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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Datroway

International non-proprietary name: Datopotamab deruxtecan

Procedure No. EMA/VR/0000316654

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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List of abbreviations

ADA	Anti-drug antibody
ADC	Antibody drug conjugate
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ASCO/CAP	American Society of Clinical Oncology/College of American Pathologists
AST	Aspartate aminotransferase
AUCtau	Area under curve (for the plasma concentration-time curve during dosing interval)
BC	Breast cancer
BCRP	Breast cancer resistance protein
BICR	Blinded independent central review
CBR	Clinical benefit rate
CDK4/6i	Cyclin-dependent kinases 4 and 6 inhibitors
CI	Confidence interval
Cmax	Maximum observed plasma concentration
COVID-19	Coronavirus disease 2019
CR	Complete response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
Dato-DXd	datopotamab deruxtecan (formerly DS 1062a)
DCO	Data cut-off
DCR	Disease control rate
DDI	Drug-drug interaction
DFI	Disease-free interval
DNA	Deoxyribonucleic acid
DoR	Duration of response
DP	Drug product
DXd	Deruxtecan
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ER	Oestrogen receptor
ESMO	European Society for Medical Oncology
FL-DP	Frozen-liquid drug product
GCP	Good Clinical Practice
geoCV%	Geometric mean coefficient of variation
GHS	Global health status
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
HR+	Hormone receptor positive
IA1	Interim analysis 1
IA2	Interim analysis 2
ICC	Investigator's choice of chemotherapy
ICH	International Council for Harmonisation
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IRR	Infusion-related reaction
ISH	In situ hybridisation
ISS	Integrated Summary of Safety
IV	Intravenous
Lyo-DP	Lyophilised powder drug product
mAb	Monoclonal antibody
MATE	Multidrug and toxin extrusion
MedDRA	Medical dictionary for regulatory activities
MRP	multidrug resistance protein
ms	Milliseconds
MTD	Maximum tolerated dose
N	Number of patients

nAb	Neutralising antibody
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non-small cell lung cancer
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
ORR	Objective response rate
OS	Overall survival
PD	Progression of disease
PDCO	Paediatric Committee
PFS	Progression-free survival
PFS2	Time from randomisation to second progression
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetics
PR	Progesterone receptor
PR	Partial response
PRO	Patient reported outcome
PT	Preferred term
Q3W	Once every 3 weeks
QLQ-C30	Quality of life questionnaire (core 30-items)
QoL	Quality of life
QT	Time on an ECG wave between the start of the Q wave and the end of the T wave
QTc	QT interval of electrocardiogram corrected for heart rate
RECIST 1.1	Response Evaluation Criteria in Solid Tumours Version 1.1
SAE	Serious adverse event
sBR	Structured benefit-risk
SD	Stable disease
SMQ	Standardised MedDRA Queries
SOC	Standard of care
t _{1/2}	Half-life
T-DXd	Trastuzumab deruxtecan (DS-8201a)
TEAE	Treatment-emergent adverse event
TFST	Time to first subsequent therapy
TNBC	Triple negative breast cancer
TROP2	Trophoblast cell surface antigen 2
TSST	Time to second subsequent therapy
TTD	Time to deterioration
TTR	Time-to-response
UGT	Uridine diphosphate glucuronosyltransferases
ULN	Upper limit of normal
V _{ss}	Volume of distribution at steady state
ΔQTc	Change from baseline in QTc

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Daiichi Sankyo Europe GmbH submitted to the European Medicines Agency on 03 December 2025 an application for a variation.

The following variation was requested:

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

Extension of indication to include, as monotherapy, the first-line treatment of adult patients with unresectable or metastatic triple-negative breast cancer (TNBC) who are not candidates for PD-1/PD-L1 inhibitor therapy for DATROWAY, based on final results from study D926PC00001 (TROPION-Breast02). This is a Phase 3, randomised, open-label, 2 arm, multicentre, international study assessing the efficacy and safety of Dato-DXd compared with investigator's choice chemotherapy in participants with locally recurrent inoperable or metastatic TNBC who are not candidates for PD-1/PD-L1 inhibitor therapy. As a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the PI. As part of the application, the MAH is requesting a 1-year extension of the market protection.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0279/2021 on the granting of a (product-specific) waiver for the treatment of breast cancer.

Information relating to orphan market exclusivity

Similarity

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

MAH request for additional market protection

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

Scientific advice

The MAH Scientific Advice from the CHMP on December 2021 (EMA/SA/0000070789). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Thalia Marie Blicher

Timetable	Actual dates
Submission date	03 December 2025
Start of procedure	27 December 2025
CHMP Rapporteur's preliminary assessment report circulated on	18 February 2026
PRAC Rapporteur's assessment report circulated on	24 February 2026
PRAC RMP advice and assessment overview adopted by PRAC	12 March 2026
Request for supplementary information and extension of timetable adopted by the CHMP on	25 March 2026
MAH's responses submitted to the CHMP on	23 April 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	31 May 2026
CHMP opinion	25 June 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Datroway (datopotamab deruxtecan) as monotherapy is indicated for the first-line treatment of adult patients with unresectable or metastatic triple-negative breast cancer (TNBC) who are not candidates for PD-1/PD-L1 inhibitor therapy (see SmPC section 5.1).

Epidemiology and risk factors

Breast cancer (BC) is one of the most common cancers globally, with approximately 2.3 million new cases in 2022 (11.6% of all new cancers) and an estimated 665,000 deaths, making it the fourth leading cause of cancer-related fatalities (Bray et al 2024). In Europe there were about 605,000 new diagnoses and 160,000 deaths due to breast cancer reported in 2023 (ECIS 2023).

Despite advances in the diagnosis and treatment of BC, around 5% to 10% of women diagnosed with BC have metastatic disease at the time of diagnosis, and up to 30% of women with early-stage non-metastatic BC will develop metastatic disease (Cardoso et al 2018, O'Shaughnessy 2005, OECD 2021).

Risk factors of TNBC include family history, longer duration of oral contraceptive use and higher breast density whereas later age at menarche, later age at first birth and breastfeeding are associated with decreased risk of TNBC.

Biologic features

The targeted disease of Triple-negative breast cancer (TNBC) is biologically heterogeneous and should be interpreted as an operational term rather than a fixed pathobiological entity. Previously these patients could only be treated with chemotherapy because of the absence or low expression of oestrogen receptor (>1%), progesterone receptor (>1%), and HER2 expression. In fact, approximately 35% of TNBCs have been reported to be HER2 low illustrating a pivotal difference between triple negative tumours and “truly” triple negative tumours and highlighting just one of several pathobiological entities within the TNBC classification. (Darekshan et al 2022)

Clinical practice classifies 3 BC subtypes, based on molecular characteristics: HER2-positive, HR-positive but HER2-negative and TNBC. Approximately 70% of all BCs are of the subtype HR-positive, HER2-negative (Howlader et al 2014). TNBC, characterized by the absence of ER, progesterone receptor and low or no HER2 protein expression, accounts for 10% to 20% of new BC diagnoses (Allison et al 2020, Wolff et al 2018, Dixon-Douglas et al 2022).

TNBC is typically more aggressive than hormone-receptor positive disease with poorer prognosis due to higher histological grades and the lack of actionable treatment targets, except in patients with PD-L1-positive disease or BRCA mutations (Bonotto et al 2014). Among patients diagnosed with metastatic TNBC, between 25.5% and 37.5% have de novo metastatic disease (Stage IV at initial diagnosis). In patients initially diagnosed with non-metastatic TNBC, up to 40% to 50% experience recurrence, primarily as distant metastases, following standard treatment (Costa and Gradishar 2017, Stewart et al 2019, Jwa et al 2016, Rugo et al 2021).

Clinical presentation, diagnosis and stage/prognosis

TNBC typically presents as a rapidly enlarging, palpable breast mass in younger women and is frequently high-grade with early nodal involvement; diagnosis is established through diagnostic imaging followed by core needle biopsy demonstrating absence of ER, PR, and HER2 expression on immunohistochemistry, with MRI and genetic testing (notably BRCA1/2) often used for disease characterization. Prognosis is strongly stage-dependent with stage I disease showing favourable outcomes and 5-year survival exceeding 85%, stage II disease showing increased recurrence risk but improved survival in patients achieving pathologic complete response after neoadjuvant chemotherapy, stage III disease associated with high rates of locoregional and distant relapse despite multimodal treatment, and stage IV disease conferring poor prognosis with median survival typically under two years and common metastases to lung, liver, brain, and bone (Liedtke et al 2008, Howlader et al 2020).

Management

Current treatment

The choice of initial systemic therapy for metastatic TNBC is individualized based on a number of factors, including PD-L1 status, BRCA status, tumour burden, rate of disease progression, previous chemotherapy exposure, medical history and patient preference. Single-agent chemotherapy remains the mainstay of first-line treatment for metastatic or locally recurrent inoperable TNBC, with the addition of checkpoint inhibitors for patients with PD-L1 positive tumours, while PARP inhibitors may be considered for those patients with germline BRCA mutations (Gradishar et al 2024, Gennari et al 2021, Cardoso et al 2024).

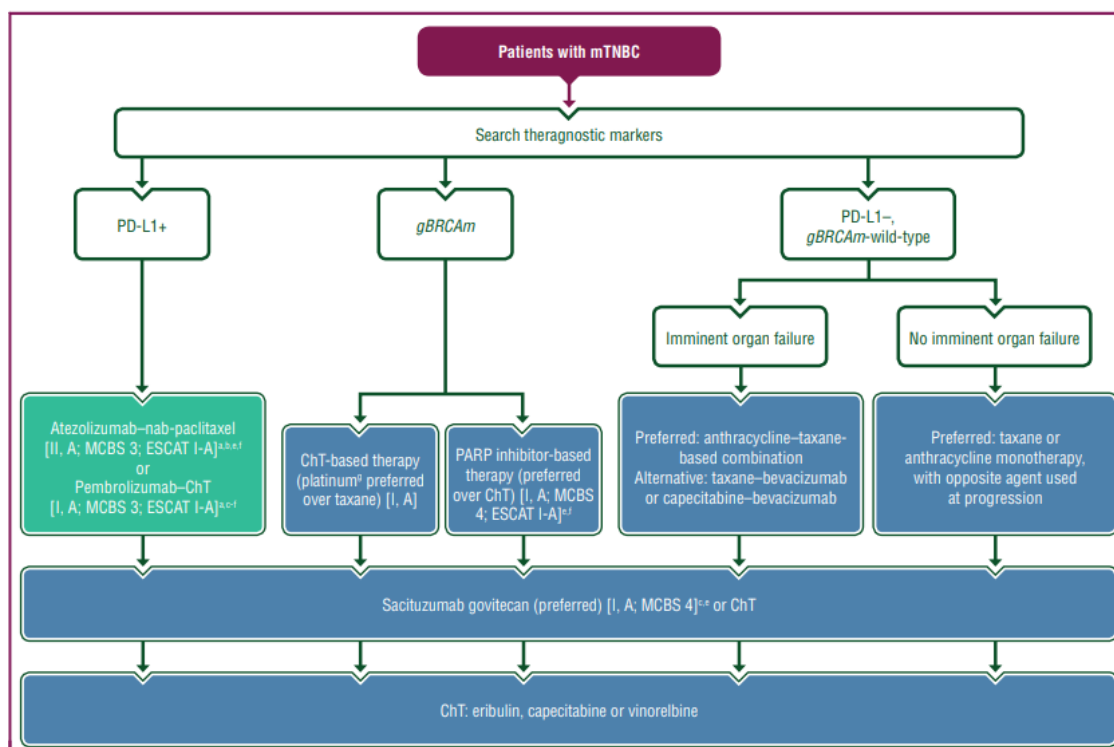


Figure 5. Treatment of mTNBC.

Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management; blue: systemic anticancer therapy.

ChT, chemotherapy; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; gBRCAm, germline BRCA1/2 mutation; ICI, immune checkpoint inhibitor; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mTNBC, metastatic triple-negative breast cancer; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed death-ligand 1.

^a May be considered as monotherapy in further lines in case of high PD-L1 positivity and no previous exposure to ICI.

^b EMA approved, not FDA approved.

^c FDA approved, not EMA approved.

^d ChT physician's choice of nab-paclitaxel, paclitaxel or gemcitabine/carboplatin.

^e ESMO-MCBS v1.1⁹³ was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (<https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1>).

For first-line treatment of metastatic TNBC, chemotherapy remains the standard, particularly for the approximately 70% of patients who are not candidates for immunotherapy, which includes those patients with PD-L1-negative disease, comorbidities precluding PD-1/PD-L1 inhibitors, or recurrence after such therapy (Gradishar et al 2024, Gennari et al 2021, Cardoso et al 2024, Punie et al 2025). In cases where immunotherapy is not an option, sequential single-agent chemotherapy is generally recommended (Gradishar et al 2024, Gennari et al 2021, Cardoso et al 2024). The preferred first-line chemotherapy is a taxane or an anthracycline, with alternatives including capecitabine, gemcitabine, eribulin, vinorelbine, and platinum (Giordano et al 2018, Gradishar et al 2024, Cardoso et al 2024). Re-challenge with taxanes is recommended, provided that there has been at least 1 year of disease-free survival (Gennari et al 2021, Cardoso et al 2024). The median PFS for patients treated with first-line chemotherapy for either recurrent or de novo metastatic TNBC is approximately 5.5 months, with median OS less than 2 years (Cortes et al 2020, Emens et al 2021, Miles et al 2021). With regard to disease-free interval (DFI) status, patients with DFI < 12 months have worse outcomes, with median PFS less than 4 months and median OS approximately 10 months (Dent et al 2024).

In patients with germline BRCA mutations, about 20% of TNBC cases (Ye et al 2021; Gonzalez-Angulo et al 2011), PARP inhibitors are an alternative treatment option to chemotherapy based on results of the OlympiAD (NCT02000622) and EMBRACA (NCT01945775) studies (Gradishar et al

2024, Gennari et al 2021, Punie et al 2025, Robson et al 2017, Litton et al 2018). If a patient had a germline BRCA mutation, eligibility for the pivotal study TB02 was dependent on the investigator assessing that another therapy (such as PARP inhibitor) was not considered the best treatment option for the patient.

For patients with metastatic TNBC with PD-L1-positive tumours, anti-PD-1/PD-L1 agents combined with chemotherapy are recommended as first-line treatments based on clinical trial data (Gradishar et al 2024, Gennari et al 2021). Some patients with PD-L1-positive disease are not candidates for immunotherapy, for reasons including comorbidities that preclude PD-1/PD-L1 inhibitor therapy or relapse after prior PD-1/PD-L1 inhibitor therapy for early-stage BC.

Sacituzumab govitecan is an anti-TROP2 ADC recommended for the treatment of adult patients with metastatic TNBC, who have received 2 or more prior systemic therapies, at least one of them for metastatic disease, but it is currently not recommended in the first-line setting (Gennari et al 2021, Gradishar et al 2024).

Finally, patients with HER2 low or ultralow expressing tumours (IHC 1+ or IHC 2+/ISH-, or HER2-ultralow tumour status, described as IHC 0 with membrane staining (IHC >0<1+)) now have the option of treatment with another ADC, trastuzumab deruxtecan, in the metastatic setting after having previously received chemotherapy after disease progression.

Unmet medical need

Treatment options for first-line metastatic TNBC (whether recurrent or de novo) are limited to single-agent chemotherapy when patients have tumors that are BRCA wild-type and do not have imminent organ failure and for those who are not candidates for immunotherapy, which includes those patients with PD-L1-negative disease, comorbidities precluding PD-1/PD-L1 inhibitors, or recurrence after such therapy (Gradishar et al 2024; Gennari et al 2021, Cardoso et al 2024, Punie et al 2025). However, single-agent chemotherapy results in poor survival outcomes and significant hematologic and gastrointestinal toxicity (Gradishar et al 2005, Miller et al 2007, Piccart-Gebhart et al 2008, Emens et al 2021, Cortes et al 2022, Brufsky et al 2012, Park et al 2019, Perez et al 2010, Pivot et al 2016). Despite advances in systemic therapies, the median overall survival for metastatic TNBC remains under 2 years, even in recent first-line clinical trials (Yao et al 2019, Kim et al 2021; Cortes et al 2022). Patients with relapse occurring within 12 months after completing chemotherapy for primary breast cancer experience rapid disease progression and extremely poor prognosis with a mOS shorter than 1 year (Dent et al 2024). Among patients with metastatic TNBC, those with brain metastases have the poorest prognosis with median OS ranging from 6 to 9 months (Yao et al 2019, Gao et al 2021, Zimmer 2021). Published real-world data indicate that only approximately 50% of patients who receive first-line TNBC treatment go on to receive second-line treatment (Punie et al 2025); therefore, the unmet need is especially pronounced for treatment options that demonstrate benefit in the first-line setting. Given the aggressive nature of metastatic TNBC and the limited efficacy of current treatments, particularly for those who are ineligible for immunotherapies, there is a need for innovative therapies that offer improved efficacy with a manageable and tolerable safety profile.

2.1.2. About the product

Datopotamab is a humanised anti-TROP2 IgG1 attached to deruxtecan, a topoisomerase I inhibitor (DXd) bound by a tetrapeptide-based cleavable linker. The antibody-drug conjugate binds to TROP2 expressed on the surface of certain tumour cells. After binding, datopotamab deruxtecan undergoes internalisation into the tumour cells and the subsequent release of DXd results in DNA damage and apoptotic cell death via topoisomerase I inhibition.

Datroway (datopotamab deruxtecan) is approved in the EU as monotherapy for the treatment of adult patients with unresectable or metastatic HR-positive, HER2-negative breast cancer who have received endocrine therapy and at least one line of chemotherapy in the advanced setting based on the results of the Phase III TROPION-Breast01 (TB01) study.

Datroway should be prescribed by a physician and administered under the supervision of a healthcare professional experienced in the use of anticancer medicinal products.

The recommended dose is 6 mg/kg (up to a maximum of 540 mg for patients ≥ 90 kg) of body weight given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

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

CHMP scientific advice concerning the development and study plan for the pivotal trial TB02 was given on December 2021 (EMA/SA/0000070789).

In summary, the CHMP advised the Sponsor to:

- *Include anthracyclines as an additional comparator option, or inclusion criteria should clarify that prior therapy must have included an anthracycline.*
- *When feasible biopsy recurrent disease to confirm histology and to re-assess tumour biology (including ER, PgR, HER2).*
- *Include pre-planned analyses of choice of chemotherapy in the control arm as this was Investigator's choice.*
- *All efforts should be made to determine PD-L1 expression prior to study inclusion, to avoid an unknown PD-L1 status.*
- *Make all efforts to be able to conclude on the TROP2 expression-response correlation data (TROP2 negative, TROP2 low and TROP2 overexpression)*
- *Evaluate the germline BRCA 1/2 mutation status (gBRCAm) of all patients as PARP inhibitors are recommended as a treatment option for gBRCAm PD-L1 negative mTNBC.*
- *Include a pre-planned analysis for taxane vs non-taxane chemotherapy.*
- *include an anthracycline (monotherapy) as an option for patients.*

CHMP scientific advice was generally followed, but not on all points. Several of these may impact the external generalizability of the trial data. Anthracycline monotherapy was not included in the Investigator's choice of chemotherapy (ICC) despite this being a standard practice referenced in the ESMO guidelines (Gennari et al, 2021). Here taxane or anthracycline monotherapy are recommended as first choices to be used with the opposite agent used at progression. However, in the pivotal study TB02, only taxanes (omitting docetaxel) were permitted and no combination treatment was possible, such as nab-paclitaxel + carboplatin. While the treatment possibilities in the Investigator's Choice arm are recommended by the ESMO guideline, the omission of anthracyclines and combination chemotherapy leaves the possibility of at least some patients receiving an inferior treatment in the control arm, which also may be implied in the difference between withdrawals in the control arm (ICC) (31 patients [9.7%]) and Dato-DXd (8 patients [2.5%]) arms. This was justified on the basis that previous studies in the first-line setting such as IMpassion130, IMpassion131 and KEYNOTE-355 studies did not include an anthracycline

monotherapy option either. While this design choice limits external generalisability of the TB02 trial's results, it does not preclude efficacy demonstration in this procedural setting and it is considered acceptable given that the TROPION-Breast02 (TB02) trial is in line with the recent clinical trial context (i.e. IMpassion130, IMpassion131 and KEYNOTE-355 studies).

