT04656652 EudraCT Number: 2020-004643-80 JRCT Identifier: jRCT2071200104		
Design	Phase 3, global, multicenter, randomized, active-controlled, open-label study. Randomization was stratified by the following: • Histology (squamous vs. non-squamous) • Most immediate prior therapy included anti PD-(L)1 immunotherapy (yes vs. no) • Geographical region (United States/Japan/Western Europe vs. Rest of World) • Documented AGA (present vs. absent)		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Variable. The study treatment continued until progressive disease, unacceptable toxicity, withdrawal of consent, or until any other discontinuation criterion was met. not applicable not applicable
Hypothesis	Superiority		
Treatments groups	**Dato-DXd**		6 mg/kg IV infusion every 3 weeks (Q3W), with variable duration 299 subjects randomized
	Docetaxel		75 mg/m^2 IV infusion Q3W, with variable duration 305 subjects randomized
Endpoints and definitions	Co-Primary endpoint	Progression free survival (PFS) blinded independent central review (BICR)	PFS by BICR: Time from randomization to the earlier of the dates of the first radiographic disease progression based on BICR assessment according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1), or death due to any cause.
		Overall Survival (OS)	OS: Time from randomization to death due to any cause.
	Key Secondary endpoints	Objective response rate (ORR) BICR	ORR: Proportion of subjects who achieved a best overall response (BOR) of complete response (CR) or partial response (PR) according to RECIST v1.1.
		Duration of response (DoR) BICR	DoR: Time from the date of the first documentation of objective response (CR or PR) to the date of the first radiographic disease progression according to RECIST v1.1, or death due to any cause, whichever occurred first.
		Disease control rate (DCR) BICR	DCR: Proportion of subjects who achieved a BOR of CR, PR, or stable disease according to RECIST v1.1.

Title: Phase 3 Randomized Study of DS-1062a Versus Docetaxel in Previously Treated Advanced or Metastatic Non-Small Cell Lung Cancer With or Without Actionable Genomic Alterations (DS1062-A-U301 [TROPION-Lung01])			
Study identifier	Sponsor's Protocol Number: DS1062-A-U301 (TROPION-Lung01 [TL01]) ClinicalTrials.gov Identifier: NCT04656652 EudraCT Number: 2020-004643-80 JRCT Identifier: jRCT2071200104		
Database lock	29 Mar 2023		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (All unique subjects randomized in the study. One subject was randomized twice in the docetaxel arm but only 1 subject ID was included for this subject in the analysis).		
Descriptive statistics and estimate variability	Treatment group	**Dato-DXd**	**Docetaxel**
	Number of subjects	299	305
	median **PFS BICR** (months), 95%CI	4.4 4.2, 5.6	3.7 2.9, 4.2
	median **OS** (months) 95%CI	12.4 10.8, 14.8	11.0 9.8, 12.5
	ORR BICR[c], % 95% CI[d]	26.4 20.0, 30.0	12.8 10.7, 18.9
	median DoR BICR[c] (months), [a] 95% CI[b]	7.1 5.6, 10.9	5.6 5.4, 8.1
Effect estimate per comparison	Co-Primary endpoint **PFS BICR**	Stratified HR, as randomized	0.75
		95%CI	0.62, 0.91
		p-value from stratified log-rank test, as randomized[f]	0.0040
		Dato-DXd vs. Docetaxel	
	Co-Primary endpoint **OS**	Stratified HR, as randomized[c]	0.90
		95% CI	0.72, 1.13
		p-value from stratified log rank test, as randomized[d]	0.3609
		Dato-DXd vs. Docetaxel	

Title: Phase 3 Randomized Study of DS-1062a Versus Docetaxel in Previously Treated Advanced or Metastatic Non-Small Cell Lung Cancer With or Without Actionable Genomic Alterations (DS1062-A-U301 [TROPION-Lung01])			
Study identifier	Sponsor's Protocol Number: DS1062-A-U301 (TROPION-Lung01 [TL01]) ClinicalTrials.gov Identifier: NCT04656652 EudraCT Number: 2020-004643-80 JRCT Identifier: jRCT2071200104		
Notes	[a] Median was based on the Kaplan-Meier method. [b] The 2-sided 95% CIs for the median and percentiles were computed using the Brookmeyer-Crowley method. [c] Cox proportional hazards model stratified by histology and geographic region (as randomized) was used to estimate the hazard ratio with the option TIES=EXACT to handle ties. [d] The pre-defined *P* value boundary: 0.018		
Analysis description	**Pre-defined Subgroup Analyses by Actionable Genomic Alteration (AGA)**		
Analysis population and time point description	Full Analysis Set DCO: 29 Mar 2023 (ie, DCO for primary analysis of PFS and interim analysis of OS)		
Descriptive statistics and estimate variability	**Treatment group**	**Dato-DXd**	**Docetaxel**
	AGA+ subpopulation		
	Number of subjects	47	50
	PFS BICR (months), median[a]	6.8	2.6
	95% CI[b]	4.2, 8.2	1.4, 4.2
	OS (months), median[a]	NE	8.4
	95% CI[b]	8.5, NE	6.2, NE
	AGA- subpopulation		
	Number of subjects	252	255
	PFS BICR (months), median[a]	4.3	4
	95% CI[b]	4.0, 5.4	3.1, 4.3
	OS (months), median[a]	12.2	11.4
	95% CI[b]	10.1, 14.4	10.1, 13.3
Effect estimate per comparison	**Comparison groups**	**Dato-DXd vs. Docetaxel**	
	AGA+ subpopulation		
	PFS BICR		
	Unstratified HR[c]	0.38	
	95% CI	0,22, 0.65	
	OS		
	Unstratified HR[c]	0.38	

Title: Phase 3 Randomized Study of DS-1062a Versus Docetaxel in Previously Treated Advanced or Metastatic Non-Small Cell Lung Cancer With or Without Actionable Genomic Alterations (DS1062-A-U301 [TROPION-Lung01])		
Study identifier	Sponsor's Protocol Number: DS1062-A-U301 (TROPION-Lung01 [TL01]) ClinicalTrials.gov Identifier: NCT04656652 EudraCT Number: 2020-004643-80 JRCT Identifier: jRCT2071200104	
	95% CI	0.17, 0.85
	AGA- subpopulation	
	PFS BICR	
	Unstratified HR[c]	0.84
	95% CI	0.68,1.03
	OS	
	Unstratified HR[c]	0.96
	95% CI	(0.76, 1.22)
Notes	[a] Median was based on the Kaplan-Meier method. [b] The 2-sided 95% CIs for the median and percentiles were computed using the Brookmeyer-Crowley method. [c]Cox proportional hazard model is used to estimate the hazard ratio with the option TIES=EXACT to handle ties DCO date: 29 Mar 2023	

3.3.4.4. Clinical studies in special populations

Table 81: Special Populations in the Controlled Study TL01 and Non-controlled Studies TL05 and TP01 (FAS)

	Controlled Study (TL01 Dato-DXd) N = 299 n (%)	**Non-Controlled Study (TL05 Dato-DXd) N = 137 n (%)**	**Non-Controlled Study (TP01 Dato-DXd NSCLC 6 mg/kg) N = 50 n (%)**
Renal impairment[a] subjects	193 (64.5)	84 (61.3)	32 (64.0)
Mild	140 (46.8)	57 (41.6)	18 (36.0)
Moderate	52 (17.4)	27 (19.7)	14 (28.0)
Severe	1 (0.3)	0	0
Hepatic impairment[b] subjects	52 (17.4)	21 (15.3)	6 (12.0)
Mild	52 (17.4)	21 (15.3)	6 (12.0)
Moderate	0	0	0
Severe	0	0	0
Pediatric subjects <18 years	0	0	0
Age 65-74	116 (38.8)	32 (23.4)	15 (30.0)
Age 75-84	21 (7.0)	14 (10.2)	5 (10.0)
Age 85+	0	0	0
Age Other (ie, 18-64)	162 (54.2)	91 (66.4)	30 (60.0)

[a] Normal renal function = CrCl ≥90 mL/min; mild renal impairment = CrCl ≥60 and <90 mL/min; moderate renal impairment = CrCl ≥30 and <60 mL/min; severe renal impairment = CrCl ≥15 and <30 mL/min.
[b] Normal hepatic function = TBL ≤ ULN and AST ≤ULN except for subjects with Gilbert syndrome, and TBL ≤3 x ULN and AST ≤ULN for subjects with Gilbert syndrome; mild hepatic impairment = (TBL >ULN and ≤1.5 × ULN and any AST except for subjects with Gilbert syndrome, and TBL >ULN and ≤3×ULN and AST>ULN for subjects with Gilbert syndrome) or (TBL ≤ULN and AST >ULN regardless of Gilbert syndrome); moderate hepatic impairment = TBL >1.5 ×ULN and ≤3.0 ×ULN and any AST except for subjects with Gilbert syndrome; severe hepatic impairment = TBL >3×ULN and any AST regardless of Gilbert syndrome.

Percentages for non-controlled trials (TL05, TP01) are based on the number of subjects treated with Dato-DXd in TL05 and TP01 NSCLC cohort 6 mg/kg dose level, respectively.
Source: Module 1, Appendix 4 MAA D120 Table Q115.1, MAA D120 Table Q115.2

3.3.4.5. In vitro biomarker test for patient selection for efficacy

Trophoblast cell surface protein 2 (TROP2), also known as tumor-associated calcium signal transducer 2, is a 36-kDa single-pass transmembrane protein expressed primarily in a variety of epithelial cells. TROP2 has several binding partners, including claudin 1, claudin 7, cyclin D1, protein kinase C, phosphatidylinositol 4,5 biphosphate, and insulin-like growth factor 1.
TROP2 is highly expressed in various epithelial tumors, including NSCLC (Kobayashi, 2010).
TROP2 expression was assessed using a validated robust prototype IHC assay (clone EPR20043, Ventana Medical Systems, Tucson, AZ, USA) in tumor biopsies obtained during the clinical trial screening period. A tumor tissue previously retrieved from a biopsy procedure performed within 2 years prior to the subject signing informed consent could be substituted for the pre-treatment screening biopsy.
Tumor biopsies were evaluated for tumor cell membrane TROP2 expression by IHC using a monoclonal antibody, EPR20043, that recognizes the intracellular domain of TROP2 (TROP2 EPR RUO Validation Report).

Table 82 Summary table of IHC Assay Validation Report

Experiment	Result
Precision	Four cases from different indication (Lung and Breast) were tested across four instruments on four non-consecutive days by four different operators. Acceptance criteria is 90% concordance. The concordance of the intensity scores for the TROP2(EPR20043) assay was 96% (29/30) for inter-day precision, inter-operator and inter-instrument precision. See attachment 6.2.1.1 for raw data
Accuracy	6 cell lines were tested for expression of TROP2(EPR20043) and all 6 stained as expected according to known expression levels. See attachment 6.2.1.2 for raw data
Specificity	A TOB-TOT TMA slide containing 30 normal cores from different organs across the human body and 29 cancer cores across different cancer types was stained and scored. The TMA stained as expected. 6 different cell lines were tested for expression of TROP2(EPR20043) and not another epitope/analyte. All 6 cell lines stained as expected. See attachment 6.2.1.3 for TOB-TOT raw data. See attachment 6.2.1.2 for cell line raw data.
Range and Linearity	Up to forty cases, from three different indications (Breast (TNBC and HR+), NSCLC, and CRC) were stained with the TROP2(EPR20043) assay to examine the prevalence of the biomarkers across different indication. See attachments 6.2.1.4-.6 for raw data.
Stability	Epitope stability and accelerated stability was examined during TROP2(EPR20043) RPA validation. Epitope stability for this biomarker passed successfully assigning a 26-week stability. Accelerate stability for this biomarker passed successfully across all treatment and conditions assigning 24 months of stability on formulated antibody. See attachments 6.2.1.7 and 6.2.1.8 for raw data.

To explore how tumor membrane TROP2 expression as measured by IHC and tumor KRAS mutation may associate with the clinical benefit from Dato-DXd compared with that of docetaxel, as measured by:

- Progression-free survival (PFS) assessed by blinded independent central review (BICR)
- Overall survival (OS)
- Best overall response (BOR) assessed by BICR
- Objective response rate (ORR) assessed by BICR
- Disease control rate (DCR) assessed by BICR
- Duration of response (DoR) assessed by BICR.

The following analysis sets were defined:

- Biomarker Full Analysis Set (BFAS): Included all subjects who were in the Full Analysis Set (defined in the study SAP). The BFAS was the primary analysis set for all efficacy analysis. Subjects were analyzed according to the treatment and strata they were assigned to at randomization.
- TROP2 IHC Biomarker Evaluable Analysis Set (IHC-EAS): Included all subjects in the BFAS whose pretreatment biopsy had adequate tumor content and quality for scoring in the TROP2 IHC assay, as indicated by a numerical value for the H-score
- TROP2 IHC Biomarker Non-Evaluable Analysis Set (IHC-NEAS): Included all subjects in the BFAS whose TROP2 IHC Scores were not available, ie, H-score was missing
- KRAS Biomarker Evaluable Analysis Set (KRAS-EAS): Included all subjects in the BFAS whose KRAS mutation status was available, either from the eCRF or by Guardant Health
- KRAS Biomarker Non-Evaluable Analysis Set (KRAS-NEAS): Included all subjects in BFAS whose KRAS mutation status was not available (ie, Unknown).

TROP2 expression:

In addition to be analyzed as continuous variables, TROP2 IHC H-score was dichotomized compared to its median level, namely the Biomarker Evaluable Analysis Set was split into 2 groups: < median and ≥ median arms. The dichotomization was performed using TROP2 Membrane H-score:

- TROP2 Membrane H-score dichotomization: H-score < median of H-score; H-score ≥ median of H-score.

In addition, TROP2 H-score was categorized into the following 3 groups: H-score < 100; 100 ≤ H-score < 200; and H-score ≥ 200.

In the BFAS, the TROP2 IHC non-evaluable (ie, TROP2 expression missing) was included as a separate category in the TROP2 analysis.

Missing TROP2 IHC data were not imputed. In the BFAS, subjects missing TROP2 IHC H-scores were identified as either samples not available for testing, samples failing the IHC quality requirement for analysis, or samples tested but TROP2 staining was found to be non-evaluable.

Table 83 Subject Disposition - Biomarker Full Analysis Set

	Treatment Arm		
	Dato-DXd N=299	Docetaxel N=305	Total N=604
Subjects in Biomarker Full Analysis Set	299	305	604
Subjects with TROP2 IHC evaluable (IHC-EAS)	207 (69.2)	205 (67.2)	412 (68.2)
Subjects with TROP2 IHC non-evaluable (IHC-NEAS)[a]	92 (30.8)	100 (32.8)	192 (31.8)
TROP2 IHC not assessed	39 (13.0)	54 (17.7)	93 (15.4)
TROP2 IHC assessment failed	53 (17.7)	46 (15.1)	99 (16.4)
KRAS mutation assessed	247 (82.6)	248 (81.3)	495 (82.0)
KRAS mutation reported from eCRF	169 (56.5)	164 (53.8)	333 (55.1)
KRAS mutation assessed from GH cfDNA	77 (25.8)	83 (27.2)	160 (26.5)
KRAS Mutation Assessed from eCRF /GH cfDNA[b]	1 (0.3)	1 (0.3)	2 (0.3)
KRAS mutation	62 (20.7)	59 (19.3)	121 (20.0)
Gly12Cys[c]	6 (2.0)	12 (3.9)	18 (3.0)
Others	56 (18.7)	47 (15.4)	103 (17.1)
KRAS wild type	185 (61.9)	189 (62.0)	374 (61.9)
KRAS unknown[d]	52 (17.4)	57 (18.7)	109 (18.0)

Source: Table 14.8.1.

cfDNA = circulating free DNA; eCRF = electronic case report form; GH = Guardant Health; IHC = immunohistochemistry; IHC-EAS = IHC Biomarker Evaluable Analysis Set; IHC-NEAS = IHC Biomarker Non-Evaluable Analysis Set; n = number of subjects.

Note: Percentages and summary statistics are based on the number of subjects in the Biomarker Full Analysis Set subgroup.

a TROP2 IHC H-score unavailable due to sample missing or invalid testing results (see Section 4.2.2).

b Two subjects had both 'eCRF' and 'Guardant Health' records.

c One subject had both 'Gly12Cys' and 'other' records, denoted only as 'Gly12Cys'.

d KRAS Unknown included both KRAS not assessed, and assessment failed.

Table 84 TROP2 Immunohistochemistry Scores by Treatment - TROP2 IHC Biomarker Evaluable Analysis Set

	Treatment Arm		
	Dato-DXd N=207	Docetaxel N= 205	Total N=412
TROP2 H-Score			
n	207	205	412
Mean	140.9	141.0	141.0
Standard deviation	75.59	77.20	76.30
Minimum	0	0	0
Median	151.0	150.0	150.0
Maximum	300	299	300

Source: Table 14.8.4.

IHC = immunohistochemistry; n = number of subjects.

Table 85 Demographic and Baseline Characteristics by TROP2 and Treatment Arm - Biomarker Full Analysis Set

	TROP2 IHC Evaluable Analysis Set			TROP2 IHC Non-Evaluable Analysis Set		
	Treatment Arm			Treatment Arm		
	Dato-DXd N=207	Docetaxel N=205	Total N=412	Dato-DXd N=92	Docetaxel N=100	Total N=192
Age (years)[a]						
n	207	205	412	92	100	192
Mean	62.6	62.1	62.4	62.8	63.5	63.2
Standard deviation	9.78	10.83	10.31	7.35	9.05	8.26
Minimum	26	24	24	43	40	40
Median	63.0	64.0	64.0	63.0	65.0	63.5
Maximum	84	88	88	81	84	84
Age group, n (%)						
< 65	111 (53.6)	107 (52.2)	218 (52.9)	51 (55.4)	48 (48.0)	99 (51.6)
≥ 65	96 (46.4)	98 (47.8)	194 (47.1)	41 (44.6)	52 (52.0)	93 (48.4)
< 75	188 (90.8)	187 (91.2)	375 (91.0)	90 (97.8)	92 (92.0)	182 (94.8)
≥ 75	19 (9.2)	18 (8.8)	37 (9.0)	2 (2.2)	8 (8.0)	10 (5.2)
Sex, n (%)						
Male	127 (61.4)	142 (69.3)	269 (65.3)	56 (60.9)	68 (68.0)	124 (64.6)
Female	80 (38.6)	63 (30.7)	143 (34.7)	36 (39.1)	32 (32.0)	68 (35.4)
Race, n (%)						
American Indian or Alaska Native	1 (0.5)	0	1 (0.2)	0	0	0
Asian	81 (39.1)	91 (44.4)	172 (41.7)	38 (41.3)	29 (29.0)	67 (34.9)
Black or African American	3 (1.4)	3 (1.5)	6 (1.5)	3 (3.3)	1 (1.0)	4 (2.1)
White	89 (43.0)	72 (35.1)	161 (39.1)	34 (37.0)	54 (54.0)	88 (45.8)
Other	28 (13.5)	33 (16.1)	61 (14.8)	14 (15.2)	14 (14.0)	28 (14.6)
Missing	5 (2.4)	6 (2.9)	11 (2.7)	3 (3.3)	2 (2.0)	5 (2.6)

	TROP2 IHC Evaluable Analysis Set			TROP2 IHC Non-Evaluable Analysis Set		
	Treatment Arm			Treatment Arm		
	Dato-DXd N=207	Docetaxel N=205	Total N=412	Dato-DXd N=92	Docetaxel N=100	Total N=192
Ethnicity, n (%)						
Hispanic or Latino	7 (3.4)	6 (2.9)	13 (3.2)	3 (3.3)	2 (2.0)	5 (2.6)
Not Hispanic or Latino	173 (83.6)	166 (81.0)	339 (82.3)	78 (84.8)	87 (87.0)	165 (85.9)
Unknown	21 (10.1)	27 (13.2)	48 (11.7)	9 (9.8)	9 (9.0)	18 (9.4)
Missing	6 (2.9)	6 (2.9)	12 (2.9)	2 (2.2)	2 (2.0)	4 (2.1)
Baseline ECOG PS, n (%)						
0	53 (25.6)	67 (32.7)	120 (29.1)	35 (38.0)	32 (32.0)	67 (34.9)
1	154 (74.4)	137 (66.8)	291 (70.6)	56 (60.9)	67 (67.0)	123 (64.1)
2	0	1 (0.5)	1 (0.2)	1 (1.1)	1 (1.0)	2 (1.0)
Baseline Body Mass Index (kg/m^2)						
n	207	205	412	92	99	191
Mean	24.13	24.45	24.29	24.48	25.29	24.90
Standard deviation	4.225	4.521	4.372	4.314	4.877	4.620
Minimum	15.3	15.1	15.1	17.4	16.2	16.2
Median	23.67	23.77	23.74	23.89	24.73	24.45
Maximum	39.0	41.9	41.9	40.1	38.3	40.1
Smoking History, n (%)						
Never	41 (19.8)	33 (16.1)	74 (18.0)	20 (21.7)	19 (19.0)	39 (20.3)
Former	138 (66.7)	140 (68.3)	278 (67.5)	61 (66.3)	69 (69.0)	130 (67.7)
Current	28 (13.5)	31 (15.1)	59 (14.3)	11 (12.0)	11 (11.0)	22 (11.5)
Missing	0	1 (0.5)	1 (0.2)	0	1 (1.0)	1 (0.5)

Source: Table 14.8.2.1.
ECOG PS = Eastern Cooperative Oncology Group performance status; IHC = immunohistochemistry; N, n = number of subjects.
Note: Percentages are based on the number of subjects in the Biomarker Full Analysis Set in each subgroup.
Baseline was defined as the last available assessment prior to the start of study treatment.
a Age in years was calculated using the informed consent date and the birth date.

Table 86 Baseline Disease Characteristics by TROP2 and Treatment - Biomarker Full Analysis Set

	TROP2 IHC Evaluable Analysis Set			TROP2 IHC Non-Evaluable Analysis Set		
	Treatment Arm			Treatment Arm		
	Dato-DXd N=207	Docetaxel N=205	Total N=412	Dato-DXd N=92	Docetaxel N=100	Total N=192
Time from diagnosis to randomization (months)						
n	207	205	412	92	100	192
Mean	22.6	21.2	21.9	24.8	23.2	24.0
Standard deviation	22.58	18.46	20.62	22.12	19.66	20.83
Minimum	3	2	2	3	2	2
Median	15.1	14.5	14.8	17.1	15.4	16.5
Maximum	176	104	176	117	104	117
Histology						
Adenocarcinoma	154 (74.4)	151 (73.7)	305 (74.0)	68 (73.9)	72 (72.0)	140 (72.9)
Squamous	44 (21.3)	47 (22.9)	91 (22.1)	21 (22.8)	24 (24.0)	45 (23.4)
Large cell	2 (1.0)	1 (0.5)	3 (0.7)	0	0	0
Small cell	0	0	0	0	0	0
Other	7 (3.4)	6 (2.9)	13 (3.2)	3 (3.3)	4 (4.0)	7 (3.6)
Not done	0	0	0	0	0	0
Actionable genomic alterations, n (%)						
Absent	181 (87.4)	175 (85.4)	356 (86.4)	71 (77.2)	80 (80.0)	151 (78.6)
Present	26 (12.6)	30 (14.6)	56 (13.6)	21 (22.8)	20 (20.0)	41 (21.4)
M stage at study entry, n (%)						
M0	5 (2.4)	9 (4.4)	14 (3.4)	4 (4.3)	7 (7.0)	11 (5.7)
M1	12 (5.8)	5 (2.4)	17 (4.1)	3 (3.3)	3 (3.0)	6 (3.1)
M1A	41 (19.8)	45 (22.0)	86 (20.9)	22 (23.9)	25 (25.0)	47 (24.5)
M1B	22 (10.6)	35 (17.1)	57 (13.8)	20 (21.7)	11 (11.0)	31 (16.1)
M1C	127 (61.4)	111 (54.1)	238 (57.8)	43 (46.7)	54 (54.0)	97 (50.5)

Source: Table 14.8.3.1.
IHC = immunohistochemistry; N, n = number of subjects.
Note: Percentages are based on the number of subjects in the Biomarker Full Analysis Set in each subgroup.

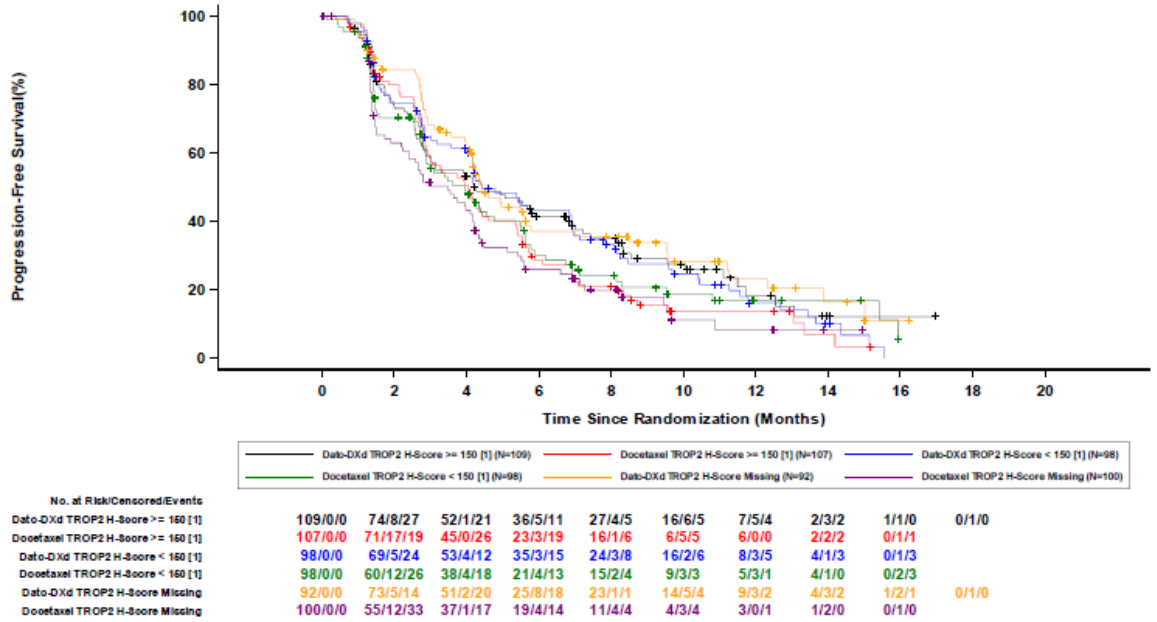
PFS

Table 87 Progression-Free Survival by TROP2 H-Score and Treatment Arm - Biomarker Full Analysis Set

	TROP2 IHC Biomarker Evaluable Analysis Set N=412						TROP2 IHC Biomarker Non-Evaluable Analysis Set N=192	
Dichotomization	H-Score ≥ 150[a]		H-Score < 150[a]		Total			
Statistics	Dato-DXd	Docetaxel	Dato-DXd	Docetaxel	Dato-DXd	Docetaxel	Dato-DXd	Docetaxel
TROP2 Membrane H-score								
n	109	107	98	98	207	205	92	100
Subjects with events, n (%)	75 (68.8)	78 (72.9)	76 (77.6)	67 (68.4)	151 (72.9)	145 (70.7)	62 (67.4)	73 (73.0)
Progressive disease	56 (51.4)	67 (62.6)	63 (64.3)	61 (62.2)	119 (57.5)	128 (62.4)	55 (59.8)	59 (59.0)
Death	19 (17.4)	11 (10.3)	13 (13.3)	6 (6.1)	32 (15.5)	17 (8.3)	7 (7.6)	14 (14.0)
Subjects censored, n (%)	34 (31.2)	29 (27.1)	22 (22.4)	31 (31.6)	56 (27.1)	60 (29.3)	30 (32.6)	27 (27.0)
Median months (95% CI)[b]	4.2 (2.9, 6.8)	4.0 (2.9, 5.4)	4.4 (4.0, 6.9)	3.9 (2.8, 5.5)	4.4 (4.0, 5.8)	3.9 (3.0, 4.4)	4.4 (4.0, 5.7)	3.5 (2.2, 4.2)
Hazard ratio (95% CI)[c]	0.80 (0.58, 1.11)		0.84 (0.60, 1.19)		0.83 (0.65, 1.04)		0.65 (0.46, 0.92)	

Source: Table 14.8.6.
BICR = blinded independent central review; CI = confidence interval; IHC = immunohistochemistry; N, n = number of subjects; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; ROW = rest of world.
Progression-free survival was based on BICR assessments according to RECIST 1.1.
a 150 was the median of TROP2 H-score for Biomarker Evaluable Set.
b Median months were based on the Kaplan-Meier method. The 95% CI for the median and percentiles were computed using the Brookmeyer-Crowley method.
c The hazard ratio of PFS by BICR was estimated from a stratified Cox proportional hazards model by TROP2 group. The stratification factors included histology (squamous versus non-squamous) and geographical region (US/Japan/Western Europe versus ROW).

Figure 59 Kaplan-Meier Plot of Dichotomized TROP2 H-score for Progression-Free Survival - Biomarker Evaluable Analysis Set



Source: Figure 14.8.10.
BICR = blinded independent central review; Grp = arm; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1.
Progression-free survival was based on BICR assessments according to RECIST 1.1.
[1] The median of TROP2 H-score was 150.0.

Table 88 Progression-Free Survival by TROP2 H-Score and Treatment Arm - Biomarker Full Analysis Set

	TROP2 IHC Biomarker Evaluable Analysis Set N=412						TROP2 IHC Biomarker Non-Evaluable Analysis Set N=192	
	H-Score < 100		≤ 100 H-Score < 200		H-Score ≥ 200			
Statistics	Dato-DXd n=53	Docetaxel n=51	Dato-DXd n=110	Docetaxel n=106	Dato-DXd n=44	Docetaxel n=48	Dato-DXd n=92	Docetaxel n=100
Subjects with events, n (%)	42 (79.2)	38 (74.5)	79 (71.8)	69 (65.1)	30 (68.2)	38 (79.2)	62 (67.4)	73 (73.0)
Progressive disease	34 (64.2)	33 (64.7)	61 (55.5)	65 (61.3)	24 (54.5)	30 (62.5)	55 (59.8)	59 (59.0)
Death	8 (15.1)	5 (9.8)	18 (16.4)	4 (3.8)	6 (13.6)	8 (16.7)	7 (7.6)	14 (14.0)
Subjects censored, n (%)	11 (20.8)	13 (25.5)	31 (28.2)	37 (34.9)	14 (31.8)	10 (20.8)	30 (32.6)	27 (27.0)
Median months (95% CI)[a]	3.6 (2.6, 6.9)	3.9 (2.8, 5.5)	5.1 (3.2, 5.9)	4.6 (3.5, 5.6)	4.9 (3.2, 11.1)	2.9 (2.6, 4.0)	4.4 (4.0, 5.7)	3.5 (2.2, 4.2)
Hazard ratio (95% CI)[b]	0.81 (0.50, 1.31)		0.96 (0.69, 1.34)		0.56 (0.34, 0.94)		0.65 (0.46, 0.92)	

Source: Table 14.8.9.
BICR = blinded independent central review; CI = confidence interval; IHC = immunohistochemistry; N, n = number of subjects; PFS = progression-free survival; ROW = rest of world.
Progression-free survival was based on BICR assessments according to RECIST 1.1.
a Median months were based on the Kaplan-Meier method. The 95% CI for the median and percentiles were computed using the Brookmeyer-Crowley method.
b The hazard ratio of PFS by BICR was estimated from a stratified Cox proportional hazards model by TROP2 group. The stratification factors included histology (squamous versus non-squamous) and geographical region (US/Japan/Western Europe versus ROW).

Table 89: PFS as Assessed by BICR by Membrane TROP2 H-score and Treatment Arm by Non-squamous Histology (FAS)

	TROP2 IHC Evaluable (N = 321)						TROP2 IHC Non-evaluable (N = 147)	
	H-Score <100		100 ≤H-Score<200		H-Score ≥200			
	Dato-DXd (n = 43)	Docetaxel (n = 42)	Dato-DXd (n = 88)	Docetaxel (n = 85)	Dato-DXd (n = 32)	Docetaxel (n = 31)	Dato-DXd (n = 71)	Docetaxel (n = 76)

Subjects with events, n (%)	34 (79.1)	31 (73.8)	62 (70.5)	58 (68.2)	21 (65.6)	25 (80.6)	42 (59.2)	56 (73.7)
Progressive disease	29 (67.4)	26 (61.9)	51 (58.0)	55 (64.7)	17 (53.1)	21 (67.7)	37 (52.1)	50 (65.8)
Death	5 (11.6)	5 (11.9)	11 (12.5)	3 (3.5)	4 (12.5)	4 (12.9)	5 (7.0)	6 (7.9)
Subjects censored, n (%)	9 (20.9)	11 (26.2)	26 (29.5)	27 (31.8)	11 (34.4)	6 (19.4)	29 (40.8)	20 (26.3)
Median months (95% CI)[a]	4.2 (2.5, 7.9)	3.6 (2.8, 5.5)	5.7 (4.2, 7.2)	4.4 (3.1, 5.7)	6.8 (2.7, 11.5)	2.9 (2.1, 4.1)	5.5 (4.3, 11.2)	2.8 (1.5, 4.2)
Hazard ratio (95% CI)[b]	0.80 (0.47, 1.35)		0.77 (0.53, 1.10)		0.47 (0.26, 0.87)		0.49 (0.32, 0.73)	

[a] The estimates are based on the Kaplan-Meier method. The 95% CIs for the median and percentiles are computed using the Brookmeyer-Crowley method.
[b] The hazard ratio of PFS by BICR is estimated from a stratified Cox proportional hazards model by TROP2 group. The stratification factor is geographical region (US/Japan/Western Europe vs. ROW).
DCO date: 29 Mar 2023
Source: Module 1, Appendix 6 Table MAA D120 Q116.2

OS

Table 90 Overall Survival by TROP2 H-Score and Treatment Arm - Biomarker Full Analysis Set

	TROP2 IHC Biomarker Evaluable Analysis Set (N = 412)						TROP2 IHC Biomarker Non-Evaluable Analysis Set (N = 192)	
Dichotomization	H-Score ≥ 150[a]		H-Score < 150[a]		Total			
Statistics	Dato-DXd	Docetaxel	Dato-DXd	Docetaxel	Dato-DXd	Docetaxel	Dato-DXd	Docetaxel
TROP2 Membrane H-score								
n	109	107	98	98	207	205	92	100
Subjects who died, n (%)	61 (56.0)	54 (50.5)	46 (46.9)	47 (48.0)	107 (51.7)	101 (49.3)	41 (44.6)	56 (56.0)
Subjects Censored, n (%)	48 (44.0)	53 (49.5)	52 (53.1)	51 (52.0)	100 (48.3)	104 (50.7)	51 (55.4)	44 (44.0)
Median Months (95% CI)[b]	12.1 (8.7, 14.8)	10.8 (8.4, 18.9)	13.4 (12.0, 20.6)	12.7 (10.1, 16.1)	12.7 (10.8, 15.1)	12.2 (9.8, 15.0)	12.4 (9.0, NE)	10.1 (6.8, 12.1)
Hazard Ratio (95% CI)[c]	1.15 (0.79, 1.67)		0.94 (0.62, 1.43)		1.03 (0.78, 1.36)		0.68 (0.45, 1.03)	

Source: Table 14.8.7.

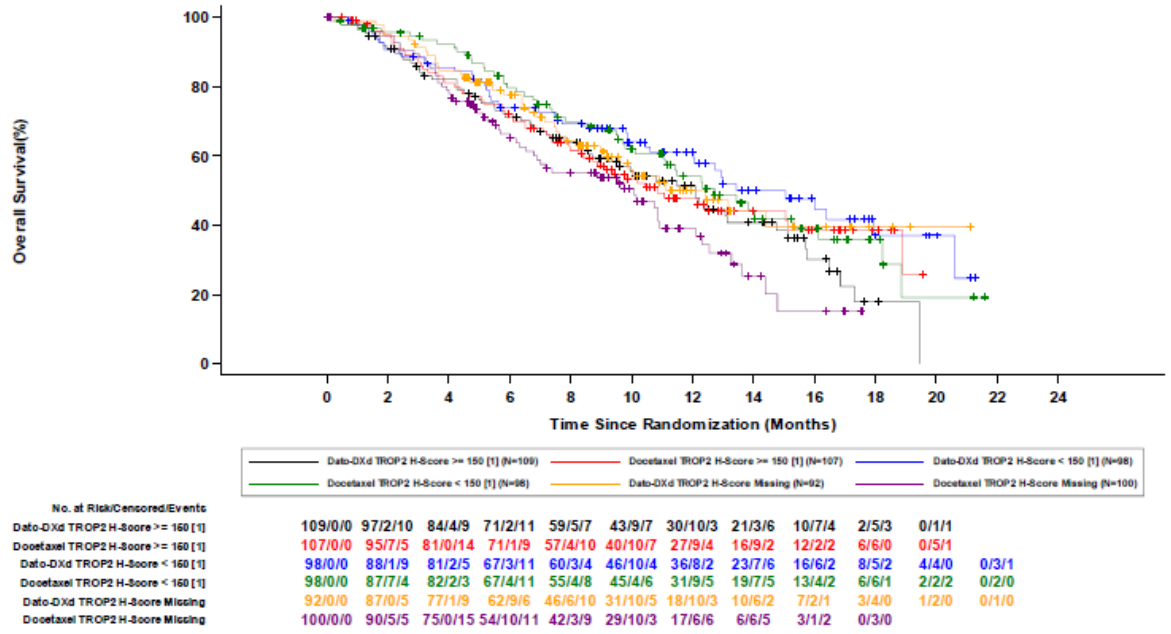
CI = confidence interval; IHC = immunohistochemistry; N, n = number of subjects; NE = not estimable; OS = overall survival; ROW = rest of world.

a 150 was the median of TROP2 H-score for Biomarker Evaluable Set.

b Median months were based on the Kaplan-Meier method. The 95% CI for the median and percentiles were computed using the Brookmeyer-Crowley method.

c The hazard ratio of OS was estimated from a stratified Cox proportional hazards model by TROP2 group. The stratification factors included histology (squamous versus non-squamous) and geographical region (US/Japan/Western Europe versus ROW).

Figure 60 Kaplan-Meier Plot of Dichotomized TROP2 H-score for Overall Survival - Biomarker Evaluable Analysis Set



No. at Risk/Censored/Events											
Dato-DXd TROP2 H-Score >= 150 [1]	109/0/0	97/2/10	84/4/9	71/2/11	59/5/7	43/9/7	30/10/3	21/3/6	10/7/4	2/5/3	0/1/1
Docetaxel TROP2 H-Score >= 150 [1]	107/0/0	95/7/5	81/0/14	71/1/9	57/4/10	40/10/7	27/9/4	16/9/2	12/2/2	6/6/0	0/5/1
Dato-DXd TROP2 H-Score < 150 [1]	98/0/0	88/1/9	81/2/5	67/3/11	60/3/4	46/10/4	36/8/2	23/7/6	16/6/2	8/5/2	4/4/0	0/3/1
Docetaxel TROP2 H-Score < 150 [1]	98/0/0	87/7/4	82/2/3	67/4/11	55/4/8	45/4/6	31/9/5	19/7/5	13/4/2	6/6/1	2/2/2	0/2/0
Dato-DXd TROP2 H-Score Missing	92/0/0	87/0/5	77/1/9	62/9/6	46/6/10	31/10/5	18/10/3	10/6/2	7/2/1	3/4/0	1/2/0	0/1/0
Docetaxel TROP2 H-Score Missing	100/0/0	90/5/5	75/0/15	54/10/11	42/3/9	29/10/3	17/6/6	6/6/5	3/1/2	0/3/0		

Source: Figure 14.8.13.

[1] The median of TROP2 H-score was 150.0.

Table 91 Overall Survival by TROP2 H-Score and Treatment Arm- Biomarker Full Analysis Set

	TROP2 IHC Biomarker Evaluable Analysis Set N=412						TROP2 IHC Biomarker Non-Evaluable Analysis Set N=192	
	H-Score < 100		≤ 100 H-Score < 200		H-Score ≥ 200			
Statistics	Dato-DXd n=53	Docetaxel n=51	Dato-DXd n=110	Docetaxel n=106	Dato-DXd n=44	Docetaxel n=48	Dato-DXd n=92	Docetaxel n=100
Subjects who died, n (%)	28 (52.8)	26 (51.0)	55 (50.0)	46 (43.4)	24 (54.5)	29 (60.4)	41 (44.6)	56 (56.0)
Subjects Censored, n (%)	25 (47.2)	25 (49.0)	55 (50.0)	60 (56.6)	20 (45.5)	19 (39.6)	51 (55.4)	44 (44.0)
Median Months (95% CI)[a]	12.7 (8.6, 17.9)	13.8 (8.4, 16.1)	13.0 (9.9, 15.7)	12.3 (10.1, 18.9)	12.1 (7.3, 17.3)	8.0 (4.7, 11.1)	12.4 (9.0, NE)	10.1 (6.8, 12.1)
Hazard Ratio (95% CI)[b]	0.95 (0.54, 1.67)		1.16 (0.78, 1.72)		0.73 (0.41, 1.30)		0.68 (0.45, 1.03)	

Source: Table 14.8.10.

CI = confidence interval; IHC = immunohistochemistry; N, n = number of subjects; NE = not estimable; OS = overall survival; ROW = rest of world.

a Median months were based on the Kaplan-Meier method. The 95% CI for the median and percentiles were computed using the Brookmeyer-Crowley method.

b The hazard ratio of OS was estimated from a stratified Cox proportional hazards model by TROP2 group. The stratification factors included histology (squamous versus non-squamous) and geographical region (US/Japan/Western Europe versus ROW).

Table 92: OS by Membrane TROP2 H-score and Treatment Arm by Non-squamous Histology (FAS)

	TROP2 IHC Evaluable (N = 321)						TROP2 IHC Non-evaluable (N = 147)	
	H-Score <100		100 ≤H-Score<200		H-Score ≥200			
	Dato-DXd (n = 43)	Docetaxel (n = 42)	Dato-DXd (n = 88)	Docetaxel (n = 85)	Dato-DXd (n = 32)	Docetaxel (n = 31)	Dato-DXd (n = 71)	Docetaxel (n = 76)
Number of subjects who died, n (%)	33 (76.7)	31 (73.8)	63 (71.6)	54 (63.5)	22 (68.8)	23 (74.2)	42 (59.2)	55 (72.4)
Subjects Censored, n (%)	10 (23.3)	11 (26.2)	25 (28.4)	31 (36.5)	10 (31.3)	8 (25.8)	29 (40.8)	21 (27.6)
Median months (95% CI)[a]	14.7 (9.8, 16.0)	13.9 (6.8, 16.8)	13.6 (10.1, 16.4)	13.4 (11.0, 18.9)	16.5 (10.0, 19.4)	10.8 (4.4, 18.3)	14.6 (10.1, 21.7)	10.7 (6.9, 12.6)
Hazard ratio (95% CI)[b]	1.11 (0.66, 1.87)		1.07 (0.74, 1.53)		0.72 (0.40, 1.32)		0.61 (0.41, 0.92)	

[a] The estimates are based on the Kaplan-Meier method. The 95% CIs for the median and percentiles are computed using the Brookmeyer-Crowley method.
[b] The hazard ratio of OS is estimated from a stratified Cox proportional hazards model by TROP2 group. The stratification factor is geographical region (US/ Japan/Western Europe versus ROW).
DCO date: 01 Mar 2024
Source: Module 1, Appendix 6 Table MAA D120 Q116.3

ORR

Table 93 TROP2 Immunohistochemistry Scores by Confirmed Best Overall Response - TROP2 IHC Biomarker Evaluable Analysis Set

	Dato-DXd						Docetaxel					
	CR N=4	PR N=52	SD N=100	PD N=33	NE N=18	Total N=207	CR N=0	PR N=28	SD N=111	PD N=37	NE N=29	Total N=205
TROP2 H-Score												
n	4	52	100	33	18	207	0	28	111	37	29	205
Mean	204.5	137.6	146.1	134.2	120.5	140.9	NA	135.3	144.8	132.4	143.1	141.0
Standard deviation	73.44	71.39	72.14	88.09	80.04	75.59	NA	79.63	78.40	73.88	77.12	77.20
Minimum	109	3	0	0	0	0	NA	4	0	3	0	0
Median	212.5	128.5	159.5	150.0	152.5	151.0	NA	145.0	155.0	131.0	162.0	150.0
Maximum	284	300	296	271	250	300	NA	291	299	280	295	299

Source: 14.8.5.
BICR = blinded independent central review; CR = complete response; IHC = immunohistochemistry; N, n = number of subjects; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SD = stable disease.
Best overall response was as assessed by BICR according to RECIST 1.1. Non-CR/non-PD were included in SD for reporting purposes.

Table 94: BOR, ORR, DCR and DoR by BICR and by Membrane TROP2 H-score by Non-squamous Histology (FAS)

	TROP2 IHC Evaluable (N = 321)						TROP2 IHC Non-evaluable (N = 147)	
	H-Score <100		100 ≤H-Score<200		H-Score ≥200			
	Dato-DXd (n = 43)	Docetaxel (n = 42)	Dato-DXd (n = 88)	Docetaxel (n = 85)	Dato-DXd (n = 32)	Docetaxel (n = 31)	Dato-DXd (n = 71)	Docetaxel (n = 76)
Best overall response, n (%)								
Complete response (CR)	0	0	2 (2.3)	0	2 (6.3)	0	0	0
Partial response (PR)	13 (30.2)	6 (14.3)	26 (29.5)	13 (15.3)	10 (31.3)	3 (9.7)	20 (28.2)	8 (10.5)
Stable disease (SD)	15 (34.9)	22 (52.4)	43 (48.9)	41 (48.2)	14 (43.8)	17 (54.8)	41 (57.7)	30 (39.5)
Non-CR/Non-PD	0	0	2 (2.3)	0	0	0	0	3 (3.9)
Progressive disease (PD)	10 (23.3)	7 (16.7)	11 (12.5)	19 (22.4)	4 (12.5)	5 (16.1)	6 (8.5)	22 (28.9)
Not evaluable (NE)	5 (11.6)	7 (16.7)	4 (4.5)	12 (14.1)	2 (6.3)	6 (19.4)	4 (5.6)	13 (17.1)
Objective response rate (ORR), n (%)	13 (30.2)	6 (14.3)	28 (31.8)	13 (15.3)	12 (37.5)	3 (9.7)	20 (28.2)	8 (10.5)
95% CI[a]	(17.2, 46.1)	(5.4, 28.5)	(22.3, 42.6)	(8.4, 24.7)	(21.1, 56.3)	(2.0, 25.8)	(18.1, 40.1)	(4.7, 19.7)
Disease control rate (DCR), n (%)	28 (65.1)	28 (66.7)	73 (83.0)	54 (63.5)	26 (81.3)	20 (64.5)	61 (85.9)	41 (53.9)
95% CI[a]	(49.1, 79.0)	(50.5, 80.4)	(73.4, 90.1)	(52.4, 73.7)	(63.6, 92.8)	(45.4, 80.8)	(75.6, 93.0)	(42.1, 65.5)
Duration of response (DoR), month								
Median (95% CI)[b]	5.7 (2.9, 9.3)	5.4 (3.6, NE)	5.6 (4.3, 7.7)	5.6 (3.3, 6.0)	11.1 (8.3, NE)	NE (5.4, NE)	10.9 (3.9, NE)	5.6 (2.1, NE)

[a] The 2-sided 95% CIs are based on the Clopper-Pearson exact binomial method.
[b] Median event time with 2-sided 95% CI using the Brookmeyer and Crowley method will be presented; DoR is based on CR/PR only.
DCO date: 29 Mar 2023
Source: Module 1, Appendix 6 Table MAA D120 Q116.1

KRAS mutation status

Tumor KRAS mutation status was measured locally using liquid or tumor tissue and reported by Investigator in the electronic case report form (eCRF). In the absence of a local KRAS test result, KRAS from cell-free DNA was tested centrally using the GuardantOMNI™ panel (Guardant, 505 Penobscot Drive Redwood City, CA 94063; DS1062 Guardant OMNI RUO Validation). Both local and central datasets were combined for analysis.