The pivotal trial required that all participants must have had a FFPE metastatic (excluding bone) or locally recurrent inoperable tumour sample available, collected ≤ 3 months prior to screening. If neither an adequate FFPE block nor the minimum of 20 slides were available from metastatic or locally recurrent inoperable tumour, or if a biopsy was not feasible for safety reasons, it was permitted to use an archival tumour specimen obtained before the diagnosis of locally recurrent inoperable or metastatic breast cancer.

2.1.4. General comments on compliance with GCP

2.2. The Sponsor's procedures, internal quality control measures, and audit programs provide reassurance that the Dato-DXd clinical development program is being conducted as per GCP. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

The dose, indication and patient population in this procedure are covered by the indication considered for the refined PEC in the previously submitted ERA during the initial MA (see [Datroway EPAR](#)).

The concerned moiety in terms of ERA of datopotamab deruxtecan is deruxtecan (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. The rest of the molecule is of protein nature, which is susceptible to rapid degradation in the environment, and, in accordance with the guideline (CHMP EMEA/CHMP/SWP/4447/00), ERA studies are not required. 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.

Table 1 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)	0.00263	µg/L	≥ 0.01 threshold: N
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2.2.2. Conclusion on the non-clinical aspects

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

Considering the above data, datopotamab deruxtecan is not expected to pose a risk to the environment

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 2 Overview of clinical studies

Study number/name Study title (Sponsor, NCT number)	Patient population	Treatment groups, dose regimen	Outcome measures	Number of patients and DCO	Status
Studies supporting clinical efficacy and safety					
Pivotal Phase III study					
D926PC00001 (TROPION-Breast02, TB02): Phase III, open-label, randomised study of datopotamab deruxtecan (Dato-DXd) versus investigator's choice of chemotherapy in patients who are not candidates for PD-1/PD-L1 inhibitor therapy in first-line locally recurrent inoperable or metastatic triple-negative breast cancer (TROPION-Breast02) (AstraZeneca; NCT05374512)	Patients with first-line locally recurrent inoperable or metastatic TNBC who are not candidates for PD-1/PD-L1 inhibitor therapy	Dato-DXd 6 mg/kg IV on Day 1 Q3W Investigator's choice of chemotherapy Paclitaxel 80 mg/m ² IV on Days 1, 8, and 15, Q3W Nab-paclitaxel 100 mg/m ² IV on Days 1, 8, and 15, Q4W Capecitabine 1000 or 1250 mg/m ² BID PO on Days 1 to 14, Q3W Carboplatin AUC6 on Day 1, Q3W Eribulin mesylate 1.4 mg/m ² IV on Days 1 and 8, Q3W (or Eribulin 1.23 mg/m ²)	Dual primary: PFS (by BICR), and OS Secondary: ORR, DoR, PFS (by investigator), DCR, safety and tolerability, PROs, tolerability, PK, immunogenicity, PFS2, TFST, TSST Key Exploratory: • TROP2 • PD-L1	Total randomized: 644 FA DCO: 25 August 2025	Completed
Supportive Phase I/II studies (also contributed data to the pooled clinical pharmacology and safety analysis)					
DS1062-A-J101 (TROPION-PanTumor01, TP01): Phase I, 2-part, multicentre, open-label, multiple dose, first in	Participants with advanced solid tumors who have relapsed or progressed following local standard treatments	Dato-DXd Dose Escalation 0.27 mg/kg IV Q3W 0.5 mg/kg IV Q3W 1 mg/kg IV Q3W 2 mg/kg IV Q3W	Primary: safety and tolerability (including AEs, DLTs) Secondary: PK, immunogenicity	NSCLC cohort: Total randomized: 210 DCO: 30 July 2021 BC cohort:	Ongoing

human study of DS-1062a in subjects with advanced solid tumors (Daiichi Sankyo; NCT03401385)		3.3 mg/kg IV Q3W 5 mg/kg IV Q3W 6.0 mg/kg IV Q3W 8 mg/kg IV Q3W 10 mg/kg IV Q3W <u>Dose Expansion</u> 4 mg/kg IV Q3W 6 mg/kg IV Q3W 8 mg/kg IV Q3W	Efficacy data from BC cohort only included as supportive evidence for efficacy	Total randomized: 85 HR+ HER2- BC: 41 TNBC: 44 DCO: 22 July 2022	
Studies contributing data only in the pooled clinical pharmacology and safety analyses:					
D9268C00001 (TROPION-Breast01, TB01): Phase III, open-label, randomized study of Dato-DXd versus investigator's choice of chemotherapy in participants with inoperable or metastatic hormone receptor-positive, HER2-negative breast cancer who have been treated with one or 2 prior lines of systemic chemotherapy (TROPION-Breast01) (AstraZeneca; NCT05104866)	Inoperable or metastatic HR+/HER2- BC that has been treated with one or 2 prior lines of systemic chemotherapy	Dato-DXd: 6 mg/kg IV on Day 1 Q3W Investigator's Choice Chemotherapy: <u>Capecitabine:</u> 1000 or 1250 mg/m ² BID PO on Days 1 to 14, Q3W <u>Gemcitabine:</u> 1000 mg/m ² IV on Days 1 and 8, Q3W <u>Eribulin mesylate:</u> 1.4 mg/m ² IV on Days 1 and 8, Q3W <u>Vinorelbine:</u> 25 mg/m ² IV on Days 1 and 8, Q3W	Dual primary: PFS by BICR, and OS Secondary: PFS by investigator, PFS2, TFST, TSST, DoR, ORR PK and immunogenicity	Total randomized: 732 Final Analysis DCO: 17 July 2024	Completed

Study number/name Study title (Sponsor, NCT number)	Patient population	Treatment groups, dose regimen	Outcome measures	Number of patients and DCO	Status
D9266C00001 (TROPION-PanTumor02, TP02): Phase I/2, Multicentre, Open-label, Multiple-cohort Study of Dato-DXd in Chinese Patients with Advanced Non-small-cell Lung Cancer, Triple-negative Breast Cancer, Gastric/Gastroesophageal Junction Cancer, Urothelial Cancer, and Other Solid Tumours (AstraZeneca; NCT05460273)	Chinese patients with advanced NSCLC, TNBC, gastric/gastroesophageal junction cancer, urothelial cancer, or other solid tumours	Dato-DXd: 6.0 mg/kg IV Q3W	Confirmed ORR by ICR	TNBC: Total randomized: 79 DCO: 06 May 2024 NSCLC: Total randomized: 40 DCO: 09 October 2023	Completed
DS1062-A-U301 (TROPION-Lung01, TL-01): Phase III randomized study of DS-1062a versus docetaxel in previously treated advanced or metastatic non-small cell lung cancer with or without actionable genomic alterations (TROPION - Lung01)	Previously treated advanced or metastatic NSCLC without AGAs	IV infusion of study drug on Day 1 of each 21-day cycle. <u>Dato-DXd:</u> 6 mg/kg <u>Docetaxel:</u> 75 mg/m ²	Data included in pooled safety and clinical pharmacology analysis only	Total randomized N = 604 299 (Dato-DXd) 305 (Docetaxel) PFS DCO: 29 Mar 2023 OS DCO: 01 Mar 2024	Completed

(Daiichi Sankyo, NCT04656652)					
DS1062-A-U202 (TROPION-Lung05, TL-05): Phase II, single - arm, open - label study of DS-1062a in advanced or metastatic non - small cell lung cancer with actionable genomic alterations and progressed on or after kinase inhibitor therapy and platinum - based chemotherapy (TROPION - Lung05)	Advanced or metastatic NSCLC with AGA and who have progressed on or after one or more kinase inhibitors and platinum - based chemotherapy	IV infusion of Dato-DXd 6 mg/kg on Day-1 of each 21-day cycle.	Data included in pooled safety and clinical pharmacology analysis only	US 90 SUR: 01 Oct 2024 Treated: 137	Completed
(Daiichi Sankyo, NCT04484142)					

Completed = Study was defined as completed if the analyses for the primary objective had been performed

AE, adverse event; AGA, actionable genomic alterations; BC, breast cancer; BICR, blinded independent central review; BID, twice daily; CSR, clinical study report; Dato-DXd, datopotamab deruxtecan (formerly DS-1062a); DCO, data cut-off; DCR, disease control rate; DLT, dose-limiting toxicity; DoR, duration of response; HER2-negative, human epidermal growth factor receptor 2 negative; HR+, hormone receptor-positive; ICR, independent central review; IV, intravenous; NCT, National Clinical Trial; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PFS2, time from randomisation to second progression; PK, pharmacokinetic(s); PO, per oral; PRO, patient-reported outcome; Q3W, once every 3 weeks; SUR, Safety Update Report; TFST, time to first subsequent therapy; TNBC, triple-negative breast cancer; TROP2, trophoblast cell surface antigen 2; TSST, time to second subsequent therapy; US, United States.

2.3.2. Pharmacokinetics

Dato-DXd and total anti-TROP2 antibody (total Dato Ab) in plasma were measured by a validated Gyrolab platform-based LBA with fluorescent detection. DXd (ADC payload) in plasma was measured by validated LC-MS/MS method.

Immunogenicity

Anti-Dato-DXd antibodies were measured by a validated MSD platform-based LBA with ECL detection. A cell-based method was used for detection of neutralising antibody (Nab).

Evaluation and qualification of models

The below table summarises the updated Pop PK and E-R analyses.

Table 3 Pharmacometrics reports

Study Number Location in Module 5	Objectives of the Studies	Studies Included in the population PK/ER Analysis
See Module 5.3.3.5 Population Pharmacokinetics Report	Population Pharmacokinetics - To characterise the PopPK of Dato-DXd and DXd - To evaluate the effects of intrinsic and extrinsic factors on the PK of Dato-DXd and DXd - To derive individual exposure metrics to enable the exposure-response analyses	TB02, TB01, TL01, TL05, TP01 (NSCLC, LCNC, and BC), and TP02 (NSCLC and BC) (0.27 to 10.0 mg/kg)
See Module 5.3.3.5 Exposure-Response Exposure-Safety analysis Report	Exposure Response - To characterise the relationship between exposure and efficacy endpoints (OS and PFS, as assessed by BICR) using Cox Proportional Hazards models - To characterise the relationship between exposure and the following safety endpoints using logistic regression models: Grade ≥ 3 treatment-related TEAEs, TEAEs associated with dose reduction, oral mucositis/stomatitis (any grade; Grade ≥ 2), ocular surface events (any grade; Grade ≥ 2), drug-related adjudicated ILD - To evaluate, for each model developed, the impact of selected covariates on clinical responses using a stepwise forward inclusion/backward elimination covariate model building strategy	Exposure-efficacy analysis: TB02 (6 mg/kg) Exposure-safety analysis: Breast pool: TB02, TB01, TP01 (BC), and TP02 (BC) (6 mg/kg and 8 mg/kg) All-solid-tumour pool: TB02, TB01, TL01, TL05, TP01, and TP02 (0.27 mg/kg to 10 mg/kg)

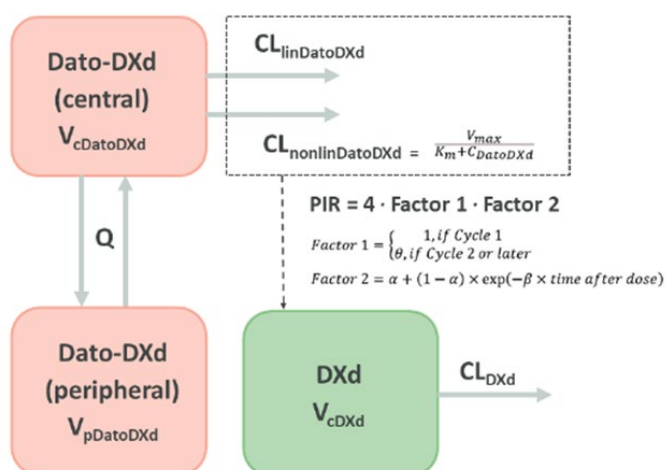
Pop PK modelling

Population PK analysis was implemented by NONMEM, version 7.3.0 (Icon Development Solutions). The FOCE inter method was primarily used for NONMEM computations. R, version 4.1.0 and above and the R packages Xpose as well as Perl-speaks-NONMEM, version 4.2.0 were used for exploratory analysis, executing NONMEM runs and post-processing of NONMEM output.

A previous Pop PK model for Dato-DXd and DXd, based on data from the TROPION-Breast01 submission (TL01, TL05, TP01, TB01), was updated to include data from two new clinical studies. TROPION-PanTumour02 (TP02) was a multiple-cohort study of Dato-DXd in Chinese patients with various cancer types including triple-negative breast cancer. TROPION-Breast02 (TB02) was a randomised study in patients not candidates for PD-1/PD-L1 inhibitor therapy in first-line (FL) locally recurrent inoperable or metastatic triple-negative breast cancer.

TP02 (N=119) and TB02 (N=319) contributed with 3359 Dato-DXd and 3307 DXd additional observations, of which 459 Dato-DXd and 442 DXd were BLQ and excluded. Most BLQ samples were taken pre-first dose. There were no outliers or duplicates identified in the additional data.

Figure 1 Model Schematic



The DatoDXd model was a two-compartmental distribution model with parallel $CL_{linDatoDXd}$ and $CL_{nonlinDatoDXd}$ from central compartment. The DXd model was a one-compartment model with CL_{DXd} from the central compartment. The release of DXd from the intact Dato-DXd was equal to the total (linear + nonlinear) elimination rate of Dato-DXd. The payload:intact ADC ratio (PIR) was decreasing with time both within the dosing cycle and between cycles (cycle 1 vs later cycles). IIV was characterised on $CL_{linDatoDXd}$, $V_{cDatoDXd}$, $V_{pDatoDXd}$, $Q_{DatoDXd}$, V_{max} , CL_{DXd} , and V_{cDXd} . The residual error was described by proportional RUV (implemented as additive on the logscale) with an exponential IIV term.

Impact of covariates were re-evaluated except for body weight which was included on all parameters with estimated IIV, except for Q and V_{max} for Dato-DXd. The final updated model also included the covariate-parameter relationships of ALB, age, region, sex and tumour type on $CL_{linDatoDXd}$; sex on $V_{cDatoDXd}$ and V_{cDXd} ; baseline tumour size on V_{max} ; ALB, AST, TBIL, and region on CL_{DXd} . All covariate relationships included in the previous model were statistically significant in this analysis, with the addition of tumour type as a covariate for $CL_{linDatoDXd}$.

The parameter estimates for the updated Dato-DXd model and DXd model are shown in the below tables.

Table 4 Parameter Estimates of the Final Model for Dato-DXd

Model Parameter	Unit	Estimate	RSE(%)	Bootstrap Median	Bootstrap 95%CI	Shrinkage(%)
WT on CLlinDato-DXd		0.75 FIX		0.75 FIX	-	-
WT on VcDato-DXd		0.409	1.670	0.458	[0.4 ; 0.49]	-
CLlinDato-DXd	L/day	0.453	0.185	0.452	[0.43 ; 0.48]	-
VcDato-DXd	L	3.036	0.126	3.024	[2.96 ; 3.08]	-
QDato-DXd	L/day	0.323	0.112	0.322	[0.3 ; 0.36]	-
VpDato-DXd	L	2.810	0.125	2.824	[2.72 ; 2.96]	-
Vmax	µg/day	5020.00	0.123	4978.775	[4111.33 ; 5982.48]	-
Km	ng/mL	2183.000	0.145	2170.660	[1466.68 ; 2998.76]	-
WT on VpDato-DXd		0.376	1.370	0.379	[0.25 ; 0.54]	-
Age on CLlinDato-DXd		-0.318	0.581	-0.309	[-0.38 ; -0.21]	-
ALB on CLlinDato-DXd		-0.644	0.286	-0.643	[-0.76 ; -0.47]	-
Japanese on CLlinDato-DXd		-0.158	1.593	-0.162	[-0.21 ; -0.13]	-
Female on CLlinDato-DXd		-0.197	0.422	-0.196	[-0.24 ; -0.16]	-
Tumor size baseline on Vmax		0.135	1.090	0.132	[0.09 ; 0.18]	-
Female on VcDato-DXd		-0.150	0.476	-0.148	[-0.16 ; -0.13]	-

Lung on CLlinDato-DXd		-0.065	4.000	-0.066	[-0.11 ; -0.03]	-
IIV RUVDato-DXd	CV	0.614	2.245	0.610	[0.53 ; 0.67]	0
IIV CLlinDato-DXd	CV	0.239	4.520	0.232	[0.21 ; 0.25]	10.67
IIV VeDato-DXd	CV	0.139	4.168	0.138	[0.13 ; 0.15]	3.2
IIV QDato-DXd	CV	0.390	4.970	0.383	[0.28 ; 0.43]	22.98
IIV VpDato-DXd	CV	0.381	5.527	0.382	[0.33 ; 0.43]	19.02
IIV Vm	CV	0.170	10.330	0.173	[0.14 ; 0.23]	44.13
RUVDato-DXd	CV	0.134	0.258	0.134	[0.13 ; 0.14]	3.04

Note: 500/500 (100%) bootstraps finished successfully

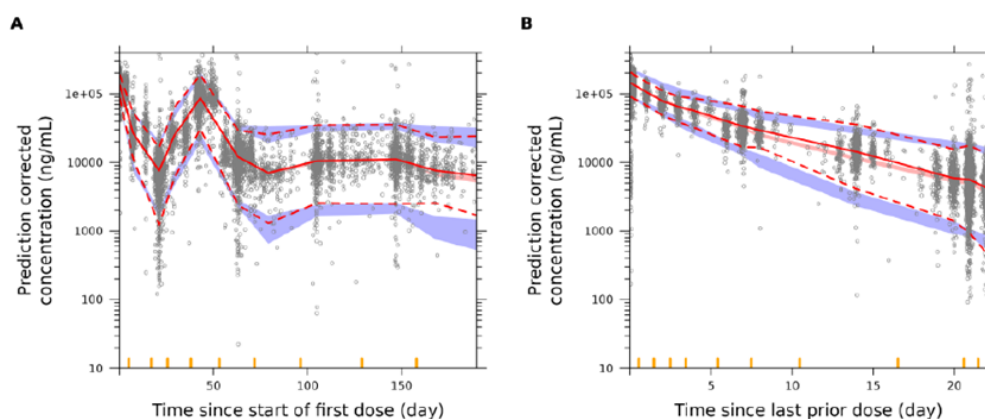
Table 5 Parameter Estimations of the Final Dato-DXd Model

Model Parameter	Unit	Estimate	RSE(%)	Bootstrap median	Bootstrap 95%CI	Shrinkage(%)
CLDXd	L/hr	2.730	0.039	2.734	[2.65 ; 2.82]	-
VeDXd	L	26.860	0.039	26.594	[25.42 ; 27.85]	-
Factor 1		0.748	0.049	0.748	[0.73 ; 0.76]	-
Beta		0.265	0.046	0.266	[0.25 ; 0.28]	-
WT on CLDXd		0.123	0.429	0.125	[0.05 ; 0.22]	-
WT on VeDXd		0.404	0.437	0.415	[0.31 ; 0.52]	-
ALB on CLDXd		0.447	0.131	0.446	[0.34 ; 0.57]	-
AST on CLDXd		-0.160	0.403	-0.160	[-0.21 ; -0.11]	-
Europe on CLDXd		0.256	0.278	0.256	[0.21 ; 0.3]	-
RoW on CLDXd		0.136	0.654	0.131	[0.09 ; 0.18]	-
Total bilirubin on CLDXd		-0.158	0.414	-0.153	[-0.2 ; -0.1]	-
Female on VeDXd		-0.205	0.172	-0.199	[-0.24 ; -0.16]	-
IIV RUVDXd	CV	0.352	3.444	0.351	[0.32 ; 0.39]	5.62
IIV CLDXd	CV	0.302	3.750	0.302	[0.28 ; 0.33]	7.84
IIV VeDXd	CV	0.327	4.963	0.327	[0.3 ; 0.35]	10.66
RUVDXd	CV	0.267	0.070	0.266	[0.26 ; 0.27]	3.87

Parameters describing Dato-DXd PK in Table 5 were fixed to estimated values.

Note: 498/500 (99.6%) bootstraps finished successfully.

Figure 2 pcVPC of the Final Dato-DXd Model (run0103500.mod) vs Time after Dose



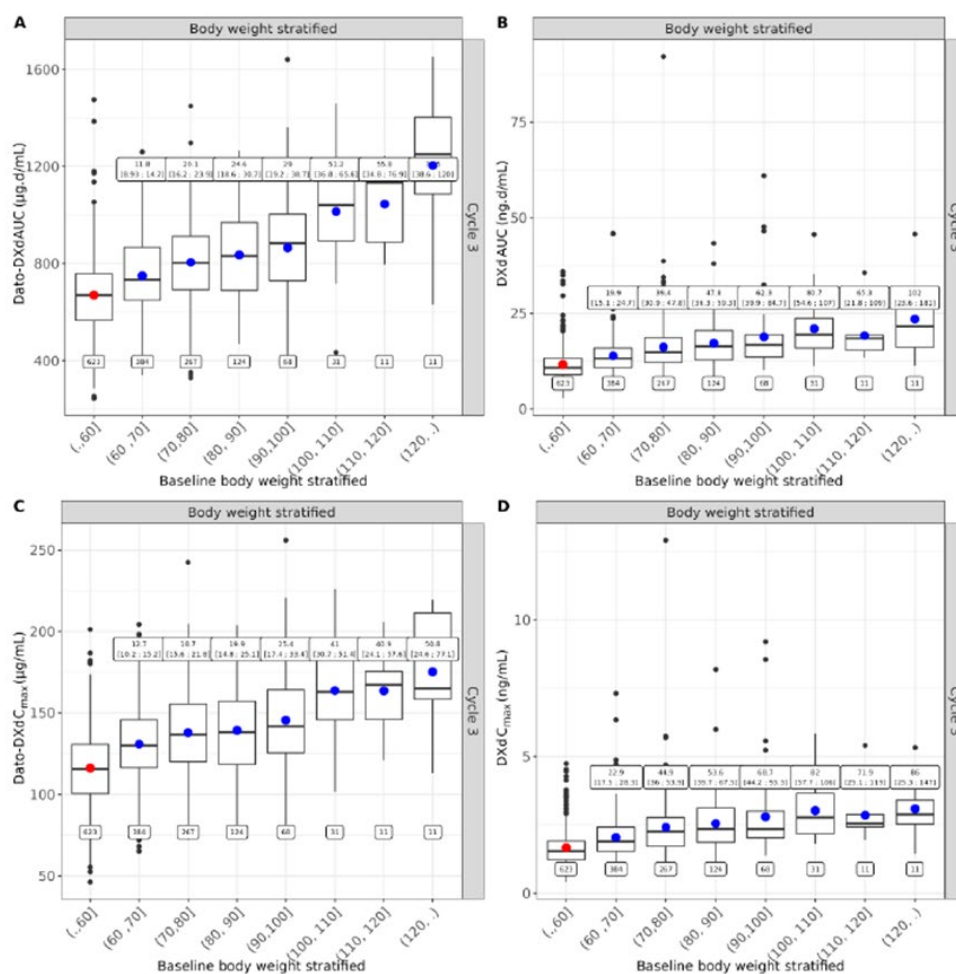
(A) Prediction corrected concentration vs. time since start of first dose

(B) Prediction corrected concentration vs. time since last prior dose

Orange vertical ticks lines on x axis represent the intervals for pcVPC; Shaded red and blue areas represent the 95% confidence interval of the median, 5th, and 95th percentiles predicted by the model, respectively; Solid and dashed lines represent the median, 5th, and 95th percentiles of the observations, respectively

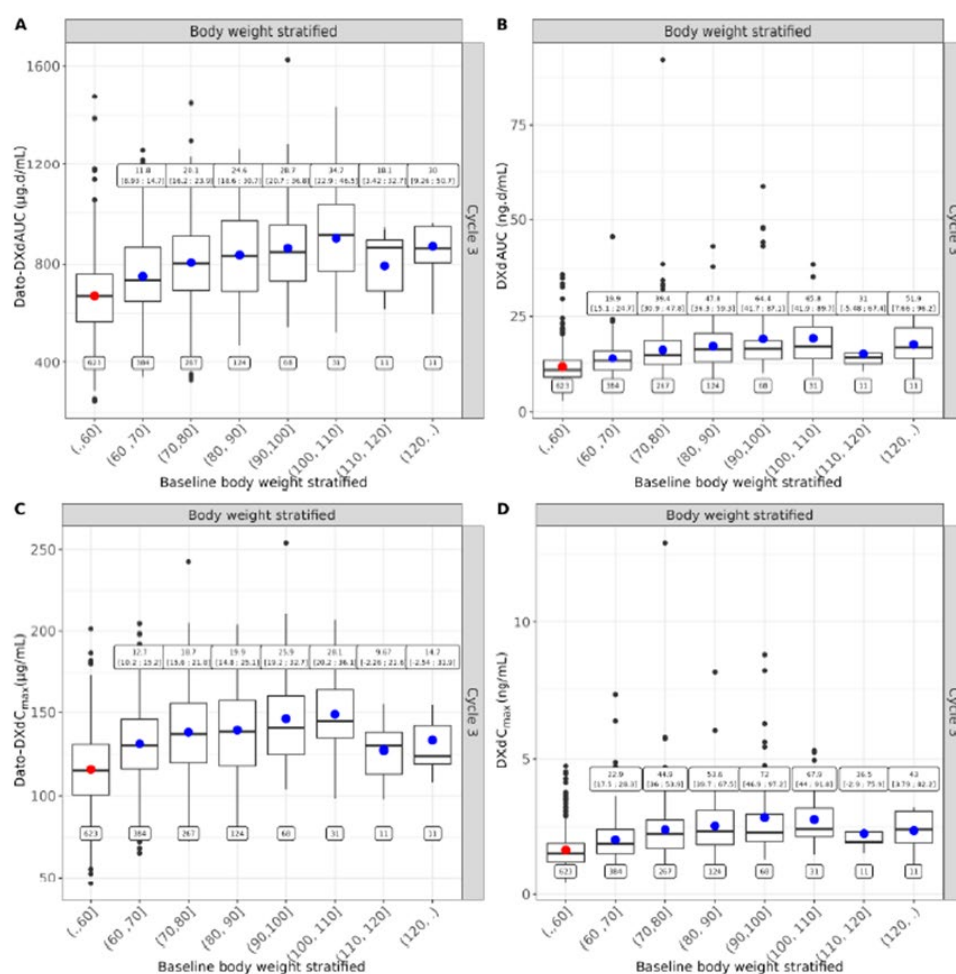
A dose capping at 90 kg body weight was applied in the approved indication. Simulations of impact on exposure without and with a dose capping at 90 kg are predicted for Cycle 3 exposure in the below figures.

Figure 3 Impact of Body Weight on Dato-DXd and DXd Cycle-3 PK Metrics



A = Third-cycle AUC of Dato-DXd by baseline body weight;
 B = Third -cycle AUC of DXd by baseline body weight;
 C = Third -cycle Cmax of Dato-DXd by baseline body weight;
 D = Third -cycle Cmax of DXd by baseline body weight;
 Numbers [brackets] above the boxes represent the percent change in AUC or Cmax (with 95% CI) in other categories relative to the most prevalent category; Numbers below represent the number of patients in each category; Red and blue dots represent the mean exposure in the most prevalent category and in other categories, respectively

Figure 4 Impact of Body Weight Cap on Dato-DXd and DXd Cycle-3 PK metrics



A = Third-cycle AUC of Dato-DXd by baseline body weight with dose capping at 90kg;
 B = Third -cycle AUC of DXd by baseline body weight with dose capping at 90kg;
 C = Third -cycle C_{max} of Dato-DXd by baseline body weight with dose capping at 90kg;
 D = Third -cycle C_{max} of DXd by baseline body weight with dose capping at 90kg;
 Numbers [brackets] above the boxes represent the percent change in AUC or C_{max} (with 95% CI) in other categories relative to the most prevalent category; Numbers below represent the number of patients in each category; Red and blue dots represent the mean exposure in the most prevalent category and in other categories, respectively

Individual exposure metrics have been derived from the individual empirical Bayes estimates (EBEs) as drivers for exposure response analysis related to safety and efficacy.

Exposure-response modelling

Exposure metrics for efficacy, Dato-DXd AUC_{C1}, and safety analyses, Dato-DXd and DXd AUC_{C1}, were derived from the updated Pop PK model. Dataset preparation and statistical analysis were performed using SAS version 9.4 and R, Version 4.0.2 or higher.

Efficacy

Exposure-efficacy analysis was performed on data from TNBC patients in study TB02 (Dato-DXd arm: N=319; ICC arm: N=321) with endpoints: progression free survival (PFS) and overall survival (OS). The maturity of the PFS and OS were 63% and 54%, respectively, at the data cut off (DCO) 25 August 2025.

Table 6 Summary of Dato-DXd AUC_{C1} by Quartiles

Variable	Label	Q1 (N =80)	Q2 (N =80)	Q3 (N =80)	Q4 (N =79)	Total (N =319)
AUC1_DA TODXd	Dato-DXd AUCC1 (µg·d/mL)	518.2 [308.5- 574.4]	613 [574.5- 643]	694.1 [643.1- 743.4]	804 [743.6- 1166.7]	643 [308.5- 1166.7]

Table 7 Summary of PFS and OS Events in the TNBC TB02 Population Set by Dato-DXd AUC_{C1} quartiles

Endpoint	Level	Q1 (N =80)	Q2 (N =80)	Q3 (N =80)	Q4 (N =79)	Total (N =319)
PFS	No-progression	28	28	30	34	120
PFS	Progressed	52	52	50	45	199
OS	Censored	28	41	41	41	151
OS	Death	52	39	39	38	168

Kaplan-Meier curves were used for initial analyses with log-rank testing. Time-to event analyses were conducted by Cox proportional hazards modelling. Model fitting was done using Maximum Likelihood Estimation. Prior to model fitting continuous covariates were centred at approximate median values. Influence of covariates was tested using a stepwise approach with forward inclusion ($p < 0.01$) followed by backward elimination ($p < 0.001$).

PFS

AUC_{C1} Dato-DXd was not statistically associated with PFS and no further covariates were evaluated.

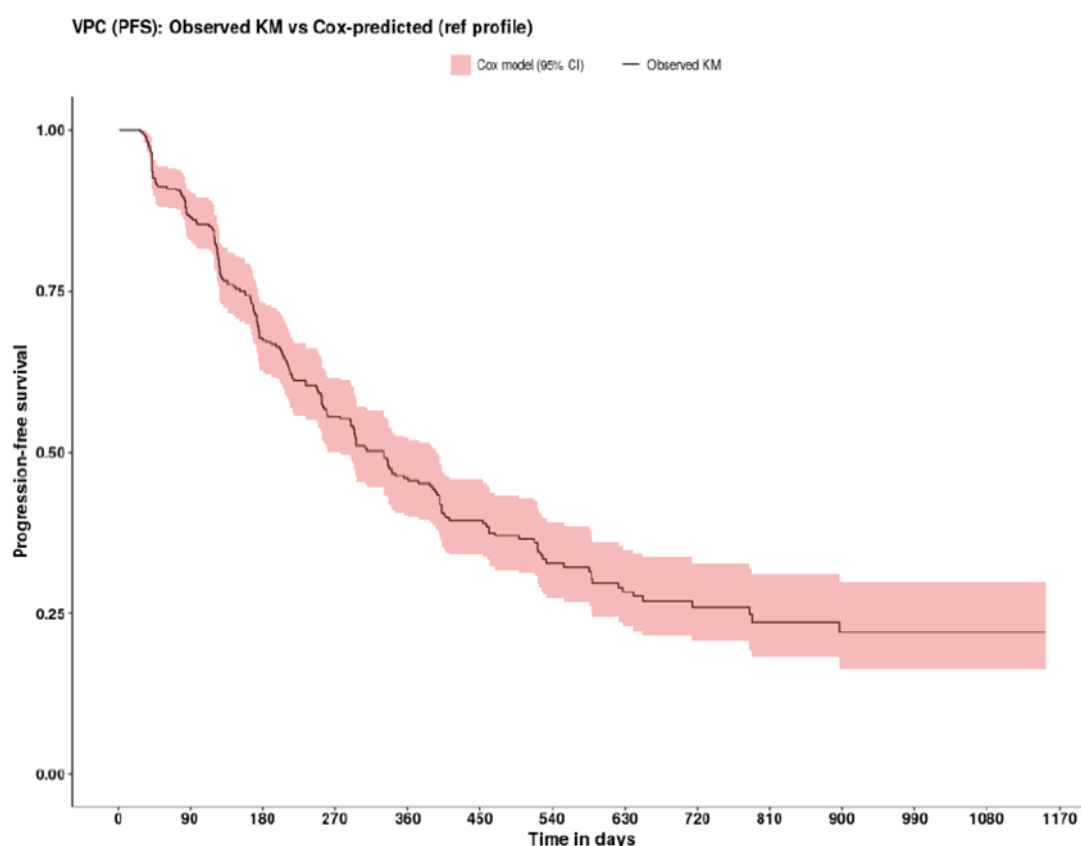
Table 8 Cox proportional hazard model for PFS

Code	Label	Hazard Ratio	Lower 95% CI	Upper 95% CI	Wald's nominal p- value
AUC1_DatoDXd	AUC C1 Dato-DXD	0.999	0.998	1	0.151

Cox proportional hazards regression analysis with area under the curve (AUC) as a continuous exposure variable. p-values are derived from the Wald test for the coefficient of the AUC term in the Cox model. Each unit increase in AUC1_DatoDXd (µg·day/mL) multiplies the hazard function by 0.999,

The PFS model diagnostics reported a Schoenfeld p-value of 0.0018 with a correlation between Schoenfeld residuals and time of 0.17. A VPC of model predicted PFS compared to observed is shown in the figure below.

Figure 5 VPC Plot: Observed vs Cox-Predicted PFS



Visual predictive check comparing the unadjusted Kaplan–Meier step estimate with the Cox model prediction generated at the mean Dato-DXd AUC_{C1} value; the Kaplan–Meier step line (solid black) is shown alongside the Cox model’s 95% confidence interval band (red band).

OS

In the univariate OS model AUC_{C1} Dato-DXd was associated with lower OS (table below).

Table 9 Summary of Hazard Ratio for the Univariate OS Model

Code	Label	Hazard Ratio	Lower 95% CI	Upper 95% CI	Wald’s nominal P-value
AUC1_DatoDXd	AUC C1 Dato- DXD	0.999	0.997	1	0.029

Cox proportional hazards regression analysis with area under the curve (AUC) as a continuous exposure variable. p-values are derived from the Wald test for the coefficient of the AUC term in the Cox model. Each unit increase in AUC1_DatoDXd (μg·day/mL) multiplies the hazard function by 0.999.

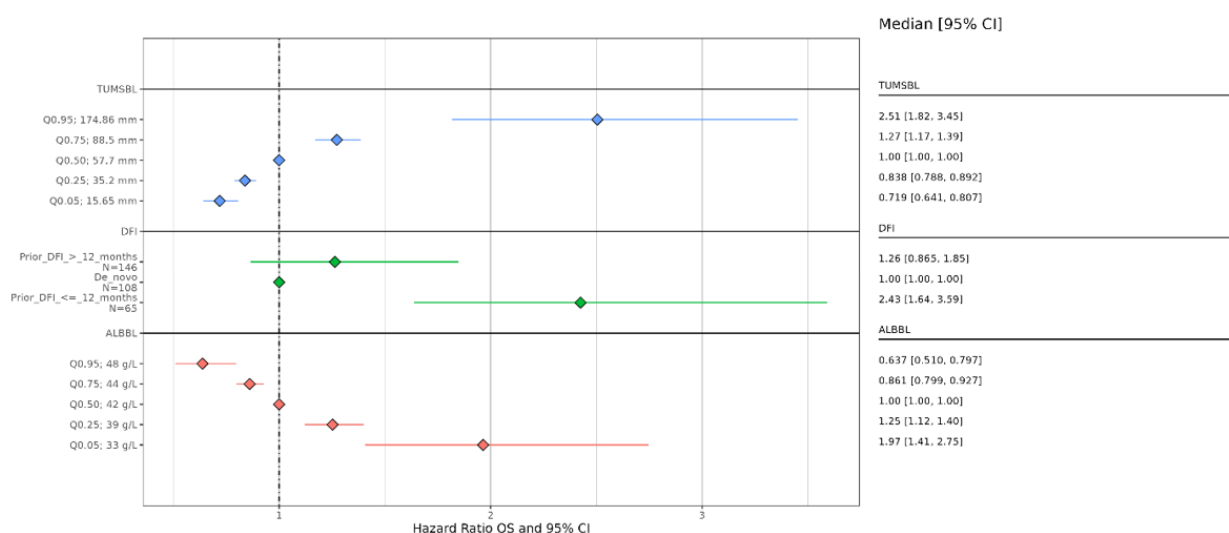
In a covariate screening confounding risk factors such as higher baseline tumor size, lower baseline albumin and prior DFI were identified as significant covariates for OS.