Clarification: InStudy TL01 there were 18 subjects with KRAS G12C mutations (6 in the Dato-DXd arm and 12 in the docetaxel arm) who had not received KRAS-targeted therapy prior to study enrolment.

Table 95 Demographic and Baseline Characteristics by KRAS Mutation and Treatment Arm - Biomarker Full Analysis Set

	KRAS Mutant, N=121									
	Gly12Cys, n=18		Others, n=103		Total, n=121		KRAS Wild Type, N=374		Unknown, N=109	
	Dato-DXd n=6	Docetaxel n=12	Dato-DXd n=56	Docetaxel n=47	Dato-DXd n=62	Docetaxel n=59	Dato-DXd n=185	Docetaxel n=189	Dato-DXd n=52	Docetaxel n=57
Age (years)[a]										
n	6	12	56	47	62	59	185	189	52	57
Mean	69.2	64.3	64.6	59.0	65.0	60.1	62.1	63.0	61.9	63.9
Standard deviation	9.62	8.26	7.51	10.60	7.76	10.32	9.80	9.66	7.49	11.88
Minimum	51	53	47	39	47	39	26	24	41	34
Median	71.0	62.5	65.0	60.0	65.0	61.0	63.0	65.0	62.0	65.0
Maximum	80	77	84	77	84	77	81	81	75	88
Age group, n (%)										
< 65	1 (16.7)	7 (58.3)	27 (48.2)	33 (70.2)	28 (45.2)	40 (67.8)	105 (56.8)	91 (48.1)	29 (55.8)	24 (42.1)
≥ 65	5 (83.3)	5 (41.7)	29 (51.8)	14 (29.8)	34 (54.8)	19 (32.2)	80 (43.2)	98 (51.9)	23 (44.2)	33 (57.9)
< 75	5 (83.3)	10 (83.3)	51 (91.1)	44 (93.6)	56 (90.3)	54 (91.5)	171 (92.4)	175 (92.6)	51 (98.1)	50 (87.7)
≥ 75	1 (16.7)	2 (16.7)	5 (8.9)	3 (6.4)	6 (9.7)	5 (8.5)	14 (7.6)	14 (7.4)	1 (1.9)	7 (12.3)
Sex, n (%)										
Male	4 (66.7)	8 (66.7)	28 (50.0)	23 (48.9)	32 (51.6)	31 (52.5)	123 (66.5)	139 (73.5)	28 (53.8)	40 (70.2)
Female	2 (33.3)	4 (33.3)	28 (50.0)	24 (51.1)	30 (48.4)	28 (47.5)	62 (33.5)	50 (26.5)	24 (46.2)	17 (29.8)
Race, n (%)										
American Indian or Alaska Native	0	0	1 (1.8)	0	1 (1.6)	0	0	0	0	0
Asian	1 (16.7)	2 (16.7)	15 (26.8)	13 (27.7)	16 (25.8)	15 (25.4)	78 (42.2)	71 (37.6)	25 (48.1)	34 (59.6)
Black or African American	0	1 (8.3)	3 (5.4)	0	3 (4.8)	1 (1.7)	2 (1.1)	2 (1.1)	1 (1.9)	1 (1.8)
White	5 (83.3)	6 (50.0)	25 (44.6)	27 (57.4)	30 (48.4)	33 (55.9)	71 (38.4)	74 (39.2)	22 (42.3)	19 (33.3)
Other	0	2 (16.7)	11 (19.6)	7 (14.9)	11 (17.7)	9 (15.3)	29 (15.7)	37 (19.6)	2 (3.8)	1 (1.8)
Missing	0	1 (8.3)	1 (1.8)	0	1 (1.6)	1 (1.7)	5 (2.7)	5 (2.6)	2 (3.8)	2 (3.5)

	KRAS Mutant, N=121									
	Gly12Cys, n=18		Others, n=103		Total, n=121		KRAS Wild Type, N=374		Unknown, N=109	
	Dato-DXd n=6	Docetaxel n=12	Dato-DXd n=56	Docetaxel n=47	Dato-DXd n=62	Docetaxel n=59	Dato-DXd n=185	Docetaxel n=189	Dato-DXd n=52	Docetaxel n=57
Ethnicity, n (%)										
Hispanic or Latino	0	0	1 (1.8)	0	1 (1.6)	0	6 (3.2)	5 (2.6)	3 (5.8)	3 (5.3)
Not Hispanic or Latino	6 (100)	9 (75.0)	45 (80.4)	43 (91.5)	51 (82.3)	52 (88.1)	155 (83.8)	149 (78.8)	45 (86.5)	52 (91.2)
Unknown	0	2 (16.7)	9 (16.1)	3 (6.4)	9 (14.5)	5 (8.5)	20 (10.8)	31 (16.4)	1 (1.9)	0
Missing	0	1 (8.3)	1 (1.8)	1 (2.1)	1 (1.6)	2 (3.4)	4 (2.2)	4 (2.1)	3 (5.8)	2 (3.5)
Baseline ECOG PS, n (%)										
0	1 (16.7)	4 (33.3)	13 (23.2)	16 (34.0)	14 (22.6)	20 (33.9)	57 (30.8)	65 (34.4)	17 (32.7)	14 (24.6)
1	5 (83.3)	8 (66.7)	43 (76.8)	31 (66.0)	48 (77.4)	39 (66.1)	127 (68.6)	122 (64.6)	35 (67.3)	43 (75.4)
2	0	0	0	0	0	0	1 (0.5)	2 (1.1)	0	0
Baseline Body Mass Index (kg/m^2)										
n	6	12	56	47	62	59	185	188	52	57
Mean	23.17	26.61	25.80	25.04	25.55	25.36	23.84	24.99	24.12	23.20
Standard deviation	2.869	5.016	4.255	5.363	4.197	5.290	4.363	4.625	3.612	3.671
Minimum	18.8	19.2	16.7	15.7	16.7	15.7	15.3	15.9	16.1	15.1
Median	22.73	25.61	25.68	23.94	25.25	24.05	23.11	24.60	24.30	23.42
Maximum	27.4	37.3	39.0	38.3	39.0	38.3	40.1	41.9	31.7	33.8
Smoking History, n (%)										
Never	0	1 (8.3)	12 (21.4)	7 (14.9)	12 (19.4)	8 (13.6)	31 (16.8)	26 (13.8)	18 (34.6)	18 (31.6)
Former	6 (100)	9 (75.0)	38 (67.9)	30 (63.8)	44 (71.0)	39 (66.1)	126 (68.1)	137 (72.5)	29 (55.8)	33 (57.9)
Current	0	2 (16.7)	6 (10.7)	9 (19.1)	6 (9.7)	11 (18.6)	28 (15.1)	26 (13.8)	5 (9.6)	5 (8.8)
Missing	0	0	0	1 (2.1)	0	1 (1.7)	0	0	0	1 (1.8)

Source: Table 14.8.2.2.

ECOG PS = Eastern Cooperative Oncology Group performance status; N, n = number of subjects.

Note: Percentages are based on the number of subjects in the Biomarker Full Analysis Set in each subgroup.

Baseline was defined as the last available assessment prior to the start of study treatment.

a Age in years was calculated using the informed consent date and the birth date.

Table 96 Baseline Disease Characteristics by KRAS Mutation and Treatment - Biomarker Full Analysis Set

	KRAS Mutant, N=121									
	Gly12Cys, n=18		Others, n=103		Total, n=121		KRAS Wild Type, N=374		Unknown, N=109	
	Dato-DXd n=6	Docetaxel n=12	Dato-DXd n=56	Docetaxel n=47	Dato-DXd n=62	Docetaxel n=59	Dato-DXd n=185	Docetaxel n=189	Dato-DXd n=52	Docetaxel n=57
Time from diagnosis to randomization										
n	6	12	56	47	62	59	185	189	52	57
Mean	37.9	26.8	19.0	17.6	20.8	19.5	21.0	20.8	34.3	28.0
Standard deviation	29.51	28.81	15.86	17.76	18.16	20.53	21.37	17.10	27.35	21.48
Minimum	4	5	3	4	3	4	3	2	5	3
Median	33.0	12.6	15.2	11.3	16.4	11.4	14.3	14.7	20.8	20.5
Maximum	76	97	84	96	84	97	176	104	109	104
Histology										
Adenocarcinoma	6 (100)	11 (91.7)	50 (89.3)	44 (93.6)	56 (90.3)	55 (93.2)	126 (68.1)	127 (67.2)	40 (76.9)	41 (71.9)
Squamous	0	1 (8.3)	4 (7.1)	1 (2.1)	4 (6.5)	2 (3.4)	50 (27.0)	55 (29.1)	11 (21.2)	14 (24.6)
Large cell	0	0	1 (1.8)	0	1 (1.6)	0	1 (0.5)	1 (0.5)	0	0
Small cell	0	0	0	0	0	0	0	0	0	0
Other	0	0	1 (1.8)	2 (4.3)	1 (1.6)	2 (3.4)	8 (4.3)	6 (3.2)	1 (1.9)	2 (3.5)
Not done	0	0	0	0	0	0	0	0	0	0
Actionable genomic alterations, n (%)										
Absent	6 (100)	12 (100)	56 (100)	47 (100)	62 (100)	59 (100)	163 (88.1)	168 (88.9)	27 (51.9)	28 (49.1)
Present	0	0	0	0	0	0	22 (11.9)	21 (11.1)	25 (48.1)	29 (50.9)
M stage at study entry, n (%)										
M0	0	0	0	2 (4.3)	0	2 (3.4)	9 (4.9)	12 (6.3)	0	2 (3.5)
M1	1 (16.7)	0	2 (3.6)	1 (2.1)	3 (4.8)	1 (1.7)	8 (4.3)	4 (2.1)	4 (7.7)	3 (5.3)
M1A	1 (16.7)	1 (8.3)	14 (25.0)	11 (23.4)	15 (24.2)	12 (20.3)	36 (19.5)	42 (22.2)	12 (23.1)	16 (28.1)
M1B	2 (33.3)	3 (25.0)	6 (10.7)	4 (8.5)	8 (12.9)	7 (11.9)	25 (13.5)	29 (15.3)	9 (17.3)	10 (17.5)
M1C	2 (33.3)	8 (66.7)	34 (60.7)	29 (61.7)	36 (58.1)	37 (62.7)	107 (57.8)	102 (54.0)	27 (51.9)	26 (45.6)

Source: Table 14.8.3.2.

N, n = number of subjects.

Note: Percentages are based on the number of subjects in the Biomarker Full Analysis Set in each subgroup.

PFS

Table 97 Progression-Free Survival by KRAS Mutation Status and Treatment Arm - Biomarker Full Analysis Set

	KRAS Mutant, N=121						KRAS Wild Type, N=374		KRAS Unknown, N=109	
	Gly12Cys, n=18		Others, n=103		Total, n=121					
	Dato-DXd n=6	Docetaxel n=12	Dato-DXd n=56	Docetaxel n=47	Dato-DXd n=62	Docetaxel n=59	Dato-DXd n=185	Docetaxel n=189	Dato-DXd n=52	Docetaxel n=57
Subjects with events, n (%)	5 (83.3)	8 (66.7)	42 (75.0)	37 (78.7)	47 (75.8)	45 (76.3)	133 (71.9)	141 (74.6)	33 (63.5)	32 (56.1)
Progressive disease	4 (66.7)	7 (58.3)	33 (58.9)	33 (70.2)	37 (59.7)	40 (67.8)	109 (58.9)	120 (63.5)	28 (53.8)	27 (47.4)
Death	1 (16.7)	1 (8.3)	9 (16.1)	4 (8.5)	10 (16.1)	5 (8.5)	24 (13.0)	21 (11.1)	5 (9.6)	5 (8.8)
Subjects censored, n (%)	1 (16.7)	4 (33.3)	14 (25.0)	10 (21.3)	15 (24.2)	14 (23.7)	52 (28.1)	48 (25.4)	19 (36.5)	25 (43.9)
Median months (95% CI)[a]	6.2 (1.4, NE)	5.6 (1.3, 8.7)	4.3 (2.7, 5.7)	3.9 (1.4, 5.4)	4.3 (2.9, 5.8)	4.2 (1.8, 5.5)	4.3 (3.3, 5.6)	3.5 (2.9, 4.1)	5.7 (4.2, 6.9)	4.5 (2.6, 5.6)
Hazard ratio (95% CI)[b]	1.27 (0.36, 4.47)		0.65 (0.40, 1.06)		0.73 (0.47, 1.14)		0.81 (0.63, 1.03)		0.73 (0.43, 1.23)	

Source: Table 14.8.12.

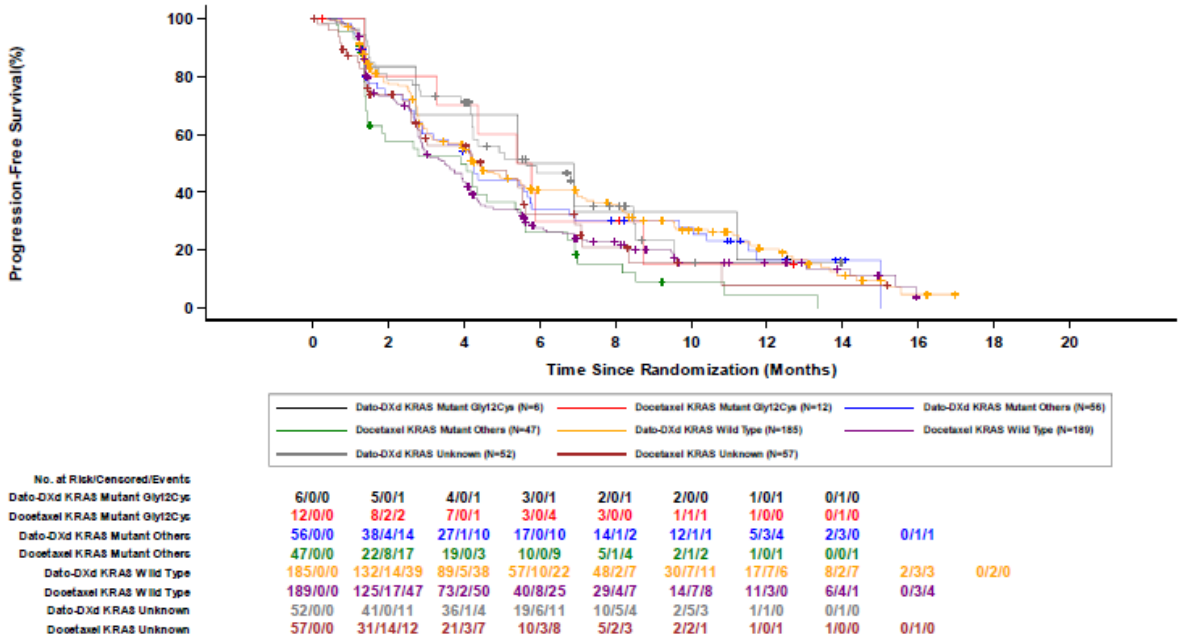
BICR = blinded independent central review; CI = confidence interval; IHC = immunohistochemistry; N, n = number of subjects; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; ROW = rest of world.

Progression-free survival was based on BICR assessments according to RECIST 1.1.

a Median months were based on the Kaplan-Meier method. The 95% CI for the median and percentiles were computed using the Brookmeyer-Crowley method.

b The hazard ratio of PFS by BICR was estimated from a stratified Cox proportional hazards model by KRAS group. The stratification factors included histology (squamous versus non-squamous) and geographical region (US/ Japan/Western Europe versus ROW).

Figure 61 Kaplan-Meier Plot of KRAS Mutation Status by Treatment Arm for Progression-Free Survival – Biomarker Evaluable Analysis Set



No. at Risk/Censored/Events										
Dato-DXd KRAS Mutant Gly12Cys	6/0/0	5/0/1	4/0/1	3/0/1	2/0/1	2/0/0	1/0/1	0/1/0		
Docetaxel KRAS Mutant Gly12Cys	12/0/0	8/2/2	7/0/1	3/0/4	3/0/0	1/1/1	1/0/0	0/1/0		
Dato-DXd KRAS Mutant Others	56/0/0	38/4/14	27/1/10	17/0/10	14/1/2	12/1/1	5/3/4	2/3/0	0/1/1	
Docetaxel KRAS Mutant Others	47/0/0	22/8/17	19/0/3	10/0/9	5/1/4	2/1/2	1/0/1	0/0/1		
Dato-DXd KRAS Wild Type	185/0/0	132/14/39	89/5/38	57/10/22	48/2/7	30/7/11	17/7/6	8/2/7	2/3/3	0/2/0
Docetaxel KRAS Wild Type	189/0/0	125/17/47	73/2/50	40/8/25	29/4/7	14/7/8	11/3/0	6/4/1	0/3/4	
Dato-DXd KRAS Unknown	52/0/0	41/0/11	36/1/4	19/6/11	10/5/4	2/5/3	1/1/0	0/1/0		
Docetaxel KRAS Unknown	57/0/0	31/14/12	21/3/7	10/3/8	5/2/3	2/2/1	1/0/1	1/0/0	0/1/0	

Source: Figure 14.8.16.

BICR = blinded independent central review; Grp = arm; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1.

Progression-free survival was based on BICR assessments according to RECIST 1.1.

OS

Table 98 Overall Survival by KRAS Mutation Status and Treatment Arm - Biomarker Full Analysis Set

	KRAS Mutant, N=121						KRAS Wild Type, N=374		KRAS Unknown, N=109	
	Gly12Cys, n=18		Others, n=103		Total, n=121					
	Dato-DXd n=6	Docetaxel n=12	Dato-DXd n=56	Docetaxel n=47	Dato-DXd n=62	Docetaxel n=59	Dato-DXd n=185	Docetaxel n=189	Dato-DXd n=52	Docetaxel n=57
Subjects who died, n (%)	2 (33.3)	7 (58.3)	30 (53.6)	28 (59.6)	32 (51.6)	35 (59.3)	99 (53.5)	99 (52.4)	17 (32.7)	23 (40.4)
Subjects censored, n (%)	4 (66.7)	5 (41.7)	26 (46.4)	19 (40.4)	30 (48.4)	24 (40.7)	86 (46.5)	90 (47.6)	35 (67.3)	34 (59.6)
Median months (95% CI)[a]	NE (6.9, NE)	10.3 (4.9, NE)	12.0 (8.7, NE)	10.1 (5.7, 14.4)	12.4 (9.2, NE)	10.1 (6.5, 14.4)	12.1 (10.0, 13.4)	11.5 (9.8, 13.3)	15.7 (15.7, NE)	10.2 (7.1, NE)
Hazard ratio (95% CI)[b]	0.63 (0.13, 3.13)		0.85 (0.49, 1.45)		0.83 (0.51, 1.37)		1.01 (0.76, 1.34)		0.80 (0.41, 1.55)	

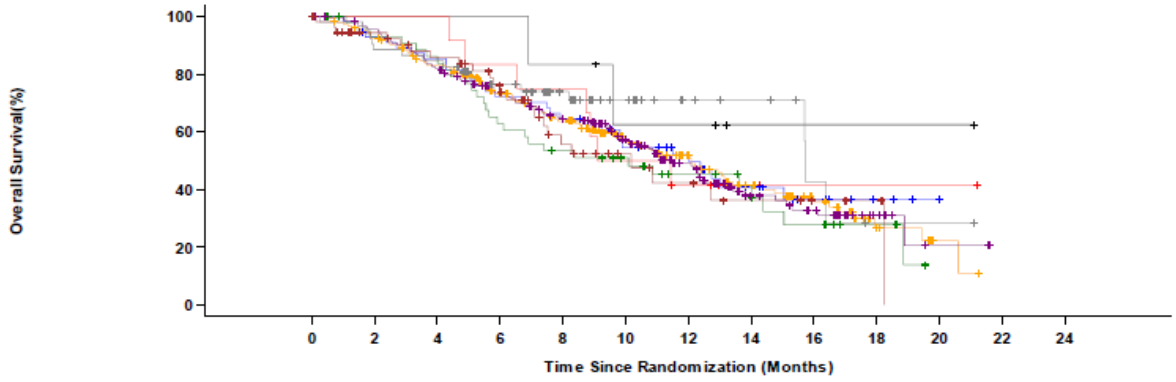
Source: Table 14.8.13.

CI = confidence interval; N, n = number of subjects; NE = not estimable; OS = overall survival; ROW = rest of world.

a Median months were based on the Kaplan-Meier method. The 95% CI for the median and percentiles were computed using the Brookmeyer-Crowley method.

c The hazard ratio of OS was estimated from a stratified Cox proportional hazards model by KRAS group. The stratification factors included histology (squamous versus non-squamous) and geographical region (US/ Japan/Western Europe versus ROW).

Figure 62 Kaplan-Meier Plot of KRAS Mutation Status by Treatment Arm for Overall Survival by KRAS Mutation -Biomarker Evaluable Analysis Set



No. at Risk/Censored/Events											
Dato-DXd KRAS Mutant Gly12Cys	6/0/0	6/0/0	6/0/0	6/0/0	5/0/1	3/1/1	3/0/0	1/2/0	1/0/0	1/0/0	0/1/0
Docetaxel KRAS Mutant Gly12Cys	12/0/0	12/0/0	12/0/0	10/0/2	9/0/1	6/0/3	4/1/1	2/2/0	1/1/0	1/0/0	0/1/0
Dato-DXd KRAS Mutant Others	56/0/0	51/1/4	45/2/4	38/0/7	34/0/4	27/2/5	20/6/1	12/4/4	7/4/1	3/4/0	1/2/0
Docetaxel KRAS Mutant Others	47/0/0	40/4/3	37/0/3	27/0/10	22/1/4	18/3/1	13/3/2	10/2/1	6/1/3	3/3/0	0/2/1
Dato-DXd KRAS Wild Type	185/0/0	169/2/14	147/5/17	122/8/17	101/6/15	75/17/9	52/16/7	34/8/10	22/9/4	8/9/4	2/5/1
Docetaxel KRAS Wild Type	189/0/0	175/6/8	150/0/25	125/10/15	106/4/15	79/16/11	50/19/10	24/16/10	18/3/3	6/11/1	1/4/1
Dato-DXd KRAS Unknown	52/0/0	46/0/6	44/0/2	34/6/4	25/8/1	15/9/1	9/6/0	7/2/0	3/2/2	1/1/1	1/0/0
Docetaxel KRAS Unknown	57/0/0	45/9/3	39/2/4	30/5/4	17/6/7	11/5/1	8/1/2	5/2/1	3/2/0	2/1/0	0/1/1

Source: Figure 14.8.17.

ORR

Table 99 Best Overall Response Objective Response Rate, Disease Control Rate, and Duration of Response by KRAS Mutation Status and Treatment Arm - Biomarker Full Analysis Set

	KRAS Mutant, N=121						KRAS Wild Type, N=374		Unknown, N=109	
	Gly12Cys, n=18		Others, n=103		Total, n=121					
	Dato-DXd n=6	Docetaxel n=12	Dato-DXd n=56	Docetaxel n=47	Dato-DXd n=62	Docetaxel n=59	Dato-DXd n=185	Docetaxel n=189	Dato-DXd n=52	Docetaxel n=57
BOR[a], n (%)										
CR	0	0	0	0	0	0	3 (1.6)	0	1 (1.9)	0
PR	2 (33.3)	2 (16.7)	13 (23.2)	7 (14.9)	15 (24.2)	9 (15.3)	42 (22.7)	23 (12.2)	18 (34.6)	7 (12.3)
SD	3 (50.0)	6 (50.0)	28 (50.0)	18 (38.3)	31 (50.0)	24 (40.7)	95 (51.4)	104 (55.0)	23 (44.2)	25 (43.9)
Non-CR/non-PD	0	0	1 (1.8)	1 (2.1)	1 (1.6)	1 (1.7)	2 (1.1)	5 (2.6)	0	0
PD	1 (16.7)	2 (16.7)	11 (19.6)	13 (27.7)	12 (19.4)	15 (25.4)	26 (14.1)	40 (21.2)	8 (15.4)	9 (15.8)
NE	0	2 (16.7)	3 (5.4)	8 (17.0)	3 (4.8)	10 (16.9)	17 (9.2)	17 (9.0)	2 (3.8)	16 (28.1)
ORR (CR + PR), n (%)	2 (33.3)	2 (16.7)	13 (23.2)	7 (14.9)	15 (24.2)	9 (15.3)	45 (24.3)	23 (12.2)	19 (36.5)	7 (12.3)
95% CI[b]	(4.3, 77.7)	(2.1, 48.4)	(13.0, 36.4)	(6.2, 28.3)	(14.2, 36.7)	(7.2, 27.0)	(18.3, 31.2)	(7.9, 17.7)	(23.6, 51.0)	(5.1, 23.7)
DCR (CR + PR + SD), n (%)	5 (83.3)	8 (66.7)	42 (75.0)	26 (55.3)	47 (75.8)	34 (57.6)	142 (76.8)	132 (69.8)	42 (80.8)	32 (56.1)
95% CI[b]	(35.9, 99.6)	(34.9, 90.1)	(61.6, 85.6)	(40.1, 69.8)	(63.3, 85.8)	(44.1, 70.4)	(70.0, 82.6)	(62.8, 76.3)	(67.5, 90.4)	(42.4, 69.3)
DoR[c], months										
Median (95% CI)[d]	NE (2.6, NE)	NE (6.0, NE)	5.6 (4.2, NE)	5.6 (2.7, NE)	5.6 (4.2, NE)	5.6 (2.7, 10.4)	9.0 (5.7, 11.1)	5.4 (3.6, 11.6)	5.6 (4.3, NE)	8.1 (5.5, NE)

Source: Table 14.8.14.

BICR = blinded independent central review; BOR = best overall response; CI = confidence interval; CR = complete response; DCR = disease control rate; DoR = duration of response; N, n = number of subjects; NE = not estimable; ORR = objective response rate; PD = progressive disease; PR = partial response; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SD = stable disease.

a Best overall response was as assessed by BICR according to RECIST 1.1. Confirmed responses required at least 2 determinations of responses ≥ 4 weeks apart before progression.

b The 2-sided 95% CIs were based on the Clopper-Pearson exact binomial method.

c DoR was only applicable for confirmed best overall response of CR or PR.

d Median months were based on the Kaplan-Meier method. The 95% CIs for the median event time were computed using Brookmeyer-Crowley method.

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

Pooled efficacy analysis was conducted to support the proposed indication in non-squamous NSCLC. TL01 and TL05 were included in the efficacy pool, TP01 was not included in the pooling due to differences in its study design, study population, and the small number of subjects with non-squamous histology treated with Dato-DXd 6 mg/kg (N=10). However, TP01 results of relevant subject groups were presented alongside the TL01/TL05 pool. Following dataset were provided:

- All non-squamous subjects (N=366): non-squamous population in TL01 treated with Dato-DXd (n=232) and non-squamous population in TL05 treated with Dato-DXd (n=134)
- All non-squamous AGA subjects (N=182): non-squamous AGA population in TL01 randomized to Dato-DXd (n=48) and non-squamous AGA population in TL05 treated with Dato-DXd (n=134)
- All subjects (N=434): all subjects in TL01 treated with Dato-DXd (n=299) and subjects in TL05 treated with Dato-DXd (n=137)

Description of TL05 is provided in section 3.7.1 below.

Table 100 Subject Disposition - All Non-squamous Subjects (Full Analysis Set)

	TL01 Dato-DXd 6 mg/kg (N=234)	TL05 Dato-DXd 6 mg/kg (N=134)	Pooled (TL01, TL05) Dato-DXd 6 mg/kg (N=366)		TP01 NSCLC Dato-DXd 6 mg/kg (N=45)
Analysis Set					
Full Analysis Set[a]	234 (100.0)	134 (100.0)	366 (100.0)		45 (100.0)
Treatment Status[b]					
Treated	232	134	366		45
Ongoing on Study Treatment	48 (20.7)	19 (14.2)	67 (18.3)		5 (11.1)
Discontinued from Study Treatment	184 (79.3)	115 (85.8)	299 (81.7)		40 (88.9)
Primary Reason for Discontinuation					
Death	5 (2.2)	0	5 (1.4)		1 (2.2)
Adverse Event	33 (14.2)	13 (9.7)	46 (12.6)		5 (11.1)
Progressive Disease	131 (56.5)	85 (63.4)	216 (59.0)		25 (55.6)
Clinical Progression	7 (3.0)	10 (7.5)	17 (4.6)		8 (17.8)
Withdrawal by Subject	4 (1.7)	6 (4.5)	10 (2.7)		1 (2.2)
Physician Decision	2 (0.9)	1 (0.7)	3 (0.8)		0
Lost to Follow-up	0	0	0		0
Pregnancy	0	0	0		0
Protocol Deviation	0	0	0		0
Study Terminated by Sponsor	0	0	0		0
Other	2 (0.9)	0	2 (0.5)		0
Study Status[c]					
Ongoing on Study	118 (50.4)	59 (44.0)	177 (48.4)		NC
Discontinued from Study	116 (49.6)	75 (56.0)	189 (51.6)		NC
Primary Reason for Discontinuation					
Lost to Follow-up	1 (0.4)	2 (1.5)	3 (0.8)		NC
Death	103 (44.0)	67 (50.0)	168 (45.9)		NC

	TL01 Dato-DXd 6 mg/kg (N=234)	TL05 Dato-DXd 6 mg/kg (N=134)	Pooled (TL01, TL05) Dato-DXd 6 mg/kg (N=366)		TP01 NSCLC Dato-DXd 6 mg/kg (N=45)
Withdrawal by Subject	11 (4.7)	6 (4.5)	17 (4.6)		NC
Study Terminated by Sponsor	0	0	0		NC
Other	1 (0.4)	0	1 (0.3)		NC
Study Duration (Months)					
Median	12.9	15.2	14.1		13.3
Min, Max	4.7, 23.9	9.2, 20.5	4.7, 23.9		9.8, 30.7

Dato-DXd=datopotamab deruxtecan; ISE=Integrated Summary of Efficacy; NA=not applicable; NC=not collected; NSCLC=non-small cell lung cancer; TL01=TROPION-Lung01; TL05=TROPION-Lung05; TP01=TROPION-PanTumor01

Note: Study duration is defined as (date of data cut-off – reference date + 1) / 30.4375, where the reference date is the date of randomization in Study TL01 and the date of first dose of study drug in Studies TL05 and TP01.

[a] The Full Analysis Set for Study TL01 includes all subjects who were randomized to the Dato-DXd arm. For Studies TL05 and TP01, the Full Analysis Set includes all subjects who received at least 1 dose of Dato-DXd. The pooled TL01 and TL05 includes all subjects who received at least 1 dose of Dato-DXd in Study TL05 and subjects who were randomized to the Dato-DXd arm and received Dato-DXd in Study TL01.

[b] Percentages are based on the number of treated subjects in the Full Analysis Set.

[c] Percentages are based on the number of subjects in the Full Analysis Set.

Source: ISE Table 1.1.1.3

Source: SCE

Table 101 Demographic and Baseline Characteristics - All Non-Squamous Subjects Full Analysis Set

	6.0 mg/kg TL01 (N=234)	6.0 mg/kg TL05 (N=134)	Pooled 6.0 mg/kg (TL01, TL05) (N=366)	6.0 mg/kg TP01 NSCLC (N=45)
Age (Years)				
n	234	134	366	45
Mean	62.3	59.4	61.2	61.3
Standard Deviation	9.29	11.16	10.11	10.15
Median	63.0	60.0	62.0	63.0
Minimum	26	29	26	38
Maximum	81	79	81	76
Age Group, n (%)				
< 65 Years	126 (53.8)	89 (66.4)	215 (58.7)	27 (60.0)
≥ 65 Years	108 (46.2)	45 (33.6)	151 (41.3)	18 (40.0)
< 75 Years	220 (94.0)	121 (90.3)	339 (92.6)	40 (88.9)
≥ 75 Years	14 (6.0)	13 (9.7)	27 (7.4)	5 (11.1)
Sex, n (%)				
Male	134 (57.3)	53 (39.6)	186 (50.8)	24 (53.3)
Female	100 (42.7)	81 (60.4)	180 (49.2)	21 (46.7)
Race, n (%)				
White	96 (41.0)	42 (31.3)	138 (37.7)	22 (48.9)
Asian	92 (39.3)	77 (57.5)	169 (46.2)	15 (33.3)
Black or African American	4 (1.7)	0	4 (1.1)	3 (6.7)
Other	36 (15.4)	14 (10.4)	49 (13.4)	5 (11.1)
Missing	6 (2.6)	1 (0.7)	6 (1.6)	0
Ethnicity, n (%)				
Hispanic or Latino	8 (3.4)	3 (2.2)	11 (3.0)	4 (8.9)
Not Hispanic or Latino	196 (83.8)	116 (86.6)	311 (85.0)	41 (91.1)
Unknown	23 (9.8)	14 (10.4)	37 (10.1)	0
Missing	7 (3.0)	1 (0.7)	7 (1.9)	0
Height (cm)				
n	234	131	363	45
Mean	166.68	164.60	165.91	167.08
Standard Deviation	9.103	9.202	9.170	9.863
Median	168.00	163.00	166.00	165.10
Minimum	144.0	147.9	144.0	151.1
Maximum	192.0	190.5	192.0	188.0
Baseline Weight (kg)				
n	234	134	366	45
Mean	67.48	65.51	66.81	69.31
Standard Deviation	13.962	15.754	14.675	16.152
Median	65.00	63.10	64.85	65.80
Minimum	37.0	39.1	37.0	38.5
Maximum	114.0	118.5	118.5	104.4
Baseline Body Mass Index (kg/m^2)				
n	234	131	363	45
Mean	24.21	24.12	24.20	24.68
Standard Deviation	4.174	4.792	4.401	4.752
Median	23.67	23.53	23.65	24.69
Minimum	16.0	15.3	15.3	16.5
Maximum	39.4	44.5	44.5	39.7
Baseline ECOG Performance Status, n (%)				
0	73 (31.2)	44 (32.8)	117 (32.0)	11 (24.4)
1	160 (68.4)	90 (67.2)	248 (67.8)	34 (75.6)
2	1 (0.4)	0	1 (0.3)	0
Smoking History, n (%)				
Never	57 (24.4)	73 (54.5)	130 (35.5)	15 (33.3)
Former	153 (65.4)	61 (45.5)	213 (58.2)	30 (66.7)
Current	24 (10.3)	0	23 (6.3)	0
Actionable Genomic Alteration [a], n (%)				
Yes	48 (20.5)	134 (100.0)	182 (49.7)	10 (22.2)
No	186 (79.5)	0	184 (50.3)	35 (77.8)

Percentages are based on the number of subjects in the Full Analysis Set.
Full Analysis Set for TL01 includes all subjects who were randomized to the Dato-DXd arm; for TL05 and TP01, it includes all subjects who received at least one dose of Dato-DXd; for pooled TL01 and TL05, all subjects received at least one dose of Dato-DXd in TL05 and subjects randomized to the Dato-DXd arm in TL01 and have been dosed were included.
Baseline for TL01 is defined as the last available assessment prior to the start of study treatment; if study treatment start date is not available, then the last available assessment prior to the randomization will be used as the baseline value. Baseline for TL05 and TP01 is defined as the last available assessment prior to the start of study treatment.
[a] Actionable genomic mutations include EGFR, ALK, ROS1, NTRK, BRAF, MET exon 14 skipping, and RET in TL01 and TL05 study, and includes EGFR, ALK, ROS1, or RET in TP01 study.

Among the overall non-squamous population in the pooled data, the median (range) time from diagnosis to study treatment was 24.25 (3.0, 181.8) months. Most subjects (29.2%) were Stage IV at initial diagnosis, and 58.2% were Stage IVB at study entry in the pooled analysis. A total of 82 (22.4%) subjects had brain metastases at study entry (Table 3.6 in SCE).

Table 102 Prior Cancer Therapy - All Non-squamous Subjects (Full Analysis Set)

	TL01 Dato-DXd 6 mg/kg (N=234)	TL05 Dato-DXd 6 mg/kg (N=134)	Pooled (TL01, TL05) Dato-DXd 6 mg/kg (N=366)		TP01 NSCLC Dato-DXd 6 mg/kg (N=45)
Any Prior Cancer Systemic Therapy, n (%)	234 (100.0)	134 (100.0)	366 (100.0)		45 (100.0)
Platinum Chemotherapy	232 (99.1)	134 (100.0)	364 (99.5)		44 (97.8)
Other Chemotherapy	233 (99.6)	133 (99.3)	364 (99.5)		45 (100.0)
Anti-PD-1/Anti-PD-L1 Immunotherapy	199 (85.0)	47 (35.1)	244 (66.7)		33 (73.3)
Targeted Therapy for Indicated AGA	45 (19.2)	134 (100.0)	179 (48.9)		12 (26.7)
Other Cancer Therapy	45 (19.2)	46 (34.3)	91 (24.9)		27 (60.0)
Intended for, n (%)[a]					
Neo-adjuvant	3 (1.3)	1 (0.7)	4 (1.1)		3 (6.7)
Adjuvant	14 (6.0)	11 (8.2)	25 (6.8)		8 (17.8)
Locally Advanced/Metastatic	233 (99.6)	134 (100.0)	365 (99.7)		43 (95.6)
Preventive	0	0	0		NC
Maintenance	69 (29.5)	16 (11.9)	85 (23.2)		NC
Palliation	NC	NC	NC		3 (6.7)
Other	0	1 (0.7)	1 (0.3)		2 (4.4)
Number of Prior Systemic Lines in Locally Advanced/Metastatic Setting					
n	234	134	366		45
Median	1.0	3.0	2.0		3.0
Min, Max	0, 6	1, 9	0, 9		0, 8
Number of Prior Systemic Lines in Locally Advanced/Metastatic Setting, n (%)					
0	1 (0.4)	0	1 (0.3)		2 (4.4)

1	127 (54.3)	4 (3.0)	130 (35.5)		4 (8.9)
2	86 (36.8)	35 (26.1)	120 (32.8)		16 (35.6)
3	15 (6.4)	42 (31.3)	57 (15.6)		11 (24.4)
4 or more	5 (2.1)	53 (39.6)	58 (15.8)		12 (26.7)
Best Responses to the Last Prior Cancer Systemic Therapy, n (%)					
CR	4 (1.7)	0	4 (1.1)		0
PR	76 (32.5)	41 (30.6)	116 (31.7)		3 (6.7)
SD	84 (35.9)	62 (46.3)	146 (39.9)		16 (35.6)
PD	48 (20.5)	24 (17.9)	71 (19.4)		15 (33.3)
Unknown	14 (6.0)	7 (5.2)	21 (5.7)		9 (20.0)
Not Applicable	2 (0.9)	0	2 (0.5)		2 (4.4)
Any Prior Cancer Radiation Therapy, n (%)	101 (43.2)	79 (59.0)	179 (48.9)		30 (66.7)
Any Prior Cancer Surgery, n (%)	76 (32.5)	44 (32.8)	120 (32.8)		12 (26.7)

CR=complete response; Dato-DXd=datopotamab deruxtecan; ISE=Integrated Summary of Efficacy; NC=not collected; PD=progressive disease; PD-L1=programmed cell death (ligand) 1; PR=partial response; SD=stable disease; TL01=TROPION-Lung01; TL05=TROPION-Lung05; TP01=TROPION-PanTumor01

Note: Percentages are based on the number of subjects in the Full Analysis Set.

The Full Analysis Set for Study TL01 includes all subjects who were randomized to the Dato-DXd arm. For Studies TL05 and TP01, the Full Analysis Set includes all subjects who received at least 1 dose of Dato-DXd. The pooled TL01 and TL05 includes all subjects who received at least 1 dose of Dato-DXd in Study TL05 and subjects who were randomized to the Dato-DXd arm and received Dato-DXd in Study TL01.

[a] A subject can be counted in multiple rows because more than 1 therapy can be taken. Within each row, a subject is counted only once.

Source: ISE Table 1.1.5.3

Table 103 Best Overall Response, Objective Response Rate, and Disease Control Rate as Assessed by Blinded Independent Central Review per RECIST v1.1 - All Non-squamous Subjects (Full Analysis Set)

	TL01 Dato-DXd 6 mg/kg (N=234)	TL05 Dato-DXd 6 mg/kg (N=134)	Pooled (TL01, TL05) Dato-DXd 6 mg/kg (N=366)		TP01 NSCLC Dato-DXd 6 mg/kg (N=45)
Response with Confirmation of CR/PR					
Best Overall Response, n (%)					
CR	4 (1.7)	4 (3.0)	8 (2.2)		0
PR	69 (29.5)	44 (32.8)	113 (30.9)		12 (26.7)
SD	113 (48.3)	55 (41.0)	168 (45.9)		17 (37.8)
Non-CR/non-PD	2 (0.9)	2 (1.5)	4 (1.1)		2 (4.4)
PD	31 (13.2)	19 (14.2)	50 (13.7)		10 (22.2)
Not Evaluable	15 (6.4)	10 (7.5)	23 (6.3)		4 (8.9)
ORR (CR + PR), n (%)	73 (31.2)	48 (35.8)	121 (33.1)		12 (26.7)
95% CI[a]	(25.3, 37.6)	(27.7, 44.6)	(28.3, 38.1)		(14.6, 41.9)
DCR (CR + PR + SD or non-CR/non-PD), n (%)	188 (80.3)	105 (78.4)	293 (80.1)		31 (68.9)
95% CI[a]	(74.7, 85.2)	(70.4, 85.0)	(75.6, 84.0)		(53.4, 81.8)

CI=confidence interval; CR=complete response; Dato-DXd=datopotamab deruxtecan; DCR=disease control rate; ISE=Integrated Summary of Efficacy; NSCLC=non-small cell lung cancer; ORR=objective response rate; PD=progressive disease; SD=stable disease; TL01=TROPION-Lung01; TL05=TROPION-Lung05; TP01=TROPION-PanTumor01

Note: Percentages are based on the number of subjects in the Full Analysis Set.

The Full Analysis Set for Study TL01 includes all subjects who were randomized to the Dato-DXd arm. For Studies TL05 and TP01, the Full Analysis Set includes all subjects who received at least one dose of Dato-DXd. The pooled TL01 and TL05 includes all subjects who received at least one dose of Dato-DXd in Study TL05 and subjects who were randomized to the Dato-DXd arm and received Dato-DXd in Study TL01.

Confirmed responses require at least 2 determinations of responses at least 4 weeks apart before progression.

[a] The 2-sided 95% CIs are based on the Clopper-Pearson exact binomial method.

Source: ISE Table 1.1.7.3

Source: SCE

Table 104 Best Overall Response, Objective Response Rate, and Disease Control Rate as Assessed by Blinded Independent Central Review (BICR) per RECIST v1.1- Non-Squamous Subjects with Actionable Genomic Alteration Full Analysis Set

	6.0 mg/kg TL01 (N=48)	6.0 mg/kg TL05 (N=134)	Pooled 6.0 mg/kg (TL01, TL05) (N=182)	(4.0, 6.0, 8.0 mg/kg) TP01 NSCLC (N=34)
Response with Confirmation of CR/PR				
Best Overall Response, n (%)				
Complete Response (CR)	1 (2.1)	4 (3.0)	5 (2.7)	0
Partial Response (PR)	17 (35.4)	44 (32.8)	61 (33.5)	11 (32.4)
Stable Disease (SD)	27 (56.3)	55 (41.0)	82 (45.1)	15 (44.1)
Non-CR/Non-PD	0	2 (1.5)	2 (1.1)	2 (5.9)
Progressive Disease (PD)	2 (4.2)	19 (14.2)	21 (11.5)	2 (5.9)
Not Evaluable (NE)	1 (2.1)	10 (7.5)	11 (6.0)	4 (11.8)
Reasons for NE				
No Baseline Tumor Assessment	0	0	0	0
No Adequate Post-Baseline Tumor Assessment [a]	1 (2.1)	7 (5.2)	8 (4.4)	2 (5.9)
SD too Early (SD<5 weeks after reference date)	0	3 (2.2)	3 (1.6)	1 (2.9)
PD too Late (PD>12 weeks after reference date)	0	0	0	1 (2.9)
Objective Response Rate (ORR, CR+PR), n (%)	18 (37.5)	48 (35.8)	66 (36.3)	11 (32.4)
95% Confidence Interval [b]	(24.0 , 52.6)	(27.7 , 44.6)	(29.3 , 43.7)	(17.4 , 50.5)
Disease Control Rate (DCR, CR+PR+SD or non-CR/non-PD), n (%)	45 (93.8)	105 (78.4)	150 (82.4)	28 (82.4)
95% Confidence Interval [b]	(82.8 , 98.7)	(70.4 , 85.0)	(76.1 , 87.7)	(65.5 , 93.2)

Percentages are based on the number of subjects in the Full Analysis Set.
Full Analysis Set for TL01 includes all subjects who were randomized to the Dato-DXd arm; for TL05 and TP01, it includes all subjects who received at least one dose of Dato-DXd; for pooled TL01 and TL05, all subjects received at least one dose of Dato-DXd in TL05 and subjects randomized to the Dato-DXd arm in TL01 and have been dosed were included.
Confirmed responses require at least 2 determinatons of responses at least 4 weeks apart before progression.
[a] No adequate post-baseline tumor assessment is defined as no post-baseline tumor assessment or all post-baseline tumor assessments are NE or new non-palliative cancer therapy started prior to the first post-baseline tumor assessment.
[b] The 2-sided 95% confidence intervals are based on the Clopper-Pearson exact binomial method.
Source: adam.adrs

Source: ISE-Tables

Table 105 Subgroup Analyses of Objective Response Rate and Duration of Response as Assessed by Blinded Independent Central Review per RECIST vl.1 - All Non-squamous Subjects (Full Analysis Set)

	Pooled (TL01, TL05) Dato-DXd 6 mg/kg		
Subgroup	**#Responder / #Subjects**	**ORR (95% CI)[a]**	**Median DoR (95% CI)[b]**
All Subjects	121 / 366	33.1 (28.3, 38.1)	7.1 (5.6, 9.8)
Age (Years)			
<65	69 / 215	32.1 (25.9, 38.8)	8.3 (5.6, 10.2)
≥65	52 / 151	34.4 (26.9, 42.6)	6.7 (5.2, 10.9)
<75	111 / 339	32.7 (27.8, 38.0)	7.1 (5.6, 9.3)
≥75	10 / 27	37.0 (19.4, 57.6)	14.5 (4.2, NE)
Sex			
Male	54 / 186	29.0 (22.6, 36.1)	8.3 (5.5, 10.2)
Female	67 / 180	37.2 (30.1, 44.7)	7.0 (5.5, 12.9)
Race			
White	39 / 138	28.3 (20.9, 36.5)	9.8 (5.5, 12.9)
Asian	63 / 169	37.3 (30.0, 45.0)	8.4 (4.4, 11.1)
Black or African American/ Other	17 / 53	32.1 (19.9, 46.3)	5.9 (4.3, 7.7)
Last ECOG Performance Status On or Prior to Reference Date[c]			
0	38 / 116	32.8 (24.3, 42.1)	8.4 (5.3, 14.0)
1	83 / 248	33.5 (27.6, 39.7)	7.0 (5.5, 9.8)

	Pooled (TL01, TL05) Dato-DXd 6 mg/kg		
Subgroup	**#Responder / #Subjects**	**ORR (95% CI)[a]**	**Median DoR (95% CI)[b]**
Smoking Status			
Former/Current Smoker	82 / 236	34.7 (28.7, 41.2)	8.3 (5.7, 10.2)
Never Smoked	39 / 130	30.0 (22.3, 38.7)	5.5 (4.2, 9.8)
Brain Metastases at Study Entry			
Yes	25 / 82	30.5 (20.8, 41.6)	8.3 (4.2, NE)
No	96 / 284	33.8 (28.3, 39.6)	7.1 (5.6, 9.8)
Prior Lines of Therapy in Locally Advanced/Metastatic Setting			
≤2	76 / 251	30.3 (24.7, 36.4)	7.7 (5.6, 11.1)
>2	45 / 115	39.1 (30.2, 48.7)	7.1 (4.4, 9.8)

DoR=duration of response; ECOG PS=Eastern Cooperative Oncology Group performance status; ISE=Integrated Summary of Efficacy; ORR=objective response rate; RECIST=Response Evaluation Criteria in Solid Tumors; TL01=TROPION-Lung01; TL05=TROPION Lung05

[a] The 2-sided 95% CIs of ORR are based on the Clopper-Pearson exact binomial method.

[b] The 2-sided 95% CIs for the median DoR are computed using the Brookmeyer-Crowley method.

[c] For last ECOG PS on or prior to reference date, the reference date is the date of randomization in Study TL01 and the date of first dose of study drug in Studies TL05 and TP01.

Source: ISE Tables 1.1.7.3, 1.1.7.3.1, 1.1.11.3, and 1.1.11.3.1

3.3.4.7. Supportive studies

3.3.4.7.1. **Study TL05 (TROPION-Lung05)**

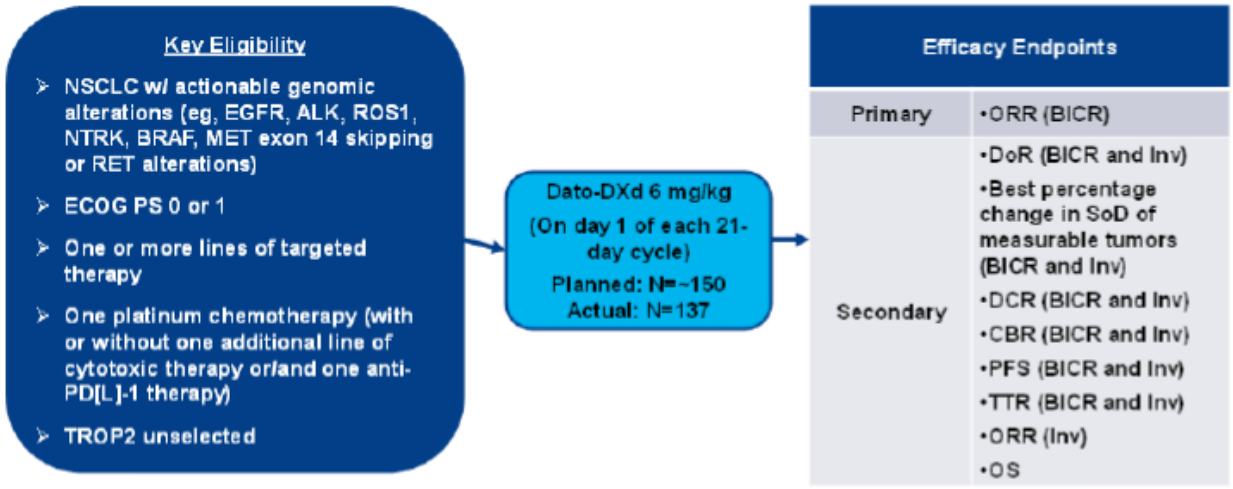
Study design: Phase 2, multicentre (North America – 15 study sites, Europe – 14 study sites, Asia Pacific region – 21 study sites), single-arm, open-label study of Dato-DXd monotherapy

First subject enrolled: 29 Mar 2021

Last subject completed: Study ongoing.

Data cut-off date: 14 Dec 2022

Figure 63 Study Design: TL05



ALK=anaplastic lymphoma kinase; BICR=blinded independent central review; BRAF=proto-oncogene B-raf; CBR=clinical benefit rate; Dato-DXd=datopotamab deruxtecan; DCR=disease control rate; DoR=duration of response; ECOG PS=Eastern Cooperative Oncology Group performance status; EGFR=epidermal growth factor receptor; Inv=investigator; MET=mesenchymal-epithelial transition factor; NSCLC=non-small cell lung cancer; NTRK=neurotrophic tyrosine receptor kinase; ORR=objective response rate; OS=overall survival; PD-(L)1=programmed cell death (ligand) 1; PFS=progression-free survival; RET=rearranged during transfection; ROS1=ROS proto-oncogene 1; SoD=sum of diameters; TROP2=trophoblast cell surface protein 2; TTR=time to response

Study population: Screened: 203

Enrolled: 137

Dosed: 137. The number of subjects with EGFR mutations was approximately 60% of the total enrolment.

Ongoing study treatment/discontinued study treatment: 20/117

Ongoing study/discontinued study: 60/77

Treatment: The study dose was Dato-DXd 6 mg/kg.

Statistical methods: The primary efficacy endpoint was BICR-assessed ORR, which was defined as the proportion of subjects who achieved a BOR of confirmed CR or confirmed PR. CR/PR was to be confirmed with a follow-up tumor assessment at least 4 weeks (28 days) apart. The ORR by BICR was summarized with the 2-sided 95% exact CI using the Clopper-Pearson method in the FAS. For the computation of ORR, subjects with a BOR of "not evaluable" were included in the FAS and were considered non-responders.

The survival distribution of DoR, PFS, and OS were summarized and presented graphically using the Kaplan-Meier method; median event times and their 2-sided 95% CI are presented using Brookmeyer-Crowley methods. In addition, the event-free probability at different time points was estimated with corresponding 2-sided 95% CIs using the Greenwood's formula for variance derivation. TTR was summarized descriptively.

Descriptive statistics for the best percentage change from baseline in SoD of measurable tumors were provided. A waterfall plot of the best percentage change in SoD was generated.

Investigator-assessed ORR, DCR, and CBR were analyzed in the same manner as for the primary efficacy endpoint.

Main inclusion and exclusion criteria:

The study population included adult subjects with a diagnosis of advanced or metastatic NSCLC with AGAs (EGFR, anaplastic lymphoma kinase [ALK], ROS proto-oncogene 1, neurotrophic tyrosine receptor kinase, proto-oncogene Braf, mesenchymal-epithelial transition exon 14 skipping, or rearranged during transfection) who have progressed on or after 1 platinum-containing therapy and 1 or more lines of targeted therapy to the applicable AGA in the study.

Subjects whose tumors harbor KRAS mutations in the absence of any of the genomic alterations specified above were excluded.

Results: The DCO date (14 Dec 2022) for the primary analysis occurred per protocol when all subjects had a minimum of 9 months of follow-up after the start of study treatment or had discontinued the study, whichever occurred first.

Table 106 Subject Disposition - All Screened Subjects

	Dato-DXd n (%)
Screened [a]	203
Screen Failure	66
Treatment Status [b]	
Treated	137
Ongoing on Study Treatment	20 (14.6)
Discontinued from Study Treatment	117 (85.4)
Primary Reason for Discontinuation	
Adverse Event	13 (9.5)
Progressive Disease	87 (63.5)
Clinical Progression	10 (7.3)
Withdrawal by Subject	6 (4.4)
Physician Decision	1 (0.7)
Study Status [b]	
Ongoing in Study	60 (43.8)
Discontinued from Study	77 (56.2)
Primary Reason for Discontinuation	
Lost to Follow-up	2 (1.5)
Death	68 (49.6)
Withdrawal by Subject	7 (5.1)
Study Duration (months) [c]	
n	137
Mean	14.9
Standard Deviation	2.85
Median	15.2
Minimum	9.1
Maximum	20.5

[a] Subjects who signed the inform consent form and were screened.
[b] Percentages are based on the number of subjects treated.
[c] Study duration is defined as (date of data cut-off – start date of study treatment +1)/30.4375.
Source: Table 14.1.1.1

Table 107 Demographic and Baseline Characteristics - Full Analysis Set

	Dato-DXd (N=137)
Age (years)	
n	137
Mean	59.5
Standard Deviation	11.15
Median	61.0
Minimum	29
Maximum	79
< 65 years, n (%)	91 (66.4)
≥ 65 years, n (%)	46 (33.6)
< 75 years, n (%)	123 (89.8)
≥ 75 years, n (%)	14 (10.2)
Sex, n (%)	
Male	54 (39.4)
Female	83 (60.6)
Race, n (%)	
American Indian or Alaska Native	0
Asian	78 (56.9)
Black or African American	0
Native Hawaiian or Other Pacific Islander	0
White	43 (31.4)
Other	15 (10.9)
Missing	1 (0.7)
Region Enrollment, n (%)	
North America	39 (28.5)
Asia	66 (48.2)
EU	32 (23.4)
Baseline ECOG Performance Status, n (%)	
0	45 (32.8)
1	92 (67.2)

Abbreviations: ECOG=Eastern Cooperative Oncology Group; EU=Europe.
Percentages are based on the number of subjects in the full analysis set.
Baseline is defined as the last available assessment prior to the start of study treatment.
Source: Table 14.1.2.1

The median time and range from initial diagnosis to study treatment was 39.66 months (range: 7.9 to 181.4). At initial diagnosis, most patients had stage IV/IVA/IVB (79.6%) NSCLC disease. At study entry, all patients had stage IV/IVA/IVB NSCLC disease (66.4% with stage IVB). In the FAS, the most common genomic alterations were EGFR, ALK, and ROS1, with 56.9%, 24.8%, and 7.3% of total patients, respectively. Among patients with EGFR mutation, 41 (29.9%) had exon 19 deletion, 26 (19.0%) had exon 20 Thr790Met mutation, and 25 (18.2%) had exon 21 Leu858Arg mutation. At study entry, 39 (28.5%) patients had brain metastasis as assessed by BICR and 31 (22.6%) patients had liver metastasis as assessed by BICR (Source: table 7.4 CSR TL05, not shown).

Table 108 Prior Cancer Therapy - Full Analysis Set

	Dato-DXd (N=137)
Any Prior Cancer Systemic Therapy, n (%)	137 (100)
Prior Platinum Chemotherapy [b]	137 (100)
Prior Other Chemotherapy [b]	136 (99.3)
Prior Anti-PD-1/Anti-PD-L1 Immunotherapy [b]	49 (35.8)
Prior Targeted Therapy for Indicated AGA [a] [b]	137 (100)
Prior Other Cancer Therapy [b]	47 (34.3)
Intended for, n (%) [b]	
Neo-Adjuvant	1 (0.7)
Adjuvant	12 (8.8)
Local Advanced	16 (11.7)
Metastatic	132 (96.4)
Preventive	0
Maintenance	17 (12.4)
Other	1 (0.7)
Number of Prior Systemic Lines for Advanced or Metastatic Disease, n (%)	
1	4 (2.9)
2	35 (25.5)
3	45 (32.8)
4 or more	53 (38.7)
Any Prior Cancer Radiation Therapy, n (%)	80 (58.4)
Intended for, n (%) [b]	
Curative	12 (8.8)
Palliative	74 (54.0)
Unknown	1 (0.7)
Other	0
Any Prior Cancer Surgery, n (%)	45 (32.8)

Abbreviations: AGA=actionable genomic alteration; PD-1=programmed cell death protein 1; PD L1=programmed cell death ligand 1.
Percentages are based on the number of subjects in the full analysis set.
[a] Indicated AGAs include epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1), neurotrophic tyrosine receptor kinase (NTRK), proto-oncogene B-raf (BRAF), or mesenchymal-epithelial transition (MET) exon 14 skipping and rearranged during transfection (RET).
[b] A subject can be counted in multiple rows since more than one therapy can be taken. Within each row, a subject is counted only once.
Source: Table 14.1.3.2

Primary endpoint ORR by BICR

Table 109 Best Overall Response, Objective Response Rate, and Disease Control Rate as Assessed by Blinded Independent Central Review per RECIST vl.1 - Full Analysis Set

	Dato-DXd (N=137) n (%)
Response with Confirmation	
Best Overall Response, n (%)	
Complete Response (CR)	4 (2.9)
Partial Response (PR)	45 (32.8)
Stable Disease (SD)	56 (40.9)
Non-CR/Non-PD	3 (2.2)
Progressive Disease (PD)	19 (13.9)
Not Evaluable (NE)	10 (7.3)
Objective Response Rate (ORR, CR+PR), n (%)	49 (35.8)
95% Confidence Interval [a]	(27.8, 44.4)
Disease Control Rate (DCR, CR+PR+SD (non-CR/non-PD), n (%)	108 (78.8)
95% Confidence Interval [a]	(71.0, 85.3)

Percentages are based on the number of subjects in the full analysis set.
Confirmed responses require at least two determinations of responses at least 4 weeks apart before progression.
[a] The 2-sided 95% confidence intervals are based on the Clopper-Pearson exact binomial method.
Source: Table 14.2.1.1

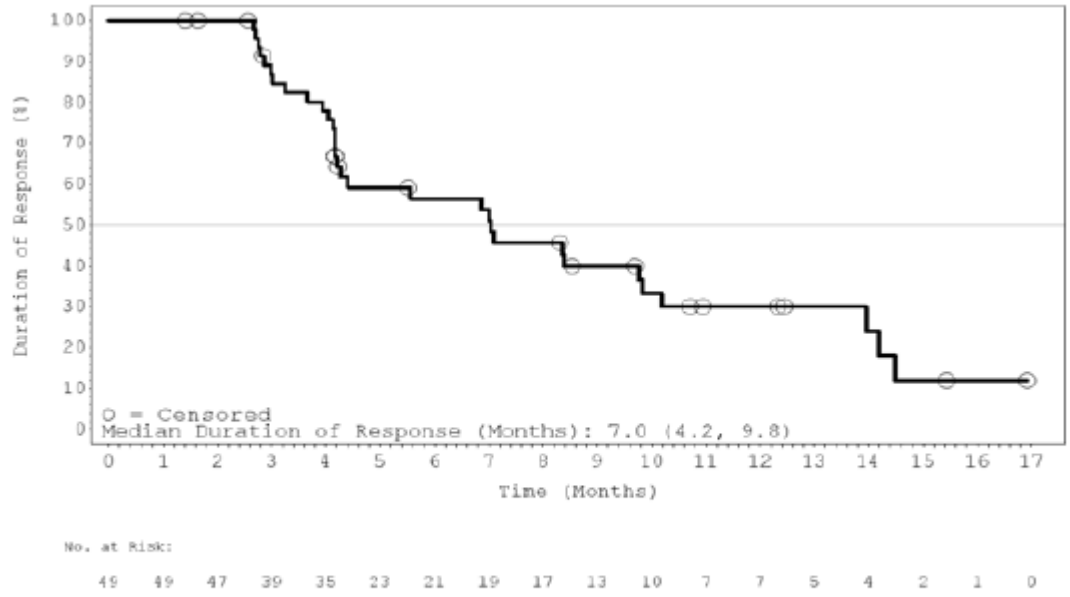
Secondary endpoints

Table 110 Duration of Response and Time to Response for Confirmed Response as Assessed by Blinded Independent Central Review per RECIST v1.1 - Full Analysis Set

	Dato-DXd (N=137) n (%)
Subjects with Confirmed CR/PR:	49
Duration of Response (Months)	
Minimum, Maximum	1.4+, 16.9+
Duration of Response, n (%)	
≥ 6 months	21 (42.9)
≥ 9 months	13 (26.5)
Subjects with Events, n (%)	31 (63.3)
Progressive Disease	29 (59.2)
Death	2 (4.1)
Subjects without Events (Censored), n (%)	18 (36.7)
Event after ≥ 2 Missing Assessments	3 (6.1)
Withdrawal of Consent*	1 (2.0)
Lost to Follow-up*	0
Adequate Tumor Assessments No Longer Available*	3 (6.1)
Ongoing Without Event*	11 (22.4)
Kaplan-Meier Estimate of Duration of Response (Months) [a]	
Median (95% CI)	7.0 (4.2, 9.8)
Kaplan-Meier Estimate Event-free Probability at (95% CI) [a]	
3 months	86.9 (73.0, 93.9)
6 months	56.5 (40.4, 69.8)
9 months	40.0 (24.9, 54.7)
12 months	30.0 (16.1, 45.3)
15 months	12.0 (2.5, 29.8)
Time to Response (Months) [b]	
n	49
Mean	2.45
Standard Deviation	1.856
Median	1.54
Minimum, Maximum	1.1, 11.3

Abbreviations: CI=Confidence Interval; CR=complete response; PR=partial response.
Percentages are based on the number of subjects in the full analysis set with best overall response of confirmed CR/PR.
Duration of response is defined as the time (months) from the date of the first documentation of objective response (confirmed CR or confirmed PR) to the date of the first documentation of progressive disease, or death due to any cause, whichever occurs first. Subjects are not censored at the initiation of new anti-cancer therapy.
[a] Median and point estimates at specific months are based on the Kaplan-Meier method. The 2-sided 95% CI for the median is computed using the Brookmeyer-Crowley method. The 2-sided 95% CIs for the event-free probability at specific months are computed using the Greenwood's formula.
[b] Time to response is defined as the time from the date from the start of study treatment to the date of the first documentation of objective response (confirmed CR or confirmed PR).
* Withdrawal of consent/lost to follow-up if withdrawal of consent from the study/lost to follow-up from end of treatment or end of study is within 2 consecutive tumor assessments from last adequate tumor assessment; ongoing without event if DCO is within 2 consecutive tumor assessments from last adequate tumor assessment; otherwise, adequate tumor assessments no longer available.

Figure 64 Kaplan-Meier Plot of Duration of Response as Assessed by Blinded Independent Central Review for Confirmed Response per RECIST v1.1 - Full Analysis Set



Only responders are included in this plot.
DCO: 2022-12-14
Source Figure 14.2.2.5

Source: Figure 14.2.2.5.

Table 111 Progression-free Survival as Assessed by Blinded Independent Central Review per RECIST v1.1 - Full Analysis Set

	Dato-DXd (N=137)
Subjects with Events, n (%)	99 (72.3)
Progressive Disease	84 (61.3)
Death	15 (10.9)
Subjects Censored, n (%)	38 (27.7)
No Baseline Tumor Assessment	0
No Post-Baseline Tumor Assessment	1 (0.7)
Event after ≥ 2 Missing Assessments	11 (8.0)
Withdrawal of Consent*	3 (2.2)
Lost to Follow-up*	0
Adequate Tumor Assessments No Longer Available*	10 (7.3)
Ongoing Without Event*	13 (9.5)
Progression-free Survival (Months) [a]	
Median (95% CI)	5.4 (4.7, 7.0)
Progression-free Survival Probability at (95% CI) [b]	
3 months	70.9 (62.3, 77.9)
6 months	44.3 (35.3, 53.0)
9 months	32.6 (24.2, 41.3)
12 months	21.4 (13.9, 29.8)
15 months	16.2 (9.6, 24.4)
18 months	7.0 (1.9, 16.7)

Percentages are based on the number of subjects in the full analysis set.
Progression-free survival is defined as the time (months) from the date of the first dose of study treatment to the earlier of the dates of the first documentation of objective progression of disease or death due to any cause.
Subjects are not censored at the initiation of new anti-cancer therapy.
[a] Median and progression-free survival probability at specific months are based on the Kaplan-Meier method. The two-sided 95% CI for the median is computed using the Brookmeyer-Crowley method.
[b] The two-sided 95% CIs for the progression-free survival at specific months are computed using the Greenwood's formula.
* Withdrawal of consent/lost to follow-up if withdrawal of consent from the study/lost to follow-up from end of treatment or end of study is within 2 consecutive tumor assessments from last adequate tumor assessment; ongoing without event if DCO is within 2 consecutive tumor assessments from last adequate tumor assessment; otherwise, adequate tumor assessments no longer available.
Source: Table 14.2.3.1

Table 112 Overall Survival - Full Analysis Set

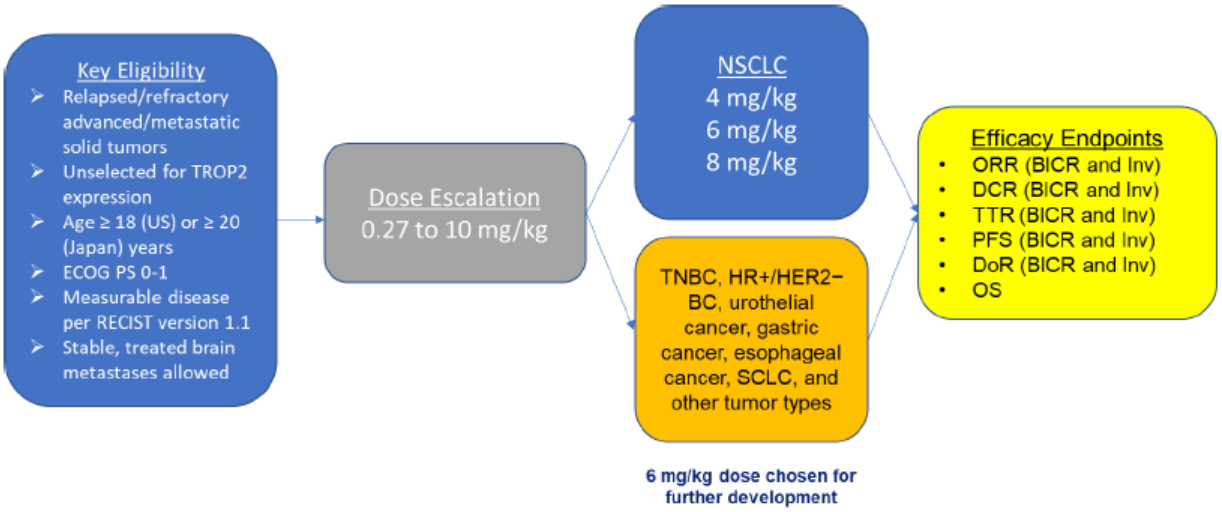
	Dato-DXd (N=137)
Number of Subjects Who Died, n (%)	68 (49.6)
Subjects Censored, n (%)	69 (50.4)
Withdrawal of Consent	7 (5.1)
Lost to Follow-up	2 (1.5)
Follow-up No Longer Available	0
Ongoing	60 (43.8)
Overall Survival (months) [a]	
Median (95% CI)	13.6 (9.9, NE)
Overall Survival Probability at (95% CI) [b]	
3 months	91.9 (85.9, 95.5)
6 months	74.6 (66.3, 81.2)
9 months	63.1 (54.3, 70.7)
12 months	55.9 (46.9, 63.9)
15 months	47.1 (37.7, 55.9)
18 months	47.1 (37.7, 55.9)

Percentages are based on the number of subjects in the full analysis set.
OS is defined as the time (months) from the date of the first dose of study treatment to the date of death due to any cause. If a subject is not known to have died, OS will be censored at the date of last contact.
[a] Median and overall survival probability at specific months are based on the Kaplan-Meier method. The two-sided 95% CI for the median is computed using the Brookmeyer-Crowley method.
[b] The two-sided 95% CIs for the overall survival at specific months are computed using the Greenwood's formula.
Source: Table 14.2.4.1

3.3.4.7.2. **Study TP01 (TROPION-PanTumor01)**

Study design: Phase 1, 2-part, multicentre (United States: 8 sites, Japan: 5 sites), open-label, multiple-dose, first-in-human study in subjects with advanced solid tumors. Study TP01 included 2 parts: 1) a dose escalation part to determine the maximum tolerated dose (MTD) and the recommended dose for expansion (RDE) of Dato-DXd on Day 1 of each 21-day cycle, and 2) a dose expansion part to investigate the safety, tolerability, and efficacy of Dato-DXd at the RDE.

Figure 65 Study design TP01



BICR=blinded independent central review; DCR=disease control rate; ECOG PS=Eastern Cooperative Oncology Group performance status; DoR=duration of response; HR(+)/HER2(-)BC=hormone receptor positive/human epidermal growth factor receptor 2 negative breast cancer; Inv=investigator; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors; SCLC=small cell lung cancer; TNBC=triple-negative breast cancer; TROP2=trophoblast cell surface protein 2; TTR=time to response; US=United States

Study population: The NSCLC cohort enrolled 210 patients, 50 patients received 6mg/m2, 10 of whom had AGAs.

First subject first visit date: 06 Feb 2018

Last subject last follow-up date: Trial ongoing

Data cut-off date (for non-small cell lung cancer [NSCLC]): 30 Jul 2021

Treatment: Dato-Dxd was given in dosage range 0.27-10 mg/m2.

Statistical methods: Efficacy analyses of Study TP01 used the FAS, which included all NSCLC subjects who received at least 1 dose of Dato-DXd. The efficacy variables were listed and summarized. ORR and DCR were summarized with the 95% CI using the Clopper-Pearson method. Time to event variables including DoR, PFS, and OS were summarized with median time using the Kaplan-Meier method with 95% CI. TTR was descriptively summarized.

Main inclusion criteria:

- Patients had relapsed or progressed following local standard treatments or for which no standard treatment was available;
- Patients were aged ≥20 years old in Japan or ≥18 years old in other countries;
- willingness and ability to provide an adequate tumor sample for tissue screening to confirm TROP2 expression level and other biomarkers;
- measurable disease assessed by the investigator based on Response Evaluation Criteria in Solid Tumors (RECIST)
- Version 1.1;
- Eastern Cooperative Oncology Group (ECOG) performance
- status (PS) of 0 to 1;

- left ventricular ejection fraction ≥50% within 28 days
- before enrollment (study drug treatment);
- adequate organ function as defined in the protocol within 7 days before enrollment (study drug
- treatment);
- adequate treatment washout period as defined in the protocol
- before enrollment (study treatment).

Results:

Table 113 Data Sets Analyzed - All Subjects Dosed

	0.27 mg/kg n (%)	0.5 mg/kg n (%)	1.0 mg/kg n (%)	2.0 mg/kg n (%)	4.0 mg/kg n (%)	6.0 mg/kg n (%)	8.0 mg/kg n (%)	10.0 mg/kg n (%)	Total n (%)
Analysis Sets[a]									
Full Analysis Set (N)	4	5	7	6	50	50	80	8	210
Safety Analysis Set	4 (100)	5 (100)	7 (100)	6 (100)	50 (100)	50 (100)	80 (100)	8 (100)	210 (100)
DLT Evaluable Set	4 (100)	5 (100)	7 (100)	6 (100)	6 (12.0)	8 (16.0)	8 (10.0)	7 (87.5)	51 (24.3)
PK Analysis Set	4 (100)	5 (100)	7 (100)	6 (100)	50 (100)	50 (100)	80 (100)	8 (100)	210 (100)

DLT = dose-limiting toxicity; PK = pharmacokinetics.
[a] Percentages and summary statistics are based on the number of subjects in the Full Analysis Set.
Source: Table 14.1.1.1

Table 114 Subject Disposition - All Screened Subjects

	0.27 mg/kg n (%)	0.5 mg/kg n (%)	1.0 mg/kg n (%)	2.0 mg/kg n (%)	4.0 mg/kg n (%)	6.0 mg/kg n (%)	8.0 mg/kg n (%)	10.0 mg/kg n (%)	Total n (%)
No. of subjects screened[a]									288
No. of screen failures									78
Treatment status[b]									
Ongoing study treatment	0	0	0	0	5 (10.0)	5 (10.0)	6 (7.5)	1 (12.5)	17 (8.1)
Discontinued from study treatment	4 (100)	5 (100)	7 (100)	6 (100)	45 (90.0)	45 (90.0)	74 (92.5)	7 (87.5)	193 (91.9)
Analysis Set[b]									
Full Analysis Set (N)	4	5	7	6	50	50	80	8	210
Safety Analysis Set	4 (100)	5 (100)	7 (100)	6 (100)	50 (100)	50 (100)	80 (100)	8 (100)	210 (100)
DLT Evaluable Set	4 (100)	5 (100)	7 (100)	6 (100)	6 (12.0)	8 (16.0)	8 (10.0)	7 (87.5)	51 (24.3)
PK Analysis Set	4 (100)	5 (100)	7 (100)	6 (100)	50 (100)	50 (100)	80 (100)	8 (100)	210 (100)
Primary reason for study treatment discontinuation									
Progressive disease per RECIST	3 (75.0)	4 (80.0)	5 (71.4)	6 (100)	29 (58.0)	26 (52.0)	34 (42.5)	1 (12.5)	108 (51.4)
Adverse event	0	0	0	0	8 (16.0)	6 (12.0)	20 (25.0)	1 (12.5)	35 (16.7)

	0.27 mg/kg n (%)	0.5 mg/kg n (%)	1.0 mg/kg n (%)	2.0 mg/kg n (%)	4.0 mg/kg n (%)	6.0 mg/kg n (%)	8.0 mg/kg n (%)	10.0 mg/kg n (%)	Total n (%)
Clinical progression	1 (25.0)	0	0	0	5 (10.0)	8 (16.0)	10 (12.5)	0	24 (11.4)
Withdrawal by subject	0	1 (20.0)	1 (14.3)	0	1 (2.0)	2 (4.0)	6 (7.5)	3 (37.5)	14 (6.7)
Physician decision	0	0	1 (14.3)	0	1 (2.0)	1 (2.0)	2 (2.5)	1 (12.5)	6 (2.9)
Other[c]	0	0	0	0	1 (2.0)	1 (2.0)	1 (1.3)	1 (12.5)	4 (1.9)
Death	0	0	0	0	0	1 (2.0)	1 (1.3)	0	2 (1.0)
Study duration (months)[b]									
n	4	5	7	6	50	50	80	8	210
Mean	41.4	37.9	35.6	33.8	16.5	17.7	20.9	26.3	20.9
Standard deviation	0.27	1.01	0.29	0.50	6.09	7.14	3.32	0.30	7.76
Minimum	41	37	35	33	11	10	14	26	10
Median	41.4	37.6	35.5	33.8	15.9	13.3	20.6	26.3	19.3
Maximum	42	39	36	34	33	31	29	27	42

PT = Principal Investigator; RECIST = Response Evaluation Criteria in Solid Tumors; TROP2 = trophoblast cell-surface antigen 2.
[a] Subjects who signed an informed consent form and were screened.
[b] Percentages and summary statistics are based on the number of subjects in the Full Analysis Set.

Table 115 Demographic and Baseline Characteristics - Full Analysis Set

	0.27 mg/kg N=4	0.5 mg/kg N=5	1.0 mg/kg N=7	2.0 mg/kg N=6	4.0 mg/kg N=50	6.0 mg/kg N=50	8.0 mg/kg N=80	10.0 mg/kg N=8	Total N=210
Age (years)[a]									
n	4	5	7	6	50	50	80	8	210
Mean	57.8	62.0	66.6	59.0	60.1	61.4	62.6	55.5	61.4
Standard deviation	20.90	10.93	5.56	10.70	11.87	9.87	10.67	15.65	11.08
Minimum	28	45	57	42	35	38	31	28	28
Median	64.0	66.0	67.0	60.5	61.0	62.5	64.0	55.5	63.0
Maximum	75	73	74	70	82	76	84	79	84
Age group (years), n (%)									
<65	2 (50.0)	2 (40.0)	2 (28.6)	3 (50.0)	32 (64.0)	30 (60.0)	43 (53.8)	6 (75.0)	120 (57.1)
≥65	2 (50.0)	3 (60.0)	5 (71.4)	3 (50.0)	18 (36.0)	20 (40.0)	37 (46.3)	2 (25.0)	90 (42.9)
Sex by age group (years), n (%)									
Male	1 (25.0)	3 (60.0)	4 (57.1)	4 (66.7)	27 (54.0)	28 (56.0)	41 (51.3)	5 (62.5)	113 (53.8)
≤18	0	0	0	0	0	0	0	0	0
>18 to <65	1 (25.0)	1 (20.0)	2 (28.6)	2 (33.3)	19 (38.0)	20 (40.0)	21 (26.3)	4 (50.0)	70 (33.3)
≥65	0	2 (40.0)	2 (28.6)	2 (33.3)	8 (16.0)	8 (16.0)	20 (25.0)	1 (12.5)	43 (20.5)
Female	3 (75.0)	2 (40.0)	3 (42.9)	2 (33.3)	23 (46.0)	22 (44.0)	39 (48.8)	3 (37.5)	97 (46.2)
≤18	0	0	0	0	0	0	0	0	0
>18 to <65	1 (25.0)	1 (20.0)	0	1 (16.7)	13 (26.0)	10 (20.0)	22 (27.5)	2 (25.0)	50 (23.8)
≥65	2 (50.0)	1 (20.0)	3 (42.9)	1 (16.7)	10 (20.0)	12 (24.0)	17 (21.3)	1 (12.5)	47 (22.4)
Race, n (%)									
White	2 (50.0)	3 (60.0)	4 (57.1)	3 (50.0)	26 (52.0)	25 (50.0)	51 (63.8)	3 (37.5)	117 (55.7)
Black or African American	0	0	0	0	2 (4.0)	3 (6.0)	1 (1.3)	0	6 (2.9)
Asian	2 (50.0)	1 (20.0)	2 (28.6)	2 (33.3)	21 (42.0)	17 (34.0)	26 (32.5)	3 (37.5)	74 (35.2)
American Indian or Alaska Native	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	1 (1.3)	0	1 (0.5)
Other	0	1 (20.0)	1 (14.3)	1 (16.7)	1 (2.0)	5 (10.0)	1 (1.3)	2 (25.0)	12 (5.7)
Ethnicity, n (%)									
Hispanic or Latino	0	0	0	2 (33.3)	2 (4.0)	4 (8.0)	0	1 (12.5)	9 (4.3)
Not Hispanic or Latino	4 (100)	4 (80.0)	6 (85.7)	4 (66.7)	48 (96.0)	46 (92.0)	80 (100)	6 (75.0)	198 (94.3)
Missing	0	1 (20.0)	1 (14.3)	0	0	0	0	1 (12.5)	3 (1.4)
Site (region), n (%)									
United States	2 (50.0)	4 (80.0)	5 (71.4)	4 (66.7)	29 (58.0)	38 (76.0)	63 (78.8)	6 (75.0)	151 (71.9)
Japan	2 (50.0)	1 (20.0)	2 (28.6)	2 (33.3)	21 (42.0)	12 (24.0)	17 (21.3)	2 (25.0)	59 (28.1)
Baseline ECOG performance status, n (%)									
0	0	0	2 (28.6)	1 (16.7)	23 (46.0)	12 (24.0)	17 (21.3)	0	55 (26.2)
1	4 (100)	5 (100)	5 (71.4)	5 (83.3)	27 (54.0)	38 (76.0)	63 (78.8)	8 (100)	155 (73.8)
Height (cm)									
n	4	5	7	6	50	50	80	8	210
Mean	165.18	166.14	165.84	164.78	166.94	167.23	166.83	167.30	166.83
Standard deviation	11.797	8.936	12.254	4.002	10.324	9.998	9.124	11.693	9.642

	0.27 mg/kg N=4	0.5 mg/kg N=5	1.0 mg/kg N=7	2.0 mg/kg N=6	4.0 mg/kg N=50	6.0 mg/kg N=50	8.0 mg/kg N=80	10.0 mg/kg N=8	Total N=210
Minimum	152.6	159.4	147.2	160.3	147.0	150.0	149.0	150.0	147.0
Median	163.50	160.00	167.60	163.20	167.90	165.40	167.40	171.00	167.10
Maximum	181.1	178.4	182.3	171.4	190.0	188.0	187.8	180.3	190.0
Baseline weight (kg)									
n	4	5	7	6	50	50	80	8	210
Mean	62.35	63.20	72.63	67.62	73.32	70.19	69.07	73.31	70.32
Standard deviation	21.227	19.413	18.119	7.016	23.052	17.039	16.753	22.149	18.584
Minimum	48.0	39.6	53.6	60.5	37.7	38.5	37.6	45.3	37.6
Median	53.95	62.30	62.50	65.25	71.95	66.40	70.45	74.45	67.70
Maximum	93.5	85.5	98.5	77.3	155.9	104.4	114.6	102.8	155.9
Baseline body mass index (kg/m²)									
n	4	5	7	6	50	50	80	8	210
Mean	22.374	22.959	26.035	24.840	25.889	24.891	24.759	25.638	25.049
Standard deviation	4.3046	7.2996	3.3823	1.4486	6.0063	4.8216	5.4168	5.1232	5.2951
Minimum	18.56	15.49	22.25	23.41	17.01	16.50	11.60	19.85	11.60
Median	21.213	24.519	26.122	24.500	24.772	25.022	24.602	26.331	24.655
Maximum	28.51	33.40	30.79	26.77	46.61	39.69	38.93	34.47	46.61
Tobacco use, n (%)									
Never	2 (50.0)	2 (40.0)	1 (14.3)	0	16 (32.0)	17 (34.0)	20 (25.0)	2 (25.0)	60 (28.6)
Current	0	1 (20.0)	0	0	1 (2.0)	0	4 (5.0)	0	6 (2.9)
Former	2 (50.0)	2 (40.0)	6 (85.7)	6 (100)	33 (66.0)	33 (66.0)	56 (70.0)	6 (75.0)	144 (68.6)

	0.27 mg/kg N=4	0.5 mg/kg N=5	1.0 mg/kg N=7	2.0 mg/kg N=6	4.0 mg/kg N=50	6.0 mg/kg N=50	8.0 mg/kg N=80	10.0 mg/kg N=8	Total N=210
Tumor size (SoD) at Baseline per BICR, n (%)									
≤5 cm	2 (50.0)	2 (40.0)	1 (14.3)	2 (33.3)	22 (44.0)	14 (28.0)	30 (37.5)	2 (25.0)	75 (35.7)
>5 to <10 cm	0	0	3 (42.9)	1 (16.7)	19 (38.0)	16 (32.0)	25 (31.3)	1 (12.5)	65 (31.0)
≥10 cm	2 (50.0)	3 (60.0)	2 (28.6)	3 (50.0)	8 (16.0)	18 (36.0)	21 (26.3)	3 (37.5)	60 (28.6)

BICR = Blinded Independent Central Review; ECOG = Eastern Cooperative Oncology Group; SoD = sum of diameters.
[a] Age in years was calculated using the informed consent date and the birth date.
Percentages are based on the number of subjects in the Full Analysis Set.
Baseline was defined as the last available assessment prior to the start of study treatment.
Source: Table 14.1.2.1

Cancer staging reported at study entry was stage IV (41.4%), stage IVa (25.2%), and stage IVb (29.0%) (Table not shown). All patients (210 [100%]) received prior cancer therapy, with >20% of patients receiving platinum compounds (97.1%), monoclonal antibodies (91.4%), folic acid analogues (77.6%), taxanes (46.0%), protein kinase inhibitors (24.8%), and pyrimidine analogues (24.3%). Themajority of patients received 2 (22.9%) or 3 (25.2%) regimens. The majority of patients (173 [82.4%]) had NSCLC with a histology of adenocarcinoma. Forty-eight patients had EGFR mutations: 17 (8.1%) patients had an exon 19 deletion and 10 (4.8%) subjects had an exon 20 Thr790Met. Five (2.4%) patients were ALK-positive.

Table 116 Best Overall Response, Objective Response Rate, and Disease Control Rate by Blinded Independent Central Review per RECIST v1.1 - Full Analysis Set

	0.27 mg/kg N=4	0.5 mg/kg N=5	1.0 mg/kg N=7	2.0 mg/kg N=6	4.0 mg/kg N=50	6.0 mg/kg N=50	8.0 mg/kg N=80	10.0 mg/kg N=8
Response with Confirmation of CR/PR								
BOR								
CR	0	0	0	0	0	0	1 (1.3)	0
PR	0	0	0	1 (16.7)	11 (22.0)	13 (26.0)	18 (22.5)	2 (25.0)
SD	0	1 (20.0)	5 (71.4)	3 (50.0)	26 (52.0)	20 (40.0)	42 (52.5)	2 (25.0)
Non-CR/non-PD	0	0	1 (14.3)	0	1 (2.0)	2 (4.0)	2 (2.5)	2 (25.0)
PD	4 (100)	3 (60.0)	1 (14.3)	2 (33.3)	7 (14.0)	10 (20.0)	8 (10.0)	0
NE	0	1 (20.0)	0	0	5 (10.0)	5 (10.0)	9 (11.3)	2 (25.0)
Reason for NE								
No Baseline tumor assessment	0	0	0	0	0	0	0	0
No adequate post-baseline tumor assessment	0	1 (20.0)	0	0	2 (4.0)	4 (8.0)	7 (8.8)	1 (12.5)
SD too early (<5 weeks after start of study treatment)	0	0	0	0	2 (4.0)	1 (2.0)	1 (1.3)	1 (12.5)
PD too late (PD >12 weeks after start of study treatment)	0	0	0	0	1 (2.0)	0	1 (1.3)	0
ORR (CR+PR)	0	0	0	1 (16.7)	11 (22.0)	13 (26.0)	19 (23.8)	2 (25.0)
95% exact CI[a]	(NE)	(NE)	(NE)	(0.4, 64.1)	(11.5, 36.0)	(14.6, 40.3)	(14.9, 34.6)	(3.2, 65.1)
DCR (CR+PR+SD+non-CR/non-PD)	0	1 (20.0)	6 (85.7)	4 (66.7)	38 (76.0)	35 (70.0)	63 (78.8)	6 (75.0)
95% exact CI[a]	(NE)	(0.5, 71.6)	(42.1, 99.6)	(22.3, 95.7)	(61.8, 86.9)	(55.4, 82.1)	(68.2, 87.1)	(34.9, 96.8)

BOR = best overall response; CI = confidence interval; CR = complete response; DCR = disease control rate; NE = non-evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease.
Percentages are based on the number of subjects in the Full Analysis Set.
[a] Using 2-sided exact (Clopper-Pearson) method.
Source: Table 14.2.1.1

Table 117 Best Overall Response, Objective Response Rate, and Disease Control Rate by Blinded Independent Central Review per RECIST vl.1 (Full Analysis Set)

	Dato-DXd 6 mg/kg N=50
Response with Confirmation of CR/PR	
BOR	
CR	0
PR	13 (26.0)
SD	20 (40.0)
Non-CR/non-PD	2 (4.0)
PD	10 (20.0)
NE	5 (10.0)
ORR (CR+PR)	13 (26.0)
95% exact CI[a]	(14.6, 40.3)
DCR (CR + PR + SD + non-CR/non-PD)	35 (70.0)
95% exact CI[a]	(55.4, 82.1)

BOR=best overall response; CI=confidence interval; CR=complete response; CSR=clinical study report; Dato-DXd=datopotamab deruxtecan; DCR=disease control rate; NE=non-evaluable; NSCLC=non-small cell lung cancer; ORR=objective response rate; PD=progressive disease; PR=partial response; SD=stable disease; RECIST=Response Evaluation Criteria in Solid Tumors
Percentages are based on the number of subjects in the Full Analysis Set.
[a] Using 2-sided exact (Clopper-Pearson) method.
Source: Adapted from Study TP01 NSCLC CSR Table 14.2.1.1

Table 118 Duration of Response and Time to Response as Assessed by Blinded Independent Central Review per RECIST v1.1 (Full Analysis Set)

	Dato-DXd 6 mg/kg N=50
Subjects with confirmed CR/PR	13
Median (95% CI) Kaplan-Meier estimate of DoR in subjects with confirmed CR/PR (months)[a]	10.5 (5.6, NE)
Median (range) TTR in subjects with confirmed CR/PR (months)	1.38 (1.2, 5.7)

BICR=blinded independent central review; CI=confidence interval; CR=confirmed response; Dato-DXd=datopotamab deruxtecan; DoR=duration of response; ISE=Integrated Summary of Efficacy; NE=not estimable; PR=partial response; RECIST v1.1=Response Evaluation Criteria in Solid Tumors Version 1.1; TTR=time to response
[a] Median is based on the Kaplan-Meier method. The 2-sided 95% CI for the median is computed using the Brookmeyer-Crowley method.
Source: Adapted from ISE Table 1.1.11.2

Table 119 Progression-free Survival as Assessed by Blinded Independent Central Review per RECIST v1.1 (Full Analysis Set)

	Dato-DXd 6 mg/kg N=50
Median (95% CI) PFS (months)[a]	6.9 (2.7, 8.8)

BICR=blinded independent central review; CI=confidence interval; CSR=clinical study report; Dato-DXd=datopotamab deruxtecan; NSCLC=non-small cell lung cancer; PFS=progression-free survival; RECIST v1.1=Response Evaluation Criteria in Solid Tumors Version 1.1

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

[a] Median is based on the Kaplan-Meier method. The 2-sided 95% CI for the median is computed using the Brookmeyer-Crowley method.

Table 120 Overall Survival (Full Analysis Set)

	Dato-DXd 6 mg/kg N=50
Median (95% CI) OS (months)[a]	11.4 (7.1, 20.6)

CI=confidence interval; CSR=clinical study report; Dato-DXd=datopotamab deruxtecan; NSCLC=non-small cell lung cancer; OS=overall survival

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

[a] Median is based on the Kaplan-Meier method. The 2-sided 95% CI for the median is computed using the Brookmeyer-Crowley method.

Source: Adapted from Study TP01 NSCLC CSR Table 14.2.4.1

Table 121 TP01 NSCLC (4, 6, and 8 mg/kg) Efficacy Results by Histology Status, ORR, DCR, DoR, and PFS as Assessed by Blinded Independent Central Review and OS (Full Analysis Set)

	Squamous Dato-DXd 4, 6, and 8 mg/kg N=24
Response with Confirmation of CR/PR	
BOR, n (%)	
CR	0
PR	2 (8.3)
SD	14 (58.3)
Non-CR/non-PD	0
PD	5 (20.8)
Not Evaluable	3 (12.5)
ORR (CR + PR), n (%)	2 (8.3)
95% CI[a]	(1.0, 27.0)
DCR (CR + PR + SD or non-CR/non-PD), n (%)	16 (66.7)
95% CI[a]	(44.7, 84.4)
Median (95% CI) DoR (months)[b]	NE (NE, NE)
PFS Events, n (%)	16 (66.7)
Median (95% CI) PFS (months)[b]	3.5 (1.3, 6.9)
OS Events, n (%)	19 (79.2)
Median (95% CI) OS (months)[b]	8.8 (3.7, 11.7)

BOR=best overall response; CI=confidence interval; CR=complete response; Dato-DXd=datopotamab deruxtecan; DCR=disease control rate; DoR=duration of response; NE=not estimable; ORR=objective response rate; OS=overall survival; PD=progressive disease; PFS=progression-free survival; PR=partial response; SD=stable disease
Percentages are based on the number of subjects in the Full Analysis Set.
Confirmed responses require at least 2 determinations of responses at least 4 weeks apart before progression.
[a] The 2-sided 95% CIs are based on the Clopper-Pearson exact binomial method.
[b] Median is based on the Kaplan-Meier method. The 2-sided 95% CIs for the median are computed using the Brookmeyer-Crowley method.
Source: Dato-DXd Ad Hoc Analysis Table 2.7 TP01, Table 2.8 TP01, Table 2.9 TP01, and Table 2.10 TP01.