Table 10 Cox Proportional Hazard Model for OS

Term	HR Parameter	Standard Error	Lower 95% CI	Upper 95% CI	Wald's p-value
TUMSBL	1.572	0.081	1.342	1.841	< 0.005
Prior DFI ≤ 12 months	2.425	0.2	1.638	3.592	< 0.005
Prior DFI > 12 months	1.264	0.193	0.865	1.847	0.226
ALBBL	0.043	0.796	0.009	0.204	< 0.005

Cox proportional hazards regression analysis with baseline tumour size (TUMSBL) and baseline albumins as continuous covariates and prior DFI as categorical covariates. Each unit increase in baseline tumour size (TUMSBL), normalized by the median 58.9 mm, multiplies the HR by 1.572. Each unit increase in baseline albumin (ALBBL), normalized by the median 40 g/L, multiplies the HR by 0.043. De novo was used as the reference level when calculating the HR parameter of prior DFS≤ 12 months and prior DFI > 12 months. Continuous covariates are standardised. p-values are derived from the Wald test for the coefficient term in the Cox proportional hazards model.

Figure 6 Covariate Effects Plot for OS Analysis (Final SCM Model)



Dot represents the median HR; bar represents the 95% CI. The reference value for continuous variables is the median; for baseline albumin, this was 42 g/L; for baseline tumour size, this was 57.7 mm. Values are shown for the 5th, 25th, 75th, and 95th percentiles. For the categorical variable prior DFI the reference value is de novo.

Safety

Exposure-safety analysis was performed on data from an all-solid-tumour pool (studies TP01, TP02, TB01, TB02, TL01, TL05; N=1527) and a breast cancer pool (studies TP01, TP02, TB01 and TB02; N=843) with endpoints: Grade 3 or higher treatment emergent adverse events (TEAEs), TEAEs leading to dose reduction, and adverse events of special interest (AESI). Patients were classified into four groups based on exposure quartiles.

Exploratory analysis of exposure and safety events in both data pools were initially depicted in boxplots. Probability of occurrence of key safety endpoints and AESIs were modelled using Dato-DXd Cycle 1 AUC and DXd Cycle 1 AUC as continuous exposure metrics in logistic regression. A

covariate search within the breast and all solid-tumour cancer pool was subsequently performed using the logistic regression model if an exposure – AE endpoints relationship was identified. Influence of covariates were tested using the stepwise approach with forward inclusion ($p < 0.01$) followed by backward elimination ($p < 0.001$). Model comparison was performed by means of AIC (Akaike Information Criterion). The modelled exposure-safety relations were quantified in Forest plots across exposure quantiles.

Breast cancer pool

The parameter estimates of safety models for key endpoints in the BC-pool are shown in the below tables.

Table 11 Summary of Logistic Regression for any TEAE Gr $\geq$ 3 in the breast cancer pool

Parameter	Estimate	StdError	exp(Estimate)	z-value	p-value
(Intercept)	-1.05639	0.174501	0.347708	-6.05381	<0.001
AUC1_DXd	0.035487	0.008988	1.036125	3.948141	7.9e-05

Logistic regression coefficients are shown with their estimate, standard error (SE), exp(estimate), z-value, and p-value. Estimates represent log-odds; p-values are from Wald tests. Significant results: $p < 0.001$. AUC1_DXd denotes DXd AUC C1 (ng/ml*day)

Table 12 Summary of Logistic Regression for any TEAE leading to dose reduction in the breast cancer pool

Parameter	Estimate	StdError	exp(Estimate)	z-value	p-value
(Intercept)	-3.26572	0.411285	0.03817	-7.94028	<0.001
AUC1_DatoDXd	0.003178	0.000586	1.003183	5.42427	<0.001

Logistic regression coefficients are shown with their estimate, standard error (SE), exp(estimate), z-value, and p-value. Estimates represent log-odds; p-values are from Wald tests. Significant results: $p < 0.001$. AUC1_DatoDXd denotes Dato-DXd AUC C1 (ug/ml*day)

Table 13 Summary of Logistic Regression for any Grade oral mucositis/stomatitis in the breast cancer pool

Parameter	Estimate	StdError	exp(Estimate)	z-value	p-value
(Intercept)	-2.43675	0.412004	0.087444	-5.91439	<0.001
AUC1_DatoDXd	0.004586	0.000634	1.004596	7.233647	<0.001

Logistic regression coefficients are shown with their estimate, standard error (SE), exp(estimate), z-value, and p-value. Estimates represent log-odds; p-values are from Wald tests. Significant results: $p < 0.001$. AUC1_DatoDXd denotes Dato-DXd AUC C1 (ug/ml*day).

Table 14 Summary of Logistic Regression for Grade ≥ 2 oral mucositis/stomatitis in the breast cancer pool

Parameter	Estimate	StdError	exp(Estimate)	z-value	p-value
(Intercept)	-2.48564	0.375253	0.083272	-6.62389	<0.001
AUC1_DatoDXd	0.00278	0.000546	1.002784	5.095597	<0.001

Logistic regression coefficients are shown with their estimate, standard error (SE), exp(estimate), z-value, and p-value. Estimates represent log-odds; p-values are from Wald tests. Significant results: $p < 0.001$. AUC1_DatoDXd denotes Dato-DXd AUC C1 (ug/ml*day).

Table 15 Summary of Logistic Regression for any Grade ocular surface events in the breast cancer pool

Parameter	Estimate	StdError	exp(Estimate)	z-value	p-value
(Intercept)	-1.31819	0.393377	0.26762	-3.35095	<0.001
AUC1_DatoDXd	0.00227	0.000542	1.002272	4.18412	2.90E-05
TUMSBL	-0.28241	0.087525	0.753969	-3.22656	0.001253

Logistic regression coefficients are shown with their estimate, standard error (SE), exp(estimate), z-value, and p-value. Estimates represent log-odds; p-values are from Wald tests. Significant results: $p < 0.001$. Tumour size at baseline (TUMSBL) in mm and normalised by the median value 55 mm. AUC1_DatoDXd denotes Dato-DXd AUC C1 (ug/ml*day)

Table 16 Summary of Logistic Regression for Grade ≥ 2 ocular surface events in the breast cancer pool

Parameter	Estimate	StdError	exp(Estimate)	z-value	p-value
(Intercept)	-4.09602	0.501235	0.016639	-8.17186	<0.001
AUC1_DatoDXd	0.002953	0.000662	1.002958	4.461192	8.00E-06
LOT0	0.988986	0.213693	2.688508	4.628074	4.00E-06
LOT1	0.435364	0.303522	1.545525	1.43437	0.151467
LOT2	-0.79182	0.752564	0.453021	-1.05216	0.292726

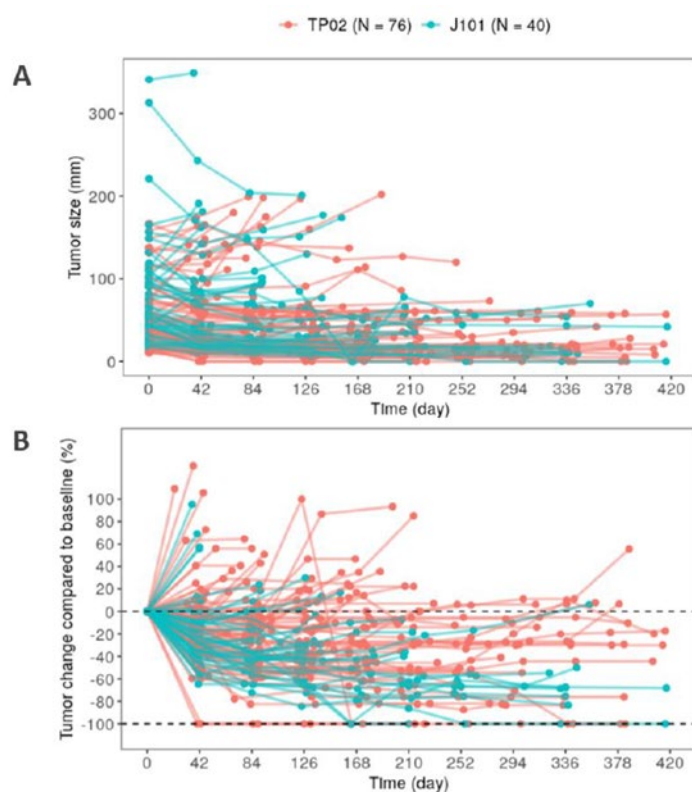
Logistic regression coefficients are shown with their estimate, standard error (SE), exp(estimate), z-value, and p-value. Estimates represent log-odds; p-values are from Wald tests. Significant results: $p < 0.001$. AUC1_DatoDXd denotes Dato-DXd AUC C1 (ug/ml*day). The reference value for prior line of therapy (LOT) is >2 .

Tumour growth inhibition model

A tumour growth inhibition (TGI) model was developed for describing the tumour size data from patients with triple-negative breast cancer (TNBC) who had received Dato-DXd at 6 or 8 mg/kg from J101 study (N = 40, Data cutoff: 22nd July 2022) or received Dato-DXd at 6 mg/kg from TP02 (N = 76, Data cutoff : 6th May 2024). A predominate part of patients originated from China (65.5%). Body weights ranged from 38 to 124 kg. Of note, no dose-capping was applied.

The analysis was performed using a SAEM approach using Monolix 2021R1 (Lixoft, France). R studio (version 4.1.3) was used in the analysis for pre- and post-processing of data and model output. Observed tumour size data is shown in the below figure.

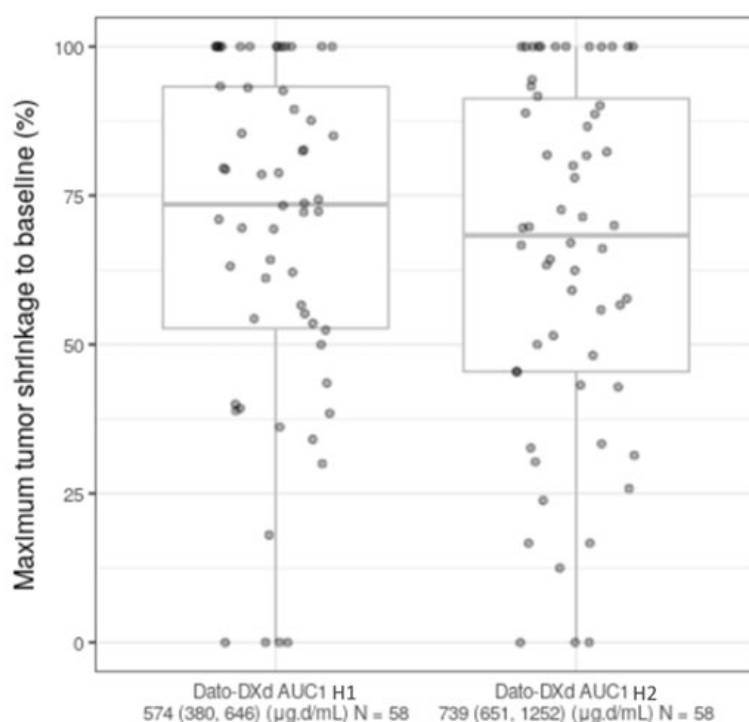
Figure 7 Tumour size time courses in patients in J101 and TP02 study



(A) longitudinal profiles of absolute tumour size; (B) longitudinal profiles of tumour size compared to baseline (%). Horizontal dash line represents baseline (100%), i.e., a 0% tumour change. Each point represents an observation, and each solid line represents one patient.

Maximum tumour reduction was greater in patients who had higher Dato-DXd PK exposure. Patients with median Dato-DXd AUC₁ at 739 ug.d/mL achieved 5% greater tumour reduction at nadir (i.e., greatest shrinkage observed) compared to the ones at 574 ug.d/mL/mL (below figure).

Figure 8 Maximum tumor shrinkage to baseline by Dato-DXd AUC1



Individual PK profiles and PK exposure metrics were predicted based on PopPK model EBE method. Evaluated PK exposure metrics in the TGI model included Cycle 1 Dato-DXd AUC (AUC1), Cycle 1 Dato-DXd Ctrough (Ctrough1), and time-varying (i.e., cycle-specific) Dato-DXd AUC.

Tumour growth inhibition was evaluated in an exposure-dependent manner. Different tumour growth models and tumour inhibition models were evaluated. Dato-DXd AUC1 to drive the tumor killing function significantly improved model performance.

The final model was parameterised by the initial tumour size (TS0), an exponential tumour growth function (kge), a linear tumour killing function (kkill) and a correlation term. IIV was evaluated on all parameters and residuals described by a proportional error function. Table 17 shows the parameter estimates of the final TGI model.

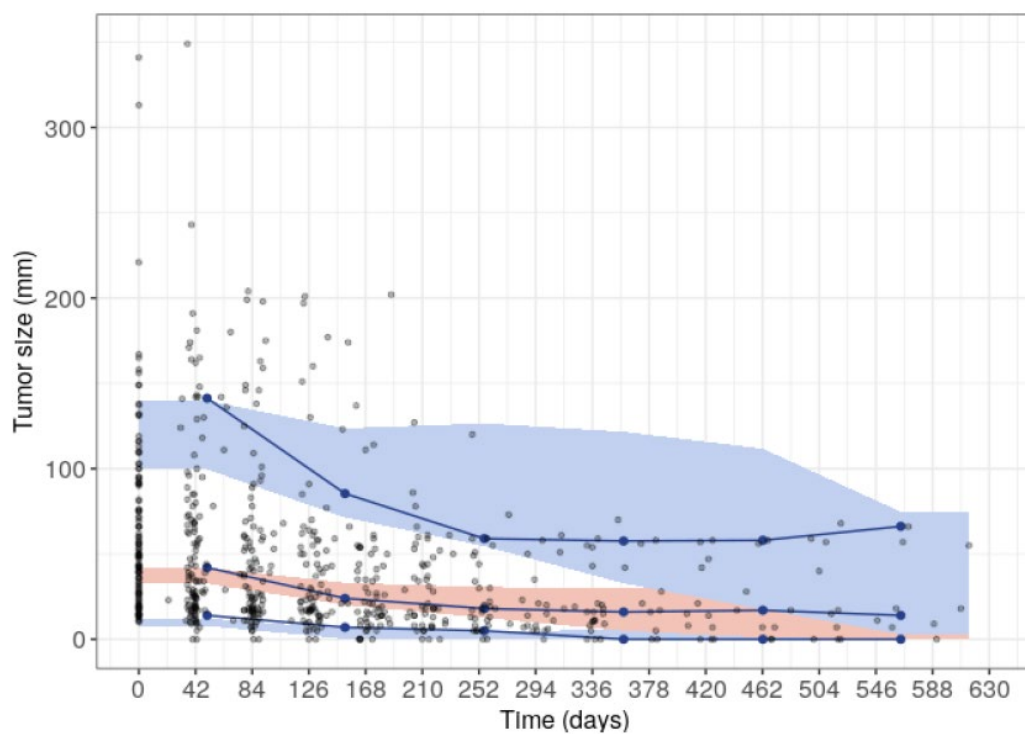
Table 17 Parameter estimates for final TGI model

PARAMETER	Description (unit)	VALUE	RSE (%)	SHRINKAGE (%)
Typical parameters				
TS0	Initial tumour size (mm)	44.28	7.81	0.865%
kge	Exponential tumour growth rate (day ⁻¹)	0.00037	26.6	2.02
kkill	linear tumour growth inhibition rate (day ⁻¹)	0.00000045	49.9	-2.55
corr_kge_TS0	Correlation between TS0 and kge	0.52	69.3	NA
Inter-individual variability				

omega_TS0	IIV on TS0	0.82	7.01	NA
omega_kge	IIV on kge	0.65	41.2	NA
omega_kkill	IIV on kkill	2.77	14.2	NA
Residual Variability				
b	Proportional error	0.3	3.46	NA

A VPC was performed based on 500 simulations (below figure).

Figure 9 VPC of the final TGI model



A total of 500 virtual trials, each including 300 virtual patients were simulated. The simulated tumor size profiles well-captured the observed data in patients with TNBC treated with Dato-DXd at 6 mg/kg (below figure).

Figure 10 Simulated vs. observed Dato-DXd tumor size profiles at 6 mg/kg

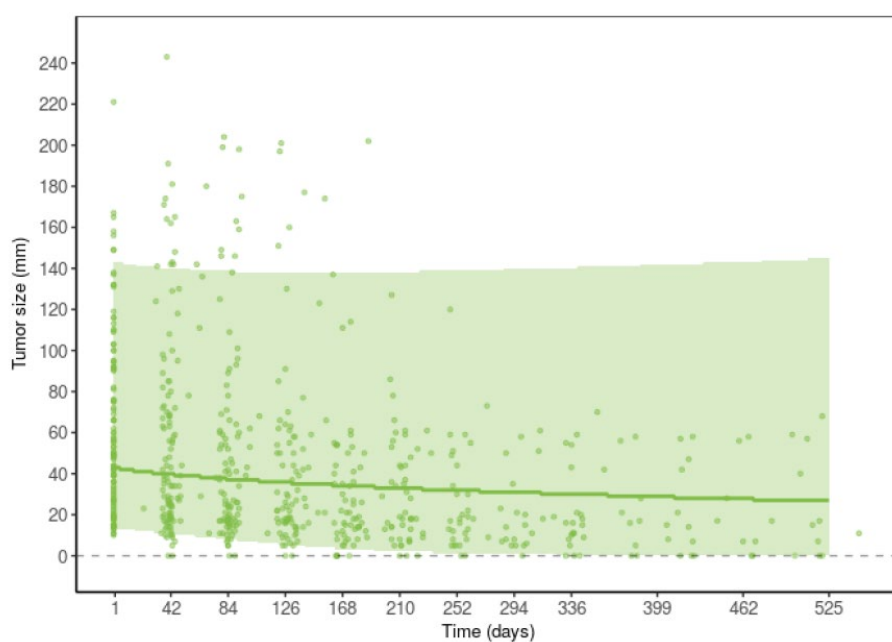
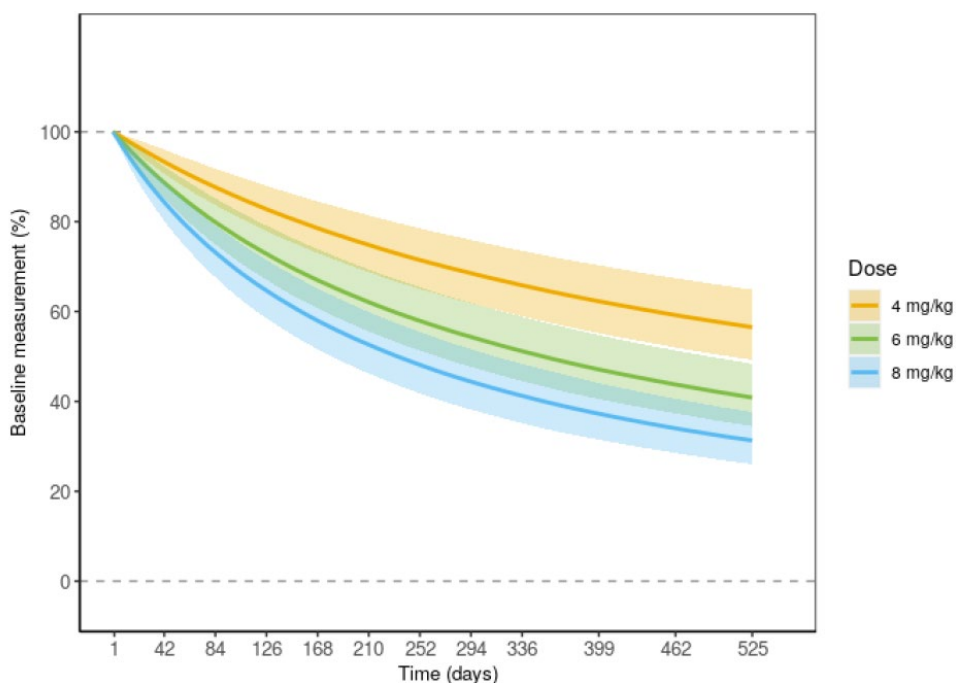


Figure 11 Simulated Dato-DXd tumor size profiles at 4, 6, and 8 mg/kg



Pharmacokinetic in the target population

Study Design

TROPION-Breast02 is a Phase III, randomised, open-label, 2-arm, multicentre, international study assessing the efficacy and safety of Dato-DXd compared with ICC in participants with locally recurrent inoperable or metastatic TNBC who are not candidates for PD-1/PD-L1 inhibitor therapy.