3.3.5. Discussion on clinical efficacy

Datopotamab deruxtecan (Dato-DXd) is an anti-TROP2 ADC. Based on results from pivotal trial TROPION-Lung01 (also known as TL01, DS1062-A-U301) and supportive data from trials TROPION-Lung05 (TL05) and TROPION-PanTumor01 (TP01), the applicant has requested a full marketing authorisation with the following indication:

Datopotamab deruxtecan Daiichi Sankyo as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) who require systemic therapy following prior treatment:

- *Patients without known actionable genomic alterations previously treated with platinum-based chemotherapy in the advanced or metastatic setting and PD-1 or PD-L1 inhibitor, either in combination or sequentially*
- *Patients with actionable genomic alterations (as listed in section 5.1) previously treated with prior platinum-based therapy and targeted therapy for the detected alteration*

Design and conduct of clinical studies

TL01 is a phase III, randomised, open-label trial where patients were assigned in a 1:1 ratio to receive either Dato-DXd 6 mg/kg or docetaxel 75 mg/m2, administered intravenously on the first day of each 21-day cycle. Randomisation was stratified by histology (squamous vs. non-squamous), whether the most immediate prior therapy included anti PD (L)1 immunotherapy (yes vs. no), geographic region (US/Japan/Western Europe vs. Rest of World), and documented actionable genomic alteration (AGA) (present vs. absent).

The initial design of TL01, intended to provide comprehensive data in the proposed therapeutic indication for Dato-DXd, was discussed with CHMP in November 2020. It was not upfront disclosed whether this trial would be open-label, and it was proposed that PFS, as assessed by investigator, would be the primary endpoint. The overall design, including patient population (i.e., advanced squamous/non-squamous NSCLC without actionable genomic alterations in progression after platinum-based chemotherapy and checkpoint immunotherapy), stratification factors and comparator arm, were found acceptable by the CHMP, but it was recommended that PFS, if retained as primary endpoint, to be assessed by BICR, to partially mitigate bias from the likely open-label design. Regarding the choice of primary endpoints in this clinical setting, the CHMP did not favour PFS as an independent primary endpoint and insisted that OS should be the prioritised primary endpoint: "a positive primary PFS analysis, if not supported by positive OS results, cannot be viewed as sufficient for a MAA."

In a follow-up scientific advice in March 2022, the applicant disclosed a major amendment in the protocol –during study conduct– that allowed inclusion of AGA+ patients (not allowed in the original protocol) while keeping the original intended sample size. By the time this amendment was disclosed with the CHMP (~24-NOV-2021), about a quarter (161 out of planned n=590) of patients had been enrolled. The CHMP was overall cautious regarding this major amendment to an ongoing open-label trial, and pointed out that the heterogeneity of the additional subpopulation (which also implied an added stratification factor) may pose interpretation challenges for efficacy in the AGA+ subgroup. Importantly, concerns were raised upon the consideration that patients with KRAS+ tumours were included in the AGA- subgroup, since Lumykras (sotorasib) had been approved for patients with KRAS G12C mutations since January 2022.

Study participants: The provided eligibility criteria reflect clinical practice, as testing for genomic alterations cannot be considered mandatory in the absence of locally approved/available targeted

treatments. Except for EGFR and ALK, for which treatments are widely available, it was not requested that patients were tested for other actionable genomic aberrations with approved targeted therapy (e.g., ROS1, NTRK, BRAFV600E, MET exon 14 skipping or RET rearrangements).

In TL01 there were 18 subjects with KRAS G12C mutations (6 in the Dato-DXd arm and 12 in the docetaxel arm) who had not received KRAS-targeted therapy prior to study enrolment. Acknowledging that KRAS G12C inhibitors are not yet widely available/reimbursed, concerns of loss of chance for these patients in TL01 seem mitigated.

Regarding the therapeutic indication wording (section 4.1 of the SmPC), it is considered to appropriately reflect the population recruited considering the eligibility criteria and the proposed restriction (non-squamous histology only) based on subgroup analyses.

Patients were tested on TROP-2 expression, but this was not regarded as an inclusion criterion or stratification factor. The effect of baseline TROP-2 on efficacy had not been investigated in earlier trials. A specific ad hoc biomarker study using the results of this phase 3 study was conducted to determine if there might be a relationship to efficacy.

Treatments: Dose and schedule of Dato-DXd are appropriately justified per dose-response results, and those for docetaxel follow standard guidelines.

Objectives/endpoints: OS and PFS (as assessed by BICR) were defined as two independent primary endpoints. The assessment of images by blinded review partly mitigates bias from the open-label nature of the trial, but concordance with investigator assessment is expected to support the external validity of the trial. The overall discordance with PFS by investigator was ~15%, which is considered acceptable. The overall Type I error rate was maintained at or below 0.05 (two-sided) by allocating alpha=0.008 to the PFS comparison and alpha=0.042 to the OS comparison – with provisions for alpha rollover based on positive interim results, which could necessitate recalibrated efficacy boundaries. According to the protocol, the study would be considered positive if the hypothesis test for either one of these primary endpoints was successful. Regardless of how alpha was handled, this approach is not endorsed. According to scientific advice, a positive primary PFS analysis, if not supported by positive OS results, could not be viewed as sufficient for a MAA. Nonetheless, a multiplicity strategy was applied to PFS and OS, making these two dual primary endpoints.

Statistical methods: The sample size estimation, including power calculation, stratification factors, and interim analysis planning is acceptable. AGA was added as a stratification factor in Protocol Version 4.0, with updates made to the randomization system (IXRS) and documentation. Patients enrolled under earlier versions were classified into the non-AGA group. Due to low event counts, AGA and another factor were removed from the primary PFS and interim OS analyses. The removal of AGA as a stratification factor due to low event counts should be carefully examined to ensure it didn't impact the study's findings. The practice of censoring progression and death after two or more missed visits was not in concurrence with regulatory expectations, but a sensitivity analysis (including the actual event times for participants who progressed or died after missing two or more tumour assessments) was provided, and its results are consistent with those of the primary analysis. RMST analyses were provided for both PFS and OS, which are robust against deviations from the PH assumption. The use of RMST strengthens the validity of the findings, and the detailed breakdown of follow-up times ensures transparency in how the analysis was conducted. The familywise error rate was maintained using an adaptive alpha recycling strategy and the Lan-DeMets spending function. The approach ensures rigorous Type I error control across both primary endpoints and during repeated testing of OS, and it is consistent with established statistical methodologies. Changes in the SAP are all justified in the protocol and thus acceptable.

Methodology for the sensitivity analyses is followed, but the subgroup and post-hoc analyses raised a number of concerns: the datasets for the planned subgroup analyses (defined by IXRS) and the post-hoc analyses (defined by eCRF) differ on account of mis-stratification of 5% of patients (20 in the Dato-Dxd arm and 11 in the docetaxel arm), and noting that the "corrected" eCRF dataset did not account for mis-stratification of prior PD-L1, raising concerns for data-driven analyses, which hampers internal validity of the results. Upon these considerations, results from the IXRS dataset were prioritised and those from the eCRF are considered supplementary.

To demonstrate reliability of the PFS results, the applicant provided a worst-case scenario sensitivity analysis and a tipping point analysis which partly mitigate concerns on statistical PFS benefit robustness in the ITT from TL01, but this does not imply that the marginal PFS gain is clinically relevant, that it relates to significant OS gains or that these hypothetical benefits outweigh the considerable toxicity risks from Dato-DXd in NSCLC. Moreover, even if PFS gains from Dato-DXd over docetaxel were considered relevant, the most problematic methodologic issues from this procedure are under no means alleviated: the required indication is for an *ad hoc* subgroup of the ITT (based on a non-prespecified analysis), addition of the ADA+ subgroup in a late major protocol amendment, multiple stratification errors and lack of OS benefit (issues not solved, see subsequent question).

Study conduct: In the first protocol amendment (Version 2.0, 03-MAR-2021), the primary objective of PFS as assessed by investigator was changed to PFS as assessed by BICR (downgrading PFS by investigator to a secondary objective), following recommendations from global regulatory authorities. In the second protocol amendment (Version 3.0, 01-OCT-2021), inclusion criterion 8 (Archival tumour tissue from initial diagnosis is required, to the extent that archival tumour tissue is available) was removed, and the requirement for tumour tissue was softened, allowing for biopsies within 2 years prior to recruitment. The third procotol amendment, which allowed the inclusion of AGA+ patients has already been discussed.

Although major protocol violations were overall balanced between both arms of U301, there was a substantial number of them: 51% in the Dato-DXd arm and 46% in the Docetaxel arm. According to the applicant, most of these violations (241 out of 291, 82%) occurred in study procedures, and concerned missing completion of PROs or image/lab tests not done at scheduled visits. Only a minority of major deviations corresponded to eligibility criteria and they were also balanced in both arms.

Cross-over was not allowed during the study, but up to 21% of patients from the Dato-DXd arm did receive subsequent docetaxel after progression.

Subject disposition: The slightly higher number of patients randomised but not treated in the docetaxel arm (15 vs. 2 in the Dato-DXd arm, most of them withdrawal by subject or physician) is as expected in an open label trial, and should not have a significant impact on overall results. At DCO (29-MAR-2023), a similar proportion of patients in both arms had discontinued treatment on account of progression (58% in the Dato-DXd arm in 62% in the Docetaxel arm) or adverse events (13% and 16%, respectively). About 42% of patients were still ongoing follow-up at DCO, and most study discontinuations were on account of death (49% in the Dato-DXd arm and 50% in the Docetaxel arm), there were only 3 patients lost to follow-up.

Baseline characteristics: Baseline demographic and disease characteristics were overall balanced between both arms of U301 and corresponded to the targeted population of patients with advanced NSCLC (with or without AGAs) in the 2L+ setting. Median age was 64 years and 65% of patients were male. About 41% were of white race, 40% Asian and 69% had ECOG 1. 22% had squamous histology and the rest non-squamous. 16.7% were AGA+ and almost all patients were in stage IV. PD-L1 expression followed standard trends (about a third with <1%) and 28% had history of brain metastases. Following inclusion criteria, almost all patients had received prior platinum-based chemotherapy, 88% had received PD-1/PD-L1 inhibitors (99% of those AGA- and 30% of AGA+) and

93% patients AGA+ had received prior targeted therapy (4 patients had genomic alterations without approved treatment, and 3 lived in countries where targeted treatment was not approved/available). 56% of patients had received one single prior line (66% AGA- and 5% AGA+), whereas 35% had received at least two (32% AGA- and 50% AGA+) and very few were in the 3L+ setting.

AGA+ patients: Considering that roughly 97 patients with AGA+ status was recruited in the trial (101 in a post hoc analysis), i.e., ~16% of the ITT, it could not be expected that the distribution of AGAs matched the known distribution of AGAs in NSCLC, but there seems to be a slight overrepresentation of EGFR+, and less than expected ALK+ patients. As pointed out in the follow-up SA from 2022, the small sample and heterogeneity of the additional AGA+ subpopulation may pose interpretation challenges for efficacy in this subgroup as a whole **(MO)**.

Efficacy data and additional analyses

The primary analysis for PFS was to be triggered after 425 BICR-PFS events. When this occurred, median follow-up time for OS (based on the inverse KM method) was 12.4 months for both arms, but it is to note that it was considerably shorter for the AGA+ patients, who started recruitment later: 7.0 months in the Dato-DXd arm and 6.7 months in the Docetaxel arm.

BICR-PFS: At DCO (29-MAR-2023), with 431 events (71% maturity; 83% of the events were progressive disease and the rest deaths), Dato-DXd showed a statistically significant improvement of BICR-PFS over docetaxel in the ITT of Study U301, noting HR for BICR-PFS of 0.75 (95% CI 0.62, 0.91), p-value 0.0040. Median PFS was 4.4 in the Dato-DXd arm vs. 3.7 in the Docetaxel arm. The K-M curves separate as of the first assessment of efficacy (around 6 weeks) and remain separated, although approaching towards the end of the follow-up period. Regarding PFS performance of docetaxel in the post-platinum post-immunotherapy NSCLC setting, it seemed as expected, noting: 3.2 months in KeyVibe-002 (Peled et al, ESMO IO 2023); 4.0 months in CONTACT-01 (Neal et al, ELCC 2023), 5.4 months in SAPPHIRE (Borghaei et al, Ann Oncol 2023); and 4.2 months in CANOPY-2 (Paz-Ares et al, Ann Oncol 2021.

OS: At the primary analysis of PFS (DCO 29-MAR-2023), and with median follow-up time for OS of 12.4 months, 305 patients (50% from the ITT) had died, about the same proportion in each arm. Although median OS from Dato-DXd was slightly superior to Docetaxel (12.4 vs. 11.0 months), the HR for OS did not show a statistically significant improvement: 0.90 (95% CI 0.72, 1.13), p-value 0.36.

The final OS analysis from Study TL01 (DCO 1-MAR-2024) did not yield a positive statistical outcome. At 72% of OS maturity and median follow-up of ~23 months, HR for OS is 0.94 (95% CI 0.78, 1.14), noting mOS 12.9 months for Dato-DXd and 11.8 months for docetaxel. The HR for OS in the IA (DCO 29-MAR-2023) was 0.90, so as data from TL01 mature, the survival benefit is no longer trending in a favourable direction. The subgroup analysis in the non-squamous population shows a similar tendency: HR for OS increased from 0.79 at the IA to 0.84 at the FA (mOS 14.6 months in Dato-DXd arm vs. 12.3 months in docetaxel arm).

The additional subgroup analysis of OS in non-squamous AGA+ vs. AGA- patients is overall consistent with the exploratory results from the IA, suggesting that any beneficial OS effects are driven by the AGA+ subgroup (HR 0.65 vs. 0.89 in AGA-), but the limited number of patients and the ad hoc nature of these analyses prevents any solid conclusions. Regardless of the promising data for Dato-DXd in non-squamous AGA+ patients progressing beyond targeted therapies, crucial methodological problems in the design and conduct of TL01 preclude concluding on established efficacy for this subpopulation.

To note, all subgroup analyses in the final OS results correspond to the eCRF dataset, in which mis-stratification was already corrected. This is not methodologically acceptable, and subgroup analyses of

final OS by IXRS (tables and KM plots) are still pending for the NSq. Vs Sq and NSq AGA+ vs. NSq AGA- patients **(OC)**.

The OS performance of docetaxel in the post-platinum post-immunotherapy NSCLC setting was within expectations, highlighting: 8.8 months in KeyVibe-002 (Peled et al, ESMO IO 2023); 10.5 months in CONTACT-01 (Neal et al, ELCC 2023), 10.6 months in SAPPHIRE (Borghaei et al, Ann Oncol 2023); 11.3 months in CANOPY-2 (Paz-Ares et al, Ann Oncol 2021); and 12.0 months in LEAP-008 (Naidoo et al, ESMO IO 2023).

Secondary endpoints: Response according to BICR was twice as likely in the Dato-DXd arm (26%) than in the Docetaxel arm (13%), but duration of response was not considerably longer for Dato-DXd (mDOR 7.1 months) vs. Docetaxel (mDOR 5.6 months). Although the concordance rate for assessment of progressive disease barely reached 80%, the analysis of PFS by investigator was overall consistent with BICR-PFS. PFS2 was also similar for both arms: HR for PFS2 was 0.85 (95% CI 0.68, 10.05), noting mPFS2 was 10 months in the Dato-DXd arm and 9 months in the docetaxel arm.

Subgroup, sensitivity and post-hoc analyses: Regarding BICR-PFS, benefit from Dato-DXd over docetaxel was seen across most predefined subgroups with a sufficient size, except in squamous histology. Concerning OS, the advantage of Dato-DXd over docetaxel across subgroups were for the most part either borderline or directly not evident, and the detrimental pattern for squamous histology was accentuated. Apparent survival detrimental effects in patients of race Black/African American/Other cannot be concluded on, because the subgroups were small in size.

Non-squamous NSCLC: To justify the histology-restricted indication to patients with non-squamous NSCLC (76% of the ITT), the applicant highlights that the benefit of Dato-DXd in BICR-PFS and OS is largely driven by these patients (HR for BICR-PFS 0.63, 95% CI 0.50, 0.78; HR for OS 0.77, 95% CI 0.59, 1.01). In fact, a detrimental effect from Dato-DXd in both BICR-PFS (HR 1.38, 95% CI 0.94, 2.02) and OS (HR 1.32, 95% CI 0.87, 2.00) vs. docetaxel is evident in patients with squamous histology. Based on these effects, the applicant proposes a restriction on non-squamous histology (76% of patients from the ITT). However, biological plausibility for this effect is not evident and this observation was not replicated in a similar clinical trial with another anti-TROP2 antibody (Paz-Ares et al, J Clin Oncol 2024). Hence, this subgroup finding, lacks external validity.

In any case, considering the biomarker all-comer (regardless of AGA presence or absence) indication, evaluation of results from AGA subgroups are mandatory for a regulatory decision. However, post-hoc subgroup analyses must be interpreted with great caution, in view of their retrospective nature and limited patient numbers. When the ITT (n=604) is split into AGA+ (n=97) and AGA- (n=507) patients, the second dataset, which started recruiting earlier, is clearly the driver of BICR-PFS maturity: 71% events in ITT (74% in AGA- vs. 60% in AGA+). The unstratified HR for BICR-PFS in AGA- patients is 0.84 (95% CI 0.68, 1.03), whereas that in AGA+ is 0.38 (95% CI 0.22, 0.65). The separation of the BICR-PFS KM curves in each dataset follows these trends, suggesting AGA+ patients obtain a higher PFS benefit from Dato-DXd vs. docetaxel. This curious finding is replicated in the OS data, despite relative immaturity of AGA+ dataset: Event maturity is again driven by AGA- patients: 49% OS events in ITT (55% in AGA- vs. 20% in AGA+); the unstratified HR for OS in AGA- patients is 0.96 (95% CI 0.76, 1.22), whereas the same in AGA+ is 0.38 (95% CI 0.17, 0.85). The behaviour of the OS KM curves in these subsets is perplexing: practically overlapping curves in the rather mature AGA- subset and completely separated curves in the AGA+. These results inevitably lead to speculation as to what the efficacy outcome of the trial would have been if the amendment that allowed AGA+ patients to enrol had not occurred. But ultimately, these data force questions upon efficacy of Dato-DXd vs. the active control in the targeted setting (particularly in AGA- patients), despite the histology restriction.

Non-squamous histology: AGA+ vs. AGA-: Another post-hoc analysis by selecting the non-squamous subgroup and splitting these patients by AGA status shows again that AGA+ patients (19% from the

non-squamous subgroup; HR for BICR-PFS 0.35; HR for OS 0.30) seem to derive most of the benefit from Dato-DXd over docetaxel. However, this interesting subgroup analysis does not mitigate abovementioned concerns of a reduced efficacy trend from Dato-DXd in AGA- patients, which happen to be the most numerous subgroup (79% from the non-squamous histology, i.e., the applied-for indication): HR for BICR-PFS 0.71 (95% 0.56, 0.91) and HR for OS 0.90 (0.68, 1.20). In the non-squamous AGA- subgroup, although the KM plot for BICR-PFS shows slightly separated curves, the one for OS shows overlapping and constantly intercrossing curves, so a survival benefit cannot be inferred in this subpopulation, emphasising it constitutes nearly 80% of the proposed therapeutic indication. The subgroup analysis of final OS results in non-squamous AGA+ vs. AGA- patients is overall consistent with the exploratory results from the IA, suggesting that any beneficial OS effects are driven by the AGA+ subgroup (HR 0.65 vs. 0.89 in AGA-), but the limited number of patients and the ad hoc nature of these analyses prevents any solid conclusions. Overall, although the PFS improvement of 1.8 months in the non-squamous AGA- subpopulation might be considered clinically relevant, the overall OS benefit is small (0.8 months). This small OS improvement might be of concern considering that patients in the Dato-DXd arm may have been more actively treated, as up to 20% of patients of the IXRS dataset received additional docetaxel after failure of Dato-DXd (although the specific proportion in the non-squamous AGA- subgroup is unknown).

By local testing, 80% of all AGA+ patients in TL01 were EGFR+, 7% were BRAF+, 6% were ROS1+, 3% were ALK+ and the rest had other alterations (NTRK, METex14, RET). Considering the small size of the subgroup, it is not surprising that the distribution did not follow the expected proportionality, but this issue obviously limits generalisation of results. Moreover, the internal distribution between arms was not balanced, e.g. all 6 ROS1+ and all 2 NTRK+ patients were in the Dato-DXd arm, whereas all 2 RET+ patients were in the docetaxel arm. Although data seems promising, considering that there are only 17 non-EGFR AGA+ patients (11 in the Dato-DXd arm and 6 in the docetaxel arm), it cannot be concluded that Dato-DXd is significantly better than docetaxel in terms of OS/PFS/ORR in all non-EGFR AGA+ patients (at most this is a positive signal for EGFR+ patients which may be used as hypothesis-generating). Subsequently, it is not considered justified to generalise the sparse results from this subpopulation as part of the proposed therapeutic indication in advanced NSCLC **(MO)**.

The sensitivity analyses for BICR-PFS and OS (stratified per CRF, unstratified, informative censoring, RMST) are overall consistent with those from the primary analysis.

Other biomarkers: Analyses of efficacy by TROP2 expression (available for about two thirds of patients from TL01) do not suggest a clear predictive effect: comparable efficacy results are observed in the high compared to the low TROP2 subpopulation. Additional analyses excluding squamous patients suggest a potential increase in treatment effect in the TROP2 H≥200 subgroup. However, this appears partly related to lower activity of docetaxel in these patients. However, results should be interpreted with great caution in view of the very limited number of patients with TROP2 H score ≥200 included in the study. Due to small size of the KRAS+ population, no conclusions on relation to efficacy from Dato-DXd can be drawn.

Supportive trials: Results of study TL05 (a single-arm trial in 157 2L+ AGA+ NSCLC patients) are supportive of efficacy of Dato-DXd in the AGA+ subgroup, but do not resolve the uncertainty of efficacy in the AGA- subpopulation from TL01.

External evidence of benefit from targeting TROP2 on NSCLC: The applicant presented 3 datasets supportive of efficacy of anti-TROP2 Dato-DXd in NSCLC. Study TP01 is part of the supportive evidence already presented. Response rates from Dato-DXd in subjects with NSq-NSCLC across TP02 (conducted solely in China) and IL01 (investigator-led) were overall consistent (57% and 33%, respectively) with those observed in TL01 (31%). Additionally, a revision on the hypothetic biological rationale that would lead TROP2 internalisation to provide efficacy benefits from Dato-DXd was presented.

However, published reports of other anti-TROP2-targeted ADCs in advanced lung cancer are already available, namely Trodelvy (sacituzumab govitecan, SG), which was evaluated in advanced 2L+ NSCLC in the EVOKE-01 study (Paz-Ares et al, J Clin Oncol 2024). This trial held an overall similar design to TROPION-Lung01 (TL01) in terms of population, randomisation, control arm and sample size, but a crucial difference in evaluation of benefit: OS was the primary endpoint, while PFS and ORR/DOR were secondary endpoints. At the primary analysis, OS was not statistically significant, noting a HR of 0.84 (95% CI 0.68, 1.04) and mOS of 11.1 months for SG vs. 9.8 months for docetaxel. PFS, although not formally tested, yielded a HR of 0.92 (95% CI 0.77, 1.11), with mPFS of 4.1 months for SG and 3.9 months for docetaxel. Interestingly however, subgroup analyses did not show a differential OS effect on the basis of histology (HR for OS in squamous 0.83 vs. 0.87 in non-squamous), whereas a higher magnitude of OS benefit was evident in patients who did not experience a response to their last anti-PD-1/PD-L1 containing regimen (HR for OS 0.75 in non-responders vs. 1.09 in responders). In summary, although a beneficial trend for OS was observed from anti-TROP2 sacituzumab govitecan in advanced NSCLC, results were not statistically significant nor clinically relevant, noting that the apparently deleterious effect of Dato-DXd on squamous histology was not replicated in such trial. Overall, external evidence does not support a clinically relevant benefit of targeting TROP2 in all-comers with advanced NSCLC.

3.3.6. Conclusions on clinical efficacy

TL01 had a positive outcome on its primary endpoint BICR-PFS in the ITT, but the magnitude of effect (2.8-week PFS advantage from Dato-DXd over docetaxel) is marginal and not supported by statistically robust nor clinically relevant OS gains as per the final analysis. Subgroup analyses identified the populations that seemed to drive PFS and OS benefits, i.e., non-squamous histology and from these the AGA+ patients (recruited as per a late major protocol amendment), but these data are at most hypothesis-generating and insufficient for evaluation of B/R and a subsequent regulatory decision. Furthermore, external evidence (Paz-Ares et al, JCO 2024) does not support a clinically relevant benefit of targeting TROP2 in all-comers with advanced NSCLC and did not replicate the apparent histology-driven differential effect from Dato-DXd. Overall, it is not considered that the marginal efficacy from Dato-DXd in non-squamous NSCLC outweighs its associated toxicities, particularly the risk of severe or even fatal ILD/pneumonitis **(MO)**.

Subgroup efficacy results are insufficient to ascertain B/R in the AGA+ subpopulation from TL01. Subsequently, it is not considered justified to generalise the sparse results from this subpopulation as part of the proposed therapeutic indication in advanced NSCLC **(MO)**.

3.3.7. Clinical safety

The table numbers refer to the numbers in the SCS unless otherwise specified.

The overall safety evaluation of Dato DXd is based on safety data derived from the 3 clinical studies conducted by Daiichi Sankyo (Table 1.1). Study TL01 has been updated with a DCO of 13.10.2023.

Table 122: List of Studies Contributing Data to the Current Submission, with Cut-off Dates

Study Number/ Status	DCO Date	Study Title (Location in Module 5)	Number of Subjects Treated
TROPION-Lung01 (TL01) DS1062-A-U301 Ongoing	29 Mar 2023	Phase 3 randomized study of DS-1062a vs. docetaxel in previously treated advanced or metastatic NSCLC with or without actionable genomic alterations (See Module 5.3.5.1 Study TL01 CSR)	297 Dato-DXd 6 mg/kg (232 non-squamous) 290 docetaxel 75 mg/m^2

Table 122: List of Studies Contributing Data to the Current Submission, with Cut-off Dates

Study Number/ Status	DCO Date	Study Title (Location in Module 5)	Number of Subjects Treated
TROPION-Lung05 (TL05) DS1062-A-U202 Completed	14 Dec 2022	Phase 2, single-arm, open-label study of DS-1062a in advanced or metastatic NSCLC with actionable genomic alterations and progressed on or after applicable targeted therapy and platinum-based chemotherapy (See Module 5.3.5.2 Study TL05 CSR)	137 Dato-DXd 6 mg/kg (134 non-squamous)
Tropion-PanTumor01 (TP01) DS1062-A-J101 Completed (NSCLC and BC)	NSCLC: 30 Jul 2021 BC: 22 Jul 2022	Phase 1, two-part, multicenter, open-label, multiple-dose, first-in-human study of DS1062a in subjects with advanced solid tumors (See Module 5.3.3.2 Study TP01 NSCLC CSR and Module 5.3.3.2 Study TP01 Breast Cancer CSR)	**NSCLC**: 4 Dato-DXd 0.27 mg/kg (4 non-squamous) 5 Dato-DXd 0.5 mg/kg (4 non-squamous) 7 Dato-DXd 1 mg/kg (6 non-squamous) 6 Dato-DXd 2 mg/kg (4 non-squamous) 50 Dato-DXd 4 mg/kg (41 non-squamous) 50 Dato-DXd 6 mg/kg (45 non-squamous) 80 Dato-DXd 8 mg/kg (70 non-squamous) 8 Dato-DXd 10 mg/kg (6 non-squamous) **BC**: 83 Dato-DXd 6 mg/kg (42 TNBC, 41 hormone receptor-positive/ human epidermal growth factor receptor 2 negative) 2 Dato-DXd 8 mg/kg (both TNBC)

The pooling strategy of presenting all NSCLC patients receiving at least one dose of the recommended dose (6 mg/kg every 21 days) as the primary safety pool is agreed (n=484). This is the safety pool presented in the SmPC consisting of 297 patients from the randomised study TL01, 137 patients from the SAT TL05, and 50 patients from the SAT TP01.

As this pool includes both non-squamous (which are the patients included in the indication; n=411) and squamous NSCLC (n=73), any differences between these two pools will be evaluated, although no major differences are expected. Furthermore, given that study TL01 is randomised, emphasis will also be made on the differences between the two arms in this study, which include 297 patients (of which 232 had non-squamous NCSLC) in the Dato-DXd arm and 290 patients (of which 221 had non-squamous NCSLC) in the docetaxel arm.

The safety assessments were generally comparable between studies TL01, TL05 and TP01.

Table 123 Summary of Pooled Datasets

Pooled Dataset	Referred to As	Description
NSCLC (6 mg/kg)	NSCLC 6 mg/kg Pool	Subjects with previously treated advanced or metastatic NSCLC who received at least 1 dose of Dato-DXd 6 mg/kg (N = 484) TL01 Dato-DXd arm (n = 297) TL05 (n = 137) TP01 NSCLC cohort (n = 50)
NSCLC Non-squamous (6 mg/kg)	NSCLC Non-squamous 6 mg/kg Pool	Subjects in the NSCLC 6 mg/kg Pool who had histology of non-squamous NSCLC (N = 411) TL01 Dato-DXd arm (n = 232) TL05 (n = 134) TP01 NSCLC cohort (n = 45)
NSCLC + BC (4.0, 6.0, 8.0 and 10.0 mg/kg)	NSCLC + BC ≥4 mg/kg Pool	All subjects who received at least 1 dose of Dato-DXd ≥4 mg/kg (N = 707) TP01 4 mg/kg: NSCLC cohort (n = 50) TP01 6 mg/kg: NSCLC cohort (n = 50) TNBC cohort (n = 42) Hormone receptor-positive BC cohort (n = 41) TP01 8 mg/kg: TNBC cohort (n = 2) TP01 8 mg/kg: NSCLC cohort (n = 80) TP01 10 mg/kg: NSCLC cohort (n = 8) TL05 6 mg/kg (n = 137) TL01 Dato-DXd arm 6 mg/kg (n = 297)

3.3.7.1. Patient exposure

Demographic and baseline characteristics have been provided for the efficacy pool for study TL01 (see the efficacy section). Generally, they were similar between the Dato-DXd and docetaxel arms of Study TL01 and the primary safety pool.

Patients with squamous NSCLC, which are not included in the indication, constitute 22% of the population in the Dato-DXd arm of study TL01. These patients had two months shorter exposure compared to non-squamous NSCLC.

Pooled data= primary safety population:

Table 124 Summary of Demographics Among Subjects Who Received Dato-DXd Across Studies and Pools (Safety Analysis Set)

	Study		Pool		
	TL01 NSCLC 6 mg/kg (N = 297)	**TL01 NSCLC Non-squamous 6 mg/kg (N = 232)**	**NSCLC 6 mg/kg (N = 484)**	**NSCLC Non-squamous 6 mg/kg (N = 411)**	**NSCLC + BC ≥4 mg/kg (N = 707)**
Age (years) [a]					
Mean	62.7	62.2	61.6	61.2	60.7

Table 124 Summary of Demographics Among Subjects Who Received Dato-DXd Across Studies and Pools (Safety Analysis Set)

	Study		Pool		
	TL01 NSCLC 6 mg/kg (N = 297)	**TL01 NSCLC Non-squamous 6 mg/kg (N = 232)**	**NSCLC 6 mg/kg (N = 484)**	**NSCLC Non-squamous 6 mg/kg (N = 411)**	**NSCLC + BC ≥4 mg/kg (N = 707)**
Std Dev	9.12	9.32	9.89	10.10	10.59
Median	63.0	63.0	63.0	62.0	62.0
Minimum, maximum	26, 84	26, 81	26, 84	26, 81	26, 84
Age group (years), n (%) [a]					
<65	162 (54.5)	126 (54.3)	283 (58.5)	242 (58.9)	436 (61.7)
≥65	135 (45.5)	106 (45.7)	201 (41.5)	169 (41.1)	271 (38.3)
<75	276 (92.9)	218 (94.0)	444 (91.7)	379 (92.2)	647 (91.5)
≥75 years	21 (7.1)	14 (6.0)	40 (8.3)	32 (7.8)	60 (8.5)
Sex, n (%)					
Male	182 (61.3)	133 (57.3)	264 (54.5)	210 (51.1)	338 (47.8)
Female	115 (38.7)	99 (42.7)	220 (45.5)	201 (48.9)	369 (52.2)
Race					
White	123 (41.4)	96 (41.4)	191 (39.5)	160 (38.9)	322 (45.5)
Asian	119 (40.1)	92 (39.7)	214 (44.2)	184 (44.8)	286 (40.5)
Black/African American	6 (2.0)	4 (1.7)	9 (1.9)	7 (1.7)	16 (2.3)
Other	42 (14.1)	35 (15.1)	62 (12.8)	54 (13.1)	75 (10.6)
Missing	7 (2.4)	5 (2.2)	8 (1.7)	6 (1.5)	8 (1.1)
Region of enrollment					
Japan	52 (17.5)	43 (18.5)	96 (19.8)	87 (21.2)	155 (21.9)
USA	33 (11.1)	24 (10.3)	110 (22.7)	95 (23.1)	274 (38.8)
Western Europe	127 (42.8)	100 (43.1)	159 (32.9)	131 (31.9)	159 (22.5)
Rest of World	85 (28.6)	65 (28.0)	119 (24.6)	98 (23.8)	119 (16.8)
Ethnicity					
Hispanic or Latino	10 (3.4)	8 (3.4)	17 (3.5)	15 (3.6)	35 (5.0)
Not Hispanic or Latino	250 (84.2)	195 (84.1)	414 (85.5)	352 (85.6)	616 (87.1)
Unknown	30 (10.1)	23 (9.9)	45 (9.3)	37 (9.0)	45 (6.4)

Table 124 Summary of Demographics Among Subjects Who Received Dato-DXd Across Studies and Pools (Safety Analysis Set)

	Study		Pool		
	TL01 NSCLC 6 mg/kg (N = 297)	**TL01 NSCLC Non-squamous 6 mg/kg (N = 232)**	**NSCLC 6 mg/kg (N = 484)**	**NSCLC Non-squamous 6 mg/kg (N = 411)**	**NSCLC + BC ≥4 mg/kg (N = 707)**
Missing	7 (2.4)	6 (2.6)	8 (1.7)	7 (1.7)	11 (1.6)

[a] Age in years is calculated using the informed consent date and the birth date.
The baseline value is defined as the last non-missing value prior to the first dose of study drug.
Percentages are based on the number of subjects in the Safety Analysis Set.
Source: Module 5.3.5.3 ISS Table 1.2.1

Table 125: Summary of Baseline Characteristics Across Studies and Pools (Safety Analysis Set)

	Study		Pool		
	TL01 NSCLC 6 mg/kg (N =297)	**TL01 NSCLC Non-squamous 6 mg/kg (N =232)**	**NSCLC 6 mg/kg (N =484)**	**NSCLC Non-squamous 6 mg/kg (N =411)**	**NSCLC + BC ≥4 mg/kg (N =707)**
Weight (kg)					
Mean	67.91	67.56	67.39	67.08	68.32
Std Dev	14.181	13.993	14.977	14.843	16.347
Median	66.00	65.30	65.00	64.90	65.80
Minimum, maximum	37.0, 127.0	37.0, 114.0	37.0, 127.0	37.0, 118.5	37.0, 155.9
Body mass index (kg/m^2) [a]					
Mean	24.27	24.24	24.26	24.25	24.74
Std Dev	4.249	4.175	4.463	4.438	4.942
Median	23.82	23.70	23.72	23.69	24.07
Minimum, maximum	15.3, 40.1	16.0, 39.4	15.3, 44.5	15.3, 44.5	11.6, 46.6
Baseline ECOG performance status, n (%)					
0	88 (29.6)	73 (31.5)	145 (30.0)	128 (31.1)	223 (31.5)
1	208 (70.0)	158 (68.1)	338 (69.8)	282 (68.6)	483 (68.3)
2	1 (0.3)	1 (0.4)	1 (0.2)	1 (0.2)	1 (0.1)
Smoking status, n (%)					
Never	61 (20.5)	57 (24.6)	154 (31.8)	145 (35.3)	255 (36.1)
Former	198 (66.7)	152 (65.5)	292 (60.3)	243 (59.1)	406 (57.4)
Current	38 (12.8)	23 (9.9)	38 (7.9)	23 (5.6)	46 (6.5)

Table 125: Summary of Baseline Characteristics Across Studies and Pools (Safety Analysis Set)

	Study		Pool		
	TL01 NSCLC 6 mg/kg (N =297)	**TL01 NSCLC Non-squamous 6 mg/kg (N =232)**	**NSCLC 6 mg/kg (N =484)**	**NSCLC Non-squamous 6 mg/kg (N =411)**	**NSCLC + BC ≥4 mg/kg (N =707)**
Renal function at baseline, n (%) [b]					
Normal function	105 (35.4)	81 (34.9)	176 (36.4)	149 (36.3)	285 (40.3)
Mild impairment	139 (46.8)	109 (47.0)	214 (44.2)	180 (43.8)	287 (40.6)
Moderate impairment	52 (17.5)	41 (17.7)	93 (19.2)	81 (19.7)	133 (18.8)
Severe impairment	1 (0.3)	1 (0.4)	1 (0.2)	1 (0.2)	2 (0.3)
Hepatic function at baseline, n (%) [c]					
Normal function	246 (82.8)	191 (82.3)	406 (83.9)	343 (83.5)	580 (82.0)
Mild impairment	51 (17.2)	41 (17.7)	78 (16.1)	68 (16.5)	126 (17.8)
Moderate impairment	0	0	0	0	1 (0.1)
Presence of brain metastases at baseline, n (%)					
Brain metastases	50 (16.8)	43 (18.5)	96 (19.8)	89 (21.7)	140 (19.8)
No brain metastases	247 (83.2)	189 (81.5)	388 (80.2)	322 (78.3)	567 (80.2)
Actionable genomic alteration at baseline, n (%)					
Present	50 (16.8)	48 (207)	197 (40.7)	192 (46.7)	221 (31.3)
Absent	247 (83.2)	184 (79.3)	287 (59.3)	219 (53.3)	486 (68.7)

[a] Body mass index = weight (kg)/height (m^2)
[b] Normal renal function = CrCl ≥90 mL/min; mild renal impairment = CrCl ≥60 and <90 mL/min; moderate renal impairment = CrCl ≥30 and <60 mL/min; severe renal impairment = CrCl ≥15 and <30 mL/min
[c] Normal hepatic function = TBL ≤ULN and AST ≤ULN; mild hepatic impairment = (TBL >ULN and ≤1.5 × ULN and any AST) or (TBL ≤ULN and AST >ULN; moderate hepatic impairment = TBL >1.5 × ULN and ≤3.0 × ULN and any AST. (For criteria for subjects with Gilbert syndrome, see Module 5.3.5.3 ISS SAP v1.0 Section 3.11.)
The baseline value is defined as the last non-missing value prior to the first dose of study drug.
Percentages are based on the number of subjects in the Safety Analysis Set.
Source: Module 5.3.5.3 ISS Table 1.2.1

Exposure:

Randomised phase 3 study TL01:

In addition to the CSR for TL01, where the DCO is 29.03.23, and the SCS, in which these data are presented, the applicant provided a document with updated safety data (+6.5 months; DCO 13.10.2023) during the first round: No further patients were included, and the median exposure for both arms are the same.

Notably, at the latter DCO the number of patients receiving Dato-DXd for >12 months had increased from 25 (8.4%) to 43 (14.5%).

An updated ISS was provided in the second round, and exposure for patients treated with Dato-DXd in the safety pool and sub-pools are presented in Table 1.3.1 (below) from this update.

Table 126 Safety Update Study Drug Exposure and Treatment Compliance by Histology Safety Analysis Set

	TL01 All Subjects Dato-DXd		TL01 All Subjects Docetaxel	
	BLA (N = 297)	120 DSU (N = 297)	BLA (N = 290)	120 DSU (N = 290)
Treatment Duration (Months) [1]				
n	297	297	290	290
Mean	5.4	6.1	3.8	4.0
Standard Deviation	4.16	5.22	3.23	3.82
Minimum	0.7	0.7	0.7	0.7
Median	4.2	4.2	2.8	2.8
Maximum	18.3	22.3	18.9	21.6
Treatment Duration Category, n (%)				
>0 to ≤ 3 Months	118 (39.7)	118 (39.7)	168 (57.9)	168 (57.9)
>3 to ≤ 6 Months	73 (24.6)	66 (22.2)	66 (22.8)	65 (22.4)
>6 to ≤ 9 Months	47 (15.8)	45 (15.2)	34 (11.7)	29 (10.0)
>9 to ≤ 12 Months	34 (11.4)	25 (8.4)	13 (4.5)	16 (5.5)
>12 Months	25 (8.4)	43 (14.5)	9 (3.1)	12 (4.1)
Total Number of Cycles Initiated				
n	297	297	290	290
Mean	7.5	8.3	5.3	5.6
Standard Deviation	5.68	7.11	4.51	5.27
Minimum	1	1	1	1
Median	6.0	6.0	4.0	4.0
Maximum	25	32	27	31

Histology subgroup is derived using data collected from CRF.
Percentages are based on the number of subjects in the Safety Analysis Set.
[1] Treatment duration (months) = (date of last dose – first dose date + 21)/30.4375.
[2] Total Dose Taken for Dato-DXd (mg/kg) = Total dose administered (mg) / weight (kg). Total Dose Taken for Docetaxel (mg/m2) = Total dose administered (mg) / body surface area (m2)
[3] Dose intensity for Dato-DXd (mg/kg/cycle) = Total amount of doses taken (mg/kg) / (Treatment duration (days)/ 21). Dose intensity for Docetaxel (mg/m2/cycle) = Total amount of doses taken (mg/m2) / (Treatment duration (days)/21).
[4] Relative dose intensity for Dato-DXd (%) = 100 x Dose intensity (mg/kg/cycle) / Planned dose intensity (mg/kg/cycle), where planned dose intensity is 6.0 mg/kg/cycle for all subjects in receiving Dato-DXd. Relative dose intensity for Docetaxel (%) = 100 x Dose intensity (mg/m2/cycle) / Planned dose intensity (mg/m2/cycle), where planned dose intensity is 75 mg/m2/cycle for all subjects receiving Docetaxel.
[5] Infusion interruption is determined by CRF collection of "Was infusion interrupted during this administration?". If there were multiple interruptions at the same dosing visit, it was counted as 1 interruption.
[6] Dose reduction is determined by CRF collection of "Was dose reduced from previous cycle?".
[7] Dose delay is determined by CRF collection of "Was dose delayed from previous cycle?".
DCO: 2023-10-13
Source: adam.adex

DCO 13.10.23.

Source: Safety-update-TL01

Primary safety population=Pooled data:

Exposure was similar between the Dato-DXd arm of Study TL01 and the NSCLC 6 mg/kg Pool (Primary safety population), with a median treatment duration of 4.2 months in both groups and between the NSCLC 6 mg/kg Pool compared with the NSCLC Non-squamous 6 mg/kg Pool (median treatment duration of 4.8 months).

Table 127 Study Drug Exposure and Treatment Compliance Safety Analysis Set

	Study		Pool		
	TL01 NSCLC 6.0 mg/kg (N=297) n(%)	TL01 NSCLC Non-Squamous 6.0 mg/kg (N=232) n(%)	NSCLC 6.0 mg/kg (N=484) n(%)	NSCLC Non-Squamous 6.0 mg/kg (N=411) n(%)	NSCLC+BC ≥ 4.0 mg/kg (N=707) n(%)
Treatment Duration (Months) [a]					
n	297	232	484	411	707
Mean	6.1	6.6	6.2	6.5	6.1
Standard Deviation	5.22	5.25	5.39	5.40	5.40
Median	4.2	4.9	4.2	4.8	4.2
Minimum	0.7	0.7	0.7	0.7	0.7
Maximum	22.3	22.3	29.9	29.9	29.9
Total Doses Taken (mg/kg) [b]					
n	297	232	484	411	707
Mean	46.23	49.83	47.02	48.99	45.99
Standard Deviation	39.516	39.592	40.462	40.253	39.345
Median	34.63	36.22	35.34	36.00	34.63
Minimum	3.7	3.7	3.7	3.7	3.7
Maximum	180.1	174.7	216.0	216.0	216.0
Dose Intensity (mg/kg/cycle) [c]					
n	297	232	484	411	707
Mean	5.47	5.43	5.49	5.47	5.57
Standard Deviation	0.806	0.811	0.791	0.791	1.133
Median	5.83	5.79	5.85	5.83	5.86
Minimum	2.6	2.6	2.6	2.6	2.3
Maximum	6.5	6.5	6.5	6.5	10.3
Relative Dose Intensity (%) [d]					
n	297	232	484	411	707
Mean	91.16	90.47	91.47	91.19	91.06
Standard Deviation	13.438	13.516	13.179	13.187	13.688
Median	97.19	96.47	97.58	97.15	97.55
Minimum	43.1	43.1	43.1	43.1	37.9
Maximum	107.8	107.8	107.8	107.8	107.8
Total Number of Cycles Initiated					
n	297	232	484	411	707
Mean	8.3	9.0	8.5	8.9	8.3
Standard Deviation	7.11	7.18	7.32	7.34	7.26
Median	6.0	7.0	6.0	7.0	6.0
Minimum	1	1	1	1	1
Maximum	32	30	36	36	40
Treatment Duration Category, n (%)					
>0 to ≤ 3 Months	118 (39.7)	79 (34.1)	199 (41.1)	157 (38.2)	292 (41.3)
>3 to ≤ 6 Months	66 (22.2)	55 (23.7)	97 (20.0)	84 (20.4)	147 (20.8)
>6 to ≤ 9 Months	45 (15.2)	38 (16.4)	68 (14.0)	60 (14.6)	104 (14.7)
>9 to ≤ 12 Months	25 (8.4)	21 (9.1)	44 (9.1)	40 (9.7)	59 (8.3)
>12 Months	43 (14.5)	39 (16.8)	76 (15.7)	70 (17.0)	105 (14.9)
Relative Dose Intensity, by Category, n (%)					

Percentages are based on the number of subjects in the Safety Analysis Set.
[a] Treatment duration (months) = (date of last dose - first dose date + 21)/30.4375.
[b] Total Dose Taken for Dato-DXd (mg/kg) = Total dose administered (mg) / weight (kg).
[c] Dose intensity for Dato-DXd (mg/kg/cycle) = Total amount of doses taken (mg/kg) / (Treatment duration (days)/ 21).
[d] Relative dose intensity for Dato-DXd (%) = 100 x Dose intensity (mg/kg/cycle) / Planned dose intensity (mg/kg/cycle), where planned dose intensity is the protocol assigned dose level for a subject.
Source: adam.adex;

Source: Updated ISS.

3.3.7.2. Adverse events

To increase the accuracy of the estimate of incidence of TEAEs, MedDRA PTs for analogous terms were combined into grouped terms as shown in Table 1.3. This is agreed.

Table 128 MedDRA (Version 26.0) Preferred Terms Combined into Grouped Terms

Grouped Term	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

Table 128 MedDRA (Version 26.0) Preferred Terms Combined into Grouped Terms

Grouped Term	MedDRA Preferred Terms	
COVID-19	Asymptomatic COVID-19 Breakthrough COVID-19 Congenital COVID-19 Coronavirus infection Coronavirus pneumonia Coronavirus test positive COVID-19 COVID-19 pneumonia COVID-19 treatment Multisystem inflammatory syndrome Multisystem inflammatory syndrome in adults Multisystem inflammatory syndrome in children	Post-acute COVID-19 syndrome SARS-CoV-2 antibody test positive SARS-CoV-2 carrier SARS-CoV-2 RNA decreased SARS-CoV-2 RNA fluctuation SARS-CoV-2 RNA increased SARS-CoV-2 sepsis SARS-CoV-2 test false negative SARS-CoV-2 test positive SARS-CoV-2 viraemia Suspected COVID-19 Vaccine derived SARS-CoV-2 infection
Hypokalemia	Blood potassium decreased	Hypokalaemia
Fatigue	Asthenia Fatigue	Lethargy Malaise
Headache	Headache Migraine	Sinus headache
Hepatic function abnormal	Alanine aminotransferase increased Aspartate aminotransferase increased Gamma-glutamyltransferase increased	Hepatic function abnormal Liver function test abnormal Transaminases increased
Hyperbilirubinaemia	Bilirubin conjugated increased Blood bilirubin increased Hyperbilirubinaemia	Blood bilirubin unconjugated increased
Keratitis	Keratitis Punctate keratitis	Ulcerative keratitis
Leukopenia	Leukopenia	White blood cell count decreased
Lymphopenia	Lymphopenia	Lymphocyte count decreased
Musculoskeletal pain	Back pain Bone pain Limb discomfort Musculoskeletal chest pain Musculoskeletal discomfort	Musculoskeletal pain Muscle spasms Myalgia Neck pain Pain in extremity
Neutropenia	Neutropenia	Neutrophil count decreased
Rash	Rash Rash popular Rash macular	Rash maculo-papular Rash pruritic Rash pustular
Skin hyperpigmentation	Pigmentation disorder Skin discolouration	Skin hyperpigmentation
Thrombocytopenia	Platelet count decreased	Thrombocytopenia
Upper respiratory tract infection	Influenza Influenza like illness	Rhinitis Sinusitis Upper respiratory tract infection

Table 128 MedDRA (Version 26.0) Preferred Terms Combined into Grouped Terms

Grouped Term	MedDRA Preferred Terms	
	Nasopharyngitis Pharyngitis	

Overview of adverse events

Phase 3 study TL01:

Despite the shorter median duration of treatment with docetaxel (2.8 months vs. 4.2 months in the Dato DXd arm), there was a higher incidence of Grade ≥3 AEs, SAEs, and discontinuations due to AEs in the docetaxel arm compared to the Dato-DXd arm.

With the updated data (DCO 13.10.23) the SAEs increased by 1% point in both arms.

There was a higher incidence of AEs associated with an outcome of death in the Dato-DXd arm; this will be discussed in the relevant section. With the updated safety data (+6.5 months) no new adverse events with an outcome of death were seen in the Dato-DXd arm (16) and 1 in the docetaxel arm (11).

When looking at histology there were relatively more deaths in the squamous population despite the shorter median duration of exposure.

Table 129 Overview of Treatment-emergent Adverse Events in Study TL01 (Safety Analysis Set)

	Number (%) of Subjects			
	Overall		Non-squamous Histology	
	Dato-DXd (N = 297)	Docetaxel (N = 290)	Dato-DXd (N = 232)	Docetaxel (N = 221)
Subjects with any TEAE	289 (97.3)	284 (97.9)	228 (98.3)	217 (98.2)
TEAEs with worst CTCAE Grade ≥3	132 (44.4)	168 (57.9)	95 (40.9)	123 (55.7)
SAEs	88 (29.6)	106 (36.6)	62 (26.7)	75 (33.9)
TEAEs associated with dose reduction	65 (21.9)	90 (31.0)	52 (22.4)	69 (31.2)
TEAEs associated with infusion interruption	7 (2.4)	15 (5.2)	6 (2.6)	13 (5.9)
TEAEs associated with dose delay	104 (35.0)	68 (23.4)	81 (34.9)	51 (23.1)
TEAEs associated with discontinuation of study drug	35 (11.8)	48 (16.6)	29 (12.5)	36 (16.3)
TEAEs associated with an outcome of death	16 (5.4)	10 (3.4)	8 (3.4)	5 (2.3)
Subjects with any drug-related TEAE	257 (86.5)	252 (86.9)	205 (88.4)	195 (88.2)
Drug-related TEAEs with worst CTCAE Grade ≥3	73 (24.6)	120 (41.4)	51 (22.0)	90 (40.7)
Drug-related SAEs	30 (10.1)	36 (12.4)	19 (8.2)	25 (11.3)

Table 129 Overview of Treatment-emergent Adverse Events in Study TL01 (Safety Analysis Set)

	Number (%) of Subjects			
	Overall		Non-squamous Histology	
	Dato-DXd (N = 297)	Docetaxel (N = 290)	Dato-DXd (N = 232)	Docetaxel (N = 221)
Drug-related TEAEs associated with dose reduction	58 (19.5)	85 (29.3)	49 (21.1)	66 (29.9)
Drug-related TEAEs associated with infusion interruption	5 (1.7)	12 (4.1)	4 (1.7)	10 (4.5)
Drug-related TEAEs associated with dose delay	49 (16.5)	31 (10.7)	38 (16.4)	24 (10.9)
Drug-related TEAEs associated with discontinuation of study drug	23 (7.7)	34 (11.7)	20 (8.6)	27 (12.2)
Drug-related TEAEs associated with an outcome of death	3 (1.0)	2 (0.7)	1 (0.4)	2 (0.9)

Percentages are based on the number of subjects in the Safety Analysis Set.
If relationship is missing, the AE is considered to be related to the study drug.
Source: Module 5.3.5.1 Study TL01 CSR Post Hoc Table 14.10.2.2

Source: SCS

Pooled results:

The overall AE profile was similar between the Dato-DXd arm of Study TL01 and the NSCLC 6 mg/kg Pool (primary safety pool), and between this pool and the NSCLC Non-squamous 6 mg/kg Pool.

Table 130 Overview of Treatment-emergent Adverse Events Among Subjects Who Received Dato-DXd Across Pools (Safety Analysis Set)

	Number (%) of Subjects Who Received Dato-DXd					
	NSCLC 6 mg/kg (N = 484)		NSCLC Non-squamous 6 mg/kg (N = 411)		NSCLC + BC ≥4 mg/kg (N = 707)	
	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU
Subjects with any TEAE	475 (98.1)	477 (98.6)	406 (98.8)	407 (99.0)	697 (98.6)	699 (98.9)
TEAEs with worst CTCAE Grade ≥3	224 (46.3)	227 (46.9)	183 (44.5)	186 (45.3)	330 (46.7)	333 (47.1)
SAEs	146 (30.2)	149 (30.8)	117 (28.5)	120 (29.2)	212 (30.0)	215 (30.4)
TEAEs associated with discontinuation of study drug	55 (11.4)	57 (11.8)	48 (11.7)	48 (11.7)	89 (12.6)	91 (12.9)
TEAEs associated with dose reduction	100 (20.7)	101 (20.9)	85 (20.7)	86 (20.9)	140 (19.8)	141 (19.9)
TEAEs associated with infusion interruption [a]	NA	NA	NA	NA	NA	NA
TEAEs associated with dose delay [a]	NA	NA	NA	NA	NA	NA
TEAEs associated with an outcome of death	23 (4.8)	23 (4.8)	14 (3.4)	14 (3.4)	35 (5.0)	35 (5.0)
Subjects with any drug-related TEAE	427 (88.2)	430 (88.8)	368 (89.5)	370 (90.0)	644 (91.1)	647 (91.5)
Drug-related TEAEs with worst CTCAE Grade ≥3	125 (25.8)	128 (26.4)	101 (24.6)	103 (25.1)	183 (25.9)	186 (26.3)
Drug-related SAEs	48 (9.9)	50 (10.3)	37 (9.0)	38 (9.2)	71 (10.0)	73 (10.3)
Drug-related TEAEs associated with discontinuation of study drug	34 (7.0)	35 (7.2)	31 (7.5)	31 (7.5)	60 (8.5)	61 (8.6)
Drug-related TEAEs associated with dose reduction	90 (18.6)	91 (18.8)	79 (19.2)	80 (19.5)	128 (18.1)	129 (18.2)
Drug-related TEAEs associated with infusion interruption [a]	NA	NA	NA	NA	NA	NA
Drug-related TEAEs associated with dose delay [a]	NA	NA	NA	NA	NA	NA
Drug-related TEAEs associated with an outcome of death	4 (0.8)	4 (0.8)	2 (0.5)	2 (0.5)	7 (1.0)	7 (1.0)

[a] Information on infusion interruption and dose delay as an outcome of the TEAE was collected separately in Study TL01 and in Study TL05, whereas Study TP01 collected this information as "study drug interruption" (ie, did not differentiate between infusion interruption and dose delay). Therefore, the pools do not include information on infusion interruption or dose delay.

Percentages are based on the number of subjects in the Safety Analysis Set.
Subjects may have more than 1 event per PT.
At each level of subject summarization, subjects are counted once if they reported at least 1 AE.
Subjects are counted once at the maximum severity if they reported at least 1 AE.
If relationship is missing, the AE is considered to be related to the study drug.
Source: 120-DSU Table 3.1.1.1

Common adverse events

Phase 3 study TL01:

The incidence of the gastrointestinal PTs stomatitis, nausea, and vomiting were higher in the Dato-DXd arm compared with the docetaxel arm.

For the docetaxel arm the PTs haematological cytopenias, febrile neutropenia, diarrhea, oedema peripheral, and neuropathy were observed with a higher frequency compared to the Dato-DXd arm.

The applicant states that "*No grouped terms had a notably higher incidence in the Dato DXd arm than in the docetaxel arm (Table 2.20). The incidence of the following grouped terms was notably higher in the docetaxel arm than in the Dato DXd arm: musculoskeletal pain (overall), neutropenia (overall and Grade ≥3), and leukopenia (overall and Grade ≥3).*" Of note, this does not include AESIs of which pneumonitis/ILD was >3 times frequent in the Dato-DXd arm; this is discussed in the relevant section. Despite the higher frequencies of *Neutropenia, Febrile neutropenia* and *Neutrophils decreased* in the

docetaxel arm, this did not lead to higher overall infection frequencies (by SOC) or for the PT Pneumonia (Table 14.3.1.2, CSR TL01), although SAEs in the SOC "Infections and Infestations" were twice as high in the docetaxel arm compared to the Dato-DXd arm (see the SAE section).

Table 131 Treatment-emergent Adverse Events Reported in At Least 5% of Subjects in Either Treatment Arm in the Overall Population of Study TL01, by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of Subjects											
	Overall				Non-squamous Histology				Squamous Histology			
	Dato-DXd (N = 297)		Docetaxel (N = 290)		Dato-DXd (N = 232)		Docetaxel (N = 221)		Dato-DXd (N = 65)		Docetaxel (N = 69)	
	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU
Subjects with any TEAE	289 (97.3)	291 (98.0)	284 (97.9)	284 (97.9)	228 (98.3)	229 (98.7)	217 (98.2)	217 (98.2)	61 (93.8)	62 (95.4)	67 (97.1)	67 (97.1)
Stomatitis	146 (49.2)	148 (49.8)	47 (16.2)	47 (16.2)	119 (51.3)	120 (51.7)	37 (16.7)	37 (16.7)	27 (41.5)	28 (43.1)	10 (14.5)	10 (14.5)
Nausea	110 (37.0)	112 (37.7)	55 (19.0)	55 (19.0)	92 (39.7)	94 (40.5)	52 (23.5)	52 (23.5)	18 (27.7)	18 (27.7)	3 (4.3)	3 (4.3)
Alopecia	95 (32.0)	95 (32.0)	101 (34.8)	101 (34.8)	83 (35.8)	83 (35.8)	82 (37.1)	82 (37.1)	12 (18.5)	12 (18.5)	19 (27.5)	19 (27.5)
Decreased appetite	86 (29.0)	86 (29.0)	61 (21.0)	63 (21.7)	66 (28.4)	66 (28.4)	45 (20.4)	47 (21.3)	20 (30.8)	20 (30.8)	16 (23.2)	16 (23.2)
Asthenia	69 (23.2)	70 (23.6)	69 (23.8)	69 (23.8)	58 (25.0)	59 (25.4)	53 (24.0)	53 (24.0)	11 (16.9)	11 (16.9)	16 (23.2)	16 (23.2)
Constipation	57 (19.2)	58 (19.5)	41 (14.1)	42 (14.5)	47 (20.3)	48 (20.7)	35 (15.8)	36 (16.3)	10 (15.4)	10 (15.4)	6 (8.7)	6 (8.7)
Dyspnoea	52 (17.5)	52 (17.5)	48 (16.6)	48 (16.6)	36 (15.5)	36 (15.5)	35 (15.8)	35 (15.8)	16 (24.6)	16 (24.6)	13 (18.8)	13 (18.8)
Anaemia	51 (17.2)	52 (17.5)	71 (24.5)	72 (24.8)	42 (18.1)	42 (18.1)	52 (23.5)	53 (24.0)	9 (13.8)	10 (15.4)	19 (27.5)	19 (27.5)
Fatigue	46 (15.5)	47 (15.8)	50 (17.2)	50 (17.2)	39 (16.8)	40 (17.2)	37 (16.7)	37 (16.7)	7 (10.8)	7 (10.8)	13 (18.8)	13 (18.8)
Vomiting	46 (15.5)	47 (15.8)	26 (9.0)	26 (9.0)	35 (15.1)	36 (15.5)	23 (10.4)	23 (10.4)	11 (16.9)	11 (16.9)	3 (4.3)	3 (4.3)
Cough	42 (14.1)	44 (14.8)	38 (13.1)	38 (13.1)	32 (13.8)	34 (14.7)	28 (12.7)	28 (12.7)	10 (15.4)	10 (15.4)	10 (14.5)	10 (14.5)
COVID-19	39 (13.1)	39 (13.1)	30 (10.3)	30 (10.3)	36 (15.5)	36 (15.5)	24 (10.9)	24 (10.9)	3 (4.6)	3 (4.6)	6 (8.7)	6 (8.7)
Rash	39 (13.1)	39 (13.1)	21 (7.2)	21 (7.2)	30 (12.9)	30 (12.9)	16 (7.2)	16 (7.2)	9 (13.8)	9 (13.8)	5 (7.2)	5 (7.2)
Diarrhoea	33 (11.1)	37 (12.5)	65 (22.4)	65 (22.4)	27 (11.6)	31 (13.4)	53 (24.0)	53 (24.0)	6 (9.2)	6 (9.2)	12 (17.4)	12 (17.4)
Pruritus	34 (11.4)	34 (11.4)	14 (4.8)	14 (4.8)	23 (9.9)	23 (9.9)	12 (5.4)	12 (5.4)	11 (16.9)	11 (16.9)	2 (2.9)	2 (2.9)
Pneumonia	30 (10.1)	32 (10.8)	30 (10.3)	31 (10.7)	21 (9.1)	22 (9.5)	17 (7.7)	17 (7.7)	9 (13.8)	10 (15.4)	13 (18.8)	14 (20.3)
Headache	26 (8.8)	28 (9.4)	11 (3.8)	14 (4.8)	24 (10.3)	26 (11.2)	8 (3.6)	11 (5.0)	2 (3.1)	2 (3.1)	3 (4.3)	3 (4.3)

MedDRA Preferred Term	Number (%) of Subjects											
	Overall				Non-squamous Histology				Squamous Histology			
	Dato-DXd (N = 297)		Docetaxel (N = 290)		Dato-DXd (N = 232)		Docetaxel (N = 221)		Dato-DXd (N = 65)		Docetaxel (N = 69)	
	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU
Arthralgia	25 (8.4)	27 (9.1)	32 (11.0)	34 (11.7)	20 (8.6)	22 (9.5)	28 (12.7)	30 (13.6)	5 (7.7)	5 (7.7)	4 (5.8)	4 (5.8)
Weight decreased	26 (8.8)	27 (9.1)	13 (4.5)	13 (4.5)	21 (9.1)	22 (9.5)	10 (4.5)	10 (4.5)	5 (7.7)	5 (7.7)	3 (4.3)	3 (4.3)
Lacrimation increased	20 (6.7)	23 (7.7)	17 (5.9)	17 (5.9)	18 (7.8)	21 (9.1)	17 (7.7)	17 (7.7)	2 (3.1)	2 (3.1)	0	0
Pyrexia	21 (7.1)	23 (7.7)	37 (12.8)	37 (12.8)	18 (7.8)	20 (8.6)	29 (13.1)	29 (13.1)	3 (4.6)	3 (4.6)	8 (11.6)	8 (11.6)
Malaise	22 (7.4)	22 (7.4)	29 (10.0)	30 (10.3)	18 (7.8)	18 (7.8)	23 (10.4)	24 (10.9)	4 (6.2)	4 (6.2)	6 (8.7)	6 (8.7)
Dry skin	21 (7.1)	21 (7.1)	9 (3.1)	9 (3.1)	20 (8.6)	20 (8.6)	6 (2.7)	6 (2.7)	1 (1.5)	1 (1.5)	3 (4.3)	3 (4.3)
Pneumonitis	19 (6.4)	20 (6.7)	10 (3.4)	10 (3.4)	15 (6.5)	15 (6.5)	7 (3.2)	7 (3.2)	4 (6.2)	5 (7.7)	3 (4.3)	3 (4.3)
Back pain	18 (6.1)	19 (6.4)	19 (6.6)	19 (6.6)	18 (7.8)	19 (8.2)	19 (8.6)	19 (8.6)	0	0	0	0
Dry eye	19 (6.4)	19 (6.4)	3 (1.0)	3 (1.0)	15 (6.5)	15 (6.5)	3 (1.4)	3 (1.4)	4 (6.2)	4 (6.2)	0	0
Chest pain	16 (5.4)	17 (5.7)	12 (4.1)	12 (4.1)	13 (5.6)	13 (5.6)	10 (4.5)	10 (4.5)	3 (4.6)	4 (6.2)	2 (2.9)	2 (2.9)
Dysgeusia	17 (5.7)	17 (5.7)	14 (4.8)	14 (4.8)	14 (6.0)	14 (6.0)	13 (5.9)	13 (5.9)	3 (4.6)	3 (4.6)	1 (1.4)	1 (1.4)
Hypo-albuminaemia	17 (5.7)	17 (5.7)	11 (3.8)	11 (3.8)	14 (6.0)	14 (6.0)	7 (3.2)	7 (3.2)	3 (4.6)	3 (4.6)	4 (5.8)	4 (5.8)
Blood creatinine increased	15 (5.1)	16 (5.4)	4 (1.4)	4 (1.4)	13 (5.6)	14 (6.0)	4 (1.8)	4 (1.8)	2 (3.1)	2 (3.1)	0	0
Dry mouth	16 (5.4)	16 (5.4)	7 (2.4)	8 (2.8)	11 (4.7)	11 (4.7)	7 (3.2)	8 (3.6)	5 (7.7)	5 (7.7)	0	0
Alanine amino-transferase increased	15 (5.1)	15 (5.1)	9 (3.1)	9 (3.1)	13 (5.6)	13 (5.6)	8 (3.6)	8 (3.6)	2 (3.1)	2 (3.1)	1 (1.4)	1 (1.4)

MedDRA Preferred Term	Number (%) of Subjects											
	Overall				Non-squamous Histology				Squamous Histology			
	Dato-DXd (N = 297)		Docetaxel (N = 290)		Dato-DXd (N = 232)		Docetaxel (N = 221)		Dato-DXd (N = 65)		Docetaxel (N = 69)	
	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU
Aspartate aminotransferase increased	14 (4.7)	15 (5.1)	8 (2.8)	8 (2.8)	13 (5.6)	14 (6.0)	8 (3.6)	8 (3.6)	1 (1.5)	1 (1.5)	0	0
Conjunctivitis	12 (4.0)	15 (5.1)	3 (1.0)	3 (1.0)	7 (3.0)	10 (4.3)	3 (1.4)	3 (1.4)	5 (7.7)	5 (7.7)	0	0
Oropharyngeal pain	14 (4.7)	15 (5.1)	4 (1.4)	4 (1.4)	12 (5.2)	13 (5.6)	4 (1.8)	4 (1.8)	2 (3.1)	2 (3.1)	0	0
Oedema peripheral	13 (4.4)	13 (4.4)	40 (13.8)	40 (13.8)	10 (4.3)	10 (4.3)	32 (14.5)	32 (14.5)	3 (4.6)	3 (4.6)	8 (11.6)	8 (11.6)
Haemoptysis	10 (3.4)	11 (3.7)	18 (6.2)	18 (6.2)	7 (3.0)	8 (3.4)	13 (5.9)	13 (5.9)	3 (4.6)	3 (4.6)	5 (7.2)	5 (7.2)
Neutrophil count decreased	8 (2.7)	9 (3.0)	41 (14.1)	41 (14.1)	7 (3.0)	8 (3.4)	33 (14.9)	33 (14.9)	1 (1.5)	1 (1.5)	8 (11.6)	8 (11.6)
Neutropenia	6 (2.0)	7 (2.4)	40 (13.8)	41 (14.1)	3 (1.3)	4 (1.7)	26 (11.8)	26 (11.8)	3 (4.6)	3 (4.6)	14 (20.3)	15 (21.7)
White blood cell count decreased	6 (2.0)	6 (2.0)	27 (9.3)	27 (9.3)	6 (2.6)	6 (2.6)	18 (8.1)	18 (8.1)	0	0	9 (13.0)	9 (13.0)
Leukopenia	5 (1.7)	5 (1.7)	20 (6.9)	20 (6.9)	4 (1.7)	4 (1.7)	15 (6.8)	15 (6.8)	1 (1.5)	1 (1.5)	5 (7.2)	5 (7.2)
Myalgia	5 (1.7)	5 (1.7)	24 (8.3)	24 (8.3)	4 (1.7)	4 (1.7)	19 (8.6)	19 (8.6)	1 (1.5)	1 (1.5)	5 (7.2)	5 (7.2)
Pain	5 (1.7)	5 (1.7)	15 (5.2)	15 (5.2)	5 (2.2)	5 (2.2)	13 (5.9)	13 (5.9)	0	0	2 (2.9)	2 (2.9)
Neuropathy peripheral	3 (1.0)	4 (1.3)	26 (9.0)	28 (9.7)	2 (0.9)	3 (1.3)	20 (9.0)	22 (10.0)	1 (1.5)	1 (1.5)	6 (8.7)	6 (8.7)
Paraesthesia	4 (1.3)	4 (1.3)	18 (6.2)	18 (6.2)	2 (0.9)	2 (0.9)	15 (6.8)	15 (6.8)	2 (3.1)	2 (3.1)	3 (4.3)	3 (4.3)
Peripheral sensory neuropathy	4 (1.3)	4 (1.3)	15 (5.2)	15 (5.2)	4 (1.7)	4 (1.7)	13 (5.9)	13 (5.9)	0	0	2 (2.9)	2 (2.9)
Febrile neutropenia	2 (0.7)	2 (0.7)	20 (6.9)	20 (6.9)	1 (0.4)	1 (0.4)	15 (6.8)	15 (6.8)	1 (1.5)	1 (1.5)	5 (7.2)	5 (7.2)

Percentages are calculated based on the number of subjects in the Safety Analysis Set.
TEAEs are sorted by decreasing frequency for the overall population in the Dato-DXd arm at the 120-DSU DCO.
If a subject had multiple occurrences of the same PT, the subject is counted once for that PT.
Source: 120-DSU Table 14.10.3.1

Table 132 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst NCI CTCAE Grade Safety Analysis Set

System Organ Class Preferred Term CTCAE Grade	Dato-DXd (N=297) n (%)	Docetaxel (N=290) n (%)
Infections and infestations		
Any Preferred Term	134 (45.1)	119 (41.0)
CTCAE Grade 1	43 (14.5)	35 (12.1)
CTCAE Grade 2	58 (19.5)	43 (14.8)
CTCAE Grade 3	26 (8.8)	31 (10.7)
CTCAE Grade 4	1 (0.3)	6 (2.1)
CTCAE Grade 5	6 (2.0)	4 (1.4)
CTCAE Grade ≥ 3	33 (11.1)	41 (14.1)
CTCAE Grade Missing	0	0
COVID-19	39 (13.1)	30 (10.3)
CTCAE Grade 1	25 (8.4)	13 (4.5)
CTCAE Grade 2	11 (3.7)	9 (3.1)
CTCAE Grade 3	2 (0.7)	6 (2.1)
CTCAE Grade 4	0	0
CTCAE Grade 5	1 (0.3)	1 (0.3)
CTCAE Grade ≥ 3	3 (1.0)	7 (2.4)
CTCAE Grade Missing	0	1 (0.3)

Infections and infestations (continued)		
Pneumonia	30 (10.1)	30 (10.3)
CTCAE Grade 1	5 (1.7)	1 (0.3)
CTCAE Grade 2	9 (3.0)	8 (2.8)
CTCAE Grade 3	14 (4.7)	16 (5.5)
CTCAE Grade 4	0	4 (1.4)
CTCAE Grade 5	2 (0.7)	1 (0.3)
CTCAE Grade ≥ 3	16 (5.4)	21 (7.2)
CTCAE Grade Missing	0	0

Source: CSR TL01

Table 133 Treatment-emergent Adverse Events, by Grouped Term (Safety Analysis Set)

Grouped Term	Number (%) of Subjects			
	Dato-DXd (N = 297)		Docetaxel (N = 290)	
	Overall	Grade ≥3	Overall	Grade ≥3
Fatigue	131 (44.1)	16 (5.4)	145 (50.0)	15 (5.2)
Anemia	51 (17.2)	12 (4.0)	72 (24.8)	14 (4.8)
Rash	49 (16.5)	1 (0.3)	29 (10.0)	1 (0.3)
COVID-19	47 (15.8)	5 (1.7)	31 (10.7)	7 (2.4)
Musculoskeletal pain	44 (14.8)	1 (0.3)	72 (24.8)	6 (2.1)
Headache	26 (8.8)	0	11 (3.8)	0
Hepatic function abnormal	20 (6.7)	6 (2.0)	11 (3.8)	3 (1.0)
Abdominal pain	18 (6.1)	1 (0.3)	20 (6.9)	1 (0.3)
Upper respiratory tract infection	17 (5.7)	1 (0.3)	11 (3.8)	0
Keratitis	14 (4.7)	5 (1.7)	1 (0.3)	0
Neutropenia	14 (4.7)	3 (1.0)	79 (27.2)	69 (23.8)
Hypokalaemia	11 (3.7)	3 (1.0)	8 (2.8)	2 (0.7)
Leukopenia	11 (3.7)	1 (0.3)	46 (15.9)	39 (13.4)
Lymphopenia	11 (3.7)	1 (0.3)	11 (3.8)	7 (2.4)
Skin hyperpigmentation	10 (3.4)	0	4 (1.4)	0
Thrombocytopenia	5 (1.7)	0	8 (2.8)	1 (0.3)
Hyperbilirubinaemia	2 (0.7)	0	2 (0.7)	0

Percentages are calculated based on the number of subjects in the Safety Analysis Set.
Grouped terms are sorted by decreasing frequency in the Dato-DXd arm.
If a subject had multiple occurrences of the PTs within a grouped term, the subject is counted once for that grouped term.
MedDRA PTs included in each grouped term are listed in Table 1.3.
Source: Module 5.3.5.1 Study TL01 CSR Table 14.3.1.6.1

DCO: 29.03.2023

Pooled results:

The incidences of the various treatment-emergent adverse events by PT were similar between the Dato-DXd arm of Study TL01 and the NSCLC 6 mg/kg Pool (primary safety pool), and between this pool and the NSCLC Non-squamous 6 mg/kg Pool.

Table 134 Treatment-emergent Adverse Events Reported in At Least 5% of Subjects Who Received Dato-DXd in the NSCLC 6 mg/kg Pool, by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of Subjects Who Received Dato-DXd					
	NSCLC 6 mg/kg (N = 484)		NSCLC Non-squamous 6 mg/kg (N = 411)		NSCLC + BC ≥4 mg/kg (N = 707)	
	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU
Subjects with any TEAE	475 (98.1)	477 (98.6)	406 (98.8)	407 (99.0)	697 (98.6)	699 (98.9)
Stomatitis	256 (52.9)	258 (53.3)	226 (55.0)	227 (55.2)	391 (55.3)	393 (55.6)
Nausea	224 (46.3)	226 (46.7)	202 (49.1)	204 (49.6)	349 (49.4)	351 (49.6)
Alopecia	186 (38.4)	186 (38.4)	170 (41.4)	170 (41.4)	272 (38.5)	272 (38.5)
Decreased appetite	136 (28.1)	136 (28.1)	114 (27.7)	114 (27.7)	185 (26.2)	185 (26.2)
Constipation	112 (23.1)	113 (23.3)	100 (24.3)	101 (24.6)	165 (23.3)	166 (23.5)
Fatigue	95 (19.6)	96 (19.8)	85 (20.7)	86 (20.9)	180 (25.5)	181 (25.6)
Asthenia	91 (18.8)	92 (19.0)	79 (19.2)	80 (19.5)	92 (13.0)	93 (13.2)
Vomiting	86 (17.8)	87 (18.0)	72 (17.5)	73 (17.8)	153 (21.6)	154 (21.8)
Anaemia	83 (17.1)	84 (17.4)	73 (17.8)	73 (17.8)	125 (17.7)	126 (17.8)
Dyspnoea	77 (15.9)	77 (15.9)	60 (14.6)	60 (14.6)	109 (15.4)	109 (15.4)
Cough	70 (14.5)	72 (14.9)	60 (14.6)	62 (15.1)	107 (15.1)	109 (15.4)
Rash	64 (13.2)	64 (13.2)	54 (13.1)	54 (13.1)	112 (15.8)	112 (15.8)
Diarrhoea	59 (12.2)	63 (13.0)	51 (12.4)	55 (13.4)	94 (13.3)	98 (13.9)
COVID-19	60 (12.4)	60 (12.4)	56 (13.6)	56 (13.6)	62 (8.8)	62 (8.8)
Pruritus	52 (10.7)	52 (10.7)	38 (9.2)	38 (9.2)	72 (10.2)	72 (10.2)
Headache	44 (9.1)	46 (9.5)	40 (9.7)	42 (10.2)	79 (11.2)	81 (11.5)
Weight decreased	45 (9.3)	46 (9.5)	39 (9.5)	40 (9.7)	67 (9.5)	68 (9.6)
Dry eye	42 (8.7)	42 (8.7)	38 (9.2)	38 (9.2)	93 (13.2)	93 (13.2)
Pneumonia	40 (8.3)	42 (8.7)	31 (7.5)	32 (7.8)	56 (7.9)	58 (8.2)
Pyrexia	37 (7.6)	39 (8.1)	33 (8.0)	35 (8.5)	66 (9.3)	68 (9.6)
Arthralgia	35 (7.2)	37 (7.6)	29 (7.1)	31 (7.5)	46 (6.5)	48 (6.8)
Malaise	36 (7.4)	36 (7.4)	32 (7.8)	32 (7.8)	51 (7.2)	51 (7.2)
Back pain	31 (6.4)	32 (6.6)	31 (7.5)	32 (7.8)	47 (6.6)	48 (6.8)
Dry skin	32 (6.6)	32 (6.6)	31 (7.5)	31 (7.5)	55 (7.8)	55 (7.8)
Pneumonitis	31 (6.4)	32 (6.6)	27 (6.6)	27 (6.6)	49 (6.9)	50 (7.1)
Dysgeusia	29 (6.0)	29 (6.0)	25 (6.1)	25 (6.1)	45 (6.4)	45 (6.4)
Blood creatinine increased	28 (5.8)	29 (6.0)	24 (5.8)	25 (6.1)	37 (5.2)	38 (5.4)
Hypoalbuminaemia	28 (5.8)	28 (5.8)	25 (6.1)	25 (6.1)	45 (6.4)	45 (6.4)
Oropharyngeal pain	26 (5.4)	27 (5.6)	22 (5.4)	23 (5.6)	46 (6.5)	47 (6.6)
Amylase increased	26 (5.4)	26 (5.4)	23 (5.6)	23 (5.6)	35 (5.0)	35 (5.0)
Aspartate aminotransferase increased	25 (5.2)	26 (5.4)	24 (5.8)	25 (6.1)	49 (6.9)	50 (7.1)
Alanine aminotransferase increased	25 (5.2)	25 (5.2)	23 (5.6)	23 (5.6)	45 (6.4)	45 (6.4)
Dizziness	25 (5.2)	25 (5.2)	22 (5.4)	22 (5.4)	48 (6.8)	48 (6.8)
Hypokalaemia	23 (4.8)	25 (5.2)	17 (4.1)	19 (4.6)	47 (6.6)	49 (6.9)
Lacrimation increased	22 (4.5)	25 (5.2)	20 (4.9)	23 (5.6)	38 (5.4)	41 (5.8)
Rash maculo-papular	25 (5.2)	25 (5.2)	23 (5.6)	23 (5.6)	41 (5.8)	41 (5.8)

Percentages are calculated based on the number of subjects in the Safety Analysis Set.
TEAEs are sorted by decreasing frequency in the NSCLC 6 mg/kg Pool at the 120-DSU DCO.
If a subject had multiple occurrences of the same PT, the subject is counted once for that PT.
Source: ISS Table 3.1.3.8, 120-DSU Table 3.1.3.8

Source: Updated ISS.

Table 135 Treatment-emergent Adverse Events Reported in At Least 5% of Subjects Who Received Dato-DXd in the NSCLC 6 mg/kg Pool, by Grouped Term (Safety Analysis Set)

Grouped Term	Number (%) of Subjects Who Received Dato-DXd					
	NSCLC 6 mg/kg (N = 484)		NSCLC Non-squamous 6 mg/kg (N = 411)		NSCLC + BC ≥4 mg/kg (N = 707)	
	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU
Fatigue	210 (43.4)	212 (43.8)	184 (44.8)	186 (45.3)	308 (43.6)	310 (43.8)
Rash	91 (18.8)	92 (19.0)	79 (19.2)	80 (19.5)	159 (22.5)	160 (22.6)
Anemia	84 (17.4)	85 (17.6)	74 (18.0)	74 (18.0)	126 (17.8)	127 (18.0)
Musculoskeletal pain	77 (15.9)	79 (16.3)	68 (16.5)	70 (17.0)	111 (15.7)	113 (16.0)
COVID-19	69 (14.3)	69 (14.3)	64 (15.6)	64 (15.6)	71 (10.0)	71 (10.0)
Headache	45 (9.3)	47 (9.7)	41 (10.0)	43 (10.5)	80 (11.3)	82 (11.6)
Hepatic function abnormal	39 (8.1)	40 (8.3)	37 (9.0)	38 (9.2)	72 (10.2)	73 (10.3)
Abdominal pain	34 (7.0)	35 (7.2)	31 (7.5)	32 (7.8)	43 (6.1)	44 (6.2)
Upper respiratory tract infection	34 (7.0)	34 (7.0)	31 (7.5)	31 (7.5)	51 (7.2)	51 (7.2)
Neutropenia	28 (5.8)	30 (6.2)	23 (5.6)	25 (6.1)	49 (6.9)	51 (7.2)
Keratitis	25 (5.2)	26 (5.4)	25 (6.1)	25 (6.1)	40 (5.7)	41 (5.8)
Hypokalemia	23 (4.8)	25 (5.2)	17 (4.1)	19 (4.6)	47 (6.6)	49 (6.9)
Leukopenia	24 (5.0)	24 (5.0)	23 (5.6)	23 (5.6)	44 (6.2)	44 (6.2)

Percentages are calculated based on the number of subjects in the Safety Analysis Set.
Grouped terms are presented in decreasing frequency in the NSCLC 6 mg/kg Pool at the 120-DSU DCO.
If a subject had multiple occurrences of the PTs within a grouped term, the subject is counted once for that grouped term.
MedDRA PTs included in each grouped term are listed in Table 1.3.
Source: ISS Table 3.1.6.1, 120-DSU Table 3.1.6.1

Table 136: TEAEs by SOC Among Subjects Who Received Dato-DXd in Study TL01 and Across Pools (Safety Analysis Set) DCO: TL01 13 Oct 2023; TL05 14 Dec 2022; TP01 NSCLC 30 Jul 2021

MedDRA SOC	Number (%) of Subjects Who Received Dato-DXd				
	Study		Pool		
	TL01 NSCLC 6 mg/kg (N = 297)	TL01 NSCLC Non-squamous 6 mg/kg (N = 232)	NSCLC 6 mg/kg (N = 484)	NSCLC Non-squamous 6 mg/kg (N = 411)	NSCLC + BC ≥4 mg/kg (N = 707)
Any TEAE	291 (98.0)	229 (98.7)	477 (98.6)	407 (99.0)	699 (98.9)
Blood and lymphatic system disorders	64 (21.5)	49 (21.1)	102 (21.1)	86 (20.9)	151 (21.4)
Cardiac disorders	20 (6.7)	15 (6.5)	38 (7.9)	33 (8.0)	57 (8.1)
Congenital, familial and genetic disorders	1 (0.3)	1 (0.4)	1 (0.2)	1 (0.2)	2 (0.3)
Ear and labyrinth disorders	10 (3.4)	8 (3.4)	14 (2.9)	12 (2.9)	22 (3.1)
Endocrine disorders	6 (2.0)	4 (1.7)	8 (1.7)	6 (1.5)	9 (1.3)
Eye disorders	59 (19.9)	50 (21.6)	110 (22.7)	100 (24.3)	202 (28.6)
Gastrointestinal disorders	229 (77.1)	184 (79.3)	395 (81.6)	343 (83.5)	591 (83.6)

MedDRA SOC	Number (%) of Subjects Who Received Dato-DXd				
	Study		Pool		
	TL01 NSCLC 6 mg/kg (N = 297)	TL01 NSCLC Non-squamous 6 mg/kg (N = 232)	NSCLC 6 mg/kg (N = 484)	NSCLC Non-squamous 6 mg/kg (N = 411)	NSCLC + BC ≥4 mg/kg (N = 707)
General disorders and administration site conditions	163 (54.9)	138 (59.5)	266 (55.0)	237 (57.7)	409 (57.9)
Hepatobiliary disorders	4 (1.3)	4 (1.7)	11 (2.3)	11 (2.7)	13 (1.8)
Immune system disorders	3 (1.0)	2 (0.9)	8 (1.7)	6 (1.5)	10 (1.4)
Infections and infestations	138 (46.5)	113 (48.7)	210 (43.4)	181 (44.0)	309 (43.7)
Injury, poisoning and procedural complications	25 (8.4)	22 (9.5)	51 (10.5)	46 (11.2)	112 (15.8)
Investigations	95 (32.0)	78 (33.6)	179 (37.0)	157 (38.2)	297 (42.0)
Metabolism and nutrition disorders	126 (42.4)	97 (41.8)	208 (43.0)	176 (42.8)	312 (44.1)
Musculoskeletal and connective tissue disorders	72 (24.2)	58 (25.0)	119 (24.6)	101 (24.6)	171 (24.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.7)	2 (0.9)	12 (2.5)	12 (2.9)	21 (3.0)
Nervous system disorders	80 (26.9)	67 (28.9)	138 (28.5)	120 (29.2)	220 (31.1)
Product issues	3 (1.0)	3 (1.3)	3 (0.6)	3 (0.7)	4 (0.6)
Psychiatric disorders	33 (11.1)	24 (10.3)	51 (10.5)	41 (10.0)	75 (10.6)
Renal and urinary disorders	16 (5.4)	10 (4.3)	29 (6.0)	23 (5.6)	47 (6.6)
Reproductive system and breast disorders	9 (3.0)	7 (3.0)	16 (3.3)	14 (3.4)	25 (3.5)
Respiratory, thoracic and mediastinal disorders	143 (48.1)	108 (46.6)	232 (47.9)	192 (46.7)	334 (47.2)
Skin and subcutaneous tissue disorders	154 (51.9)	124 (53.4)	272 (56.2)	237 (57.7)	411 (58.1)
Surgical and medical procedures	1 (0.3)	0	1 (0.2)	0	1 (0.1)
Vascular disorders	19 (6.4)	12 (5.2)	38 (7.9)	30 (7.3)	64 (9.1)

BC = breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; SOC = system organ class; TEAE = treatment-emergent adverse event
Percentages are based on the number of subjects in the Safety Analysis Set.
Source: Module 5.3.5.3 ISS 120 DSU Table 3.1.2.1

Source: D120 response to Q120.

Grade ≥3 Treatment-emergent adverse events

Phase 3 study TL01:

Grade ≥3 neutropenia and neutrophil count decreased were reported in ≥10% of subjects in the docetaxel arm leading to febrile neutropenia in 6.6%. The most frequent Grade ≥3 PTs in the Dato-DXd arm was stomatitis and pneumonia of which the latter was slightly more frequent in the docetaxel arm.

Table 137 Treatment-emergent Adverse Events of At Least Grade 3 Reported in At Least 5% of Subjects in Either Treatment Arm of the Overall Population of Study TL01, by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of Subjects											
	Overall				Non-squamous Histology				Squamous Histology			
	Dato-DXd (N = 297)		Docetaxel (N = 290)		Dato-DXd (N = 232)		Docetaxel (N = 221)		Dato-DXd (N = 65)		Docetaxel (N = 69)	
	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU
Subjects with any CTCAE Grade ≥3 TEAE	132 (44.4)	135 (45.5)	168 (57.9)	171 (59.0)	95 (40.9)	98 (42.2)	123 (55.7)	125 (56.6)	37 (56.9)	37 (56.9)	45 (65.2)	46 (66.7)
Stomatitis	19 (6.4)	20 (6.7)	3 (1.0)	3 (1.0)	16 (6.9)	17 (7.3)	3 (1.4)	3 (1.4)	3 (4.6)	3 (4.6)	0	0
Pneumonia	16 (5.4)	17 (5.7)	21 (7.2)	21 (7.2)	9 (3.9)	10 (4.3)	12 (5.4)	12 (5.4)	7 (10.8)	7 (10.8)	9 (13.0)	9 (13.0)
Anaemia	12 (4.0)	13 (4.4)	13 (4.5)	13 (4.5)	11 (4.7)	12 (5.2)	9 (4.1)	9 (4.1)	1 (1.5)	1 (1.5)	4 (5.8)	4 (5.8)
Febrile neutropenia	2 (0.7)	2 (0.7)	19 (6.6)	19 (6.6)	1 (0.4)	1 (0.4)	15 (6.8)	15 (6.8)	1 (1.5)	1 (1.5)	4 (5.8)	4 (5.8)
Neutropenia	2 (0.7)	2 (0.7)	33 (11.4)	34 (11.7)	1 (0.4)	1 (0.4)	20 (9.0)	20 (9.0)	1 (1.5)	1 (1.5)	13 (18.8)	14 (20.3)
Neutrophil count decreased	1 (0.3)	1 (0.3)	38 (13.1)	38 (13.1)	0	0	30 (13.6)	30 (13.6)	1 (1.5)	1 (1.5)	8 (11.6)	8 (11.6)
White blood cell count decreased	1 (0.3)	1 (0.3)	25 (8.6)	25 (8.6)	1 (0.4)	1 (0.4)	18 (8.1)	18 (8.1)	0	0	7 (10.1)	7 (10.1)

Percentages are calculated based on the number of subjects in the Safety Analysis Set.
TEAEs are sorted by decreasing frequency for the overall population in the Dato-DXd arm at the 120-DSU DCO.
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.
Source: 120-DSU Table 14.10.5.1

Source: Updated ISS.

Pooled results:

The only PT of Grade ≥3 reported in ≥5% of subjects in the NSCLC 6 mg/kg Pool was stomatitis, which was reported in a similar proportion of subjects in the Dato-DXd arm of Study TL01 and the NSCLC Non-squamous 6 mg/kg Pool.

Table 138 TEAEs Grade 23 Among Subjects Who Received Dato-DXd in Study TL01 and Across Pools, Reported in at Least 2% of Subjects in the TL01 NSCLC 6.0 mg/kg Arm by SOC and Preferred Term (Safety Analysis Set) DCO: TL01 13 Oct 2023; TL05 14 Dec 2022; TP01 NSCLC 30 Jul 2021

MedDRA SOC Preferred Term	Number (%) of Subjects Who Received Dato-DXd				
	Study		Pool		
	TL01 NSCLC 6.0 mg/kg (N = 297)	TL01 NSCLC Non-squamous 6.0 mg/kg (N = 232)	NSCLC 6.0 mg/kg (N = 484)	NSCLC Non-squamous 6.0 mg/kg (N = 411)	NSCLC + BC ≥ 4.0 mg/kg (N = 707)
Subjects with any TEAE Grade ≥3	135 (45.5)	98 (42.2)	227 (46.9)	186 (45.3)	333 (47.1)
Blood and lymphatic system disorders	15 (5.1)	13 (5.6)	31 (6.4)	28 (6.8)	45 (6.4)
Anaemia	13 (4.4)	12 (5.2)	23 (4.8)	21 (5.1)	33 (4.7)
Gastrointestinal disorders	35 (11.8)	26 (11.2)	59 (12.2)	50 (12.2)	83 (11.7)
Stomatitis	20 (6.7)	17 (7.3)	34 (7.0)	31 (7.5)	48 (6.8)
Nausea	7 (2.4)	5 (2.2)	12 (2.5)	10 (2.4)	14 (2.0)
General disorders and administration site conditions	21 (7.1)	15 (6.5)	30 (6.2)	24 (5.8)	47 (6.6)
Asthenia	11 (3.7)	10 (4.3)	14 (2.9)	13 (3.2)	14 (2.0)
Infections and infestations	36 (12.1)	23 (9.9)	46 (9.5)	33 (8.0)	66 (9.3)
Pneumonia	17 (5.7)	10 (4.3)	20 (4.1)	13 (3.2)	29 (4.1)
Investigations	24 (8.1)	18 (7.8)	50 (10.3)	42 (10.2)	85 (12.0)
Amylase increased	7 (2.4)	6 (2.6)	19 (3.9)	16 (3.9)	22 (3.1)
Respiratory, thoracic and mediastinal disorders	32 (10.8)	17 (7.3)	46 (9.5)	31 (7.5)	65 (9.2)
Dyspnoea	9 (3.0)	4 (1.7)	15 (3.1)	10 (2.4)	22 (3.1)
Pneumonitis	9 (3.0)	4 (1.7)	11 (2.3)	6 (1.5)	16 (2.3)

BC = breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; SOC = system organ class; TEAE = treatment-emergent adverse event
Source: Module 1, Appendix 5 MAA D120 Table Q121.1

Source: D120 response to Q121.