Pharmacokinetic Results

The two comparable drug products, to-be-marketed Lyo-DP and clinical Lyo-DP, was used in the TB02 study. A total of 319 participants from the Dato-DXd arm were included in the PK analysis set. No formal non-compartmental analysis was conducted due to the sparse PK sampling scheme in this study. After repeated IV administration of Dato-DXd 6 mg/kg Q3W, minimal accumulation was observed. Steady-state concentrations of Dato-DXd, anti-TROP2 antibody, and DXd were generally reached by Cycle 4 and maintained thereafter. For the summary of plasma concentrations of Dato-DXd, anti-TROP2 antibody, and DXd by visits/timepoints, see below table.

Table 18 Plasma Concentrations of Dato-DXd, Anti-TROP2 Antibody, and DXd at Selected Visits (PK Analysis Set)

Visit/ Statistic	Analyte		
	Dato-DXd (µg/mL)	Anti-TROP2 Antibody (µg/mL)	DXd (ng/mL)
	(N = 319)	(N = 319)	(N = 318)
Cycle 1, Day 1, pre-dose			
n (n < LLOQ)	311 (303)	311 (308)	305 (303)
Mean	NC	NC	NC
SD	NC	NC	NC
Geometric mean	NC	NC	NC
Geometric CV (%)	NC	NC	NC
Cycle 1, Day 1, EOI			
n (n < LLOQ)	289 (5)	287 (3)	281 (4)
Mean	147.4	147.8	1.495
SD	40.73	36.33	0.7533
Geometric mean	126.1	133.4	1.259
Geometric CV (%)	137.2	97.88	88.52
Cycle 1, Day 1, 5 hours post start of infusion			
n (n < LLOQ)	252 (5)	251 (4)	247 (3)
Mean	145.2	143.4	2.691
SD	35.85	35.49	1.252
Geometric mean	125.6	126.9	2.329
Geometric CV (%)	139.2	118.6	84.94
Cycle 2, Day 1, pre-dose			
n (n < LLOQ)	306 (7)	305 (5)	301 (1)
Mean	4.626	5.488	0.1437
SD	7.806	3.318	0.09768
Geometric mean	3.149	4.090	0.1228
Geometric CV (%)	128.7	123.0	62.33
Cycle 2, Day 1, EOI			
n (n < LLOQ)	270 (1)	268 (0)	263 (0)
Mean	145.7	144.9	1.322

Visit/ Statistic	Analyte		
	Dato-DXd (µg/mL)	Anti-TROP2 Antibody (µg/mL)	DXd (ng/mL)
	(N = 319)	(N = 319)	(N = 318)
SD	45.89	40.35	1.273
Geometric mean	127.1	133.1	1.016
Geometric CV (%)	94.45	60.73	88.06
Cycle 4, Day 1, pre-dose			
n (n < LLOQ)	262 (1)	259 (0)	257 (0)
Mean	9.178	10.75	0.2038
SD	18.83	16.40	0.1475
Geometric mean	5.686	7.387	0.1715
Geometric CV (%)	121.3	110.4	63.57
Cycle 4, Day 1, EOI			
n (n < LLOQ)	246 (0)	244 (0)	241 (0)
Mean	151.3	146.2	1.118
SD	43.22	41.77	0.7807
Geometric mean	134.5	133.4	0.8998
Geometric CV (%)	84.83	62.06	80.40
Cycle 8, Day 1, pre-dose			
n (n < LLOQ)	174 (2)	172 (0)	172 (1)
Mean	9.573	11.13	0.2198
SD	15.19	11.75	0.131
Geometric mean	6.446	8.466	0.1909
Geometric CV (%)	119.4	97.43	60.96
Cycle 8, Day 1, EOI			
n (n < LLOQ)	158 (1)	160 (1)	158 (1)
Mean	155.6	153.5	1.045
SD	37.92	33.58	0.6448
Geometric mean	143.9	144.2	0.8660
Geometric CV (%)	74.76	68.53	77.05

PK concentrations collected outside of protocol defined window or associated with dose reduction/incomplete dosing are excluded from the summary table.

LLOQ is 0.1 µg/mL for Dato-DXd and anti-TROP2 antibody, and 0.01 ng/mL for DXd.

N = number of participants with at least one non-missing PK concentration across all visits; n = number of PK observations at a specific visit.

Impact of anti-drug antibodies (ADAs) on PK

The geometric mean peak and trough plasma concentrations of Dato-DXd were comparable among TE-ADA-positive, nAb-positive, and ADA-negative participants across all time points, and within the variabilities of data observed in ADA-negative participants. Overall, there was no apparent effect of ADA or nAb on the PK of Dato-DXd.

Special populations

On the basis of the updated PopPK model (see above) the effect of relevant covariates on the Dato-DXd exposures at Cycle 3 (AUC_3 and C_{max3}) at 6.0 mg/kg administered on Day 1 of each 21-day cycle were re-evaluated.

The impact of baseline albumin, age, sex, region, baseline tumour size, hepatic impairment, renal impairment, tumour type, TROP2 expression and treatment emergent ADA on Dato-DXd and DXd PK exposure (first-cycle and third-cycle Dato-DXd and DXd AUC and C_{max}) were not deemed to be clinically relevant, as the impacts were generally within the 80% to 125% range therefore no dose adjustment is needed based on baseline patient characteristics. Body weight was identified as a clinically relevant covariate. Participants with body weight ≥ 90 kg are recommended to receive a flat dose of 540 mg.

Elderly

Table 19 Age ranges studied in the elderly population

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
TROPION-Breast02 (TB02) Dato-DXd arm	61/323	17/323	0/323

2.3.3. Pharmacodynamics

Mechanism of action

Dato-DXd is a TROP2-targeted antibody and DNA topoisomerase I inhibitor conjugate. The anti-TROP2 component is a humanised IgG1 κ mAb. 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 active metabolite of irinotecan. The mAb is covalently conjugated to a drug-linker, MAAA-1162a, which is composed of a cleavable maleimide tetrapeptide linker and the payload (DXd).

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. It has been reported that ADCs with DXd can exhibit a bystander effect, where the payload can diffuse out of a targeted cell into adjacent cells (Ogitani et al 2016).

Primary and secondary pharmacology

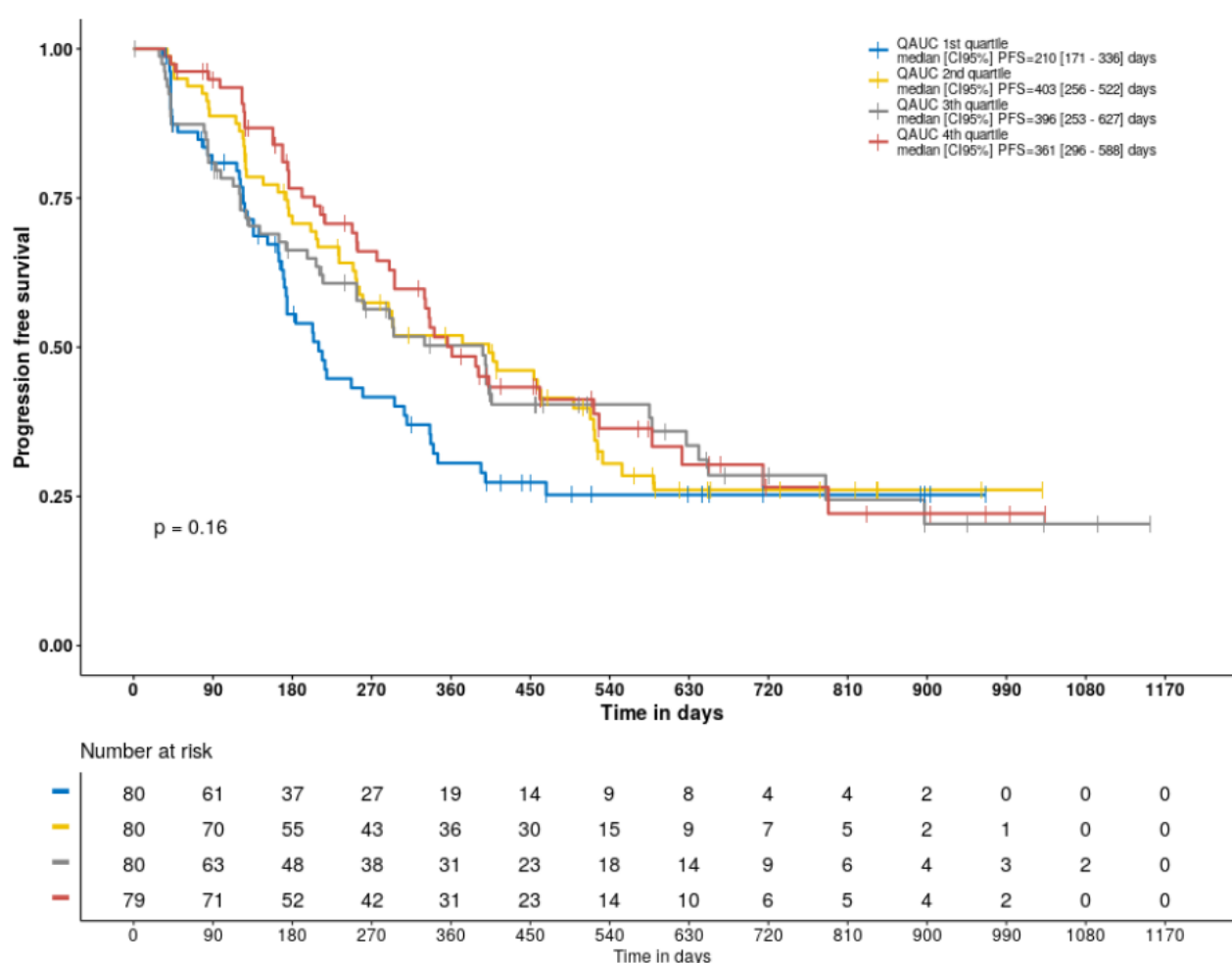
No new studies were conducted that significantly inform these parts of the assessment.

2.3.4. PK/PD modelling

Exposure-response models

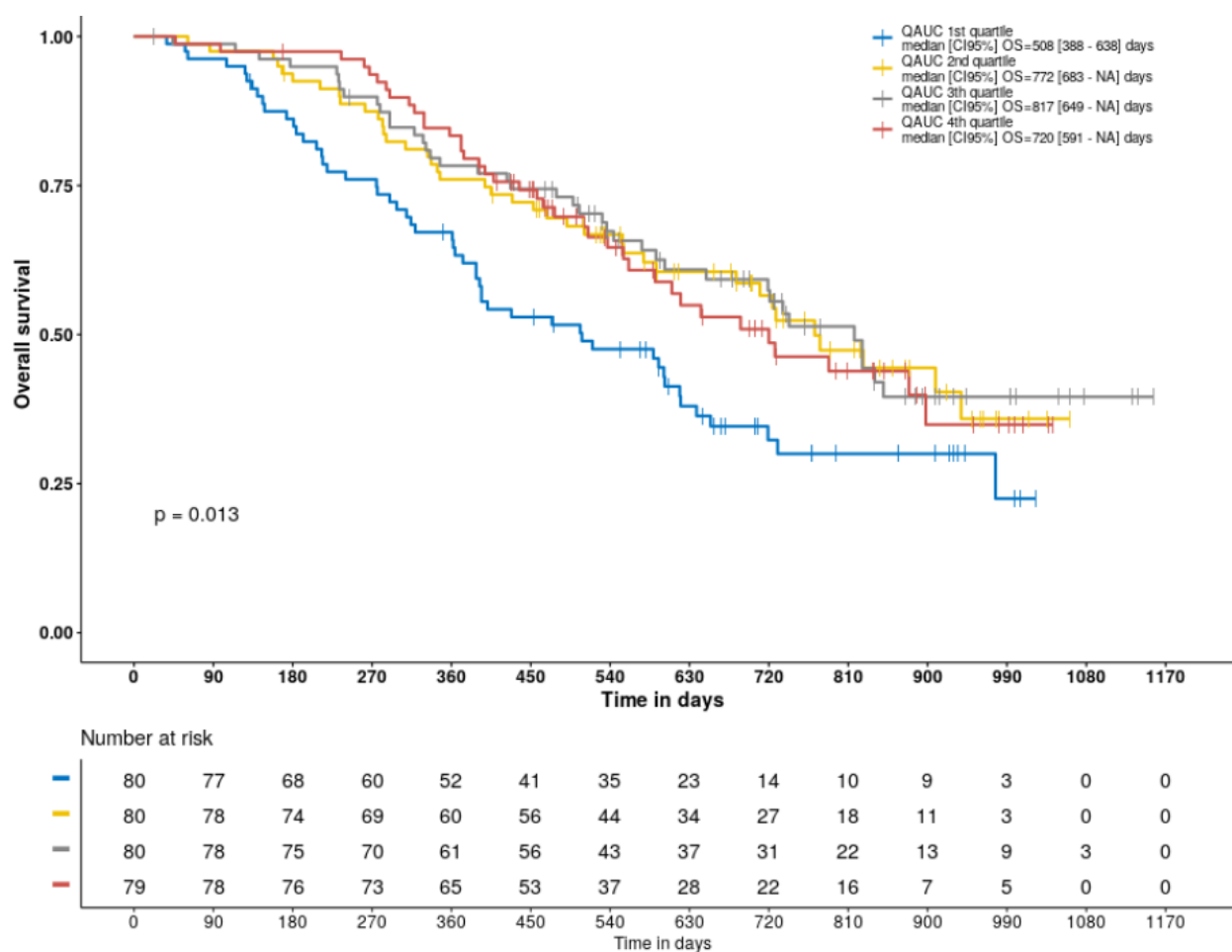
The analysis of efficacy endpoints encompassed all TNBC participants in the PK analysis set (n=319) from TB02. The exposure metrics for all participants included in the exposure efficacy and exposure safety datasets were derived from the popPK model of Dato-DXd using individual empirical Bayes estimates. Models were performed on AUC in cycle 1.

Figure 12 PFS by blinded independent central review (BICR) by Dato-DXd AUC Quartiles at Cycle1



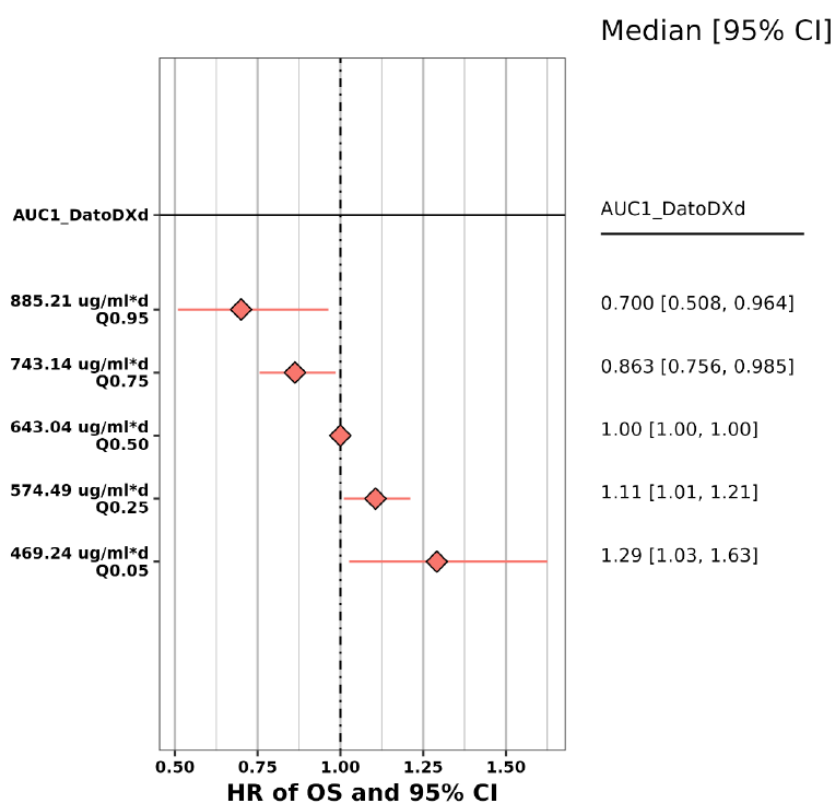
Kaplan–Meier estimates of PFS stratified by quartiles of Dato-DXd AUC C1; p value from the log rank test is shown. Numbers at risk at each time point are displayed below the plot. Dato-DXd AUC1 quartiles were predicted based on population PK TB-02 model; censored observations are indicated by tick marks.

Figure 13 OS Kaplan-Meier by Dato-DXd AUC Quartiles at Cycle 1



Kaplan–Meier estimates of OS stratified by quartiles of Dato-DXd AUC C1; p-value from the log-rank test is shown. Numbers at risk at each time point are displayed below the plot. Dato-DXd AUC C1 quartiles were predicted based on population PK TB-02 model; censored observations are indicated by tick marks.

Figure 14 Covariate Effects Plot for Exposure OS Analysis



~/Documents/d926/pkpd002/scripts/s11_fp_ee.R
2025-10-21

Dot represents the hazard ratio (HR), Bar represents the 95% CI

The reference value for continuous variables is the median; for Dato-DXd AUC C1 (AUC1_DatoDXd), this was 643.04 ug*day/ml. Values are shown for the 5th, 25th, 75th, and 95th percentiles.

Table 20 Covariate Distribution by the Quartiles of Dato-DXd AUC in Cycle 1

Variable	Label	Q1	Q2	Q3	Q4	Total
N	Number of subjects	80	80	80	79	319
TUMSBL	Tumour size	68.8 [10-280.2]	50 [10-309.6]	57.8 [10.1-233.2]	48.3 [10-295.5]	57.7 [10-309.6]
ALBBL	Albumin	40 [24-51.1]	42 [32-52.5]	43 [29-49.8]	42 [32-50.1]	42 [24-52.5]
Prior DFI	De novo	34 (42.5)	24 (30.0)	28 (35.0)	22 (27.8)	108 (33.9)
	Prior DFI ≤ 12 months	14 (17.5)	16 (20.0)	16 (20.0)	19 (24.1)	65 (20.4)
	Prior DFI > 12 months	32 (40.0)	40 (50.0)	36 (45.0)	38 (48.1)	146 (45.8)
Liver metastases	Not present	50 (62.5)	56 (70.0)	57 (71.2)	63 (79.7)	226 (70.8)
	Present	30 (37.5)	24 (30.0)	23 (28.8)	16 (20.3)	93 (29.2)

Continuous covariates are summarized as median (range) (missing values excluded). Categorical covariates are presented as N (%). Covariate distributions are shown by quartiles of Dato-DXd AUC in Cycle 1.

Exposure-safety models

The exposure-safety analysis was performed in two pools: all-solid-tumour pool and the BC only pool.

- A total of 1527 participants were included in the all-solid-tumour pool: 4 at 0.27 mg/kg, 5 at 0.5 mg/kg, 7 at 1 mg/kg, 6 at 2 mg/kg, 50 at 4 mg/kg, 1365 at 6 mg/kg, 82 at 8 mg/kg and 8 at 10 mg/kg.
- A total of 843 participants were included in the BC only pool: 841 at 6 mg/kg, and 2 at 8 mg/kg.

AUC₁ of Dato-DXd and DXd are used as the exposure metrics for all safety endpoints. Logistic regression model was used to derive the exposure-safety relationship.

Table 21 Overview of Exposure-safety Analysis

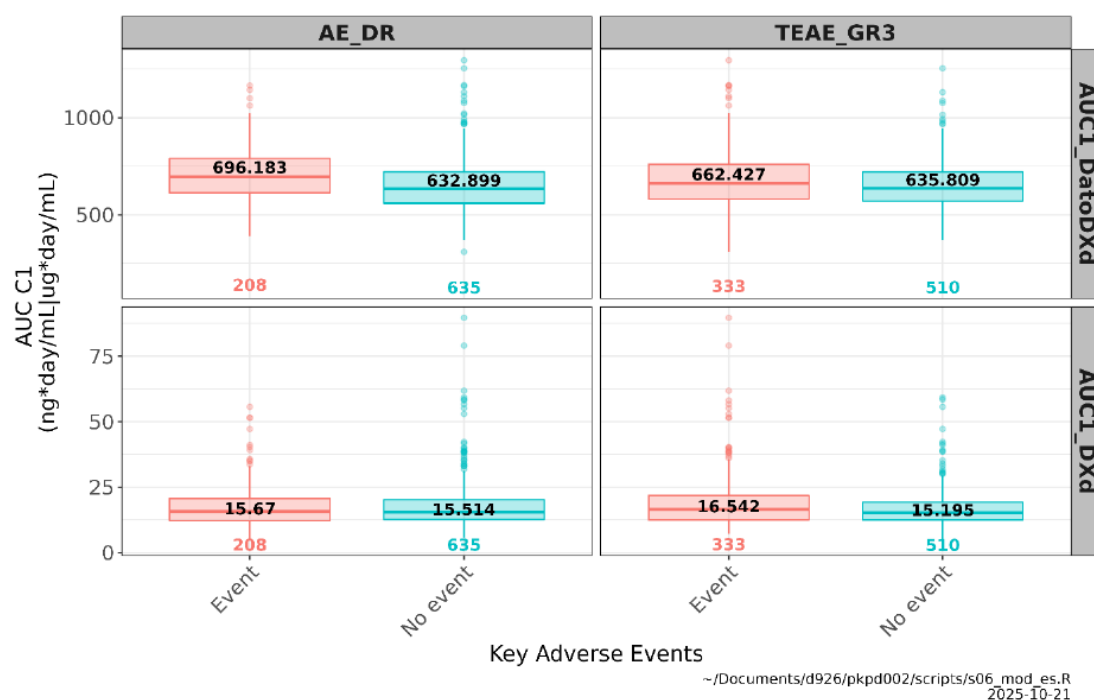
ER endpoint	Studies included	Methods	Exposure metrics tested	Covariates included
Grade $\geq$ 3 TEAEs	All-solid-tumour pool: TP01, TP02, TL01, TL05, TB01, and TB02 BC pool: TP01 (BC), TP02 (TNBC), TB01, and TB02	Graphical exploration and logistic regression	AUC ₁ of Dato-DXd AUC ₁ of DXd	tumour type (all-solid-tumour pool only), sex (all-solid-tumour pool), race, ethnicity, age, region, tumour size, albumin, body weight, ECOG performance status, number of prior line therapy, history of CNS metastases, presence of liver metastases, renal function ^a , hepatic function ^a
TEAE leading to dose reduction				
Oral mucositis/stomatitis (any grade; Grade $\geq$ 2)				
Adjudicated drug-related ILD				
Ocular surface events (any grade; Grade $\geq$ 2)				

^a Only for Grade $\geq$ 3 TEAEs.

Continuous covariate relationships will be implemented as linear models and categorical covariate relationships as a difference from the most common category. Other parameterizations of any covariate relationships may be considered if indicated by the data.

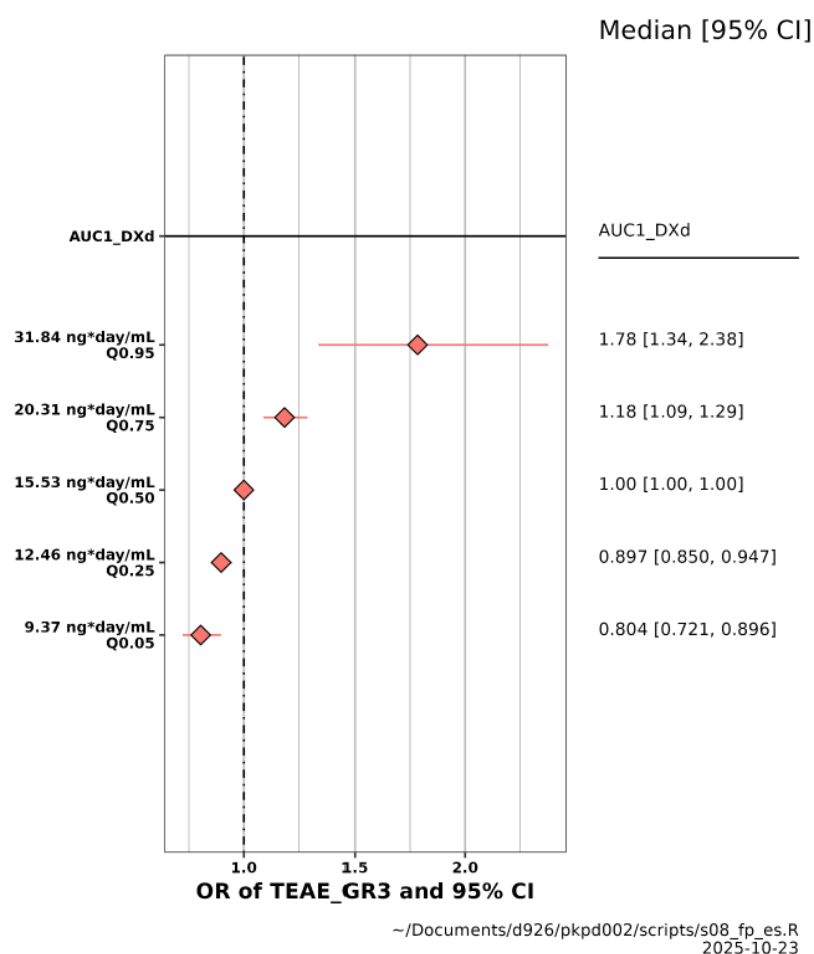
Only exposure-safety models from BC populations are carried forward in this assessment.

Figure 15 Box Plot Distribution of AUC C1 Dato-DXd and DXd by key AEs in breast cancer pool



Boxplot showing AUC cycle 1 for Dato-DXd (AUC1_DatoDXd) and DXd (AUC1_DXd) faceted by AEs (AEs resulting in dose reduction [AE_DR] and TEAE Grade 3 or higher [TEAE_GR3]) in the BC pool; boxes indicate median and interquartile range, whiskers extend to $1.5 \times$ IQR, and points beyond are plotted as outliers. Data represent N subjects per event; AUCs were estimated using the TB-02 Dato-DXd PopPK model.

Figure 16 Forest plot of OR for any TEAE Gr $\geq$ 3 in the breast cancer pool



Dot represents the median OR, Bar represents the 95% CI
The reference value is the median for continuous variables. The reference value for continuous variables is the median; for DXd AUC C1, this was 15.53 ng·day/ml. Values are shown for the 5th, 25th, 75th, and 95th percentiles

Table 22 Overview of Significant Exposure Metrics and Covariates in the Final Logistic Regression Models for the Breast Cancer Pool

Safety endpoints	Significant exposure metrics	Significant covariates
Grade $\geq$ 3 TEAEs	+ DXd_AUC_C1 + Dato_DXd_AUC_C1 ^a	-
TEAE-associated dose reduction	+ Dato_DXd_AUC_C1	-
Oral mucositis/stomatitis (any grade)	+ Dato_DXd_AUC_C1	-
Oral mucositis/stomatitis (Grade $\geq$ 2)	+ Dato_DXd_AUC_C1	-
Adjudicated drug-related ILD	-	-
Ocular surface events any grade	+ Dato_DXd_AUC_C1	- TUMSBL
Ocular surface events (Grade $\geq$ 2)	+ Dato_DXd_AUC_C1	+ LOT0 - LOT1 + LOT2

Significant covariates obtained a nominal p-value < 0.01 when selected from forward addition, and a nominal p-value < 0.001 when removed from backward elimination. The sign (+ or -) indicates a positive or negative effect on the logistic model.

^a Both DXd AUC C1 and Dato-DXd AUC C1 were associated with an increased incidence of any Grade $\geq$ 3 TEAE in the breast cancer pool. However, DXd AUC at Cycle 1 showed a stronger association (nominal p-value < 0.001).

Immunogenicity

Table 23 Summary of ADA Responses to Dato-DXd (ADA Analysis Set)

ADA category	TB02 (6 mg/kg)	BC Pool (6 mg/kg)	BC + NSCLC Pool (6 mg/kg)
ADA-evaluable patients, n (%)	319	833	1350
ADA+ at any visit (ADA prevalence), n (%)	65 (20.4)	167 (20.0)	291 (21.6)
Median of maximum titer	120.0	120.0	90.0
TE-ADA+ (ADA incidence), n (%)	47 (14.7)	124 (14.9)	222 (16.4)
Median of maximum titer	120.0	120.0	120.0
ADA+ post-baseline only (treatment-induced ADA+), n (%)	43 (13.5)	115 (13.8)	207 (15.3)
Median of maximum titer	120.0	120.0	105.0
Treatment-boosted ADA+, n (%)	4 (1.3)	9 (1.1)	15 (1.1)
Median of maximum titer	180.0	240.0	240.0
Non-TE-ADA+, n (%)	18 (5.6)	43 (5.2)	69 (5.1)
Median of maximum titer	30.0	60.0	60.0
ADA+ both at baseline and post-baseline, n (%)	9 (2.8)	22 (2.6)	39 (2.9)
Median of maximum titer	240.0	240.0	240.0
Only ADA positive at baseline and no ADA detected post-baseline, n (%)	13 (4.1)	30 (3.6)	45 (3.3)
Median of maximum titer	30.0	30.0	30.0
Persistently TE-ADA+, n (%)	0 (0)	0 (0)	0 (0)
Median of maximum titer	NA	NA	NA
Transiently TE-ADA+, n (%)	47 (14.7)	118 (14.2)	130 (9.6)
Median of maximum titer	120.0	120.0	120.0
nAb+ at baseline and/or post-baseline (nAb prevalence), n (%)	12 (3.8)	25 (3.0)	42 (3.1)
Median of maximum titer	120.0	240.0	240.0
TE-nAb+ (nAb incidence), n (%)	10 (3.1)	22 (2.6)	37 (2.7)
Median of maximum titer	300.0	420.0	240.0

Treatment-induced ADA+, defined as ADA positive post-baseline and not detected at baseline (negative or missing).

Treatment-boosted ADA+, defined as a baseline positive ADA titer that was boosted to a 4-fold or higher level following drug administration.

TE-ADA+ are patients who were either treatment-boosted ADA+ or treatment-induced ADA+.

Non-TE-ADA+ are patients who are ADA positive but not fulfilling the conditions for TE-ADA+.

ADA- is defined as patients who were ADA- at all assessments, including baseline and post-baseline.

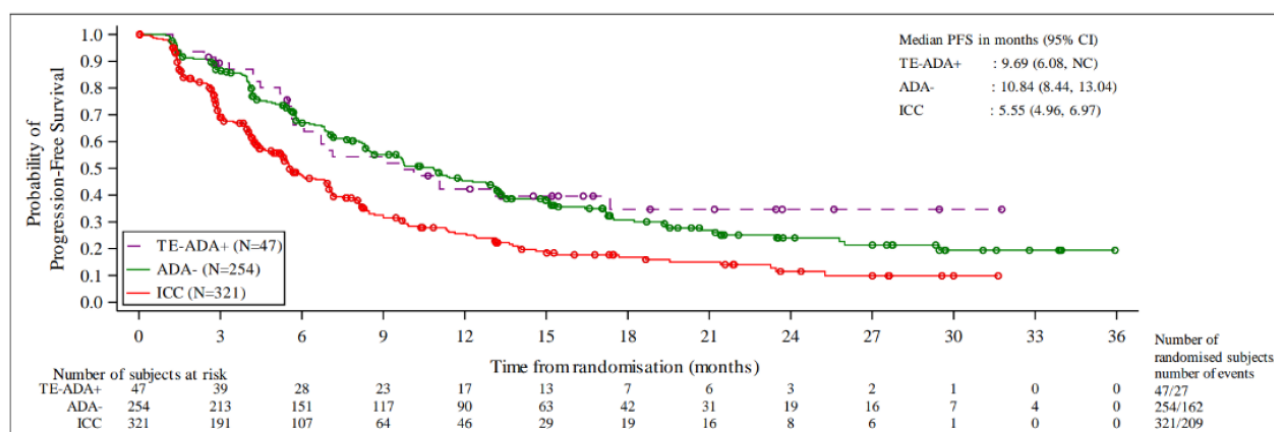
nAb+ is defined as patients with positive nAb assessment at any visit.

TE persistently ADA+, defined as being TE-ADA+ and having at least 2 post-baseline ADA+ measurements with ≥ 16 weeks between first and last positive, post-baseline (Not applicable for TL01, TP01, TP02, and TL05).

TE-nAb+ (nAb incidence), defined as TE-ADA+ patients with a positive nAb assessment.

If a patient had more than one titer result, the maximum post-baseline titer result was used, except for the category 'ADA+ at baseline only'.

Figure 17 Kaplan-Meier PFS (BICR) Curve for Dato-DXd Stratified by ADA Status (ADA Evaluable Set, TB02)



Only the ADA categories with at least 20 events are presented.

Progression is determined by BICR assessment, RECIST 1.1. Only includes progression events that occur within 2 assessments of the last evaluable assessment.

TE-ADA+: either treatment-induced ADA positive (ADA negative or missing at baseline and post-baseline ADA positive) or treatment-boosted ADA positive (ADA positive at baseline and boosted the pre-existing titer 4-fold or higher following drug administration).

Non-TE-ADA+: having at least one ADA positive assessment and not fulfilling the conditions of TE-ADA+.

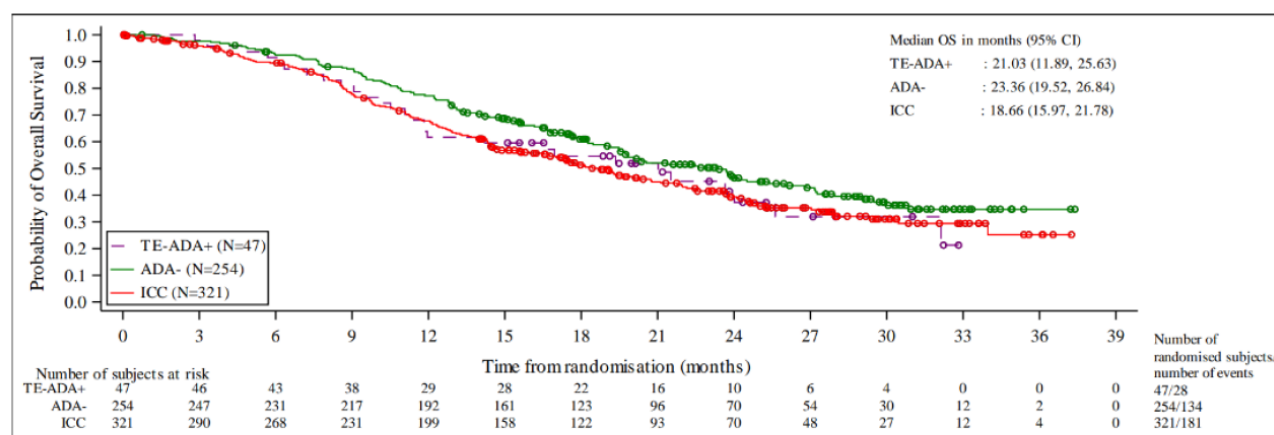
ADA-: ADA negative at all assessments.

nAb+: nAb positive at any assessment.

ICC from Full Analysis Set.

Non-TE-ADA+ and nAb+ groups are missing due to event number < 20.

Figure 18 Kaplan-Meier OS Curve for Dato-DXd Stratified by ADA Status (ADA Evaluable Set, TB02)



Only the ADA categories with at least 20 events are presented.

TE-ADA+: either treatment-induced ADA positive (ADA negative or missing at baseline and post-baseline ADA positive) or treatment-boosted ADA positive (ADA positive at baseline and boosted the pre-existing titer 4-fold or higher following drug administration).

Non-TE-ADA+: having at least one ADA positive assessment and not fulfilling the conditions of TE-ADA+.

ADA-: ADA negative at all assessments.

nAb+: nAb positive at any assessment.

ICC from Full Analysis Set.

Non-TE-ADA+ and nAb+ groups are missing due to event number < 20.

2.3.5. Discussion on clinical pharmacology

In this variation, the MAH is applying for use of the antibody-drug conjugate Datoway (datopotamab deruxtecan, Dato-DXd) as monotherapy for first-line treatment of adult patient with unresectable or metastatic triple-negative breast cancer (TNBC) who are not candidates for PD-

1/PD-L1 inhibitor therapy. The clinical pharmacology of Dato-DXd has been previously characterised and presented in the initial approval in BC (EPAR EMA/CHMP/78522/2025) and is reflected in the current product information.

The current application is primarily based on the pivotal study TROPION-Breast02 (TB02) in TNBC patients. The study's dosing regimen, 6 mg/kg IV infusion once every 3 weeks (21-day cycle), was the same as in approved BC indication of Datroway, which was based on the pivotal study TB01. Dato-Dxd, total anti-trop-2 antibody (total Ab) and Dxd in plasma were quantified with the validated methods applied in the initial Datroway MA. The conducted bioanalysis in TB02 study was in accordance with regulatory requirements. Pharmacokinetics in TB02 study was investigated using sparse PK-sampling. Overall, exposure of Dato-DXd and DXd, on basis of mean Ceoi (end of infusion) and Cpre-dose plasma concentrations values, were similar in TNBC patients as in BC patients in study TB01. Variability was also comparable.

In conclusion, the **pharmacokinetics** of Dato-DXd and DXd in TNBC patients in TB02 study is considered as supportive for the recommended dosing regimen. There was no apparent effect on ADAs on Dato-DXd PK, consistent with previous conclusions. An analysis of intrinsic and extrinsic factors utilizing the updated PopPK model was in line with previous investigations and these are adequately reported in SmPC.