Adverse drug reactions

Phase 3 study TL01:

Table 139 Drug-related Treatment-emergent Adverse Events Reported in At Least 5% of Subjects in Either Treatment Arm of Study TL01, by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of Subjects											
	Overall				Non-squamous Histology				Squamous Histology			
	Dato-DXd (N = 297)		Docetaxel (N = 290)		Dato-DXd (N = 232)		Docetaxel (N = 221)		Dato-DXd (N = 65)		Docetaxel (N = 69)	
	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU
Subjects with any drug-related TEAE	257 (86.5)	260 (87.5)	252 (86.9)	252 (86.9)	205 (88.4)	207 (89.2)	195 (88.2)	195 (88.2)	52 (80.0)	53 (81.5)	57 (82.6)	57 (82.6)
Stomatitis	140 (47.1)	141 (47.5)	45 (15.5)	45 (15.5)	114 (49.1)	114 (49.1)	35 (15.8)	35 (15.8)	26 (40.0)	27 (41.5)	10 (14.5)	10 (14.5)
Nausea	100 (33.7)	101 (34.0)	48 (16.6)	48 (16.6)	83 (35.8)	84 (36.2)	45 (20.4)	4 (20.4)	17 (26.2)	17 (26.2)	3 (4.3)	3 (4.3)
Alopecia	95 (32.0)	95 (32.0)	101 (34.8)	101 (34.8)	83 (35.8)	83 (35.8)	82 (37.1)	82 (37.1)	12 (18.5)	1 (18.5)	19 (27.5)	19 (27.5)
Decreased appetite	68 (22.9)	68 (22.9)	45 (15.5)	46 (15.9)	54 (23.3)	54 (23.3)	34 (15.4)	35 (15.8)	14 (21.5)	14 (21.5)	11 (15.9)	11 (15.9)
Asthenia	55 (18.5)	56 (18.9)	55 (19.0)	55 (19.0)	45 (19.4)	46 (19.8)	42 (19.0)	42 (19.0)	10 (15.4)	10 (15.4)	13 (18.8)	13 (18.8)
Anaemia	43 (14.5)	44 (14.8)	59 (20.3)	59 (20.3)	37 (15.9)	37 (15.9)	46 (20.8)	46 (20.8)	6 (9.2)	7 (10.8)	13 (18.8)	13 (18.8)
Vomiting	38 (12.8)	39 (13.1)	22 (7.6)	22 (7.6)	28 (12.1)	29 (12.5)	21 (9.5)	21 (9.5)	10 (15.4)	10 (15.4)	1 (1.4)	1 (1.4)
Rash	36 (12.1)	36 (12.1)	18 (6.2)	18 (6.2)	27 (11.6)	27 (11.6)	14 (6.3)	14 (6.3)	9 (13.8)	9 (13.8)	4 (5.8)	4 (5.8)
Fatigue	34 (11.4)	34 (11.4)	40 (13.8)	40 (13.8)	30 (12.9)	30 (12.9)	30 (13.6)	30 (13.6)	4 (6.2)	4 (6.2)	10 (14.5)	10 (14.5)
Diarrhoea	28 (9.4)	30 (10.1)	55 (19.0)	55 (19.0)	24 (10.3)	26 (11.2)	45 (20.4)	45 (20.4)	4 (6.2)	4 (6.2)	10 (14.5)	10 (14.5)
Pruritus	30 (10.1)	30 (10.1)	12 (4.1)	12 (4.1)	21 (9.1)	21 (9.1)	10 (4.5)	10 (4.5)	9 (13.8)	9 (13.8)	2 (2.9)	2 (2.9)
Constipation	29 (9.8)	29 (9.8)	30 (10.3)	30 (10.3)	23 (9.9)	23 (9.9)	26 (11.8)	26 (11.8)	6 (9.2)	6 (9.2)	4 (5.8)	4 (5.8)
Lacrimation increased	16 (5.4)	19 (6.4)	14 (4.8)	14 (4.8)	15 (6.5)	18 (7.8)	14 (6.3)	14 (6.3)	1 (1.5)	1 (1.5)	0	0
Dry eye	18 (6.1)	18 (6.1)	2 (0.7)	2 (0.7)	14 (6.0)	14 (6.0)	2 (0.9)	2 (0.9)	4 (6.2)	4 (6.2)	0	0
Malaise	18 (6.1)	18 (6.1)	28 (9.7)	29 (10.0)	14 (6.0)	14 (6.0)	22 (10.0)	23 (10.4)	4 (6.2)	4 (6.2)	6 (8.7)	6 (8.7)
Dry skin	17 (5.7)	17 (5.7)	7 (2.4)	7 (2.4)	16 (6.9)	16 (6.9)	6 (2.7)	6 (2.7)	1 (1.5)	1 (1.5)	1 (1.4)	1 (1.4)
Pneumonitis	16 (5.4)	17 (5.7)	9 (3.1)	9 (3.1)	12 (5.2)	12 (5.2)	6 (2.7)	6 (2.7)	4 (6.2)	5 (7.7)	3 (4.3)	3 (4.3)

MedDRA Preferred Term	Number (%) of Subjects											
	Overall				Non-squamous Histology				Squamous Histology			
	Dato-DXd (N = 297)		Docetaxel (N = 290)		Dato-DXd (N = 232)		Docetaxel (N = 221)		Dato-DXd (N = 65)		Docetaxel (N = 69)	
	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU
Dysgeusia	16 (5.4)	16 (5.4)	13 (4.5)	13 (4.5)	13 (5.6)	13 (5.6)	13 (5.9)	13 (5.9)	3 (4.6)	3 (4.6)	0	0
Weight decreased	15 (5.1)	15 (5.1)	6 (2.1)	6 (2.1)	11 (4.7)	11 (4.7)	5 (2.3)	5 (2.3)	4 (6.2)	4 (6.2)	1 (1.4)	1 (1.4)
Conjunctivitis	11 (3.7)	14 (4.7)	1 (0.3)	1 (0.3)	7 (3.0)	10 (4.3)	1 (0.5)	1 (0.5)	4 (6.2)	4 (6.2)	0	0
Dry mouth	12 (4.0)	12 (4.0)	5 (1.7)	6 (2.1)	7 (3.0)	7 (3.0)	5 (2.3)	6 (2.7)	5 (7.7)	5 (7.7)	0	0
Dyspnoea	12 (4.0)	12 (4.0)	8 (2.8)	8 (2.8)	8 (3.4)	8 (3.4)	5 (2.3)	5 (2.3)	4 (6.2)	4 (6.2)	3 (4.3)	3 (4.3)
Arthralgia	8 (2.7)	8 (2.7)	18 (6.2)	19 (6.6)	6 (2.6)	6 (2.6)	16 (7.2)	17 (7.7)	2 (3.1)	2 (3.1)	2 (2.9)	2 (2.9)
Lymphocyte count decreased	7 (2.4)	7 (2.4)	10 (3.4)	10 (3.4)	6 (2.6)	6 (2.6)	6 (2.7)	6 (2.7)	1 (1.5)	1 (1.5)	4 (5.8)	4 (5.8)
Neutropenia	6 (2.0)	7 (2.4)	35 (12.1)	36 (12.4)	3 (1.3)	4 (1.7)	23 (10.4)	23 (10.4)	3 (4.6)	3 (4.6)	12 (17.4)	13 (18.8)
Neutrophil count decreased	6 (2.0)	7 (2.4)	41 (14.1)	41 (14.1)	6 (2.6)	7 (3.0)	33 (14.9)	33 (14.9)	0	0	8 (11.6)	8 (11.6)
White blood cell count decreased	5 (1.7)	5 (1.7)	26 (9.0)	26 (9.0)	5 (2.2)	5 (2.2)	18 (8.1)	18 (8.1)	0	0	8 (11.6)	8 (11.6)
Peripheral sensory neuropathy	4 (1.3)	4 (1.3)	14 (4.8)	14 (4.8)	4 (1.7)	4 (1.7)	12 (5.4)	12 (5.4)	0	0	2 (2.9)	2 (2.9)
Leukopenia	3 (1.0)	3 (1.0)	19 (6.6)	19 (6.6)	3 (1.3)	3 (1.3)	14 (6.3)	14 (6.3)	0	0	5 (7.2)	5 (7.2)
Neuropathy peripheral	2 (0.7)	3 (1.0)	23 (7.9)	25 (8.6)	1 (0.4)	2 (0.9)	17 (7.7)	19 (8.6)	1 (1.5)	1 (1.5)	6 (8.7)	6 (8.7)
Myalgia	2 (0.7)	2 (0.7)	21 (7.2)	21 (7.2)	2 (0.9)	2 (0.9)	17 (7.7)	17 (7.7)	0	0	4 (5.8)	4 (5.8)
Nail disorder	2 (0.7)	2 (0.7)	12 (4.1)	12 (4.1)	2 (0.9)	2 (0.9)	12 (5.4)	12 (5.4)	0	0	0	0
Febrile neutropenia	1 (0.3)	1 (0.3)	19 (6.6)	19 (6.6)	0	0	15 (6.8)	15 (6.8)	1 (1.5)	1 (1.5)	4 (5.8)	4 (5.8)
Oedema peripheral	1 (0.3)	1 (0.3)	29 (10.0)	29 (10.0)	1 (0.4)	1 (0.4)	26 (11.8)	26 (11.8)	0	0	3 (4.3)	3 (4.3)

Percentages are calculated based on the number of subjects in the Safety Analysis Set.
TEAEs are sorted by decreasing frequency for the overall population in the Dato-DXd arm at the 120-DSU DCO.
If a subject had multiple occurrences of the same PT, the subject is counted once for that PT.
If relationship is missing, the AE is considered to be related to the study drug.
Source: 120-DSU Table 14.10.4.1

Source: Updated ISS.

Pooled results:

Table 140 Drug-related Treatment-emergent Adverse Events Reported in At Least 5% of Subjects Who Received Dato-DXd in the NSCLC 6 mg/kg Pool, by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of Subjects Who Received Dato-DXd					
	NSCLC 6 mg/kg (N = 484)		NSCLC Non-squamous 6 mg/kg (N = 411)		NSCLC + BC ≥4 mg/kg (N = 707)	
	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU
Subjects with any drug-related TEAE	427 (88.2)	430 (88.8)	368 (89.5)	370 (90.0)	644 (91.1)	647 (91.5)
Stomatitis	242 (50.0)	243 (50.2)	214 (52.1)	214 (52.1)	376 (53.2)	377 (53.3)
Nausea	200 (41.3)	201 (41.5)	179 (43.6)	180 (43.8)	319 (45.1)	320 (45.3)
Alopecia	181 (37.4)	181 (37.4)	166 (40.4)	166 (40.4)	265 (37.5)	265 (37.5)
Decreased appetite	104 (21.5)	104 (21.5)	89 (21.7)	89 (21.7)	145 (20.5)	145 (20.5)
Asthenia	71 (14.7)	72 (14.9)	60 (14.6)	61 (14.8)	71 (10.0)	72 (10.2)
Fatigue	71 (14.7)	71 (14.7)	65 (15.8)	65 (15.8)	144 (20.4)	144 (20.4)
Anaemia	64 (13.2)	65 (13.4)	57 (13.9)	57 (13.9)	96 (13.6)	97 (13.7)
Vomiting	61 (12.6)	62 (12.8)	50 (12.2)	51 (12.4)	116 (16.4)	117 (16.5)
Rash	57 (11.8)	57 (11.8)	48 (11.7)	48 (11.7)	101 (14.3)	101 (14.3)
Constipation	54 (11.2)	54 (11.2)	48 (11.7)	48 (11.7)	80 (11.3)	80 (11.3)
Diarrhoea	44 (9.1)	46 (9.5)	40 (9.7)	42 (10.2)	72 (10.2)	74 (10.5)
Pruritus	43 (8.9)	43 (8.9)	32 (7.8)	32 (7.8)	58 (8.2)	58 (8.2)
Dry eye	37 (7.6)	37 (7.6)	33 (8.0)	33 (8.0)	78 (11.0)	78 (11.0)
Malaise	30 (6.2)	30 (6.2)	26 (6.3)	26 (6.3)	43 (6.1)	43 (6.1)
Dysgeusia	28 (5.8)	28 (5.8)	24 (5.8)	24 (5.8)	43 (6.1)	43 (6.1)
Pneumonitis	26 (5.4)	27 (5.6)	22 (5.4)	22 (5.4)	43 (6.1)	44 (6.2)
Dry skin	26 (5.4)	26 (5.4)	25 (6.1)	25 (6.1)	44 (6.2)	44 (6.2)

Percentages are calculated based on the number of subjects in the Safety Analysis Set.
TEAEs are sorted by decreasing frequency in the NSCLC 6 mg/kg Pool at the 120-DSU DCO.
If a subject had multiple occurrences of the same PT, the subject is counted once for that PT.
If relationship is missing, the AE is considered to be related to the study drug.
Source: ISS Table 3.1.3.2, 120-DSU Table 3.1.3.2

Source: Updated ISS.

Generally, the ADRs are agreed with a few exceptions:

Neutropenia/ neutrophil count decreased:

First of all, the fact that an AE is more frequent in the control arm does not exclude this AE from being an ADR in the experimental arm, and thus from the need to report it in section 4.8. In addition, *neutropenia/ neutrophil count decreased* were adjudicated as TRAEs with a frequency of 2.4% (7/297) for either term.

Furthermore, based on the terms used by the applicant to decide upon whether a term should be regarded as an ADR it is considered, that the grouped term *Neutropenia/ neutrophil count decreased* is an ADR:

- Biological plausibility: Since Anemia is Very common, a general effect on bone marrow function could be envisaged.
- Severity: Grade 3 observed.
- In-class effect: Listed both in TROP2 (Trodelvy) and deruxtecan (Enhertu) medicines as Very common.
- Designated Medical Event (DME) list: Granulocytopenia, under which neutropenia belongs.

Neuropathy peripheral/ peripheral sensory neuropathy

The AE frequencies were 1.3% (4/297) for either term. TRAE were seen in 3/297 (1%) and 4/397 (1.3%), respectively.

See also OC regarding ILD.

3.3.7.3. Serious adverse events, deaths, and other significant events

Serious adverse events:

Phase 3 study TL01:

A total of 30.6% subjects in the Dato-DXd arm and 37.6% of subjects in the docetaxel arm had at least 1 SAE (Table 14.10.10.1/u301 safety update). No event was reported in ≥10% of subjects in either treatment arm. The incidence of febrile neutropenia was >2-fold higher in the docetaxel arm than in the Dato-DXd arm, and the incidence of ILD/pneumonitis using the pooled term was >3-fold higher in the Dato-DXd arm.

The main preferred terms leading to an SAE were within the SOC 'Infections and Infestations' and the AESI ILD/pneumonitis with at least 21/297 patients in the Dato-DXd arm and 8/290 patients in the docetaxel arm experiencing the latter.

Table 141 Serious Treatment-Emergent Adverse Events Reported in ≥1% of Subjects in either Treatment Group by Preferred Term and Histology Safety Analysis Set

	TL01 All Subjects Dato-DXd		TL01 All Subjects Docetaxel	
Preferred Term	BLA (N = 297) n (%)	120 DSU (N = 297) n (%)	BLA (N = 290) n (%)	120 DSU (N = 290) n (%)
Any Serious Treatment-Emergent Adverse Events (TEAE)	88 (29.6)	91 (30.6)	106 (36.6)	109 (37.6)
Pneumonia	14 (4.7)	15 (5.1)	23 (7.9)	23 (7.9)
Pneumonitis	11 (3.7)	12 (4.0)	6 (2.1)	6 (2.1)
COVID-19	5 (1.7)	5 (1.7)	8 (2.8)	8 (2.8)
Stomatitis	5 (1.7)	5 (1.7)	0	0
Dyspnoea	4 (1.3)	4 (1.3)	2 (0.7)	2 (0.7)
Pulmonary embolism	4 (1.3)	4 (1.3)	2 (0.7)	2 (0.7)
Anaemia	3 (1.0)	3 (1.0)	0	0
Interstitial lung disease	3 (1.0)	3 (1.0)	0	0
Respiratory failure	3 (1.0)	3 (1.0)	2 (0.7)	2 (0.7)
Vomiting	3 (1.0)	3 (1.0)	0	0
Febrile neutropenia	2 (0.7)	2 (0.7)	10 (3.4)	10 (3.4)
Pleural effusion	2 (0.7)	2 (0.7)	4 (1.4)	5 (1.7)
Sepsis	2 (0.7)	2 (0.7)	3 (1.0)	3 (1.0)
Haemoptysis	1 (0.3)	2 (0.7)	4 (1.4)	4 (1.4)
Pyrexia	1 (0.3)	1 (0.3)	3 (1.0)	3 (1.0)
Bacterial infection	0	0	3 (1.0)	3 (1.0)
Cancer pain	0	0	3 (1.0)	3 (1.0)

Histology subgroup is derived using data collected from CRF
Percentages are based on the number of subjects in the Safety Analysis Set. TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0.
If a subject has more than one event per preferred term, the subject is counted only once within preferred term.
A TEAE is defined as an adverse event with a start or worsening date on or after the start of study treatment until 35 days since the last dose of study treatment.
Table is sorted by decreasing frequency in All Subjects Dato-DXd BLA column.
DCO: 2023-10-13
Source: adam.adae

Source: Updated ISS.

For SAEs by SOC in study TL01 see the Pooled results-section below.

Pooled results:

The proportion of subjects with SAEs was similar between the Dato-DXd arm of Study TL01 and the NSCLC 6 mg/kg Pool.

SAEs by SOC:

Table 142 Treatment-emergent SAEs by SOC Among Subjects Who Received Dato-DXd in Study TL01 and Across Pools (Safety Analysis Set) DCO: TL01 13 Oct 2023; TL05 14 Dec 2022; TP01 NSCLC 30 Jul 2021

MedDRA SOC	Number (%) of Subjects Who Received Dato-DXd				
	Study		Pool		
	TL01 NSCLC 6 mg/kg (N = 297)	TL01 NSCLC Non-squamous 6 mg/kg (N = 232)	NSCLC 6 mg/kg (N = 484)	NSCLC Non-squamous 6 mg/kg (N = 411)	NSCLC + BC ≥4 mg/kg (N = 707)
Any serious TEAE	91 (30.6)	65 (28.0)	149 (30.8)	120 (29.2)	215 (30.4)
Blood and lymphatic system disorders	5 (1.7)	3 (1.3)	5 (1.0)	3 (0.7)	5 (0.7)
Cardiac disorders	10 (3.4)	6 (2.6)	12 (2.5)	8 (1.9)	19 (2.7)
Ear and labyrinth disorders	0	0	0	0	1 (0.1)
Endocrine disorders	1 (0.3)	0	1 (0.2)	0	1 (0.1)
Eye disorders	2 (0.7)	2 (0.9)	4 (0.8)	4 (1.0)	5 (0.7)
Gastrointestinal disorders	14 (4.7)	9 (3.9)	19 (3.9)	14 (3.4)	28 (4.0)
General disorders and administration site conditions	8 (2.7)	6 (2.6)	10 (2.1)	8 (1.9)	17 (2.4)
Hepatobiliary disorders	1 (0.3)	1 (0.4)	3 (0.6)	3 (0.7)	4 (0.6)
Immune system disorders	0	0	1 (0.2)	1 (0.2)	1 (0.1)

MedDRA SOC	Number (%) of Subjects Who Received Dato-DXd				
	Study		Pool		
	TL01 NSCLC 6 mg/kg (N = 297)	TL01 NSCLC Non-squamous 6 mg/kg (N = 232)	NSCLC 6 mg/kg (N = 484)	NSCLC Non-squamous 6 mg/kg (N = 411)	NSCLC + BC ≥4 mg/kg (N = 707)
Infections and infestations	37 (12.5)	26 (11.2)	50 (10.3)	38 (9.2)	68 (9.6)
Injury, poisoning and procedural complications	1 (0.3)	1 (0.4)	2 (0.4)	2 (0.5)	7 (1.0)
Investigations	3 (1.0)	1 (0.4)	7 (1.4)	4 (1.0)	10 (1.4)
Metabolism and nutrition disorders	1 (0.3)	0	2 (0.4)	1 (0.2)	5 (0.7)
Musculoskeletal and connective tissue disorders	3 (1.0)	2 (0.9)	5 (1.0)	3 (0.7)	13 (1.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	3 (0.6)	3 (0.7)	5 (0.7)
Nervous system disorders	4 (1.3)	3 (1.3)	13 (2.7)	11 (2.7)	20 (2.8)
Psychiatric disorders	0	0	2 (0.4)	2 (0.5)	2 (0.3)
Renal and urinary disorders	1 (0.3)	1 (0.4)	2 (0.4)	2 (0.5)	3 (0.4)
Respiratory, thoracic and mediastinal disorders	33 (11.1)	19 (8.2)	52 (10.7)	37 (9.0)	70 (9.9)
Skin and subcutaneous tissue disorders	0	0	1 (0.2)	0	1 (0.1)
Vascular disorders	2 (0.7)	0	4 (0.8)	2 (0.5)	5 (0.7)

BC = breast cancer; MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; SOC = system organ class; TEAE = treatment-emergent adverse event
Percentages are based on the number of subjects in the Safety Analysis Set.
Source: Module 5.3.5.3 ISS 120 DSU Table 3.1.2.3

SAEs by Preferred Term:

Table 143: Treatment-emergent SAEs Among Subjects Who Received Dato-DXd in Study TL01 and Across Pools, Reported in At Least 1% of Subjects in the NSCLC 6 mg/kg Pool by SOC and Preferred Term (Safety Analysis Set) DCO: TL01 13 Oct 2023; TL05 14 Dec 2022; TP01 NSCLC 30 Jul 2021

MedDRA SOC Preferred Term	Number (%) of Subjects Who Received Dato-DXd				
	Study		Pool		
	TL01 NSCLC 6 mg/kg (N = 297)	TL01 NSCLC Non-squamous 6 mg/kg (N = 232)	NSCLC 6 mg/kg (N = 484)	NSCLC Non-squamous 6 mg/kg (N = 411)	NSCLC + BC ≥4 mg/kg (N = 707)
Subjects with any serious TEAE	91 (30.6)	65 (28.0)	149 (30.8)	120 (29.2)	215 (30.4)
Blood and lymphatic system disorders	5 (1.7)	3 (1.3)	5 (1.0)	3 (0.7)	5 (0.7)
Cardiac disorders	10 (3.4)	6 (2.6)	12 (2.5)	8 (1.9)	19 (2.7)
Gastrointestinal disorders	14 (4.7)	9 (3.9)	19 (3.9)	14 (3.4)	28 (4.0)
Stomatitis	5 (1.7)	5 (2.2)	6 (1.2)	6 (1.5)	8 (1.1)
General disorders and administration site conditions	8 (2.7)	6 (2.6)	10 (2.1)	8 (1.9)	17 (2.4)
Infections and infestations	37 (12.5)	26 (11.2)	50 (10.3)	38 (9.2)	68 (9.6)
Pneumonia	15 (5.1)	9 (3.9)	19 (3.9)	13 (3.2)	27 (3.8)

MedDRA SOC Preferred Term	Number (%) of Subjects Who Received Dato-DXd				
	Study		Pool		
	TL01 NSCLC 6 mg/kg (N = 297)	TL01 NSCLC Non-squamous 6 mg/kg (N = 232)	NSCLC 6 mg/kg (N = 484)	NSCLC Non-squamous 6 mg/kg (N = 411)	NSCLC + BC ≥4 mg/kg (N = 707)
COVID-19	5 (1.7)	5 (2.2)	7 (1.4)	7 (1.7)	7 (1.0)
Investigations	3 (1.0)	1 (0.4)	7 (1.4)	4 (1.0)	10 (1.4)
Musculoskeletal and connective tissue disorders	3 (1.0)	2 (0.9)	5 (1.0)	3 (0.7)	13 (1.8)
Nervous system disorders	4 (1.3)	3 (1.3)	13 (2.7)	11 (2.7)	20 (2.8)
Respiratory, thoracic and mediastinal disorders	33 (11.1)	19 (8.2)	52 (10.7)	37 (9.0)	70 (9.9)
Pneumonitis	12 (4.0)	7 (3.0)	18 (3.7)	13 (3.2)	23 (3.3)
Dyspnoea	4 (1.3)	1 (0.4)	9 (1.9)	5 (1.2)	16 (2.3)
Pulmonary embolism	4 (1.3)	0	5 (1.0)	1 (0.2)	7 (1.0)
Respiratory failure	3 (1.0)	3 (1.3)	5 (1.0)	5 (1.2)	7 (1.0)

BC = breast cancer; COVID-19 = coronavirus disease 2019; Dato-DXd = datopotamab deruxtecan; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; SAE = serious adverse event; SOC = system organ class; TEAE = treatment-emergent adverse event
Percentages are based on the number of subjects in the Safety Analysis Set.
Preferred terms are sorted by decreasing frequency in the NSCLC 6 mg/kg Pool.
Source: Module 5.3.5.3 ISS 120 DSU Table 3.1.2.3

Source: D120 response, Q123.

Deaths

Phase 3 study TL01:

With the updated data a total of 16 (5.4%) of subjects in the Dato-DXd arm and 11 (3.8%) of subjects in the docetaxel arm had AEs associated with an outcome of death.

Based on the ILD AC's adjudication there were 7 deaths due to ILD/pneumonitis in the Dato-DXd arm and 1 in the docetaxel arm.

Table 144 Treatment-emergent Adverse Events with an Outcome of Death in Study TL01, by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of Subjects											
	Overall				Non-squamous Histology				Squamous Histology			
	Dato-DXd (N = 297)		Docetaxel (N = 290)		Dato-DXd (N = 232)		Docetaxel (N = 221)		Dato-DXd (N = 65)		Docetaxel (N = 69)	
	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU
Subjects with any TEAE associated with an outcome of death	16 (5.4)	16 (5.4)	10 (3.4)	11 (3.8)	8 (3.4)	8 (3.4)	5 (2.3)	5 (2.3)	8 (12.3)	8 (12.3)	5 (7.2)	6 (8.7)
Pneumonia	2 (0.7)	2 (0.7)	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	1 (0.5)	1 (0.5)	1 (1.5)	1 (1.5)	0	0
Pneumonitis	2 (0.7)	2 (0.7)	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	1 (0.5)	1 (0.5)	1 (1.5)	1 (1.5)	0	0
Sepsis	2 (0.7)	2 (0.7)	0	0	1 (0.4)	1 (0.4)	0	0	1 (1.5)	1 (1.5)	0	0
Cardiac arrest	1 (0.3)	1 (0.3)	0	0	0	0	0	0	1 (1.5)	1 (1.5)	0	0
Cardio-respiratory arrest	1 (0.3)	1 (0.3)	0	0	0	0	0	0	1 (1.5)	1 (1.5)	0	0
Chronic obstructive pulmonary disease	1 (0.3)	1 (0.3)	0	0	0	0	0	0	1 (1.5)	1 (1.5)	0	0
COVID-19	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	0	0	0	0	1 (1.4)	1 (1.4)
COVID-19 pneumonia	1 (0.3)	1 (0.3)	0	0	1 (0.4)	1 (0.4)	0	0	0	0	0	0
Disease progression	1 (0.3)	1 (0.3)	0	0	1 (0.4)	1 (0.4)	0	0	0	0	0	0
Dyspnoea	1 (0.3)	1 (0.3)	0	0	1 (0.4)	1 (0.4)	0	0	0	0	0	0
General physical condition abnormal	1 (0.3)	1 (0.3)	0	0	0	0	0	0	1 (1.5)	1 (1.5)	0	0
Multiple organ dysfunction syndrome	1 (0.3)	1 (0.3)	0	0	0	0	0	0	1 (1.5)	1 (1.5)	0	0
Respiratory failure	1 (0.3)	1 (0.3)	0	0	1 (0.4)	1 (0.4)	0	0	0	0	0	0
Death	0	0	2 (0.7)	2 (0.7)	0	0	1 (0.5)	1 (0.5)	0	0	1 (1.4)	1 (1.4)
Haemoptysis	0	0	1 (0.3)	1 (0.3)	0	0	0	0	0	0	1 (1.4)	1 (1.4)
Hydrothorax	0	0	1 (0.3)	1 (0.3)	0	0	0	0	0	0	1 (1.4)	1 (1.4)
Respiratory tract infection	0	0	1 (0.3)	1 (0.3)	0	0	0	0	0	0	1 (1.4)	1 (1.4)
Septic shock	0	0	1 (0.3)	1 (0.3)	0	0	1 (0.5)	1 (0.5)	0	0	0	0
Sudden death	0	0	1 (0.3)	1 (0.3)	0	0	1 (0.5)	1 (0.5)	0	0	0	0
General physical health deterioration	0	0	0	1 (0.3)	0	0	0	0	0	0	0	1 (1.4)

Percentages are based on the number of subjects in the Safety Analysis Set.
TEAEs are sorted by decreasing frequency for the overall population in the Dato-DXd arm at the 120-DSU DCO.
A death could be associated with multiple PTs.
Source: 120-DSU Table 14.10.6.2

Pooled results:

The proportion of subjects with TEAEs associated with an outcome of death was similar between the Dato-DXd arm of Study TL01 and the NSCLC 6 mg/kg Pool. With regards to the AESI ILD/pneumonitis there were fewer in the SATs. It is considered, that a randomised trial more accurately reflects the frequencies of AEs.

Table 145 Treatment-emergent Adverse Events with an Outcome of Death Among Subjects Who Received Dato-DXd Across Studies and Pools, by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of Subjects Who Received Dato-DXd				
	Study		Pool		
	TL01 NSCLC 6 mg/kg (N = 297)	TL01 NSCLC Non-squamous 6 mg/kg (N = 232)	NSCLC 6 mg/kg (N = 484)	NSCLC Non-squamous 6 mg/kg (N = 411)	NSCLC + BC ≥4 mg/kg (N = 707)
Subjects with any TEAE associated with an outcome of death	16 (5.4)	8 (3.4)	23 (4.8)	14 (3.4)	35 (5.0)
Pneumonitis	2 (0.7)	1 (0.4)	3 (0.6)	2 (0.5)	5 (0.7)
Dyspnoea	1 (0.3)	1 (0.4)	2 (0.4)	2 (0.5)	4 (0.6)
Pneumonia	2 (0.7)	1 (0.4)	2 (0.4)	1 (0.2)	2 (0.3)
Respiratory failure	1 (0.3)	1 (0.4)	2 (0.4)	2 (0.5)	4 (0.6)
Sepsis	2 (0.7)	1 (0.4)	2 (0.4)	1 (0.2)	3 (0.4)
COVID-19	1 (0.3)	1 (0.4)	1 (0.2)	1 (0.2)	1 (0.1)
COVID-19 pneumonia	1 (0.3)	1 (0.4)	1 (0.2)	1 (0.2)	1 (0.1)
Cardiac arrest	1 (0.3)	0	1 (0.2)	0	1 (0.1)
Cardio-respiratory arrest	1 (0.3)	0	1 (0.2)	0	1 (0.1)
Cardiomyopathy	0	0	1 (0.2)	1 (0.2)	1 (0.1)
Chronic obstructive pulmonary disease	1 (0.3)	0	1 (0.2)	0	1 (0.1)
Death	0	0	1 (0.2)	1 (0.2)	1 (0.1)
Disease progression	1 (0.3)	1 (0.4)	1 (0.2)	1 (0.2)	4 (0.6)
General physical condition abnormal	1 (0.3)	0	1 (0.2)	0	1 (0.1)
Multiple organ dysfunction syndrome	1 (0.3)	0	1 (0.2)	0	1 (0.1)
Neck pain	0	0	1 (0.2)	0	1 (0.1)
Non-small cell lung cancer	0	0	1 (0.2)	1 (0.2)	1 (0.1)
Pulmonary embolism	0	0	1 (0.2)	1 (0.2)	2 (0.3)
Acute respiratory failure	0	0	0	0	1 (0.1)
Respiratory tract infection	0	0	0	0	1 (0.1)

Percentages are based on the number of subjects in the Safety Analysis Set.
Preferred terms are sorted by decreasing frequency in the NSCLC 6 mg/kg Pool.
A death could be associated with multiple PTs.
Source: Module 5.3.5.3 ISS Table 3.1.3.5

Adverse events of special interest

Table 146 Selected MedDRA (Version 26.0) Preferred Terms for Adverse Events of Special Interest

Category	MedDRA Preferred Terms		
ILD/pneumonitis (PTs to be submitted to the ILD AC for adjudication)	Acute interstitial pneumonitis Acute respiratory failure Alveolar lung disease Alveolar proteinosis Alveolitis Alveolitis necrotising Autoimmune lung disease Bronchiolitis Bronchiolitis obliterans syndrome Chronic graft versus host disease in lung Combined pulmonary fibrosis and emphysema Confirmed e-cigarette or vaping product use associated lung injury Diffuse alveolar damage Eosinophilia myalgia syndrome Eosinophilic granulomatosis with polyangiitis	Eosinophilic pneumonia Eosinophilic pneumonia acute Eosinophilic pneumonia chronic Hypersensitivity pneumonitis Low lung compliance Necrotising bronchiolitis Obliterative bronchiolitis Pleuroparenchymal fibroelastosis Pneumonitis Probable e-cigarette or vaping product use associated with lung injury Progressive massive fibrosis Pulmonary fibrosis Pulmonary necrosis Pulmonary radiation injury Pulmonary toxicity Pulmonary vasculitis Radiation alveolitis	Radiation fibrosis – lung Radiation pneumonitis Rheumatoid arthritis-associated interstitial lung disease Small airways disease Transfusion-related acute lung injury Acute respiratory distress syndrome Allergic eosinophilia Granulomatous pneumonitis Organising pneumonia Pulmonary sarcoidosis Radiation bronchitis Restrictive pulmonary disease Rheumatoid lung Sarcoidosis Respiratory failure
Oral mucositis/stomatitis	Aphthous ulcer Dysphagia Glossitis Lip erosion Lip ulceration Mouth ulceration Oral mucosa erosion	Oral mucosal blistering Pharyngeal inflammation Palatal ulcer Pharyngeal ulceration Pharyngeal erosion Oropharyngeal blistering Oropharyngeal pain	Oral pain Odynophagia Stomatitis Stomatitis haemorrhagic Stomatitis necrotising Tongue blistering Tongue ulceration
Mucosal inflammation other than oral mucositis/stomatitis	Mucosal inflammation		
Infusion-related reaction (defined as any of these pre-selected PTs within the same day of an infusion at any cycle)	Anaphylactic reaction Anaphylactic shock Anaphylactic transfusion reaction Anaphylactoid reaction Anaphylactoid shock Angioedema Bronchospasm Circulatory collapse Dyspnoea	Flushing Hypersensitivity Hypotension Infusion related reaction Oedema Polymers allergy Procedural shock Pruritus	Rash Rash maculo-papular Shock Shock symptom Skin exfoliation Type I hypersensitivity Urticaria Wheezing
Ocular surface toxicity	Abnormal sensation in eye Acquired corneal	Corneal erosion Corneal exfoliation	Keratitis sclerosing Keratopathy

Table 146 Selected MedDRA (Version 26.0) Preferred Terms for Adverse Events of Special Interest

Category	MedDRA Preferred Terms		
	dystrophy Blepharitis Conjunctivalisation Conjunctival haemorrhage Conjunctival hyperaemia Conjunctivitis Chalazion Contact lens intolerance Cornea verticillata Corneal cyst Corneal decompensation Corneal defect Corneal degeneration Corneal deposits Corneal disorder Corneal endothelial cell loss Corneal endotheliitis Corneal epithelial microcysts Corneal epithelial wrinkling Corneal epithelium defect	Corneal infiltrates Corneal irritation Corneal lesion Corneal oedema Corneal opacity Corneal perforation Corneal thinning Corneal toxicity Dellen Diffuse lamellar keratitis Dry eye Eye disorder Eye inflammation Eye irritation Eye opacity Eye ulcer Foreign body sensation in eyes Keratitis Keratitis interstitial	Keratouveitis Lacrimation increased Limbal stem cell deficiency Limbal swelling Meibomian gland dysfunction Ocular toxicity Ophthalmological examination abnormal Photophobia Punctate keratitis Slit-lamp tests abnormal Superior limbic keratoconjunctivitis Tear break up time decreased Terrien's marginal degeneration Topography corneal abnormal Ulcerative keratitis Vision blurred Visual impairment Visual acuity reduced Xerophthalmia

Interstitial lung disease/ pneumonitis

An independent, external ILD AC (Adjudication Committee) was established for the program and adjudicated all events of potential ILD reported by investigators on an ongoing basis to ensure a comprehensive assessment of the ILD events and an adequate management plan for ongoing studies.

Phase 3 study TL01:

Events of adjudicated drug-related ILD were reported in 25 (8.4%) subjects in the Dato DXd arm, compared with 12 (4.1%) subjects in the docetaxel arm.

The incidence of adjudicated drug-related ILD was slightly higher in study TL01 compared to the primary safety pool; 8.4% and 6.8%, respectively. Furthermore, deaths adjudicated as ILD were seen in 7/297 (2.4%) in the randomised study TL01 but only in 1/137 for the remainder of the primary safety pool (single arm trials). This could indicate, that the true incidence is higher than presented in the SmPC. With the randomised study in breast cancer (assessment ongoing), this will presumably be clarified.

Regarding study TL01, the applicant states that "In the Dato DXd arm, the incidence of Grade 5 adjudicated drug-related ILD was lower among subjects with non-squamous histology (1.7%) than subjects in the overall population (2.4%)." It is considered, that the small size of squamous NSCLC patients (n=65) adds a lot of uncertainty to this statement and no conclusion may be drawn.

In study TL01 at the time of the DCO, the drug-related events had resolved in 11/25 (44.0%) subjects, was resolving in 3/25 (12.0%) subjects, was not resolved in 7/25 (28.0%) subjects, and was fatal in 3/25 (12.0%) subjects. Outcome was unknown for 1 subject.

All patients adjudicated as having ILD/pneumonitis (for what-ever reason) are considered to constitute the all-causality pneumonitis/ILD frequency, which amounts to 26 patients in study TL01, see comment in the Pooled safety section below.

It is clear that ILD (includes several PTs) is a serious risk with a frequency of Common and with a potentially fatal outcome with the treatment of Dato-DXd. In line with this, ILD/pneumonitis is listed as an Important identified risk in the RMP, which is agreed.

ILD/pneumonitis is described in section 4.2, 4.4, and 4.8 of the SmPC, which is satisfactory.

Table 147 Results of Adjudication of ILD Events in Study TL01 (Safety Analysis Set)

	Number (%) of Subjects with Events of Each CTCAE Grade by the ILD Adjudication Committee					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Overall						
Dato-DXd (N = 297)						
BLA						
Subjects with any event of potential ILD (ie, event sent for adjudication) [a]	13 (4.4)	4 (1.3)	9 (3.0)	2 (0.7)	6 (2.0)	34 (11.4)
Adjudicated as not ILD [a]	5 (1.7)	0	2 (0.7)	0	3 (1.0)	10 (3.4)
Adjudicated as ILD [b]	4 (1.3)	12 (4.0)	2 (0.7)	1 (0.3)	7 (2.4)	26 (8.8)
Adjudicated as drug-related ILD [b]	3 (1.0)	12 (4.0)	2 (0.7)	1 (0.3)	7 (2.4)	25 (8.4)
Adjudicated as not drug-related ILD [b]	1 (0.3)	0	0	0	0	1 (0.3)
120-DSU						
Subjects with any event of potential ILD (ie, event sent for adjudication) [a]	13 (4.4)	4 (1.3)	11 (3.7)	2 (0.7)	6 (2.0)	36 (12.1)
Adjudicated as not ILD [a]	5 (1.7)	0	4 (1.3)	0	3 (1.0)	12 (4.0)
Adjudicated as ILD [b]	3 (1.0)	12 (4.0)	3 (1.0)	1 (0.3)	7 (2.4)	26 (8.8)
Adjudicated as drug-related ILD [b]	2 (0.7)	12 (4.0)	3 (1.0)	1 (0.3)	7 (2.4)	25 (8.4)
Adjudicated as not drug-related ILD [b]	1 (0.3)	0	0	0	0	1 (0.3)
Docetaxel (N = 290)						
BLA						
Subjects with any event of potential ILD (ie, event sent for adjudication) [a]	5 (1.7)	3 (1.0)	6 (2.1)	1 (0.3)	1 (0.3)	16 (5.5)
Adjudicated as not ILD [a]	0	0	3 (1.0)	1 (0.3)	0	4 (1.4)
Adjudicated as ILD [b]	0	8 (2.8)	3 (1.0)	0	1 (0.3)	12 (4.1)
Adjudicated as drug-related ILD [b]	0	8 (2.8)	3 (1.0)	0	1 (0.3)	12 (4.1)
Adjudicated as not drug-related ILD [b]	0	0	0	0	0	0

	Number (%) of Subjects with Events of Each CTCAE Grade by the ILD Adjudication Committee					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
120-DSU						
Subjects with any event of potential ILD (ie, event sent for adjudication) [a]	5 (1.7)	3 (1.0)	6 (2.1)	1 (0.3)	1 (0.3)	16 (5.5)
Adjudicated as not ILD [a]	0	0	3 (1.0)	1 (0.3)	0	4 (1.4)
Adjudicated as ILD [b]	0	8 (2.8)	3 (1.0)	0	1 (0.3)	12 (4.1)
Adjudicated as drug-related ILD [b]	0	8 (2.8)	3 (1.0)	0	1 (0.3)	12 (4.1)
Adjudicated as not drug-related ILD [b]	0	0	0	0	0	0

[a] Grade as reported by the investigator.
[b] Grade as assigned by the ILD AC. An additional subject in the Dato-DXd arm (one subject with non-squamous histology, had Grade 2 adjudicated drug-related ILD (PT of pneumonitis). This event was initially reported as an AE that was entered into the clinical database and sent to the AC for adjudication.
The investigator subsequently determined this event to be disease progression and withdrew it as an AE; therefore, this subject is not included in this table.
Percentages are based on the number of subjects in the Safety Analysis Set.
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 a subject had more than 1 ILD event, the CTCAE grade is for the event with the worst grade.

If a subject had more than 1 event of potential ILD, with some adjudicated as ILD and others adjudicated as not ILD, the subject is counted once in each
corresponding row.

Table 148 Overview of Adjudicated Drug-related ILD in Study TL01 (Safety Analysis Set)

	Number (%) of Subjects			
	Overall		Non-squamous Histology	
	Dato-DXd (N = 297)	Docetaxel (N = 290)	Dato-DXd (N = 232)	Docetaxel (N = 221)
Subjects with any event adjudicated as drug-related ILD	25 (8.4)	12 (4.1)	20 (8.6)	7 (3.2)
CTCAE Grade ≥2 [a]	22 (7.4)	12 (4.1)	16 (6.9)	7 (3 .2)
CTCAE Grade ≥3 [a]	10 (3.4)	4 (1.4)	5 (2.2)	4 (1.8)
Serious events	16 (5.4)	5 (1.7)	10 (4.3)	4 (1.8)
Events associated with dose reduction [b]	2 (0.7)	2 (0.7)	2 (0.9)	1 (0.5)
Events associated with infusion interruption [b]	0	0	0	0
Events associated with dose delay [b]	8 (2.7)	2 (0.7)	7 (3.0)	2 (0.9)
Events associated with study drug discontinuation [b]	15 (5.1)	7 (2.4)	12 (5.2)	4 (1.8)
Events associated with an outcome of death [a]	7 (2.4)	1 (0.3)	4 (1.7)	1 (0.5)

[a] Based on ILD AC assessment
[b] Based on investigator assessment
Percentages are based on the number of subjects in the Safety Analysis Set.
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.
Source: Module 5.3.5.1 Study TL01 CSR Table 10.18, Module 5.3.5.1 Study TL01 CSR Post Hoc Table 14.10.12.1

Pooled results:

Table 149 Adjudicated Interstitial Lung Disease/Pneumonitis Among Subjects Who Received Dato-DXd Across Pools (Safety Analysis Set)

	Number (%) of Subjects with Events of Each CTCAE Grade by ILD Adjudication Committee/Investigator					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
NSCLC 6 mg/kg (N = 484)						
BLA						
Subjects with any event of potential ILD (ie, event sent for adjudication) [a]	18 (3.7)	10 (2.1)	12 (2.5)	2 (0.4)	10 (2.1)	52 (10.7)
Adjudicated as not ILD [a]	7 (1.4)	2 (0.4)	4 (0.8)	0	6 (1.2)	19 (3.9)
Adjudicated as ILD [b]	5 (1.0)	18 (3.7)	2 (0.4)	2 (0.4)	8 (1.7)	35 (7.2)
Adjudicated as drug-related ILD [b]	4 (0.8)	17 (3.5)	2 (0.4)	2 (0.4)	8 (1.7)	33 (6.8)
Adjudicated as not drug-related ILD [b]	1 (0.2)	1 (0.2)	0	0	0	2 (0.4)
120-DSU						
Subjects with any event of potential ILD (ie, event sent for adjudication) [a]	18 (3.7)	10 (2.1)	14 (2.9)	2 (0.4)	10 (2.1)	54 (11.2)
Adjudicated as not ILD [a]	7 (1.4)	2 (0.4)	6 (1.2)	0	6 (1.2)	21 (4.3)
Adjudicated as ILD [b]	4 (0.8)	18 (3.7)	3 (0.6)	2 (0.4)	8 (1.7)	35 (7.2)
Adjudicated as drug-related ILD [b]	3 (0.6)	17 (3.5)	3 (0.6)	2 (0.4)	8 (1.7)	33 (6.8)
Adjudicated as not drug-related ILD [b]	1 (0.2)	1 (0.2)	0	0	0	2 (0.4)

[a] Grade based on investigator assessment
[b] Grade based on ILD AC assessment
Percentages are based on the number of subjects in the Safety Analysis Set.
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 a subject had more than 1 PT, the subject was counted once at each level of summation.
An additional subject in the Dato-DXd arm (with non-squamous histology and non-AGA status) had a Grade 2 adjudicated drug-related ILD/pneumonitis (PT of pneumonitis). This event was initially reported as an AE that was entered into the clinical database and sent to the ILD AC for adjudication. The investigator subsequently determined this event to be disease progression and withdrew it as an AE; therefore, this subject is not included in this table.

In the overall safety pool 35 patients were adjudicated as having ILD/pneumonitis of which 33 were considered drug-related ILD by the AC. The fact that ILD/pneumonitis was causally associated to Dato-DXd by means of an adjudication committee is acknowledged, but not acceptable for defining the *true* proportion of patients with ILD/pneumonitis in relation to Dato-DXd. From a clinical and regulatory perspective, it is the actual incidence of ILD/pneumonitis, regardless of its causal association with Dato-DXd or other causes, that matters for clinicians to anticipate when they consider treatment with Dato-DXd. Accordingly, considering the challenges of causality assessment in Oncology, the latest revision of EMA's anticancer guideline clearly states: "Thus, while investigator assessments of causality may often provide useful clinical insights, the all-causality AE frequencies may be expected to be the measure least biased by preformed understanding." Thus, all 35/484 patients adjudicated as having

ILD/pneumonitis (for whatever reason) are considered to constitute the all-causality pneumonitis/ILD frequency and relevant tables and the SmPC should be updated accordingly. **(OC)**

Table 150 Results of Adjudication of Interstitial Lung Disease/Pneumonitis Across Studies and Pools (Safety Analysis Set)

	Number (%) of Subjects Who Received Dato-DXd				
	Study		Pool		
	TL01 NSCLC 6 mg/kg (N = 297)	TL01 NSCLC Non-squamous 6 mg/kg (N = 232)	NSCLC 6 mg/kg (N = 484)	NSCLC Non-squamous 6 mg/kg (N = 411)	NSCLC + BC ≥4 mg/kg (N = 707)
Subjects with any event adjudicated as drug-related ILD	25 (8.4)	19 (8.2)	33 (6.8)	27 (6.6)	50 (7.1)
Worst CTCAE grade [a]					
Grade 1	3 (1.0)	3 (1.3)	4 (0.8)	4 (1.0)	7 (1.0)
Grade 2	12 (4.0)	11 (4.7)	17 (3.5)	16 (3.9)	25 (3.5)
Grade 3	2 (0.7)	1 (0.4)	2 (0.4)	1 (0.2)	5 (0.7)
Grade 4	1 (0.3)	0	2 (0.4)	1 (0.2)	2 (0.3)
Grade 5	7 (2.4)	4 (1.7)	8 (1.7)	5 (1.2)	11 (1.6)
CTCAE Grade ≥2	22 (7.4)	16 (6.9)	29 (6.0)	23 (5.6)	43 (6.1)
CTCAE Grade ≥3	10 (3.4)	5 (2.2)	12 (2.5)	7 (1.7)	18 (2.5)
Serious events [b]	16 (5.4)	10 (4.3)	20 (4.1)	14 (3.4)	26 (3.7)
Events associated with dose reduction [b]	2 (0.7)	2 (0.9)	2 (0.4)	2 (0.5)	2 (0.3)
Events associated with infusion interruption [b]	0	0	NA	NA	NA
Events associated with dose delay [b]	8 (2.7)	6 (2.6)	NA	NA	NA
Events associated with study drug discontinuation [b]	15 (5.1)	12 (5.2)	20 (4.1)	17 (4.1)	35 (5.0)
Events associated with an outcome of death [a]	7 (2.4)	4 (1.7)	8 (1.7)	5 (1.2)	11 (1.6)

[a] Based on ILD AC assessment
[b] Based on investigator assessment
Percentages are based on the number of subjects in the Safety Analysis Set.
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.
Source: Module 5.3.5.3 ISS Table 3.1.4.1

There were no new cases of fatal or serious adjudicated drug-related ILD/pneumonitis or adjudicated drug-related ILD/pneumonitis leading to withdrawal, dose reduction, or delay in Study TL01 at the updated DCO (13 Oct 2023).

Infusion-related reaction

Phase 3 study TL01:

Table 151 Overview of Treatment-emergent AESI of Infusion-related Reaction in Study TL01 (Safety Analysis Set)

	Number (%) of Subjects			
	Overall		Non-squamous Histology	
	Dato-DXd (N = 297)	Docetaxel (N = 290)	Dato-DXd (N = 232)	Docetaxel (N = 221)
Subjects with an AESI of IRR	24 (8.1)	24 (8.3)	18 (7.8)	19 (8.6)
CTCAE Grade ≥2	8 (2.7)	13 (4.5)	5 (2.2)	10 (4.5)
CTCAE Grade ≥3	1 (0.3)	0	0	0
Serious events	0	0	0	0
Drug-related events	21 (7.1)	17 (5.9)	16 (6.9)	15 (6.8)
Events associated with dose reduction	0	1 (0.3)	0	0
Events associated with infusion interruption	1 (0.3)	8 (2.8)	1 (0.4)	7 (3.2)
Events associated with dose delay	0	1 (0.3)	0	1 (0.5)
Events associated with study drug discontinuation	0	3 (1.0)	0	3 (1.4)
Events associated with an outcome of death	0	0	0	0

Percentages are based on the number of subjects in the Safety Analysis Set.
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.
Source: Module 5.3.5.1 Study TL01 CSR Post Hoc Table 14.10.12.2

For the primary safety pool (n=484) the frequency was higher (12.2%), as listed in the ADR table of the SmPC (Very common) with two SAEs (0.4%).

In the SmPC risk-mitigation for IRR is described.

Oral mucositis / stomatitis

Phase 3 study TL01:

In study TL01 PTs in the AESI of oral mucositis/stomatitis were higher in the Dato-DXd arm compared to the docetaxel arm [163 (54.9%) vs. 59 (20.3%)], with the corresponding Grade ≥3 incidences 6.7% and 1.4%, respectively.

Pooled results:

The incidence of the individual PTs that comprise oral mucositis/stomatitis were reported in similar proportions of subjects in the Dato-DXd arm of Study TL01 and the Primary safety pool.

Table 152 Overview of Treatment-emergent AESI of Oral Mucositis/Stomatitis Among Subjects Who Received Dato-DXd Across Pools (Safety Analysis Set)

	Number (%) of Subjects Who Received Dato-DXd					
	NSCLC 6 mg/kg (N = 484)		NSCLC Non-squamous 6 mg/kg (N = 411)		NSCLC + BC ≥4 mg/kg (N = 707)	
	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU
Subjects with an AESI of oral mucositis/stomatitis	284 (58.7)	287 (59.3)	250 (60.8)	252 (61.3)	432 (61.1)	435 (61.5)
CTCAE Grade ≥2	141 (29.1)	142 (29.3)	124 (30.2)	124 (30.2)	215 (30.4)	216 (30.6)
CTCAE Grade ≥3	35 (7.2)	36 (7.4)	32 (7.8)	33 (8.0)	50 (7.1)	51 (7.2)
Serious events	8 (1.7)	8 (1.7)	8 (1.9)	8 (1.9)	10 (1.4)	10 (1.4)
Drug-related events	260 (53.7)	262 (54.1)	229 (55.7)	230 (56.0)	404 (57.1)	406 (57.4)
Events associated with dose reduction	45 (9.3)	45 (9.3)	41 (10.0)	41 (10.0)	62 (8.8)	62 (8.8)
Events associated with infusion interruption [a]	NA	NA	NA	NA	NA	NA
Events associated with dose delay [a]	NA	NA	NA	NA	NA	NA
Events associated with study drug discontinuation	3 (0.6)	3 (0.6)	3 (0.7)	3 (0.7)	4 (0.6)	4 (0.6)
Events associated with an outcome of death	0	0	0	0	0	0

[a] Information on infusion interruption and dose delay as an outcome of the TEAE was collected separately in Study TL01 and in Study TL05, whereas Study TP01 collected this information as "study drug interruption" (ie, did not differentiate between infusion interruption and dose delay). Therefore, the pools do not include information on infusion interruption or dose delay.

Percentages are based on the number of subjects in the Safety Analysis Set.

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.

Source: ISS Table 3.1.4.1, 120-DSU Table 3.1.4.1

Source: Updated ISS.

Stomatitis is clearly an adverse event with impact on quality of life but not on mortality.

Stomatitis is described in section 4.2, 4.4 (including risk-mitigation), and 4.8 of the SmPC, which is satisfactory.

Mucosal inflammation other than oral mucositis/stomatitis

Although this is considered an AESI the incidence was very low. One could speculate that this group clinically is overlapping with the Oral mucositis/stomatitis AESI.

Table 153 Overview of Treatment-emergent AESI of Mucosal Inflammation Other than Oral Mucositis/Stomatitis Among Subjects Who Received Dato-DXd Across Pools (Safety Analysis Set)

	Number (%) of Subjects Who Received Dato-DXd					
	NSCLC 6 mg/kg (N = 484)		NSCLC Non-squamous 6 mg/kg (N = 411)		NSCLC + BC ≥4 mg/kg (N = 707)	
	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU
Subjects with an AESI of mucosal inflammation other than oral mucositis/stomatitis	9 (1.9)	10 (2.1)	7 (1.7)	8 (1.9)	35 (5.0)	36 (5.1)
CTCAE Grade ≥2	6 (1.2)	7 (1.4)	5 (1.2)	6 (1.5)	25 (3.5)	26 (3.7)
CTCAE Grade ≥3	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	7 (1.0)	7 (1.0)
Serious events	0	0	0	0	2 (0.3)	2 (0.3)
Drug-related events	7 (1.4)	8 (1.7)	6 (1.5)	7 (1.7)	32 (4.5)	33 (4.7)
Events associated with dose reduction	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	9 (1.3)	9 (1.3)
Events associated with infusion interruption [a]	NA	NA	NA	NA	NA	NA
Events associated with dose delay [a]	NA	NA	NA	NA	NA	NA
Events associated with study drug discontinuation	0	0	0	0	0	0
Events associated with an outcome of death	0	0	0	0	0	0

[a] Information on infusion interruption and dose delay as an outcome of the TEAE was collected separately in Study TL01 and in Study TL05, whereas Study TP01 collected this information as "study drug interruption" (ie, did not differentiate between infusion interruption and dose delay). Therefore, the pools do not include information on infusion interruption or dose delay.

Percentages are based on the number of subjects in the Safety Analysis Set.

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.

Source: ISS Table 3.1.4.1, 120-DSU Table 3.1.4.1

Source: Updated ISS.

Ocular surface toxicity

Current risk mitigation strategies include mandatory ophthalmologic assessments at baseline (as clinically needed) and at the end of treatment, and preventative measures such as use of artificial tears. Management guidelines were provided in all protocols for clinical studies, with information in the ICF about the risk of ocular surface toxicity.

Phase 3 study TL01:

In study TL01 PTs in the AESI of ocular surface toxicity were higher in the Dato-DXd arm compared to the docetaxel arm (20.9%) vs. 27 (9.3%)], with the corresponding Grade ≥3 incidences 1.7% and 0%, respectively. For Grade ≥3 events the PTs were keratitis, ulcerative keratitis, and visual acuity reduced.

Pooled safety:

The incidence of the individual PTs that comprise ocular surface toxicity were reported in similar proportions of subjects in the Dato-DXd arm of Study TL01 and the Primary safety pool.

Table 154 Overview of Treatment-emergent AESI of Ocular Surface Toxicity Among Subjects Who Received Dato-DXd Across Pools (Safety Analysis Set)

	Number (%) of Subjects Who Received Dato-DXd					
	NSCLC 6 mg/kg (N = 484)		NSCLC Non-squamous 6 mg/kg (N = 411)		NSCLC + BC ≥4 mg/kg (N = 707)	
	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU
Subjects with an AESI of ocular surface toxicity	105 (21.7)	110 (22.7)	94 (22.9)	98 (23.8)	188 (26.6)	193 (27.3)
CTCAE Grade ≥2	39 (8.1)	41 (8.5)	35 (8.5)	37 (9.0)	68 (9.6)	70 (9.9)
CTCAE Grade ≥3	9 (1.9)	9 (1.9)	9 (2.2)	9 (2.2)	12 (1.7)	12 (1.7)
Serious events	2 (0.4)	2 (0.4)	2 (0.5)	2 (0.5)	3 (0.4)	3 (0.4)
Drug-related events	86 (17.8)	90 (18.6)	78 (19.0)	82 (20.0)	154 (21.8)	158 (22.3)
Events associated with dose reduction	8 (1.7)	8 (1.7)	8 (1.9)	8 (1.9)	14 (2.0)	14 (2.0)
Events associated with infusion interruption [a]	NA	NA	NA	NA	NA	NA
Events associated with dose delay [a]	NA	NA	NA	NA	NA	NA
Events associated with study drug discontinuation	4 (0.8)	4 (0.8)	4 (1.0)	4 (1.0)	9 (1.3)	9 (1.3)
Events associated with an outcome of death	0	0	0	0	0	0

[a] Information on infusion interruption and dose delay as an outcome of the TEAE was collected separately in Study TL01 and in Study TL05, whereas Study TP01 collected this information as "study drug interruption" (ie, did not differentiate between infusion interruption and dose delay). Therefore, the pools do not include information on infusion interruption or dose delay.
Percentages are based on the number of subjects in the Safety Analysis Set.
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.
Source: ISS Table 3.1.4.1, 120-DSU Table 3.1.4.1

Source: Updated ISS.

Keratitis is listed as an Important identified risk in the RMP, which is agreed.

Keratitis is described in section 4.2, 4.4, and 4.8 of the SmPC, which is satisfactory.

3.3.7.4. Laboratory findings

Haematology:

Phase 3 study TL01:

The main differences between the Dato-DXd arm and docetaxel arm in study TL01 were seen for neutrophils: **Neutropenia (grouped term)** reported as a Grade 3 AE, was observed with a frequency of 1.0% in the Dato-DXd arm compared to 23.8% in the docetaxel arm (DCO 29.03.2023).

In study TL01 4.0% in the Dato-DXd arm and 4.8% in the docetaxel arm had **anemia (grouped term)** Grade ≥3 (DCO 29.03.2023).

No patient in the Dato-DXd arm had a Grade ≥3 event of **thrombocytopenia (grouped term)** and 1 (0.3%) patient in the docetaxel arm had a Grade 4 event (DCO 29.03.2023).

Table 155 Summary of Shifts from Baseline to Worst Post-baseline CTCAE Grade in Neutrophil Count in Study TL01 (Safety Analysis Set)

Treatment Arm	Baseline CTCAE Grade	Number (%) of Subjects with Each Worst Post-baseline CTCAE Grade (Low)							
		0	1	2	3	4	3 or 4	Total	Missing
Dato-DXd (N = 297)	0	233 (81.8)	22 (7.7)	20 (7.0)	3 (1.1)	1 (0.4)	4 (1.4)	279 (97.9)	12
	1	1 (0.4)	3 (1.1)	0	0	0	0	4 (1.4)	0
	2	0	0	2 (0.7)	0	0	0	2 (0.7)	0
	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
	3 or 4	0	0	0	0	0	0	0	0
	Total	234 (82.1)	25 (8.8)	22 (7.7)	3 (1.1)	1 (0.4)	4 (1.4)	285 (100.0)	12
Docetaxel (N = 290)	0	191 (68.7)	12 (4.3)	7 (2.5)	13 (4.7)	48 (17.3)	61 (21.9)	271 (97.5)	12
	1	2 (0.7)	1 (0.4)	0	0	2 (0.7)	2 (0.7)	5 (1.8)	0
	2	0	0	0	0	0	0	0	0
	3	1 (0.4)	0	0	0	0	0	1 (0.4)	0
	4	1 (0.4)	0	0.20	0	0	0	1 (0.4)	0
	3 or 4	2 (0.7)	0	0	0	0	0	2 (0.7)	0
	Total	195 (70.1)	13 (4.7)	7 (2.5)	13 (4.7)	50 (18.0)	63 (22.7)	278 (100.0)	12

Baseline value is defined as the last non-missing value prior to the first dose of study drug.
On-treatment period is defined as the interval from the date of the first dose up to 35 days after the last dose of study drug (inclusive).
All on-treatment visits, including repeat and unscheduled visits, were included.
The grade for a reported laboratory value was derived based on the numeric component of CTCAE v5.0.
Percentages for each treatment arm are based on the number of subjects in the Safety Analysis Set who had both a baseline assessment and at least 1 post-baseline assessment. (ie, the number of subjects in the intersection of the Total row and the Total column) as the denominator
Source: Module 5.3.5.1 Study TL01 CSR Table 14.3.4.3

Pooled results:

Table 156 Summary of Shifts from Baseline to Worst Post-baseline CTCAE Grade in Neutrophil Count Among Subjects Who Received Dato-DXd Across Studies and Pools (Safety Analysis Set)

Study/Pool	Baseline CTCAE Grade	Number (%) of Subjects with Each Worst Post-baseline CTCAE Grade (Low)							
		0	1	2	3	4	3 or 4	Total	Missing
TL01 NSCLC 6 mg/kg (N = 297)	0	233 (81.8)	22 (7.7)	20 (7.0)	3 (1.1)	1 (0.4)	4 (1.4)	279 (97.9)	12
	1	1 (0.4)	3 (1.1)	0	0	0	0	4 (1.4)	0
	2	0	0	2 (0.7)	0	0	0	2 (0.7)	0
	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
	3 or 4	0	0	0	0	0	0	0	0
	Total	234 (82.1)	25 (8.8)	22 (7.7)	3 (1.1)	1 (0.4)	4 (1.4)	285 (100.0)	12
TL01 NSCLC Non-squamous 6 mg/kg (N = 232)	0	180 (80.4)	17 (7.6)	18 (8.0)	2 (0.9)	1 (0.4)	3 (1.3)	218 (97.3)	8
	1	1 (0.4)	3 (1.3)	0	0	0	0	4 (1.8)	0
	2	0	0	2 (0.9)	0	0	0	2 (0.9)	0
	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
	3 or 4	0	0	0	0	0	0	0	0
	Total	181 (80.8)	20 (8.9)	20 (8.9)	2 (0.9)	1 (0.4)	3 (1.3)	224 (100.0)	8
NSCLC 6 mg/kg (N = 484)	0	384 (81.9)	39 (8.3)	27 (5.8)	6 (1.3)	2 (0.4)	8 (1.7)	458 (97.7)	15
	1	1 (0.2)	4 (0.9)	3 (0.6)	1 (0.2)	0	1 (0.2)	9 (1.9)	0
	2	0	0	2 (0.4)	0	0	0	2 (0.4)	0
	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
	3 or 4	0	0	0	0	0	0	0	0
	Total	385 (82.1)	43 (9.2)	32 (6.8)	7 (1.5)	2 (0.4)	9 (1.9)	469 (100.0)	15

Table 156 Summary of Shifts from Baseline to Worst Post-baseline CTCAE Grade in Neutrophil Count Among Subjects Who Received Dato-DXd Across Studies and Pools (Safety Analysis Set)

Study/Pool	Baseline CTCAE Grade	Number (%) of Subjects with Each Worst Post-baseline CTCAE Grade (Low)							
		0	1	2	3	4	3 or 4	Total	Missing
NSCLC Non-squamous 6 mg/kg (N = 411)	0	325 (81.3)	32 (8.0)	25 (6.3)	5 (1.3)	2 (0.5)	7 (1.8)	389 (97.3)	11
	1	1 (0.3)	4 (1.0)	3 (0.8)	1 (0.3)	0	1 (0.3)	9 (2.3)	0
	2	0	0	2 (0.5)	0	0	0	2 (0.5)	0
	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
	3 or 4	0	0	0	0	0	0	0	0
	Total	326 (81.5)	36 (9.0)	30 (7.5)	6 (1.5)	2 (0.5)	8 (2.0)	400 (100.0)	11
NSCLC + BC ≥4 mg/kg (N = 707)	0	580 (83.8)	57 (8.2)	34 (4.9)	7 (1.0)	2 (0.3)	9 (1.3)	680 (98.3)	15
	1	1 (0.1)	4 (0.6)	4 (0.6)	1 (0.1)	0	1 (0.1)	10 (1.4)	0
	2	0	0	2 (0.3)	0	0	0	2 (0.3)	0
	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
	3 or 4	0	0	0	0	0	0	0	0
	Total	581 (84.0)	61 (8.8)	40 (5.8)	8 (1.2)	2 (0.3)	10 (1.4)	692 (100.0)	15

Baseline value is defined as the last non-missing value prior to the first dose of study drug.
On-treatment period is defined as the interval from the date of the first dose up to 35 days after the last dose of study drug (inclusive).
All on-treatment visits, including repeat and unscheduled visits, were included.
The grade for a reported laboratory value was derived based on the numeric component of CTCAE v5.0.
Percentages are based on the number of subjects in the Safety Analysis Set who had both a baseline assessment and at least 1 post-baseline assessment (ie, the number of subjects in the intersection of the Total row and the Total column) as the denominator.
Source: Module 5.3.5.3 ISS Table 3.3.3

See also the Common adverse events-section for neutropenia, grouped term.

Clinical chemistry

Few patients had shifts in **LFT value**. No patients met the criteria for Hy's Law. Only patients with normal and mild **hepatic** impairment were included. No recommendation regarding use in patients with moderate or severe hepatic impairment can thus be given.

Table 157 Hepatic Function Abnormalities Among Subjects Who Received Dato-DXd Across Studies and Pools (Safety Analysis Set)

Maximum Post-baseline Value for Laboratory Parameters	Number (%) of Subjects Who Received Dato-DXd					
	NSCLC 6 mg/kg (N = 484)		NSCLC Non-squamous 6 mg/kg (N = 411)		NSCLC + BC ≥4 mg/kg (N = 707)	
	BLA	120-DSU	BLA	120-DSU	BLA	120-DSU
Alanine aminotransferase (ALT)						
≥3 × ULN	15 (3.1)	15 (3.1)	15 (3.6)	15 (3.6)	27 (3.8)	27 (3.8)
≥5 × ULN	6 (1.2)	6 (1.2)	6 (1.5)	6 (1.5)	8 (1.1)	8 (1.1)
≥8 × ULN	4 (0.8)	4 (0.8)	4 (1.0)	4 (1.0)	5 (0.7)	5 (0.7)
≥10 × ULN	2 (0.4)	2 (0.4)	2 (0.5)	2 (0.5)	3 (0.4)	3 (0.4)
≥20 × ULN	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Aspartate aminotransferase (AST)						
≥3 × ULN	15 (3.1)	15 (3.1)	13 (3.2)	13 (3.2)	29 (4.1)	29 (4.1)
≥5 × ULN	6 (1.2)	6 (1.2)	5 (1.2)	5 (1.2)	10 (1.4)	10 (1.4)
≥8 × ULN	3 (0.6)	3 (0.6)	2 (0.5)	2 (0.5)	6 (0.8)	6 (0.8)
≥10 × ULN	3 (0.6)	3 (0.6)	2 (0.5)	2 (0.5)	5 (0.7)	5 (0.7)
≥20 × ULN	0	0	0	0	0	0
ALT or AST						
≥3 × ULN	22 (4.5)	22 (4.5)	20 (4.9)	20 (4.9)	40 (5.7)	40 (5.7)
≥5 × ULN	7 (1.4)	7 (1.4)	6 (1.5)	6 (1.5)	12 (1.7)	12 (1.7)
≥8 × ULN	5 (1.0)	5 (1.0)	4 (1.0)	4 (1.0)	8 (1.1)	8 (1.1)
≥10 × ULN	4 (0.8)	4 (0.8)	3 (0.7)	3 (0.7)	6 (0.8)	6 (0.8)
≥20 × ULN	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Total bilirubin (TBL)						
≥1.5 × ULN	5 (1.0)	6 (1.2)	4 (1.0)	4 (1.0)	13 (1.8)	14 (2.0)
≥2 × ULN	0	0	0	0	6 (0.8)	6 (0.8)
≥3 × ULN	0	0	0	0	4 (0.6)	4 (0.6)
Alkaline phosphatase (ALP)						
≥1.5 × ULN	103 (21.3)	104 (21.5)	85 (20.7)	86 (20.9)	163 (23.1)	164 (23.2)
≥2 × ULN	53 (11.0)	53 (11.0)	44 (10.7)	44 (10.7)	84 (11.9)	84 (11.9)
Concurrent (ALT or AST ≥3 × ULN) and (TBL ≥2 × ULN) [a]	0	0	0	0	4 (0.6)	4 (0.6)
Concurrent (ALT or AST ≥3 × ULN), (TBL ≥2 × ULN), and (ALP <2 × ULN) [a]	0	0	0	0	1 (0.1)	1 (0.1)

[a] Concurrent is defined as abnormalities occurring within a 28-day window.
Percentages are calculated using n as the denominator.
Each subject is counted for only the worst case observed post-baseline.
Categories are cumulative; eg, a subject with an elevation of ALT >8 × ULN also appears in the categories of ALT >5 × ULN and ALT >3 × ULN).
Source: 120-DSU Table 3.3.6

Source: Updated ISS.

Few patients had shifts in serum **creatinine values** and most were <Gr. 3. Patients with normal to moderate **renal** impairment were included. No recommendations for patients with severe renal

impairment can thus be given. Shifts in serum creatinine values among subjects with non-squamous histology were similar to those among all subjects.

Table 96 Summary of Shifts from Baseline to Worst Post-Baseline Value in Creatinine Clearance Among Subjects Who Received Dato-DXd Across Studies and Pools (Safety Analysis Set)

Study/Pool	Baseline	Number (%) of Subjects with Each Worst Post-baseline Renal Function					
		Normal	Mild	Moderate	Severe	Total	Missing
TL01 NSCLC 6 mg/kg (N = 297)	Normal	47 (16.4)	48 (16.8)	4 (1.4)	2 (0.7)	101 (35.3)	4
	Mild	3 (1.0)	89 (31.1)	40 (14.0)	3 (1.0)	135 (47.2)	4
	Moderate	0	2 (0.7)	45 (15.7)	2 (0.7)	49 (17.1)	3
	Severe	0	0	1 (0.3)	0	1 (0.3)	0
	Total	50 (17.5)	139 (48.6)	91 (31.5)	7 (2.4)	286 (100.0)	11
TL01 NSCLC Non-squamous 6 mg/kg (N = 232)	Normal	38 (17.0)	36 (16.1)	3 (1.3)	1 (0.4)	78 (34.8)	3
	Mild	0	70 (31.3)	34 (15.2)	1 (0.4)	105 (46.9)	4
	Moderate	0	2 (0.9)	37 (16.5)	1 (0.4)	40 (17.9)	1
	Severe	0	0	1 (0.4)	0	1 (0.4)	0
	Total	38 (17.0)	108 (48.2)	75 (33.5)	3 (1.3)	224 (100.0)	8
NSCLC 6 mg/kg (N = 484)	Normal	80 (17.0)	81 (17.2)	8 (1.7)	2 (0.4)	171 (36.4)	5
	Mild	4 (0.9)	132 (28.1)	67 (14.3)	5 (1.1)	208 (44.3)	6
	Moderate	0	2 (0.4)	84 (17.9)	4 (0.9)	90 (19.1)	3
	Severe	0	0	1 (0.2)	0	1 (0.2)	0
	Total	84 (17.9)	215 (45.7)	160 (34.0)	11 (2.3)	470 (100.0)	14
NSCLC Non-squamous 6 mg/kg (N = 411)	Normal	70 (17.5)	68 (17.0)	6 (1.5)	1 (0.3)	145 (36.3)	4
	Mild	1 (0.3)	112 (28.0)	59 (14.8)	2 (0.5)	174 (43.5)	6
	Moderate	0	2 (0.5)	75 (18.8)	3 (0.8)	80 (20.0)	1
	Severe	0	0	1 (0.3)	0	1 (0.3)	0
	Total	71 (17.8)	182 (45.5)	141 (35.3)	6 (1.5)	400 (100.0)	11
NSCLC + BC ≥4 mg/kg (N = 707)	Normal	143 (20.6)	125 (18.0)	10 (1.4)	2 (0.3)	280 (40.4)	5
	Mild	5 (0.7)	173 (25.0)	96 (13.9)	7 (1.0)	281 (40.5)	6
	Moderate	0	4 (0.6)	120 (17.3)	6 (0.9)	130 (18.8)	3
	Severe	0	0	2 (0.3)	0	2 (0.3)	0
	Total	148 (21.4)	302 (43.6)	228 (32.9)	15 (2.2)	693 (100.0)	14

Baseline value is defined as the last non-missing value prior to the first dose of study drug.
On-treatment period is defined as the interval from the date of the first dose up to 35 days after the last dose of study drug (inclusive).
All on-treatment visits, including repeat and unscheduled visits, were included.
The grade for a reported laboratory value was derived based on the numeric component of CTCAE v5.0.
Percentages are based on the number of subjects in the Safety Analysis Set who had both a baseline assessment and at least 1 post-baseline assessment.
Normal renal function = CrCl ≥90 mL/min; mild renal impairment = CrCl ≥60 and <90 mL/min; moderate renal impairment = CrCl ≥30 and <60 mL/min; severe renal impairment = CrCl ≥15 and <30 mL/min
One subject who was classified with moderate renal impairment at baseline had a worst post-baseline renal function of end stage (CrCl <15 mL/min) and is included in the severe category.

Source: Module 5.3.5.3 ISS Table 3.3.7

3.3.7.5. In vitro biomarker test for patient selection for safety

Not applicable.

3.3.7.6. Safety in special populations

Age:

In Study TL01, the Dato-DXd subgroup ≥65 years had a higher incidence of Grade ≥3 AEs compared to the <65 years group (43.5% vs 51.7%). This was also reflected in the safety pool (40.7% vs 51.1%). Despite these differences the frequencies of SAEs were comparable.

Table 158 TEAEs by Age Range for Dato-DXd Among Subjects Who Received Dato-DXd in Study TL01 and the NSCLC 6 mg/kg Pool (Safety Analysis Set) DCO: TL01 13 Oct 2023; TL05 14 Dec 2022; TP01 NSCLC 30 Jul 2021

	Number (%) of Subjects who Received Dato-DXd			
	TL01 Dato-DXd (N = 297)		Pool NSCLC 6 mg/kg (N = 484)	
	<65 (N = 162)	≥65 (N = 135)	<65 (N = 283)	≥65 (N = 201)
Subjects with any TEAE	159 (98.1)	132 (97.8)	280 (98.9)	197 (98.0)
Drug-related TEAE	143 (88.3)	117 (86.7)	256 (90.5)	174 (86.6)
TEAE CTCAE Grade ≥3	66 (40.7)	69 (51.1)	123 (43.5)	104 (51.7)
Drug-related TEAE CTCAE Grade ≥3	36 (22.2)	40 (29.6)	66 (23.3)	62 (30.8)
Serious TEAE	49 (30.2)	42 (31.1)	85 (30.0)	64 (31.8)
Drug-related serious TEAE	17 (10.5)	15 (11.1)	25 (8.8)	25 (12.4)
TEAE associated with study drug discontinuation	20 (12.3)	17 (12.6)	31 (11.0)	26 (12.9)
TEAE associated with dose reduction	42 (25.9)	24 (17.8)	62 (21.9)	39 (19.4)
TEAE associated with infusion interruption[a]	6 (3.7)	1 (0.7)	NA	NA
TEAE associated with dose delay[a]	49 (30.2)	58 (43.0)	NA	NA
TEAE associated with an outcome of death	9 (5.6)	7 (5.2)	14 (4.9)	9 (4.5)

CTCAE = Common toxicity criteria for adverse events; Dato-DXd = datopotamab deruxtecan; NA = not applicable; NSCLC = non-small cell lung cancer; TEAE = treatment-emergent adverse event
[a] Information on infusion interruption and dose delay as action taken associated with TEAE was collected separately in Study TL01 and in Study TL05, whereas Study TP01 did not differentiate between infusion interruption and dose delay; therefore, the number (%) of subjects at the Pool columns are not available.
Source: Module 1, Appendix 5 MAA D120 Table Q125.1

Source: D120 response, Q125.

SEX: No differences were noted among male subjects and female subjects in study TL01 or in the primary safety pool (NSCLC 6 mg/kg Pool; Table 5.3/SCS).

RACE: In study TL01 and the primary safety pool (n=484) AEs of Grade ≥3 and SAEs occurred more frequently in Caucasian patients compared to Asian, although the corresponding drug-related events were of the same magnitude. There were few Black/Other patients (Table 5.4/SCS).

ECOG

In study TL01 and the primary safety pool (n=484) AEs of Grade ≥3 and SAEs occurred more frequently in patients with ECOG 1 compared to ECOG 0, although the corresponding drug-related events were of the same magnitude. All adverse events-related deaths occurred in the patients with ECOG 1. Poorer ECOG PS is a negative prognostic factor in patients with NSCLC and the majority of AEs associated with death in study TL01 were not considered to be drug related.

Table 159 Overview of Treatment-emergent Adverse Events Among Subjects Who Received Dato-DXd, by ECOG Performance Status (Safety Analysis Set)

	Number (%) of Subjects Who Received Dato-DXd			
	Study TL01 NSCLC 6 mg/kg (N = 297)		NSCLC 6 mg/kg Pool (N = 484)	
	ECOG PS 0 (n = 86)	ECOG PS 1 (n = 209)	ECOG PS 0 (n = 143)	ECOG PS 1 (n = 339)
Subjects with any TEAE	84 (97.7)	203 (97.1)	141 (98.6)	332 (97.9)
Drug-related TEAE	82 (95.3)	173 (82.8)	138 (96.5)	287 (84.7)
TEAE CTCAE Grade ≥3	30 (34.9)	102 (48.8)	55 (38.5)	169 (49.9)
Drug-related TEAE CTCAE Grade ≥3	21 (24.4)	52 (24.9)	37 (25.9)	88 (26.0)
Serious TEAE	15 (17.4)	73 (34.9)	29 (20.3)	117 (34.5)
Drug-related serious TEAE	9 (10.5)	21 (10.0)	16 (11.2)	32 (9.4)
TEAE associated with study drug discontinuation	10 (11.6)	25 (12.0)	14 (9.8)	41 (12.1)
TEAE associated with dose reduction	20 (23.3)	45 (21.5)	33 (23.1)	67 (19.8)
TEAE associated with infusion interruption [a]	1 (1.2)	6 (2.9)	NA	NA
TEAE associated with dose delay [a]	31 (36.0)	73 (34.9)	NA	NA
TEAE associated with an outcome of death [b]	0	16 (7.7)	0	23 (6.8)

[a] Information on infusion interruption and dose delay as an action taken for the TEAE was collected separately in Study TL01 and in Study TL05, whereas Study TP01 collected this information as "study drug interrupted" (ie, did not differentiate between infusion interruption and dose delay). Therefore, the NSCLC 6 mg/kg Pool does not include information on infusion interruption, dose delay, or study drug interruption.

[b] For specific TEAEs associated with an outcome of death, see Table 2.14.

Percentages are calculated based on the number of subjects in the subgroup in the Safety Analysis Set.

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 relationship is missing, the AE is considered to be related to the study drug.

Source: Module 5.3.5.3 ISS Table 3.1.1.2

Actionable genomic alterations at baseline: In the Dato-DXd arm of Study TL01 AEs of Grade ≥3 (any and drug-related) occurred more frequently in subjects without AGA (n = 247), although uncertainties exist due to the relative low number of patients with AGA (n = 50) at baseline. In the Primary safety population, no major differences were noted among subjects with AGA (n = 197) and subjects without AGA (n = 287) at baseline (Table 5.7/SCS).

Table 160 Overview of Treatment-emergent Adverse Events Among Subjects Who Received Dato-DXd, by AGA Status at Baseline (Safety Analysis Set)

	Number (%) of Subjects Who Received Dato-DXd			
	Study TL01 NSCLC 6 mg/kg (N = 297)		NSCLC 6 mg/kg Pool (N = 484)	
	AGA (n = 50)	Non-AGA (n = 247)	AGA (n = 197)	Non-AGA (n = 287)
Subjects with any TEAE	48 (96.0)	241 (97.6)	195 (99.0)	280 (97.6)
Drug-related TEAE	47 (94.0)	210 (85.0)	184 (93.4)	243 (84.7)
TEAE CTCAE Grade ≥3	16 (32.0)	116 (47.0)	88 (44.7)	136 (47.4)
Drug-related TEAE CTCAE Grade ≥3	7 (14.0)	66 (26.7)	51 (25.9)	74 (25.8)
Serious TEAE	11 (22.0)	77 (31.2)	50 (25.4)	96 (33.4)
Drug-related serious TEAE	2 (4.0)	28 (11.3)	14 (7.1)	34 (11.8)
TEAE associated with study drug discontinuation	2 (4.0)	33 (13.4)	16 (8.1)	39 (13.6)
TEAE associated with dose reduction	15 (30.0)	50 (20.2)	45 (22.8)	55 (19.2)
TEAE associated with dose interruption [a]	1 (2.0)	6 (2.4)	NA	NA
TEAE associated with dose delay [a]	19 (38.0)	85 (34.4)	NA	NA
TEAE associated with an outcome of death [b]	0	16 (6.5)	3 (1.5)	20 (7.0)

[a] Information on infusion interruption and dose delay as an action taken for the TEAE was collected separately in Study TL01 and in Study TL05, whereas Study TP01 collected this information as "study drug interrupted" (ie, did not differentiate between infusion interruption and dose delay). Therefore, the NSCLC 6 mg/kg Pool does not include information on infusion interruption, dose delay, or study drug interruption.
[b] For specific TEAEs associated with an outcome of death, see Table 2.14.
AGA subjects are those with at least 1 documented AGA in epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1), neurotrophic receptor tyrosine kinase (NTRK), B-rapidly accelerated fibrosarcoma (BRAF), MET exon 14 skipping, or rearranged during transfection (RET).
Percentages are calculated based on the number of subjects in the subgroup in the Safety Analysis Set.
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 relationship is missing, the AE is considered to be related to the study drug.
Source: Module 5.3.5.3 ISS Table 3.1.1.2

Brain metastases at baseline: In the Primary safety population, no differences were noted between subjects with brain metastases (n = 96) and subjects without brain metastases (n = 388) (Table 5.8/SCS).

Renal function at baseline: In the Primary safety population, drug-related Grade ≥3 AEs and drug-related SAEs occurred more frequently in subjects with moderate renal impairment at baseline (n = 93) than in subjects with normal renal function (n = 176) or mild renal impairment (n = 214) although the corresponding overall frequencies were comparable (Table 5.9/SCS).

The PTs seen in all three categories were stomatitis, alopecia, gastrointestinal PTs and general PTs such fatigue and asthenia.

Hepatic function at baseline: In the Primary safety population, no differences were noted among subjects with normal hepatic function (n = 406) or mild hepatic impairment (n = 78), at baseline.

Geographic region: For the Primary safety population, the applicant has pooled Japan/USA/Western Europe (n=365) and compared to the rest of the world (n=119). Upon request additional pooling was performed showing the results for Western Europe and USA and pooled. Across the Study TL01 geographic subgroups receiving Dato-DXd, AEs associated with an outcome of death was the only category to show a notable difference across the region subgroups (a notable difference was defined as a difference of ≥10 percentage points and/or clinically relevant ≥2-fold difference in incidence), with a lower rate in Japan compared with all of the other regions, which all had similar rates. Other differences were lower.

Table 161 TEAEs by Region in Subjects Receiving Dato-DXd in Study TL01 and the NSCLC 6 mg/kg Pool (Safety Analysis Set) DCO: TL01 13 Oct 2023; TL05 14 Dec 2022; TP01 NSCLC 30 Jul 2021

	Number (%) Subjects Who Received Dato-DXd									
	TL01 Dato-DXd (N = 297)					NSCLC 6.0 mg/kg Pool (N = 484)				
Subjects with	Japan (n = 52)	USA (n = 33)	Western Europe (n = 127)	USA/ Western Europe (n = 160)	Rest of World (n = 85)	Japan (n = 96)	USA (n = 110)	Western Europe (n = 159)	USA/ Western Europe (n = 269)	Rest of World (n = 119)
Any TEAE	51 (98.1)	32 (97.0)	125 (98.4)	157 (98.1)	83 (97.6)	95 (99.0)	108 (98.2)	157 (98.7)	265 (98.5)	117 (98.3)
Drug-related TEAE	50 (96.2)	30 (90.9)	114 (89.8)	144 (90.0)	66 (77.6)	93 (96.9)	98 (89.1)	145 (91.2)	243 (90.3)	94 (79.0)
TEAE CTCAE Grade ≥3	26 (50.0)	15 (45.5)	61 (48.0)	76 (47.5)	33 (38.8)	43 (44.8)	61 (55.5)	77 (48.4)	138 (51.3)	46 (38.7)
Drug-related TEAE CTCAE Grade ≥3	18 (34.6)	9 (27.3)	35 (27.6)	44 (27.5)	14 (16.5)	33 (34.4)	31 (28.2)	43 (27.0)	74 (27.5)	21 (17.6)
Serious TEAE	15 (28.8)	8 (24.2)	42 (33.1)	50 (31.3)	26 (30.6)	23 (24.0)	42 (38.2)	52 (32.7)	94 (34.9)	32 (26.9)
Drug-related serious TEAE	8 (15.4)	3 (9.1)	14 (11.0)	17 (10.6)	7 (8.2)	14 (14.6)	11 (10.0)	18 (11.3)	29 (10.8)	7 (5.9)
TEAE associated with study drug discontinuation	7 (13.5)	4 (12.1)	15 (11.8)	19 (11.9)	11 (12.9)	12 (12.5)	15 (13.6)	17 (10.7)	32 (11.9)	13 (10.9)
TEAE associated with dose reduction	14 (26.9)	8 (24.2)	29 (22.8)	37 (23.1)	15 (17.6)	20 (20.8)	19 (17.3)	41 (25.8)	60 (22.3)	21 (17.6)
TEAE associated with infusion interruption[a]	1 (1.9)	0	4 (3.1)	4 (2.5)	2 (2.4)	NA	NA	NA	NA	NA
TEAE associated with dose delay[a]	20 (38.5)	13 (39.4)	47 (37.0)	60 (37.5)	27 (31.8)	NA	NA	NA	NA	NA
TEAE associated with an outcome of death	1 (1.9)	2 (6.1)	8 (6.3)	10 (6.3)	5 (5.9)	1 (1.0)	8 (7.3)	8 (5.0)	16 (5.9)	6 (5.0)

CTCAE = common toxicity criteria for adverse events; Dato-DXd = datopotamab deruxtecan; NSCLC = non-small cell lung cancer; TEAE = treatment-emergent adverse event

[a] Information on infusion interruption and dose delay as action taken associated with TEAE was collected separately in Study TL01 and in Study TL05, whereas Study TP01 did not differentiate between infusion interruption and dose delay; therefore the number of subjects (%) at the pools columns are not available

Source: Module 1, Appendix 5 MAA D120 Table Q127.1

Source: D120 responses, Q127.

Histology:

Despite shorter exposure SAEs and ≥Grade 3 adverse events were seen with a noticeable higher frequency in the squamous NSCLC compared to the non-squamous NSCLC. The applicant has restricted the indication to the latter, which from a safety point of view is agreed.

Table 162 Overview of Treatment-emergent Adverse Events in Study TL01, by Histology (Safety Analysis Set)

	Overall		Non-squamous Histology		Squamous Histology	
	Dato-DXd (N = 297)	Docetaxel (N = 290)	Dato-DXd (N = 232)	Docetaxel (N = 221)	Dato-DXd (N = 65)	Docetaxel (N = 69)
Median treatment duration (months)	4.2	2.8	4.9	2.8	2.2	2.8
Subjects with any TEAE	289 (97.3)	284 (97.9)	228 (98.3)	217 (98.2)	61 (93.8)	67 (97.1)
Drug-related TEAE	257 (86.5)	252 (86.9)	205 (88.4)	195 (88.2)	52 (80.0)	57 (82.6)
TEAE CTCAE Grade ≥3	132 (44.4)	168 (57.9)	95 (40.9)	123 (55.7)	37 (56.9)	45 (65.2)
Drug-related TEAE CTCAE Grade ≥3	73 (24.6)	120 (41.4)	51 (22.0)	90 (40.7)	22 (33.8)	30 (43.5)
Serious TEAE	88 (29.6)	106 (36.6)	62 (26.7)	75 (33.9)	26 (40.0)	31 (44.9)
Drug-related serious TEAE	30 (10.1)	36 (12.4)	19 (8.2)	25 (11.3)	11 (16.9)	11 (15.9)
TEAE associated with study drug discontinuation	35 (11.8)	48 (16.6)	29 (12.5)	36 (16.3)	6 (9.2)	12 (17.4)
TEAE associated with dose reduction	65 (21.9)	90 (31.0)	52 (22.4)	69 (31.2)	13 (20.0)	21 (30.4)
TEAE associated with infusion interruption [a]	7 (2.4)	15 (5.2)	6 (2.6)	13 (5.9)	1 (1.5)	2 (2.9)
TEAE associated with dose delay [a]	104 (35.0)	68 (23.4)	81 (34.9)	51 (23.1)	23 (35.4)	17 (24.6)
TEAE associated with an outcome of death[b]	16 (5.4)	10 (3.4)	8 (3.4)	5 (2.3)	8 (12.3)	5 (7.2)

[a] Information on infusion interruption and dose delay as an outcome of the TEAE was collected separately in Study TL01 and in Study TL05, whereas Study TP01 collected this information as "study drug interrupted" (ie, did not differentiate between infusion interruption and dose delay). Therefore, the NSCLC 6 mg/kg Pool does not include information on infusion interruption, dose delay, or study drug interruption.

[b] For specific TEAEs associated with an outcome of death, see Table 2.14.

Percentages are based on the number of subjects in the subgroup in the Safety Analysis Set.

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 relationship is missing, the AE is considered to be related to the study drug.

Source: Module 5.3.5.1 Study TL01 CSR Post Hoc Table 14.10.1.1 and Table 14.10.2.2

3.3.7.7. Immunological events

See the pharmacology section, pharmacodynamics.

3.3.7.8. Safety related to drug-drug interactions and other interactions

See the pharmacology section.

3.3.7.9. Discontinuation due to adverse events

In study TL01 AEs were associated with discontinuation of study drug in 37 (12.5%) subjects in the Dato-DXd arm and 50 (17.2%) subjects in the docetaxel arm. The most frequent reason for discontinuation in the Dato-DXd arm was pneumonitis/ILD whereas in the docetaxel arm it was

pneumonia, pneumonitis, asthenia, and peripheral neuropathy in declining order. The results for the Dato-DXd arm were similar in the overall safety pool (11.8%).

Table 163: TEAEs Associated with Study Drug Discontinuation in Study TL01 - Reported in At Least 1% of Subjects in Either Treatment Arm by SOC and Preferred Term (Safety Analysis Set) DCO: ISS 120 DSU 13 Oct 2023

MedDRA SOC Preferred Term	Study TL01 Number (%) of Subjects	
	Dato-DXd 6 mg/kg (N = 297)	Docetaxel (N = 290)
Subjects with any TEAE associated with study drug discontinuation	37 (12.5)	50 (17.2)
General disorders and administration site Conditions	3 (1.0)	14 (4.8)
Asthenia	2 (0.7)	5 (1.7)
Fatigue	0	3 (1.0)
Infections and infestations	7 (2.4)	14 (4.8)
Pneumonia	2 (0.7)	6 (2.1)
Nervous system disorders	0	9 (3.1)
Neuropathy peripheral	0	4 (1.4)
Respiratory, thoracic and mediastinal disorders	19 (6.4)	10 (3.4)
Pneumonitis	12 (4.0)	5 (1.7)
Interstitial lung disease	4 (1.3)	2 (0.7)

Dato-DXd = datopotamab deruxtecan; MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; SOC = system organ class; TEAE = treatment-emergent adverse event
Source: Module 1, Appendix 5 MAA D120 Table Q128.7

Source: D120 responses, Q128. In study TL01 the frequencies of dose reduction in the Dato-DXd arm was 22.2% compared to 31.0% in the docetaxel arm. The most frequent reason for discontinuation in the Dato-DXd arm was stomatitis (10.1%), whereas in the docetaxel arm it was PTs related to neutropenia. The results for the Dato-DXd arm were similar in the overall safety pool (20.9%). The frequencies of dose delay in the Dato-DXd arm was 36.0% compared to 24.1% in the docetaxel arm with COVID-19 infection being the most common in both arms (7.7% in the Dato-DXd arm and 4.1% in the docetaxel arm). The most commonly reported AEs associated with dose delay in the NSCLC 6 mg/kg (Study TL01 + TL05) Pool were COVID-19 (8.8%) and stomatitis (4.8%).

Table 164 TEAEs Associated with Study Drug Discontinuation Among Subjects Who Received Dato-DXd in Study TL01 and Across Pools, Reported in At Least 1% of Subjects in the NSCLC 6 mg/kg Pool by SOC and Preferred Term (Safety Analysis Set) DCO: TL01 13 Oct 2023; TL05 14 Dec 2022; TP01 NSCLC 30 Jul 2021

MedDRA SOC Preferred Term	Number (%) of Subjects Who Received Dato-DXd				
	Study TL01		Pool		
	NSCLC 6 mg/kg (N = 297)	NSCLC Non-squamous 6 mg/kg (N = 232)	NSCLC 6 mg/kg (N = 484)	NSCLC Non-squamous 6 mg/kg (N = 411)	NSCLC + BC ≥4 mg/kg (N = 707)
Subjects with any TEAE associated with study drug discontinuation	37 (12.5)	29 (12.5)	57 (11.8)	48 (11.7)	91 (12.9)
Respiratory, thoracic and mediastinal disorders	19 (6.4)	14 (6.0)	28 (5.8)	23 (5.6)	46 (6.5)
Pneumonitis	12 (4.0)	9 (3.9)	18 (3.7)	15 (3.6)	33 (4.7)
Interstitial lung disease	4 (1.3)	4 (1.7)	5 (1.0)	5 (1.2)	6 (0.8)

BC = breast cancer; Dato-DXd = datopotamab deruxtecan; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; SOC = system organ class; TEAE = treatment-emergent adverse event
Percentages are based on the number of subjects in the Safety Analysis Set.
Preferred terms are sorted by decreasing frequency in the NSCLC 6 mg/kg Pool.
Source: Module 1 Appendix 5 MAA D120 Table Q128.1

Table 165 Adjudicated Drug-related ILD/Pneumonitis Associated with Study Drug Discontinuation Reported in At Least 1% of Subjects in the TL01 NSCLC 6 mg/kg Pool by Preferred Term, Among Subjects Who Received Dato-DXd in Study TL01, and Across Pools (Safety Analysis Set) DCO: TL01 13 Oct 2023; TL05 14 Dec 2022; TP01 NSCLC 30 Jul 2021; TP01 BC 22 Jul 2022

	Number (%) of Subjects Who Received Dato-DXd				
	Study TL01		Pool		
	NSCLC 6 mg/kg (N = 297)	NSCLC Non-squamous 6 mg/kg (N = 232)	NSCLC 6 mg/kg (N = 484)	NSCLC Non-squamous 6 mg/kg (N = 411)	NSCLC + BC ≥4 mg/kg (N = 707)
Adjudicated drug-related ILD/pneumonitis events associated with study drug discontinuation	15 (5.1)	12 (5.2)	20 (4.1)	17 (4.1)	35 (5.0)
Pneumonitis	10 (3.4)	7 (3.0)	15 (3.1)	12 (2.9)	27 (3.8)
Interstitial lung disease	3 (1.0)	3 (1.3)	3 (0.6)	3 (0.7)	4 (0.6)

BC = breast cancer; Dato-DXd = datopotamab deruxtecan; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; TEAE = treatment-emergent adverse event
Percentages are based on the number of subjects in the Safety Analysis Set.
Source: Module 1, Appendix 5 MAA D120 Table Q128.5

3.3.7.10. Post-marketing experience

Not applicable.