A previous **Pop PK model** developed for Dato-DXd and DXd was re-estimated after addition of the sparse data from two clinical studies, TROPION-PanTumour02 (TP-02) and TROPION-Breast02 (TB02) where patients had received Dato-DXd IV 6 mg/kg Q3W. The updated Pop PK model was used to derive individual exposure metrics based on empirical Bayes estimates for evaluation of PK in patients with TNBC in special populations and for exposure-response analyses. Overall the updated Pop PK model is considered adequate for support of PK and for E-R analyses in TNBC patients. Of note, the clinical studies were conducted without a dose cap for individuals of ≥ 90 kg, applied to reduce occurrence of safety issues such as ocular surface events shown to be exposure dependent. Body weights ranged from 38 to 99.6 kg in TP-02 and 36 to 150 kg in TB02. Dato-DXd and DXd exposure with and without a dose cap was predicted and indicated individuals with a body weight ≥ 90 kg and dose-cap (fixed 540 mg) would achieve exposures in the same range as individuals with a body weight < 90 kg who received 6 mg/kg.

The **mechanism of action** is that datopotamab deruxtecan (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 so that DXd can exhibit a bystander effect, where the payload can diffuse out of a targeted cell into adjacent cells (Ogitani et al 2016).

No new studies were conducted that significantly informs primary or secondary pharmacology in this extension of indication. However, new dose-response analyses for efficacy and safety were conducted based on the TB02 trial.

Although no significant associations were identified in **exposure-efficacy analyses** (PFS or OS) at Cycle 1 Dato-DXd AUC, numerical differences between lower and upper AUC1 quartiles for PFS and OS could suggest that efficacy in the lowest quartile (Q1) is lower than for the other quartiles (Q2-4). For Q2 to Q4, median PFS was 403 days, 396 days and 361 days, respectively, whereas the median PFS for Q1 was 210 days. Per quartile median OS was 772 days, 817 days and 720 days for Q2-4 with a shorter OS for Q1 (508 days). Additional p-value of response relationship remained below the significance threshold with a p-value of 0.023. Furthermore, Cox Proportional Hazard

modelling showed the OS difference is less attributed to low exposure in Cycle 1 but suggested important influence by confounding risk factors such as higher baseline tumor size, lower baseline albumin and prior DFI which were identified as significant covariates ($p < 0.005$) for OS. Thus, it can be concluded that there is no dose-efficacy relationship for Dato-DXd. It is considered that in this dataset an unbalanced distribution between Q1-4 in major prognostic variables such as tumour size, liver metastases and de novo disease status indicate a confounded relationship between AUC1 quartiles and OS. Diagnostics were provided for the updated OS CPH model that did not indicate any violation of the PH assumption for any of the variables TUMSBL (tumour size at baseline), DFI (disease free interval) or ALBBL (baseline albumin). Univariate KM-VPCs, stratified by ALBBL and TUMSBL quartiles showed concordance between observed and model-derived survival probability (data not shown).

The **exposure–safety analyses** are acceptable and conclusions supported. The exposure-safety models were based on data from BC clinical trial populations, where the vast majority ($n=841/843$) received the intended dose of 6mg/kg. Exposure-safety relationship were found between Dato-DXd dose at AUC1 and Grade ≥ 3 TEAEs, TEAEs, dose reduction, oral mucositis/stomatitis, and ocular surface events in the BC pool. No exposure–safety relationship between Dato-DXd and/or DXd and adjudicated, drug-related ILD was established in any pool.

Immunogenicity was investigated based on data from the TB02 study. It is concluded that ADA prevalence was numerically similar across Study TB02 and the reference BC pools (range: 20.0% to 21.6%). In addition, the data indicate that the majority of ADA positive participants were classified as treatment-emergent-nAb positive (14.7%). The percentage of participants who were ADA positive at baseline ranged from 3.3% to 4.1% and the number of patients with treatment-boosted antibodies was similarly low in the TB02 study ($n=4$, 1.3%).

Patients with TE-ADA positive status showed similar PFS as patients with ADA negative status, while visual inspection of the KM curves for TE-ADA positives and ICC seemed to cross multiple times. Given the low number of patients in the TE-ADA positives ($n=47$) especially at median PFS/OS ($n \sim 20$), efficacy outputs are overall non-informative and it is accepted that TE-ADA positive status shows similar efficacy as ADA negatives.

2.3.6. Conclusions on clinical pharmacology

The pharmacokinetics and immunogenicity of Dato-DXd in adult patients with TNBC have been sufficiently determined in the clinical study TB-02 and shown to be comparable to Dato-DXd in other approved BC indications. In conclusion, the obtained clinical pharmacology data is overall supportive for approval of the use of Dato-DXd in TNBC.

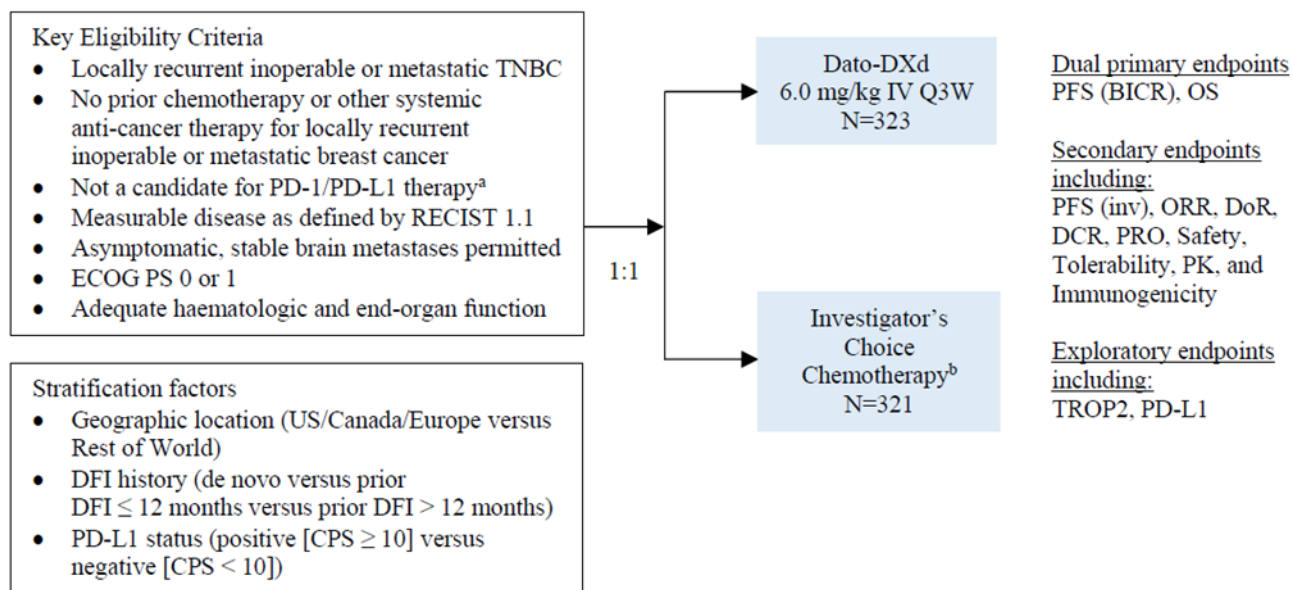
2.4. Clinical efficacy

2.4.1. Main study(ies)

TROPION-Breast02 (TB02) is a Phase III, randomized, open-label, 2-arm, multicentre, international study assessing the efficacy and safety of Dato-DXd compared with investigator's Choice of Chemotherapy (ICC) in participants with locally recurrent inoperable or metastatic TNBC who are not candidates for PD-1/PD-L1 inhibitor therapy.

Methods

Figure 19 Schematic of Study Design



^a Participants whose tumours are PD-L1-negative, or participants whose tumours are PD-L1-positive and have: 1) relapsed after prior PD-1/PD-L1 inhibitor therapy for early-stage breast cancer, 2) comorbidities precluding PD-1/PD-L1 inhibitor therapy, or 3) no regulatory access to pembrolizumab (participant's country does not have regulatory approval at the time of screening).

^b If no prior taxane, or prior taxane in the (neo)adjuvant setting and DFI > 12 months, paclitaxel or nab-paclitaxel; if prior taxane and DFI ≤ 12 months: capecitabine, carboplatin, or eribulin. For participants who relapse after being treated for early-stage breast cancer, DFI will be measured as the time between completion of treatment with curative intent (either date of primary breast tumour surgery or date of last dose of systemic anti-cancer therapy [not including endocrine therapy], whichever occurred last) and the first documented local or distant disease recurrence (either by biopsy or imaging). Adjuvant radiation therapy is not considered treatment with curative intent for the purpose of calculating DFI.

Study participants

The most important criteria are listed here. The complete list will be available in the published clinical study results.

Key inclusion criteria:

- Participant must be ≥ 18 years at the time of screening.
- Histologically or cytologically documented locally recurrent inoperable TNBC, which cannot be treated with curative intent, or metastatic TNBC (ER with < 1%, PR < 1% and HER2 with 0 or 1+ intensity on IHC or 2+ intensity on IHC and negative by in situ hybridization)
- No prior chemotherapy or other systemic anti-cancer therapy for metastatic or locally recurrent inoperable breast cancer.
- Not a candidate for PD-1/PD-L1 inhibitor therapy, defined as:
 - Participants whose tumours are PD-L1-negative, or
 - Participants whose tumours are PD-L1-positive and have: 1) relapsed after prior PD-1/PD-L1 inhibitor therapy for early-stage breast cancer, 2) comorbidities precluding PD-1/PD-L1 inhibitor therapy, or 3) no regulatory access to pembrolizumab [participant's country does

not have regulatory approval at the time of screening]), additionally, participants eligible for atezolizumab in countries with regulatory approval of atezolizumab should be excluded.

5. At least 1 measurable lesion not previously irradiated (based on RECIST 1.1)
 6. ECOG PS 0 or 1 with no deterioration over the previous 2 weeks prior to baseline or day of first dosing.
 7. Eligible for one of the chemotherapy options listed as ICC (paclitaxel, nab-paclitaxel, capecitabine, carboplatin, or eribulin) based on DFI and prior taxane exposure, per investigator assessment.
- Note 1: Participants with locally recurrent inoperable or relapsed metastatic TNBC are expected to have been treated with (neo)adjuvant anthracycline, unless anthracycline was contraindicated or not considered the best treatment option for the participant in the opinion of the treating physician.
- Note 2: Participants presenting with de novo metastatic TNBC are eligible for the study, if anthracycline is contraindicated or not considered the best treatment option for the participant in the opinion of the treating physician.
- Note 3: Participants with known germline BRCA pathogenic variants (based on testing performed as part of routine clinical practice) presenting with metastatic or locally recurrent inoperable TNBC are eligible for the study, if another therapy (such as poly adenosine diphosphate-ribose polymerase [PARP] inhibitor) is not considered the best treatment option for the participant in the opinion of the treating physician.
10. Participants with a history of previously treated neoplastic spinal cord compression or asymptomatic, stable brain metastases, who require no treatment with corticosteroids or anticonvulsants may be included in the study, if they are no longer symptomatic and have recovered from acute toxic effects of radiotherapy. A minimum of 2 weeks must have elapsed between the end of radiotherapy and Cycle 1 Day 1. A minimum of 3 days must have elapsed between the end of corticosteroid therapy for central nervous system metastatic disease and Cycle 1 Day 1.
 11. Adequate organ and bone marrow function within 7 days before randomisation

Key exclusion criteria:

7. Uncontrolled or significant cardiac disease including:
 - Myocardial infarction or uncontrolled/unstable angina within 6 months prior to Cycle 1 Day 1
 - Congestive heart failure (New York Heart Association Class II to IV), or
 - Uncontrolled or significant cardiac arrhythmia, or
 - Uncontrolled hypertension (resting systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg).
15. Prior exposure to:
 - Any treatment (including ADC) containing a chemotherapeutic agent targeting topoisomerase I – TROP2-targeted therapy
 - Prior treatment with same ICC agent

- Chloroquine/hydroxychloroquine without an adequate treatment washout period of > 14 days prior to randomisation.

Note: Participants are eligible for enrolment into this study if they are able to receive treatment with another ICC agent not previously received. Participants who have DFI > 12 months and have received prior taxane in the (neo)adjuvant setting can still receive paclitaxel or nab-paclitaxel.

Treatments

The study intervention arms were:

- Arm 1: Dato-DXd (6 mg/kg IV on Day 1, Q3W)
- Arm 2: ICC:

If no prior taxane, or prior taxane in the (neo)adjuvant setting and DFI > 12 months:

- Paclitaxel (80 mg/m² IV on Day 1, Day 8 and Day 15, Q3W)
- Nab-paclitaxel (100 mg/m² IV Day 1, Day 8 and Day 15, every 4 weeks [Q4W])

If prior taxane and DFI ≤ 12 months:

- Capecitabine (1000 or 1250 mg/m² oral BID on Days 1 to 14, Q3W); choice between the 2 doses will be determined by standard institutional practice.
- Eribulin mesylate (1.4 mg/m² IV on Day 1 and Day 8, Q3W).
- Carboplatin (AUC 6 [using Calvert formula] IV Day 1, Q3W)

Objectives

Primary:

- To demonstrate superiority of Dato-DXd relative to ICC by assessment of PFS, by BICR
- To demonstrate superiority of Dato-DXd relative to ICC by assessment of OS

Main secondary:

- To demonstrate superiority of Dato-DXd relative to ICC by assessment of PFS, by investigator assessment.
- To demonstrate superiority of Dato-DXd relative to ICC by assessment of objective response rate (ORR)
- To demonstrate the superiority of Dato-DXd relative to ICC by assessment of duration of response (DoR)
- To demonstrate the superiority of Dato-DXd relative to ICC by assessment of disease control rate (DCR)

Several secondary outcomes concerning patient reported outcomes (PROs), safety, PK and immunogenicity are not described here. Complete list can be found in the Clinical Study Report.

Outcomes/endpoints

Primary endpoints

The dual primary endpoints of the study are:

- PFS by BICR according to RECIST 1.1, defined as the time from the date of randomisation until progression per RECIST 1.1 as assessed by BICR, or death due to any cause.
- OS in the ITT population, defined as the time from the date of randomisation until death due to any cause regardless of whether the participant withdraws from randomised therapy or receives another anti-cancer therapy (i.e. date of death or censoring – date of randomisation +1).

The study was to be considered positive if either the PFS or the OS analysis results were statistically significant.

Secondary endpoints

Main secondary endpoints:

ORR is defined as the proportion of participants who have a confirmed CR or PR, as determined by BICR/investigator assessment, per RECIST 1.1.

DoR is defined as the time from the date of first documented confirmed response until date of documented progression per RECIST 1.1, as assessed by BICR/investigator assessment or death due to any cause.

PFS by investigator assessment is defined as the time from the date of randomisation until the date of PD per RECIST 1.1 by investigator assessment or death by any cause in the absence of progression.

DCR at 12 weeks is defined as the percentage of participants who have a CR or PR or who have SD, per RECIST 1.1, as assessed by BICR/investigator assessment and derived from the raw tumour data for at least 11 weeks after randomisation.

PROs: PRO questionnaires to assess secondary participant-reported pain, breast and arm symptoms, physical functioning and global health status (GHS)/quality of life (QoL) endpoints, assessed using selected items from the European Organisation for Research and Treatment of Cancer (EORTC) item library (IL), as well as participant-reported symptomatic AEs measured by selected items from the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)/EORTC IL reflecting overall influence of the benefits and toxicity of the treatment from the participant's perspective.

Safety and tolerability of Dato-DXd is assessed in terms of AEs (graded by CTCAE version 5.0) and in terms of ECOG PS, vital signs, body weight, physical examination, Clinical chemistry, haematology, and urinalysis assessments, and Ophthalmologic assessments.

Sample size

Approximately 1100 participants were to be screened/enrolled to achieve approximately 600 randomised to study intervention.

The primary (and final) PFS analysis for superiority was planned to occur after approximately 422 BICR PFS events across the Dato-DXd and ICC treatment groups (70% maturity). The final OS analysis for superiority was planned to occur after approximately 340 OS events from the intent-to-treat (ITT) population across the Dato-DXd and the ICC arms (57% maturity).

The study was sized for dual primary endpoints to assess the efficacy of Dato-DXd versus ICC in the ITT population in terms of PFS; as assessed by BICR and OS.

Assuming the true PFS treatment effect under the alternative hypothesis is the hazard ratio (HR) of 0.6 for Dato-DXd versus ICC and the median PFS in ICC was 5.6 months, 422 PFS events from the ITT population (70% maturity) were estimated to provide greater than 99% power to demonstrate statistical significance at the 2-sided alpha level of 1.0%. Assuming the true OS treatment effect under the alternative hypothesis was the HR of 0.72 and the median OS in ICC is 20.6 months, 340 OS events (57% maturity) were estimated to provide approximately 82.7% power to demonstrate statistical significance at the 2-sided alpha level of 4.0%. If the PFS by BICR dual primary analysis crosses the efficacy threshold, OS was to be tested at the 2-sided alpha level of 5.0% and the analysis would provide approximately 85% power to demonstrate statistical significance.

Randomisation

A total of 1277 participants were screened. Of these, 644 were randomised in a 1:1 ratio to one of the 2 treatment arms; 323 in the Dato-DXd arm and 321 in the ICC arm.

Randomisation was stratified by the following prognostic factors:

- Geographic region (Region 1 [US, Canada, Europe] vs Region 2 [Rest of World])
- DFI history (de novo vs prior DFI $\leq$ 12 months vs prior DFI $>$ 12 months)
- PD-L1 status (positive [CPS $\geq$ 10] vs negative [CPS $<$ 10])

A recruitment cap of approximately 20% of the randomised participants was applied to participants with a DFI $\leq$ 12 months.

A recruitment cap of approximately 10% of the randomised participants was applied to participants with PD-L1-positive tumours who would otherwise have been eligible for pembrolizumab but did not have regulatory access to pembrolizumab (participant's country did not have regulatory approval at the time of screening).

Blinding (masking)

The study was an open-label study for the personnel at study sites, however the trial was conducted as a sponsor-blind..

Statistical methods

Analysis set for efficacy

The full analysis set (FAS) will include all randomised participants. The FAS will be used for all efficacy analyses and treatment groups will be compared on the basis of randomised study treatment, regardless of the treatment actually received. Participants who were randomised but did not subsequently receive treatment are included in the FAS in the treatment group to which they were randomised. The analysis of data will be done using the FAS population that follows the principles of ITT. Of note, the safety analysis set will include participants who received at least one dose of study medication.

PFS primary analysis

PFS is defined as the time from the date of randomisation until the date of objective disease progression, as defined by RECIST 1.1, or death (by any cause in the absence of progression) regardless of whether the participant withdraws from randomised therapy, receives another anti-

cancer therapy or clinically progresses prior to RECIST 1.1 progression (i.e. date of PFS event or censoring – date of randomisation + 1).

Table 5 Outcome and date of event for primary PFS

Situation	Date of PD/ Death event or Censoring	PFS Outcome
First progression or death after at most 1 missed scheduled visit, regardless of whether the patient withdraws from randomised therapy, receives another anti-cancer therapy or clinically progresses prior to RECIST 1.1 progression	Date of assessment of first progression or death (by any cause in the absence of progression)	Event
No baseline or evaluable RECIST assessments post baseline and no death within 2 scheduled RECIST visits after the date of randomisation	Day 1 (Date of randomisation)	Censored
No PD or death at time of data cut-off	Date of last evaluable RECIST assessment	Censored
Death or progression after two or more missed scheduled RECIST visits	Date of last evaluable RECIST assessment prior to the 2 missed scheduled visits	Censored

OS

Overall survival (OS) is defined as the time from the date of randomisation until death due to any cause regardless of whether the participant withdraws from randomised therapy or receives another anti-cancer therapy (i.e. date of death or censoring – date of randomisation + 1).