3.3.8. Discussion on clinical safety

The safety profile of Dato-DXd for NSCLC was evaluated in the ongoing phase 3 randomised study TL01 consisting of 297 patients in the Dato DXD arm and 290 patients in the docetaxel arm. The **Primary safety population (n=484)** is agreed with the applicant: this comprises the Dato-DXd arm of study TL01 and 187 NSCLC patients from two single arm trials (TL05; n=137 and TP01; n=50)

receiving Dato-DXd in the recommended dose of 6 mg/kg. In study TL01 78% had non-squamous NSCLC, whereas in the two SATs together >95% had non-squamous NSCLC. As the proposed indication is restricted to subjects with non-squamous histology, safety data have also been presented separately for this population.

In the randomised study TL01 (DCO 13.10.23), the median **duration of treatment** was longer in the Dato DXd arm than in the docetaxel arm (4.2 months vs. 2.8 months), with 14.5% and 4.1% of subjects, respectively, receiving >12 months of study drug. Exposure was longer for patients with non-squamous NSCLC (4.9 months) compared to squamous NSCL (2.2 months).

In the Primary safety population, the median duration of exposure was also 4.2 months and 76 patients (15.7%) received >12 months of Dato-DXd. Updated safety data was provided during the review process.

Demographic and baseline characteristics were similar between the Dato DXd and docetaxel arms of Study TL01 and the Primary safety pool. The primary safety pool includes more subjects with actionable genomic alterations compared to the randomised study TL01 (AGA, 46.7% vs. 16.8%, respectively), a higher proportion of subjects from the USA (22.7% vs. 11.1%), and a higher proportion who had never smoked (31.8% vs. 20.5%) compared to the pivotal study.

Overall, the safety database is sufficient to characterise the safety profile of Dato-DXd in the target population. The pooled safety data allows assessment of less frequently occurring AEs and as well as in subgroups. Long term safety data is limited, which is not of major concern given that most subjects (about 80%) already discontinued treatment, mainly due to progressive disease.

Adverse events:

In the phase 3 study TL01 there was a higher incidence of Grade ≥3 AEs, SAEs, and discontinuations due to AEs in the docetaxel arm compared to the Dato-DXd arm despite the shorter median duration of treatment with docetaxel. There was a higher incidence of AEs associated with an outcome of death in the Dato-DXd arm (discussed below). With the updated safety data (+6.5 months) no new adverse events with an outcome of death were seen in the Dato-DXd arm (16) and 1 in the docetaxel arm (11). When looking at histology it seems there were relatively more deaths in the squamous NSCLC arm despite the shorter median duration of exposure. The results were similar for the Primary safety pool.

For study TL01, adverse events in the gastrointestinal SOC (stomatitis, nausea, and vomiting) were higher in the Dato-DXd arm compared with the docetaxel arm although in most instances they were grade 1-2. For the docetaxel arm cytopenias, febrile neutropenia, diarrhea, oedema peripheral, and neuropathy were observed with a higher frequency compared to the Dato-DXd arm. Grade ≥3 neutropenia and neutrophil count decreased were reported in ≥10% of subjects in the docetaxel arm leading to febrile neutropenia in 6.6%. Despite the higher frequencies of these preferred terms, this did not lead to higher overall infection frequencies (by SOC).

Adverse events of special interest (AESI):

Several AESIs that include many preferred terms were described. In the following those with the most impact on safety are described.

The incidence of **ILD/pneumonitis** was slightly higher in study TL01 compared to the primary safety pool; 8.8% vs 7.4%, respectively, for adjudicated ILD regardless of relatedness to Dato-DXd. Based on the ILD AC's adjudication there were 7/297 deaths due to ILD/pneumonitis in the Dato-DXd arm and 1/290 in the docetaxel arm. At least 5.4% experienced an SAE and 5.1% discontinued due to ILD. No new ILD events were seen with the 6.5 months updated data from study TL01. Median time to onset of the first event was 69.5 days (range: 12-379). Events were managements with steroid treatment (not specified) and dose modifications. Fifteen (5.1%) subjects discontinued treatment with Dato-DXd due

to adjudicated drug-related ILD. At the time of the DCO, the event had resolved/was resolving in 14/25 (56.0%) of subjects. Appropriate warnings have been included in section 4.4 of the SmPC. In addition, information is included in section 4.2, 4.4, and 4.8 of the SmPC. The correct frequency to be presented in the SmPC is the all-cause ILD/pneumonitis, and not the drug-related AE, as proposed by the applicant.

It is clear that ILD (includes several PTs) is a serious risk with a frequency of Common and with a potentially fatal outcome with the treatment of Dato-DXd. When ILD occurs, prompt action is needed, and in patients with their disease already located in the lungs, recognising ILD from for instance pneumonia and exacerbation of COPD, is challenging, and may contribute to delayed treatment with potentially fatal consequences. This concern needs to be considered in the B/R evaluation. ILD/pneumonitis is listed as an Important identified risk in the RMP and described in the relevant sections in the SmPC.

Infusion-related reactions (IRR) was comparable between the two arms in study TL01 (8.1% in the Dato-DXd arm and 8.3% in the docetaxel arm). For the primary safety pool (n=484) the frequency was higher (12.2%), as listed in the ADR table of the SmPC (Very common) with two SAEs (0.4%). Most common IRR by PT in the Dato-DXd arm were rash (3.0%), pruritis (2.7%), and IRR (1.3%). Most were Grade 1 or Grade 2 events, and only 1 Grade 3 event was reported in the Dato-DXd arm. At the time of the DCO, the event had resolved or resolved with sequelae in 20/24 (83.3%) subjects, was resolving in 1/24 (4.2%) subject, and was not resolved in 3/24 (12.5%) subjects. In the SmPC risk-mitigation for IRR is described.

In study TL01 PTs in the AESI of **oral mucositis/stomatitis** were higher in the Dato-DXd arm (and similar in the primary safety pool), compared to the docetaxel arm 54.9% vs. 20.3%, with the corresponding Grade ≥3 incidences 6.7% and 1.4%, respectively. Median time to onset of the first event was 15 days (range: 1 to 313). At the time of the DCO, the event had resolved/were resolving in 111/160 (69.4%) subjects. Dose modifications for stomatitis are included in section 4.2, as well as recommendations for prophylaxis and treatment in section 4.4 of the SmPC. The proposed risk minimization measures are in line with that of the pivotal study and acceptable/appropriate. Stomatitis is clearly an adverse event with impact on quality of life but not on mortality.

In study TL01 PTs in the AESI of **ocular surface toxicity** were higher in the Dato-DXd arm compared to the docetaxel arm although with few Grade ≥3 in the Dato-DXd arm. At the time of the DCO, 37/62 (59.7%) subjects in the Dato-DXd arm had events that had resolved or were resolving. The risk of ocular surface toxicity increased with exposure time. Within the NSCLC 6 mg/kg pool, 11.5% subjects with exposure <6 months and 36.6% with exposure >6 months ≤12 months had ocular surface toxicity. Keratitis (Grouped term) was reported in 4.7% of subjects in the randomised study vs. 0.3% in the comparator arm. The median time to onset for keratitis was 6.3 months (section 4.8 SmPC). Dose modifications have been included in the SmPC section 4.2 for keratitis and precautionary measures/warnings are included in section 4.4. These are in line with the study protocol and appropriate. However, patients with clinically significant corneal disease were excluded from the study (see section 5.1 SmPC). A statement that these patients may be at an increased risk and need careful monitoring has been added to the SmPC, section 4.4. The incidence was similar in the Primary safety pool. Keratitis is listed as an Important identified risk in the RMP.

SAE, Death, and discontinuation/dose reduction:

In the randomised study TL01 a total of 30.6% subjects in the Dato-DXd arm and 37.6% of subjects in the docetaxel arm had at least 1 **serious AE**. Pneumonia (5.1%) and pneumonitis (4.0%) were the most frequently reported SAEs by PT in the Dato-DXd arm, followed by stomatitis (1.7%). No event was reported in ≥10% of subjects in either treatment arm. The proportion of subjects with SAEs was similar between the Dato-DXd arm of Study TL01 (n=297) and the Primary safety population (n=484).

In study TL01 the main preferred terms leading to an SAE were within the SOC 'Infections and Infestations' and the AESI ILD/pneumonitis.

With the updated safety data for study TL01 (DCO 13-10-23), three additional SAEs in each arm were observed including one case of pneumonitis in the Dato-DXd arm.

In study TL01 a total of 16 (5.4%) patients in the Dato-DXd arm and 11 (3.8%) patients in the docetaxel arm had AEs associated with an outcome of **death**. Based on the ILD AC's adjudication there were 7 deaths due to ILD/pneumonitis in the Dato-DXd arm and 1 in the docetaxel arm, indicating that ILD/pneumonitis remains a major issue with these types of products. There was 1 additional Grade 5 event in the NSCLC 6 mg/kg pool (overall incidence 1.7%). In 5 out of 8 subjects, the investigator assessed the primary cause of death to be disease progression.

The proportion of subjects with AEs associated with an outcome of **death** was similar between the Dato-DXd arm of Study TL01 and the NSCLC 6 mg/kg Pool. With regards to the AESI ILD/pneumonitis there were fewer in the SATs. It is considered that a randomised trial more accurately reflects the frequencies of AEs. The applicant states that 4 cases of drug related fatal TEAEs were reported in the safety pool; 3 of pneumonitis and 1 sepsis. However, 2 additional cases treated with Dato-DXd were also identified, one Grade 5 pneumonitis and one Grade 5 pulmonary toxicity. Both cases were considered by the applicant non-TEAEs but assessed as drug related. If the additional cases are counted, 6 drug-related fatal TEAEs were observed in the Dato-DXd arm. The two additional cases of Grade 5 pneumonitis and Grade 5 pulmonary toxicity assessed as drug related should be counted as drug-related fatal TEAEs, and the related tables in Overview and CSR should be updated accordingly. (**OC**).

To justify a higher treatment-related mortality a substantial benefit is considered required.

In study TL01 AEs were associated with **discontinuation** of study drug in 37 (12.5%) subjects in the Dato-DXd arm and 50 (17.2%) subjects in the docetaxel arm. The most frequent reason for discontinuation in the Dato-DXd arm was pneumonitis/ILD. The results for the Dato-DXd arm were similar in the overall safety pool (11.8%).

The frequency of **dose reduction** in the Dato-DXd arm was 22.2% compared to 31.0% in the docetaxel arm. The most frequent reason for discontinuation in the Dato-DXd arm was stomatitis (10.1%), whereas in the docetaxel arm it was PTs related to neutropenia. The results for the Dato-DXd arm were similar in the overall safety pool (20.9% overall dose reduction).

The frequencies of **dose delay** in the Dato-DXd arm were 36.0% compared to 24.1% in the docetaxel arm with COVID-19 infection being the most common in both arms (7.7% in the Dato-DXd arm and 4.1% in the docetaxel arm). The most commonly reported AEs associated with dose delay in the NSCLC 6 mg/kg (Study TL01 + TL05, n= 434) Pool were COVID-19 (8.8%) and stomatitis (4.8%).

Safety in special populations.

Age: In study TL01 the Dato-DXd subgroup ≥65 years had a higher incidence of Grade ≥3 AEs compared to the <65 years group (43.5% vs 51.7%). This was also reflected in the safety pool (40.7% vs 51.1%). Despite these differences the frequencies of SAEs were comparable. Overall, data in elderly (≥75 years) is limited but tolerability appears lower and a statement reflecting this should be included in section 4.8 SmPC (**SmPC comment**).

Sex: No differences were noted among male subjects and female subjects in study TL01 or in the primary safety pool.

Race: In study TL01 and the primary safety pool (n=484) AEs of Grade ≥3 and SAEs occurred more frequently in Caucasian patients compared to Asian.

ECOG: In study TL01 and the primary safety pool (n=484) AEs of Grade ≥3 and SAEs occurred more frequently in patients with ECOG 1 compared to ECOG 0. All adverse events-related deaths occurred in the patients with ECOG 1: poorer ECOG PS is a negative prognostic factor in patients with NSCLC and the majority of AEs associated with death in study TL01 were not considered to be drug related. ,

Brain metastases at baseline: In the Primary safety population, no differences were noted between subjects with brain metastases (n = 96) and subjects without brain metastases (n = 388).

Renal function at baseline: In the Primary safety population, drug-related Grade ≥3 AEs and drug-related SAEs occurred more frequently in subjects with moderate renal impairment at baseline (n = 93) than in subjects with normal renal function (n = 176) or mild renal impairment (n = 214). The PTs seen in all three categories were stomatitis, alopecia, gastrointestinal PTs and general PTs such fatigue and asthenia. A statement on higher incidence of AEs in patients with moderate renal impairment should be considered in section 4.2 SmPC, as for Enhertu (**SmPC comment**).

Hepatic function at baseline: In the Primary safety population, no differences were noted among subjects with normal hepatic function (n = 406) or mild hepatic impairment (n = 78), at baseline. Patients with moderate or severe hepatic impairment were excluded. AEs of Grade ≥3 and SAEs occurred more frequently in subjects with mild hepatic impairment. As metabolism and biliary excretion are the primary routes of elimination of the topoisomerase I inhibitor, DXd, a warning in section 4.4 reflecting the limited/lack of data is considered justified in line with that of Enhertu **(SmPC comment)**.

Results by histology: The overall safety profile in the non-squamous subgroup was in general comparable to that of the safety set and somewhat worse in the subgroup with squamous histology, especially with regard to Grade ≥3 TEAEs and SAEs. This was seen in both treatment arms and may be related to differences in the population with squamous NSCLC having more comorbidity, and subjects generally being older.

Geographic region: For the Primary safety population, the applicant has pooled Japan/USA/Western Europe (n=365) and compared to the rest of the world (n=119), which is not agreed, and an OC has been raised.

ADR table section 4.8 SmPC: ADRs were based on the pivotal trial, the supportive studies TP01 and TL05, clinical pharmacology data including the ER analysis, non-clinical data, an epidemiology/literature review was performed as well as review of in-class or similar class product labels (e.g. trastuzumab deruxtecan, Sacituzumab govitecan). The identification of ADRs is not fully agreed as it appears that in certain cases events that were an ADR for the comparator arm and observed at lower frequencies in the Dato-DXd arm, could not be an ADR for Dato-DXd. Furthermore, several AEs (e.g. dyspnoea, cough, dysgeusia) were not selected as ADR whereas these are included as ADR for Enhertu and a justification has been requested.

Laboratory findings:

Haematological events are known for ADCs due to their payload, however, except for anaemia appear less frequent with Dato-DXd. Though observed at low frequencies (≤2.4%), AEs of leukopenia, lymphocyte count decreased, neutropenia and neutrophil count decreased as well as white blood cell count decreased were reported as drug-related adverse events. A further justification is requested why these were not considered ADRs for inclusion in section 4.8 SmPC has been requested (**SmPC comment)**. The main differences between the Dato-DXd arm and docetaxel arm in study TL01 were

seen for neutrophils: **Neutropenia** (grouped term) reported as a Grade 3 AE, was observed with a frequency of 1.0% in the Dato-DXd arm compared to 23.8% in the docetaxel arm. Clinically, though, this did not lead to a higher frequency of all-grades infections (by SOC) with similar frequencies for the PT Pneumonia (10.1% vs. 10.3%) although 5.4% vs 7.2%, respectively, for ≥Grade 3 Pneumonia., although SAEs related to infections were twice as high in the docetaxel arm compared to Dato-DXd.

Few patients had shifts in LFT value. No patients met the criteria for Hy's Law. Only patients with normal and mild **hepatic impairment** were included. Increases in ALT and AST were reported in about 5% of subjects but were not classified as ADR. This should be further justified by the applicant given that increases in transaminases are known side effects of topoisomerase inhibitors (**SmPC comment**). No recommendation regarding use in patients with moderate or severe hepatic impairment can thus be given, and this is listed as Missing information in the Summary of safety concerns in the RMP.

Few patients had shifts in serum creatinine values and most were <Gr. 3. Patients with normal to moderate **renal impairment** were included. No recommendations for patients with severe renal impairment can thus be given.

3.3.9. Conclusions on clinical safety

The safety profile of Dato-DXd in the proposed indication of locally advanced or metastatic non-squamous NSCLC is non-negligible: in the randomised study TL01, SAEs and ≥ Grade 3 AEs were more frequent in the docetaxel arm compared to the Dato-DXd arm, whereas deaths due to adverse events were seen more frequently in the Dato-DXd arm; 16 (5.4%) compared to 11 (3.8%) in the docetaxel arm. Of the 16 AE-related deaths in the Dato-DXd arm 7 were due to the AESI ILD/pneumonitis, which is considered the safety issue of greatest concern. In addition, GI events, skin toxicities, and ocular surface toxicity were frequently observed with SAEs related to infections being the main concern in the docetaxel arm.

3.4. Risk management plan

3.4.1. Safety specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 166 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Interstitial lung disease / pneumonitis Keratitis
Important potential risks	Embryo-foetal toxicity
Missing information	Use in patients with moderate or severe hepatic impairment

3.4.1.1. Discussion on safety specification

The Safety Concerns for inclusion in the RMP are agreed:

Important identified risks:

Interstitial **lung disease/pneumonitis** is a potentially life-threatening event that requires immediate medical evaluation/intervention, as if not recognised or managed appropriately, may result in a fatal outcome.

Whilst ILD/pneumonitis is not completely preventable, actions can be taken to reduce the risk of serious adverse outcomes.

Keratitis, if not recognised or managed appropriately, may lead to persistent or significant disability (impaired vision or loss of sight).

Actions can be taken to reduce the possibility of events of keratitis progressing to a more severe outcome.

Important potential risks:

It is possible that exposure to Dato-DXd during pregnancy may cause severe **foetal harm**.

Contraception guidelines for both women of childbearing potential and men with female partners of childbearing potential are provided in the Dato-DXd SmPC and PL. The pregnancy status of females of childbearing potential should be verified prior to the initiation of Dato-DXd, and females of childbearing potential and male patients with female partners of childbearing potential should be advised to use effective contraception.

Missing information:

No dedicated **hepatic impairment** study has been conducted, and only a limited number of patients with moderate or severe hepatic impairment have received Dato-DXd in the clinical development programme to date (see Table II-SII.1).

Based on the evidence that the DXd payload is primarily hepatically excreted, it is unknown whether moderate or severe hepatic impairment may have an effect on Dato-DXd elimination and exposure in humans. The safety profile of Dato-DXd may therefore be different in patients with moderate or severe hepatic impairment.

Population in need of further characterisation

Patients with advanced/unresectable HR-positive, HER2-negative breast cancer, and patients with locally advanced/metastatic non-squamous NSCLC, who have moderate or severe hepatic impairment.

Data from ongoing studies will be reviewed to further characterise the safety profile of Dato-DXd in these patient populations.

3.4.1.2. Conclusions on the safety specification

Having considered the data in the safety specification t is agreed that the safety concerns listed by the applicant are appropriate.

3.4.2. Pharmacovigilance plan

3.4.2.1. Routine pharmacovigilance activities

Regarding routine pharmacovigilance activities, the applicant proposes, beyond adverse reactions reporting and signal detection, as follows:

- **Specific adverse reaction follow-up questionnaires**: Follow-up questionnaire for spontaneous ILD/pneumonitis and keratitis events that captures additional details, including clinical course and presentation, relevant medical history, concomitant medications, and details of laboratory/diagnostic test results (where relevant) for enhanced safety surveillance and monitoring of these important identified risks.

The applicant did not concur recommendation to remove follow-up questionnaires for ILD/pneumonitis and keratitis and is of opinion that such questionnaires may help to collect additional information ADRs of interest. However, follow-up questionnaires are not considered warranted. Although inclusion of these questionnaires to the RMP is not supported, the follow-up of cases ILD/pneumonitis and keratits is considered part of the routine pharmacovigilance and it is expected that the applicant will follow-up on these safety concerns but there is no need for specific questionnaires in the RMP **(OC)**.

3.4.2.2. Summary of additional PhV activities

Not applicable – there are currently no planned additional pharmacovigilance activities.

3.4.2.3. Overall conclusions on the PhV Plan

The applicant included 'Use in patients with moderate or severe hepatic impairment' as missing information but has not proposed any additional pharmacovigilance activities. The applicant informed that patients with severe hepatic impairment were excluded from the clinical trials. The patients with mild and moderate hepatic impairment could have been included; however, the number of patients with moderate hepatic impairment was very limited: 5 patients were included in the TB01 study, and none were enrolled in the TL01 study. The applicant has also stated that based on the epidemiological data, the number of patients with moderate/severe hepatic impairment in applied indication is very low. Having said that the applicant acknowledged that the collection of meaningful data may be limited by the low occurrence of moderate hepatic impairment amongst patients in the target study populations. In addition, the applicant admits that patients with moderate hepatic impairment are unlikely to experience a different safety profile to those with normal hepatic function.

Given that the number of patients is quite limited, and that a study to evaluate safety in these patients is not warranted, this safety concern should not be included as missing information in the safety specification. It can be followed in the PSURs. **(OC)**

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC Rapporteur also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

3.4.3. Plans for post-authorisation efficacy studies

None

3.4.3.1. Summary of Post authorisation efficacy development plan

None

3.4.4. Risk minimisation measures

3.4.4.1. Routine Risk Minimisation Measures

3.4.4.2. Summary of additional risk minimisation measures

For the important identified risk of ILD/pneumonitis, an HCP Guide and a Patient Guide (Including Patient Alert Card) are proposed as additional risk minimisation measures.

Healthcare professional guide

Objectives

To ensure HCPs can promptly recognise and diagnose ILD/pneumonitis to enable its appropriate management.

Rationale for the additional risk minimisation activity

Appropriate recognition and management of ILD/pneumonitis can mitigate worsening of the condition and reduce the risk of serious adverse outcomes.

Target audience and planned distribution path:

Information will be made available to HCPs in a manner appropriate to each market in which Dato-DXd is launched.

Plans to evaluate the effectiveness of the interventions and criteria for success

Routine pharmacovigilance is in place to evaluate the effectiveness of risk minimisation measures. Other suitable measures may be added, if deemed necessary, in a specific country.

Patient guide (including patient alert card)

Objectives

To ensure patients are able to recognise the symptoms of ILD/pneumonitis to enable prompt and appropriate management.

Rationale for the additional risk minimisation activity

Appropriate recognition and management of ILD/pneumonitis can mitigate worsening of the condition and reduce the risk of serious adverse outcomes.

Target audience and planned distribution path:

Information will be made available to patients/caregivers in a manner appropriate to each market in which Dato-DXd is launched.

Plans to evaluate the effectiveness of the interventions and criteria for success

Routine pharmacovigilance is in place to evaluate the effectiveness of risk minimisation measures.

Table 167 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 Sections 4.2, 4.4, and 4.8 • PL Sections 2 and 4 • Legal status: Prescription-only medicine Additional risk minimisation measures: • HCP guide • Patient Guide (including Patient Alert Card)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None
Keratitis	Routine risk minimisation measures: • SmPC Sections 4.2, 4.4, and 4.8 • PL Sections 2 and 4 • Legal status: Prescription-only medicine Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None
Important Potential Risks		
Embryo-foetal toxicity	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.6 • PL Section 2 • Legal status: Prescription-only medicine Additional risk minimisation measures: • None	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 • Legal status: Prescription-only medicine Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

The need of additional risk minimisation measures has been questioned in the first round. The justification provided by the applicant to keep HCP Guide and a Patient Guide for ILD/pneumonitis is not convincing. Reference to Enhertu (trastuzumab deruxtecan) is not considered relevant. ILD is very common for Entertu but is common for datopotamab deruxtecan. Of note, in the SmPC of datopotamab deruxtecan, information related to ILD is described in section 4.2 (dose modification in case of ILD), section 4.4 (diagnostic symptoms and management), section 4.8 (listed ADR in table with more details provided below the table). The current characterisation of ILD and described RMM are deemed adequate, and risk proportionate. This ADR is also in detail described in section 2 and 4 of the PL.

Given the fact that ILD is well characterised in the Product information with appropriate risk minimisation measures, the proposed additional risk minimisation is deemed unnecessary and is not supported. **(OC)**

3.4.4.3. Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that:

The proposed risk minimisation measures need further revision. The proposed additional risk minimisation measures are considered redundant and duplicate information provided in the Product information.

3.4.5. Summary of the risk management plan

The public summary of the RMP may require revision.

3.4.6. PRAC Outcome

PRAC discussed the following points from the Rapporteurs' AR, and recommended changes to the outcomes:

Safety specification and advice to CHMP:

The PRAC considered that 'Use in patients with moderate or severe hepatic impairment' does not need to be included to the RMP as missing information. Given that the number of patients is quite limited, and that a study to evaluate safety in these patients is not warranted, this safety concern cannot be regarded as important. should not be included as missing information in the safety specification.

Pharmacovigilance plan:

The PRAC maintained its previous recommendation to remove follow-up questionnaires for ILD/pneumonitis and keratitis from the routine pharmacovigilance activities, considering that both are well characterized. Nonetheless, the follow-up of cases ILD/pneumonitis and keratits is considered part of the routine pharmacovigilance and it is expected that the applicant will follow-up on these but there is no need for specific questionnaires in the RMP.

Risk minimisation measures:

Given the fact that ILD is well characterised in the Product information with appropriate routine risk minimisation measures, the proposed additional risk minimisation is deemed unnecessary and is not supported (patient card and HCP guide).

3.4.7. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 0.2 could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the list of questions in section 6.3.

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3.5.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list, and a new entry will be required. The new EURD list entry uses the IBD to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request an alignment of the PSUR cycle with the international birth date (IBD). The IBD is {DD.MM.YYYY.}

The first periodic safety update report should cover the six-month period following the initial scientific opinion for this product on <date of initial scientific opinion>.

Subsequently, the scientific opinion holder shall submit periodic safety update reports for this product every 6 months until otherwise agreed.

4. Non-conformity with agreed paediatric investigation plan

Not applicable.

5. Benefit risk assessment

5.1. Therapeutic context

5.1.1. Disease or condition

Marketng authorization is sought for the following indication: *Datopotamab deruxtecan Daiichi Sankyo as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) who require systemic therapy following prior treatment:*

- *Patients without known actionable genomic alterations previously treated with platinum-based chemotherapy in the advanced or metastatic setting and PD-1 or PD-L1 inhibitor, either in combination or sequentially*
- *Patients with actionable genomic alterations (as listed in section 5.1) previously treated with prior platinum-based therapy and targeted therapy for the detected alteration.*

The aim of the therapy of locally advanced/metastatic NSCLC is to prolong overall survival (OS) and progression free survival. Additionally, improvements in symptom control are desirable.

5.1.2. Available therapies and unmet medical need

The standard of care first-line treatment in advanced/metastatic NSCLC without actionable genomic alterations (AGAs) in the US and Europe usually involves an immune checkpoint inhibitor as a monotherapy or in combination with a platinum-based chemotherapy (NCCN 2022, ESMO 2023 guidelines). The use of anti-PD-(L)1 agents has significantly improved outcomes in advanced NSCLC without AGA.

A number of AGAs identified in NSCLC have an impact on therapy selection. These include EGFR mutations, ALK gene rearrangements, KRAS, and more rarely, ROS1 gene rearrangements, NTRK gene fusions, MET exon 14 skipping, RET gene fusions, BRAF V600E mutation, and ERBB2 (HER2) mutations. For patients with AGAs, targeted therapies have become the standard of care in the frontline setting. However, once patients develop acquired resistance to the various targeted therapies, treatment options are limited. After targeted agents have been exhausted, therapy for NSCLC patients with AGAs generally mirrors that used for those without AGA.

For patients with advanced AGA- NSCLC whose tumors progress after frontline therapy with platinum-based chemotherapy and immunotherapy and for AGA+ patients whose tumors progress on targeted

therapies and platinum-based chemotherapy, standard treatment options usually comprise chemotherapy, such as docetaxel, either alone or in combination with other agents.

Overall, 2L+ therapies for advanced NSCLC, regardless of AGA status, only slightly prolong overall survival and progression-free survival (benefit of about 3–6 months compared to best supportive care; source table 1.1 Clinical Overview) and consequently an unmet medical need exists for improving the outcomes for patients who progressed on first line treatment.

5.1.3. Main clinical studies

The current application is based on the results of study TROPION-Lung01 (also known as TL01, DS1062-A-U301), an open-label, randomized 1:1, phase III trial that compared Dato-DXd monotherapy to docetaxel monotherapy in patients with locally advanced or metastatic NSCLC in 2L+ setting (both AGA+ and AGA-). A total of 605 patients were randomized (one patient was counted twice as a result of inclusion error): 299 patients to Dato-DXd and 306 patients to docetaxel (FAS consisted of 299 patients in Dato-DXd arm and 305 patients in docetaxel arm). The study had dual-primary endpoints: overall survival (OS) and progression-free survival by blinded independent reviewer (PFS BICR). Main secondary endpoints were PFS by Investigator (PFS INV), ORR/DoR by BICR.

The safety profile of Dato-DXd in NSCLC was evaluated in the ongoing phase 3 randomised study TL01 consisting of 297 patients in the Dato DXD arm and 290 patients in the docetaxel arm having received at least one dose of the study drug. The primary safety population (n=484) comprises the Dato-DXd arm of study TL01 and 187 NSCLC patients from two single arm trials (TL05; n=137 and TP01; n=50) receiving Dato-DXd at the recommended dose of 6 mg/kg every 21 days.

5.2. Favourable effects

- At DCO (29-MAR-2023), with 431 events (71% maturity; 83% of the events were progressive disease and the rest deaths), Dato-DXd showed a statistically significant improvement of BICR-PFS over docetaxel in the ITT of Study U301, noting HR for BICR-PFS of 0.75 (95% CI 0.62, 0.91), p-value 0.0040. Median PFS was 4.4 in the Dato-DXd arm vs. 3.7 in the docetaxel arm.
- At the primary analysis of PFS, and with median follow-up time for OS of 12.4 months, 305 patients (50% from the ITT) had died, about the same proportion in each arm. Although median OS from Dato-DXd was slightly numerically superior to docetaxel (12.4 vs. 11.0 months), the HR for OS did not reach statistical significance: 0.90 (95% CI 0.72, 1.13), p-value 0.36. The final OS analysis from Study TL01 (DCO 1-MAR-2024) did not yield a positive statistical outcome. At 72% of OS maturity and median follow-up of ~23 months, HR for OS is 0.94 (95% CI 0.78, 1.14), noting mOS 12.9 months for Dato-DXd and 11.8 months for docetaxel.
- Response according to BICR was twice as likely in the Dato-DXd arm (26%) than in the Docetaxel arm (13%), but duration of response was not considerably longer for Dato-DXd (mDOR 7.1 months) vs. docetaxel (mDOR 5.6 months).
- The benefit of Dato-DXd in BICR-PFS and OS seems largely driven by patients with non-squamous histology: HR for BICR-PFS 0.63, 95% CI 0.50, 0.78; HR for OS 0.77, 95% CI 0.59, 1.01.
- Post hoc analyses based on the eCRF dataset for the non-squamous subpopulation confirmed the analyses of the initial efficacy dataset, including the AGA- and AGA+ subgroups
    - Non-squamous AGA- (n= 370): Dato-DXd shows a numerical improvement in mPFS of 1.8 months over docetaxel, which is supported by a 0.8 month improvement in mOS.

The KM curves for PFS show an early separation, whereas those for OS are overlapping.

- mPFS: 5.3 vs. 3.5 months, HR 0.70 (95% CI 0.56, 0.89)
- mOS: 13.1 vs. 12.3 months, HR 0.90 (95% CI 0.68, 1.20)

- Non-squamous AGA+ (n= 98): Dato-DXd shows a numerical improvement in mPFS of 3.6 months over docetaxel, mOS in the Dato-DXd arm is not yet reached. The KM curves for both PFS and OS are clearly separated.
  - mPFS: 5.7 vs. 2.1 months, HR 0.42 (95% CI 0.25, 0.69)
  - mOS: NE vs. 7.5 months, HR 0.30 (95% CI 0.14, 0.65).

5.3. Uncertainties and limitations about favourable effects

- The post hoc subgroup analyses are based on a different dataset (eCRF) than the one for planned analyses (IXRS) on account of mis-stratification, but not all mis-stratified factors were accounted for, raising concerns over internal validity.
- A detrimental effect from Dato-DXd in both BICR-PFS (HR 1.38, 95% CI 0.94, 2.02) and OS (HR 1.32, 95% CI 0.87, 2.00) vs. docetaxel is evident in patients with squamous histology.
- AGA+ patients were allowed to participate as of protocol V4 (20-JAN-2022), when a substantial amount of the originally intended AGA- population had already been randomised. Despite this major protocol amendment, sample size and primary analysis assumptions were not changed.
- Subgroup analyses by AGA status, in both ITT and non-squamous subpopulation suggest that AGA+ patients (19% from the non-squamous subgroup; HR for BICR-PFS 0.35; HR for OS 0.30) seem to drive most of the efficacy from Dato-DXd over docetaxel, whereas their AGA- counterparts, despite representing 79% of the non-squamous subgroup, derive an uncertain efficacy: HR for BICR-PFS 0.71 (95% 0.56, 0.91) and HR for OS 0.90 (0.68, 1.20).
- Up to 80% of patients in supportive study TP05 and the non-squamous AGA+ subgroup (n=98) had EGFR mutations. Therefore, only limited comparative data is available for the other 7 targetable genomic aberrations known in NSCLC.

5.4. Unfavourable effects

In the randomised study TL01 the system organ classes with the most frequently reported AEs (>50%) in both treatment arms were Gastrointestinal Disorders, General Disorders and Administration Site Conditions, and Skin and Subcutaneous Tissue Disorders. The most commonly reported TEAEs (>15%) by preferred term (PT) for Dato-DXd were (in decreasing order) stomatitis (49.8%), nausea (37.7%), alopecia (32.0%), decreased appetite (29.0%), asthenia (23.6%), constipation (19.5%), dyspnoea (17.5%), anaemia (17.5%), fatigue, and vomiting (each 15.8%). Stomatitis and nausea were also among the TEAEs with a ≥10% higher incidence compared to docetaxel.

In the randomised study TL01, **SAE**s and ≥ Grade 3 AEs were more frequent in the docetaxel arm compared to the Dato-DXd arm, whereas **deaths due to adverse events** were seen more frequently in the Dato-DXd arm; 16 (5.4%) compared to 11 (3.8%) in the docetaxel arm. Of the 16 AE-related deaths in the Dato-DXd arm 7 were due to the AESI ILD/pneumonitis. With the updated safety data for study TL01 (DCO 13-10-23), three additional SAEs in each arm were observed including one case of pneumonitis in the Dato-DXd arm.

For the **ECOG** subgroups there was a marked difference in SAEs and deaths in the randomised study with 15/86 (17.4%) with ECOG 0 and 73/209 (34.9%) with ECOG 1 experiencing a SAE, and all 16 deaths due to AE were seen in the ECOG 1 subgroup. Poorer ECOG PS is a negative prognostic factor in patients with NSCLC and the majority of AEs associated with death in study TL01 were not considered to be drug related.

The incidence of the AESI **ILD/pneumonitis** was 8.8% in study TL01 for adjudicated ILD regardless of relatedness to Dato-DXd. Based on the ILD AC's adjudication there were 7/297 deaths due to ILD/pneumonitis in the Dato-DXd arm and 1/290 in the docetaxel arm. At least 5.4% experienced a SAE and 5.1% discontinued due to ILD.

The AESI **ocular surface toxicity**, which is mainly keratitis-related PTs, was seen in 20.9 % in study TL01 and 22.7% in the primary safety pool. Keratitis (Grouped term) was reported in 4.7% of Dato-DXd-treated subjects in study TL01 vs. 0.3% in the comparator arm.

The AESI **oral mucositis/stomatitis** was seen in ≥ 50%, and although mainly grade 1-2, this is an AE with a high impact on QoL.

In study TL01 **infections (SOC)** were seen in 46.5% and 41.0% in the Dato-DXd and docetaxel arm, respectively, with the corresponding ≥Grade 3 observed in 12.1% and 14.1%.

In study TL01 AEs were associated with **discontinuation** in 12.5% in the Dato-DXd arm and 17.2% in the docetaxel arm. The most frequent reason for discontinuation in the Dato-DXd arm was pneumonitis/ILD.

The frequencies of **dose reduction** in the Dato-DXd arm were 22.2% compared to 31.0% in the docetaxel arm. The most frequent reason for discontinuation in the Dato-DXd arm was stomatitis (10.1%), whereas in the docetaxel arm it was PTs related to neutropenia.

The frequencies of **dose delay** in the Dato-DXd arm were 36.0% compared to 24.1% in the docetaxel arm with COVID-19 infection being the most common in both arms (7.7% in the Dato-DXd arm and 4.1% in the docetaxel arm).

The results for the Dato-DXd arm were generally similar in the overall safety pool.

5.5. Uncertainties and limitations about unfavourable effects

Although the larger primary safety pool (n=484) is considered the correct safety pool, uncertainties remain for the results based on the two single-arm trials (n=187).

The risk of ILD in patients with a history of non-infectious ILD/pneumonitis that required steroids is unknown as these were excluded from the trials. Proposed mitigating strategies for ILD (section 4.2 and 4.4 SmPC) appear adequate to reduce the risk of severe/fatal ILD for these patients, but fatal events were still reported.

Patients with clinically significant corneal disease were excluded from the study.

Both ILD and ocular surface toxicity can occur over a longer period of time, and the current frequencies may be somewhat underestimated. However, most subjects were off-treatment at the time of DCO.

There were more Grade ≥3 events and SAEs in subjects >75 years, however the safety data is limited (n=40 pooled safety data).

No safety data is available in patients with moderate/severe hepatic impairment where the safety profile may be different as the drug is primarily hepatically eliminated.

No safety data are available in patients with severe renal impairment.

5.6. Effects table

Table 168 Effects Table for Datopotamab deruxtecan Daiichi Sankyo (Datopotamab deruxtecan) for advanced non-squamous NSCLC (data cut-off: 29 Mar 2023)

Effect	Short Description	Unit	Treatment Dato-DXd N=229	Control Docetaxel N=232	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS by BICR NSQ	Progression free survival	Events n(%) Median in months (95%CI)	156 (68.21) 5.6 (4.4, 7.0)	168 (72.4) 3.7 (2.9, 4.2)	Median FU 10.9 months (95% CI: 9.8, 12.5) for Dato-DXd and 9.6 months (95% CI: 8.2, 11.9) for docetaxel.	CSR
		HR (95%CI)	0.63 (0.50, 0.78)			
PFS by BICR NSQ AGA+		Events n (%) Median in months (95%CI)	25 (52.1) 5.7 (4.2, 8.2)	35 (70) 2.6 (1.4, 3.7)	Relatively small sample size (N=48 Dato-DXd; N=50 Docetaxel) These results come from the post hoc eCRF dataset, after corrections for mis-stratification	
		Unstratified HR (95%CI)	0.35 (0.21, 0.60)			
PFS by BICR NSQ AGA-		Events n (%) Median in months (95%CI)	134 (72) 5.1 (4.2, 6.9)	135 (73.4) 4.0 (3.0, 4.4)	Dato-DXd N=186; Docetaxel N=184 Patients with KRAS mutation or unknown KRAS status were included in this subpopulation.	
		Unstratified HR (95%CI)	0.71 (0.56, 0.91)			
OS NSQ	Overall survival	Events n(%) Median in months (95%CI)	102 (44.5) 13.4 (12.1,16.4)	115(49.6) 11.4 (10.1,14.0)		CSR
		HR (95%CI)	0.77 (0.59, 1.01)			
OS NSQ AGA+		Events n(%) Median in months (95%CI)	9(18.8) NE (8.5, NE)	21(42) 7.5 (6.0, NE)	OS immaturity, relatively small sample size	
		Unstratified HR (95%CI)	0.30 (0.14, 0.65)			

Effect	Short Description	Unit	Treatment Dato-DXd N=229	Control Docetaxel N=232	Uncertainties/ Strength of evidence	References
OS NSQ AGA-		Events n(%) Median in months (95%CI)	96 (51.6) 13.1 (11.5,16.4)	95 (51.6) 12.3 (10.8,14.8)		
		Unstratified HR (95%CI)	0.90 (0.68, 1.20)			
ORR by BICR NSQ	Overall response rate	n(%) (95%CI)	73 (31.2) (25.3,37.6)	30(12.8) (8.8, 17.8)		
DOR by BICR NSQ Responders	Duration of response	Median in months (95%CI)	7.7 (5.6, 11.1)	5.6 (5.4, 6.0)	Dato-DXd N=73; Docetaxel N=30	

Abbreviations: BICR- Blinded independent central review; NSQ – non-squamous; AGA – actionable genomic aberrations.
Notes:
*: Grouped term.

Unfavourable Effects		Unit	Dato-DXd N=297	Docetaxel N=290	Primary safety population N=484/ Uncertainties	Non-squamous histology N=411
Unfavourable Effects						
SAE		N (%)	91 (30.6)	109 (37.6)	149 (30.8)/	120 (29.2)
≥Grade 3 AEs		N (%)	135 (45.5)	171 (59.0)	227 (46.9)	186 (45.3)
Death due to AE		N (%)	16 (5.4)	11 (3.8)	23 (4.8)/	14 (3.4)
Discont. due to AE		N (%)	37 (12.5)	50 (17.2)	57 (11.8)	48 (11.7)
COVID-19*	All grades: Grade ≥3:	N (%)	47 (15.8) 5 (1.7)	31 (10.7) 7 (2.4)	69 (14.3)/ Study performed during the pandemic	64 (15.6)
Neutropenia*	All grades: Grade ≥3:	N (%)	14 (4.7) 3 (1.0)	79 (27.2) 69 (23.8)	30 (6.2)	25 (6.1)
Infections (SOC) Pneumonia (PT):	All grades: Grade ≥3: All grades: Grade ≥3:	N (%)	138 (46.5) 36 (12.1) 32 (10.8) 17 (5.7)	119 (41.0) 41 (14.1) 31 (10.7) 21 (7.2)	210 (43.4) 46 (9.5) 42 (8.7) 20 (4.1)	181 (44.0) 33 (8.0) 32 (7.8) 13 (3.2)
AESIs: (selected)						

Unfavourable Effects		Unit	Dato-DXd N=297	Docetaxel N=290	Primary safety population N=484/ Uncertainties	Non-squamous histology N=411
Pneumonitis/ILD*+	All grades: Deaths:	N (%)	26 (8.8) 7 (2.4)	12 (4.1) 1 (0.3)	35 (7.2) 8 (1.7)/ drug-related; adjudicated by ILD AC. 187 patients from SAT.	29 (7.1) 5 (1.2)
Ocular surface toxicity*	All grades: Grade ≥3:	N (%)	62 (20.9) 5 (1.7)	27 (9.3) 0	110 (22.7) 9 (1.9)	98 (23.8) 9 (2.2)
Keratitis*	All grades: Grade ≥3:	N (%)	15 (5.1) 5 (1.7)	1 (0.3) 0	26 (5.4) 7 (1.4)	25 (6.1) 7 (1.7)
Oral mucositis / stomatitis *	All grades: Grade ≥3:	N (%)	163 (54.9) 20 (6.7)	60 (20.7) 4 (1.4)	287 (59.3) 36 (7.4)	252 (61.3) 33 (8.0)

Notes: *: Grouped term. +All patients adjudicated as ILD/pneumonitis by the ILD AC; not only drug-related, as presented by the applicant.

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

Treatment options for patients with advanced NSCLC after failure of immunotherapy and platinum-based chemotherapy (and after exhausting targeted treatments and failing platinum-based chemotherapy in patients with actionable genomic aberrations, AGA+) are scant, with docetaxel often regarded as the standard-of-care, albeit with limited efficacy.

Per initial design, TL01 was intended to allow recruitment of AGA- patients only, whose treatment approach is completely different than that for AGA+ patients. For AGA- patients the usual approach in the advanced stage (locally advanced unresectable disease not amenable for chemoradiotherapy or metastatic disease) is platinum-based chemotherapy with or without immune checkpoint inhibitors. In AGA+ patients, targeted treatment with selective oral tyrosine kinase inhibitors or bispecific antibodies is prioritised, whereas platinum-based chemotherapy (usually without immune checkpoint inhibitors) is used when targeted treatments have been exhausted.

When the applicant decided on a major amendment of the protocol to allow recruitment of AGA+ patients (by the time overall recruitment was relative close to its end), the CHMP warned about all the risks and caveats from the excessive heterogeneity of results this amendment could imply, and insisted that PFS benefits on their own would likely not suffice for regulatory approval: it was emphasised that substantial survival improvements from a mature dataset would be necessary to consider a positive B/R in the targeted 2L+ setting.

Results from the primary analysis show a clinically borderline (although statistically significant) PFS benefit from Dato-DXd over docetaxel in the ITT (one of the primary endpoints), but methodological issues challenge the validity of these results. Additionally, this marginal PFS benefit is not supported by clinically relevant survival gains (the other primary endpoint). Even when a restricted indication to non-squamous histology is based on evident results from subgroup analyses, the remaining non-squamous dataset still lacks robustness of results to endorse regulatory approval, considering also that

the claimed differential activity on histology was not replicated externally (Paz-Ares et al, J Clin Oncol 2024). The same concerns apply for the presented results of subgroup analyses according to AGA status. The final OS analysis from TL01, rather than addressing these major uncertainties, failed to demonstrate any statistical or clinical benefit from Dato-DXd over docetaxel in NSCLC.

Furthermore, the safety profile from Dato-DXd is of concern: it is characterised by gastrointestinal toxicities and skin and subcutaneous tissue toxicities, which are frequently occurring events from topoisomerase inhibitors. Ocular surface toxicities were also frequently reported events and known for ADCs. Noting that a considerable proportion of lung cancer patients are former or current smokers, and often presents with varying degrees of baseline pulmonary disease, the major safety concern from Dato-DXd is the risk of ILD/pneumonitis, which in many cases led to drug discontinuation. Despite extensive monitoring and risk minimisation measures in line with established clinical guidelines, several fatal events from ILD/pneumonitis were observed.

5.7.2. Balance of benefits and risks

TL01 had a positive outcome on its primary endpoint BICR-PFS in the ITT, but the statistical robustness of the efficacy demonstration is limited, as the p-value is close to the decision-making limit; there was considerable attrition in the control arm; and there were protocol amendments of concern in an open-label study. This efficacy demonstration is not supported by statistically significant nor clinically relevant OS gains as per the final analysis. Subgroup analyses identified the populations that seemed to drive PFS and OS benefits, i.e., non-squamous histology and from these the AGA+ patients (recruited as per a late major protocol amendment), but these data are not deemed reliable nor robust due to the risk of chance finding and the absence of external data corroborating them. Moreover, Dato-DXd exhibits non-negligible toxicities, particularly the risk of severe or even fatal ILD/pneumonitis. In summary, a positive B/R has neither been established in the overall study population nor in any subpopulation thereof. **(MO)**.

5.7.3. Additional considerations on the benefit-risk balance

Subgroup efficacy results provided are inadequate to ascertain B/R in the AGA+ subpopulation. Subsequently, it is not considered justified to generalise the sparse results from this subpopulation as part of the proposed therapeutic indication in advanced NSCLC **(MO)**.

5.8. Conclusions

The overall benefit/risk balance of Datopotamab deruxtecan Daiichi Sankyo is negative.