Any participant not known to have died at the time of analysis will be censored based on the last recorded date on which the participant was known to be alive.

Statistical methods and sensitivity analyses

Endpoints Analysed	Notes
PFS per BICR*	Primary analysis stratified log-rank test Sensitivity analyses ^a 1. Evaluation-time bias (midpoint analysis) 2. Attrition bias 3. Ascertainment bias 4. Subsequent anti-cancer therapy being censored 5. Stratification according to eCRF 6. No censoring to events 7. Subsequent anti-cancer therapy being event 8. Evaluation-time bias (Interval censoring analysis) Subgroup analysis
OS *	Stratified log-rank test Sensitivity analyses 1. Attrition bias 2. Stratification according to eCRF 3. Inverse probability censoring weighted analysis Subgroup analysis
PFS by investigator	Stratified log-rank test
ORR	Logistic regression model, Miettinen-Nurminen method
DoR	Kaplan-Meier estimates
DCR at 12 weeks	Logistic regression model, Miettinen-Nurminen method

The dual primary endpoint of PFS (by BICR) was stratified by DFI history and PD-L1 status, and the dual primary endpoint of OS was stratified by DFI history.

Of note, geographic region was not included as a stratification factor in the analysis although it remains a randomisation factor. For OS, only DFI was included in the stratified analysis. Selected stratification factors were removed from the stratified analysis in accordance with the pre-specified SAP rules because of the small number of events within certain strata. This pooling was implemented to ensure that the resulting strata contained sufficient number of events to support robust and reliable analyses.

The HRs together with their 95% confidence intervals (CIs) and p values were presented (a HR less than 1 favoured the Dato-DXd arm). The HR was estimated from a stratified Cox Proportional Hazards model (with ties = Efron), and the CI calculated using a profile likelihood approach.

Details about attrition and ascertainment sensitivity analysis.

Table 24 Change of censoring rules for PFS attrition bias sensitivity analysis

Scenario	Date of PD/ Death event or Censoring	PFS Outcome
Progresses or dies immediately after two or more consecutive missed visits	Disease progression date, or death date if no PD	Event
Take subsequent therapy prior to their last evaluable RECIST assessment or progression or death	Last evaluable assessment prior to taking the subsequent therapy	Censored

Ascertainment bias was assessed by analysing the site investigator data which is a secondary efficacy endpoint.

Sensitivity for OS

Sensitivity Analysis 1- Attrition bias: A sensitivity analysis for OS examining the censoring patterns to rule out attrition bias with regard to the primary treatment comparisons will be achieved by a KM plot of time to censoring where the censoring indicator of OS is reversed.

Sensitivity Analysis 2 – Stratification according to eCRF

Sensitivity Analysis 3 – Inverse probability censoring weighted analysis. To better understand the impact of subsequent anti-cancer therapies on OS, a sensitivity analysis of OS using the inverse probability censoring weights (IPCW) method (Mosier 2023, Xue & Lai 2023) will be performed accounting for the impact of subsequent anti-cancer of interest. The subsequent anti-cancer therapies of interest include:

- SACITUZUMAB GOVITECAN,
- SACITUZUMAB GOVITECAN HZIY,
- TRASTUZUMAB DERUXTECAN,
- TRASTUZUMAB DERUXTECAN NXXI,
- "SACITUZUMAB TIRUMOTECAN", "SKB264", "SKB-264", "MK2870", "MK-2870", or any variants thereof.

Standardized weights are estimated using the ratio of the probabilities estimated from two models, one containing only baseline covariates, the other containing baseline and time dependent covariates. The numerator of the weights is estimated using the baseline covariate model and the denominator of the weights is estimated using the baseline and time-dependent covariate model. Covariates were suggested by the clinical study team. Sponsor may add or remove one or more baseline or time-dependent covariates as appropriate. For example, if there are insufficient numbers of subjects receiving subsequent therapies of interest to fit a model with all the listed covariates, covariates may be removed. Or if inclusion of one of the covariates violates the positivity assumption, covariates may be dropped. The final model will be specified in the output.

The baseline covariates include:

- Age at randomisation
- Stratifications factors (geographic region, DFI history, and PD-L1 status)
- HER2 status at baseline
- Number of metastatic sites
- Brain metastases
- Liver metastases

The time-dependent covariates include:

- ECOG
- AE (G3 or greater)
- PFS by investigator

Subgroups

Subgroup analyses will be conducted comparing PFS by BICR and OS between the treatments in the following subgroups of the FAS:

1. Stratification factors at randomisation:

- Geographic region (Region 1 [US, Canada, Europe] versus Region 2 [Rest of World])
- DFI history (de novo versus prior DFI ≤ 12 months versus prior DFI > 12 months)
- PD-L1 status (positive [CPS ≥ 10] versus negative [CPS < 10])

2. Exploratory factors:

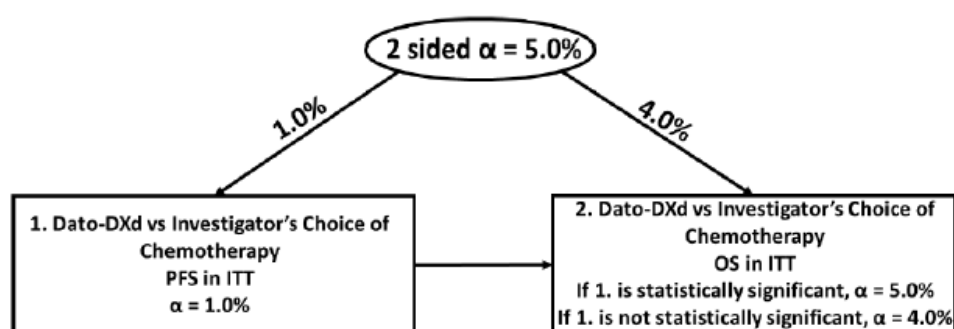
- Age at randomisation (<65 versus ≥ 65 years of age)
- Race (Asian versus non-Asian).
- Brain metastases (Yes versus No)
- Liver metastases (Yes versus No)
- Pre-selected choice of chemotherapy (paclitaxel, nab-paclitaxel, capecitabine, carboplatin, eribulin mesylate/eribulin)
- HER2 (IHC 0 versus IHC 1+ and IHC 2+/FISH/ISH -ve)
- ECOG performance status at baseline (0 versus 1)
- Number of metastatic sites at baseline (<3 versus ≥ 3)
- Prior anti-PD-(L)1 therapy for breast cancer (Yes versus No)

Multiplicity

To preserve the overall type 1 error (familywise error rate), a multiple testing procedure (MTP) including the dual primary endpoints was implemented. Hypotheses were tested in the MTP using alpha (test mass) splitting and alpha recycling, where the test mass that becomes available to the OS analyses (recycled) if the PFS dual primary analysis null hypothesis is rejected. Implementation of this pre-defined ordered testing procedure, including recycling, will control type I error at 5.0% (2-sided), among all dual primary hypotheses.

The overall alpha for this study is 0.05, which is split with 0.01 to evaluate PFS and 0.04 to evaluate OS. If the PFS dual primary analysis crosses the efficacy threshold, the 1.0% type I error allocated to the PFS endpoint will be reallocated (Burman et al 2009) to the OS endpoint for a total type I error of 5.0%. The MTP for the dual primary endpoints is described in Figure 20.

Figure 20 Multiple testing procedure



No interim analyses performed

This clinical study report (CSR) presents the final analysis (FA) of this study, which includes FA of both PFS and OS. No previous interim analysis has been conducted nor reported. The primary analysis of PFS (presented in this CSR) was planned to occur after approximately 422 BICR PFS events across the Dato-DXd and ICC treatment groups, and the FA of OS (presented in this CSR) was planned to occur after approximately 340 OS events from the ITT population across the Dato-DXd and ICC treatment groups. The required approximate number of BICR PFS and OS events to trigger the primary PFS and final OS analyses, respectively, had occurred as of the 25 August 2025 data cut off (DCO).

Planned interim analyses:

Two IAs for OS analysis are planned. The first OS IA will occur at the primary PFS analysis (approximately 57% of target OS events) and the second when approximately 80% of the target OS events have occurred. The Haybittle-Peto procedure (Haybittle 1971, Peto et al 1976) will be used to calculate the alpha spending at the first IA, resulting in a large critical value and small nominal p-value (2-sided nominal p-value 0.0001). For both the second IA and the final OS analyses, the Lan DeMets approach that approximates the O'Brien and Fleming spending function will be used (Lan and DeMets 1983).

Table 25 Summary of Planned Timings of the Interim and Final OS Analyses

	IA 1		IA 2		Final analysis	
Projected timing	26 months ^a		33.4 months		41.6 months	
Number of deaths ^b	195		272		340	
Information fraction	57%		80%		100%	
Maturity	33%		45%		57%	
Recommendation	Continue	Reject Null Hypothesis	Continue	Reject Null Hypothesis	Do not reject null hypothesis	Reject null hypothesis
<i>At 4.0% 2-sided alpha ^c</i>						
2-sided nominal p-value	≥ 0.0001	< 0.0001	≥ 0.0195	< 0.0195	≥ 0.0340	< 0.0340
Estimated HR	≥ 0.571	< 0.571	≥ 0.752	< 0.752	≥ 0.793	< 0.793
<i>At 5% 2-sided alpha ^c</i>						
2-sided nominal p-value	≥ 0.0001	< 0.0001	≥ 0.0244	< 0.0244	≥ 0.0429	< 0.0429
Estimated HR	≥ 0.572	< 0.572	≥ 0.760	< 0.760	≥ 0.802	< 0.802

^a Timing of first IA based on PFS.

There were 3 versions of the SAP.

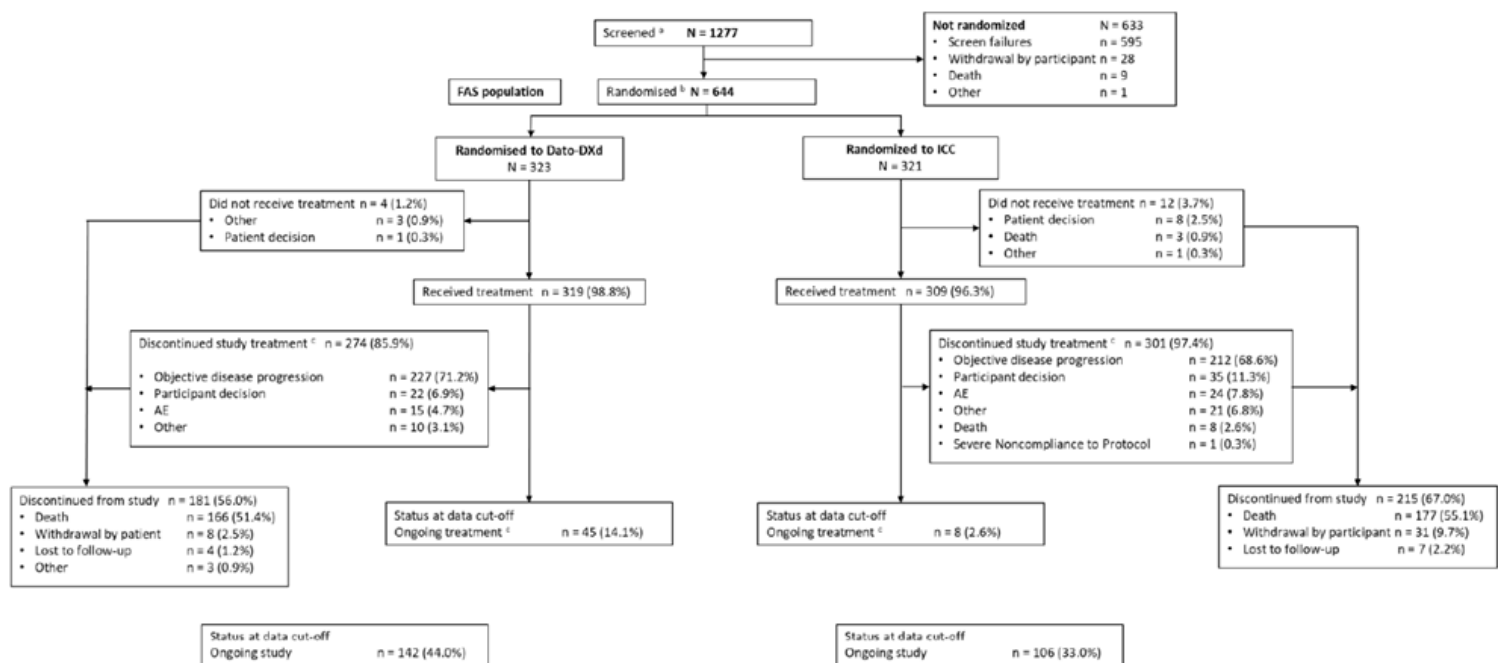
Table 26 **Changes to the SAP**

Statistical Analysis Plan Number	Date
Statistical Analysis Plan, Edition 3.0	21 Aug 2025
Statistical Analysis Plan, Edition 2.0	07 Feb 2025
Statistical Analysis Plan, Edition 1.0	10 Aug 2022

Results

Participant flow

Figure 21 Study CONSORT Diagram



^a Screened participants are those who signed informed consent.

^b For ICC arms, percentages are based on the total number of participants randomised to ICC. For the Dato-DXd arm, percentages are based on the total number of participants randomised to Dato-DXd.

^c Percentages are based on the number of participants who started treatment.

Participants are summarised in the arm to which they were randomised.

Percentages are based on the number of participants randomised, with the exception of those marked (b) and (c).

n = Number of participants per category.

Recruitment

The study was conducted at 198 active sites in 23 countries.

First patient was screened 16 May 2022. Start date submitted to EudraCT is listed as 16 June 2022. Study completion according to National Clinical Trials was 3 December 2025. The final clinical data lock date was 19 September 2025 and the study was unblinded on 22 September 2025.

A total of 248 (38.5%) participants remained on study follow-up at the time of the DCO (25 August 2025), including 142 (44.0%) participants in the Dato-DXd arm and 106 (33.0%) participants in the ICC arm.

Table 27 Disposition – All Participants

Table 7 Disposition – All Participants

	Dato-DXd n (%)	ICC n (%)	Paclitaxel n (%)	Nab-paclitaxel n (%)	Capecitabine n (%)	Carboplatin n (%)	Eribulin mesylate/ Eribulin n (%)	Total n (%)
Participants screened ^a								1277
Not randomised								633
Participants randomised ^b	323 (100)	321 (100)	89 (27.7)	174 (54.2)	7 (2.2)	15 (4.7)	36 (11.2)	644 (100)
Participants randomised, not treated	4 (1.2)	12 (3.7)	4 (4.5)	6 (3.4)	0	2 (13.3)	0	16 (2.5)
Participant decision	1 (0.3)	8 (2.5)	2 (2.2)	5 (2.9)	0	1 (6.7)	0	9 (1.4)
Death	0	3 (0.9)	2 (2.2)	0	0	1 (6.7)	0	3 (0.5)
Other	3 (0.9)	1 (0.3)	0	1 (0.6)	0	0	0	4 (0.6)
Participants started treatment	319 (98.8)	309 (96.3)	85 (95.5)	168 (96.6)	7 (100)	13 (86.7)	36 (100)	628 (97.5)
Participants ongoing treatment at DCO date ^c	45 (14.1)	8 (2.6)	2 (2.4)	5 (3.0)	0	0	1 (2.8)	53 (8.4)
Participants discontinued treatment ^c	274 (85.9)	301 (97.4)	83 (97.6)	163 (97.0)	7 (100)	13 (100)	35 (97.2)	575 (91.6)
Participant decision	22 (6.9)	35 (11.3)	12 (14.1)	19 (11.3)	1 (14.3)	1 (7.7)	2 (5.6)	57 (9.1)
AE	15 (4.7)	24 (7.8)	14 (16.5)	7 (4.2)	0	2 (15.4)	1 (2.8)	39 (6.2)
Severe non-compliance to protocol	0	1 (0.3)	0	1 (0.6)	0	0	0	1 (0.2)
Objective disease progression	227 (71.2)	212 (68.6)	49 (57.6)	119 (70.8)	4 (57.1)	9 (69.2)	31 (86.1)	439 (69.9)
Death	0	8 (2.6)	4 (4.7)	4 (2.4)	0	0	0	8 (1.3)
Other	10 (3.1)	21 (6.8)	4 (4.7)	13 (7.7)	2 (28.6)	1 (7.7)	1 (2.8)	31 (4.9)
Participants ongoing in study at DCO date	142 (44.0)	106 (33.0)	33 (37.1)	64 (36.8)	1 (14.3)	1 (6.7)	7 (19.4)	248 (38.5)
Participants withdrawn from study	181 (56.0)	215 (67.0)	56 (62.9)	110 (63.2)	6 (85.7)	14 (93.3)	29 (80.6)	396 (61.5)
Death	166 (51.4)	177 (55.1)	45 (50.6)	91 (52.3)	6 (85.7)	13 (86.7)	22 (61.1)	343 (53.3)
Lost to follow-up	4 (1.2)	7 (2.2)	0	6 (3.4)	0	0	1 (2.8)	11 (1.7)
Withdrawal by participant	8 (2.5)	31 (9.7)	11 (12.4)	13 (7.5)	0	1 (6.7)	6 (16.7)	39 (6.1)
Other	3 (0.9)	0	0	0	0	0	0	3 (0.5)

^a Screened participants are those who signed informed consent.

^b For ICC arms, percentages are based on the total number of participants randomised to ICC. For Dato-DXd and total arms, percentages are based on the number of participants randomised.

^c Percentages are based on the number of participants who started treatment.

Participants are summarised in the arm to which they were randomised.

Percentages are based on the number of participants randomised, with the exception of those marked (b) and (c).

ICC categories are based on planned chemotherapy choice from IRT system (at time of randomisation).

n = Number of participants per category.

Source: Table 14.1.1

Conduct of the study

Protocol amendments:

DOCUMENT HISTORY	
Document	Date of Issue
Amendment 3 (Version 4.0)	30 Jul 2024
Amendment 2 (Version 3.0)	11 Apr 2023
Amendment 1 (Version 2.0)	13 Jan 2022
Original Protocol (Version 1.0)	29 Nov 2021

From version 3 to 4 no important changes were made.

From version 2 to 3 the following important changes were made:

- Exclusion of participants eligible for atezolizumab in countries with regulatory approval of atezolizumab.

- Increase of target screening number from 800 to 1100 participants
- Clarification of wording for PD-L1 testing and removal of the possibility for use of local PD-L1 IHC 22C3 pharmDx assay results until the central laboratory was set up
- Changed end of study definition, text added to clarify FDA and EU requirements, and to specify the relevant statistical considerations

From version 1 to 2 the following important changes were made (before study start):

- Removal of hormone receptor low population. To ensure that definition of TNBC is in accordance with published guidelines.
- Removal of unknown PD-L1 status and clarification of which participants are not candidates for PD-1/PD-L1 inhibitor therapy.

Table 28 Changes to Planned Analyses

Key details of change	Reason for change	SAP amendment?
Changes made before unblinding of study data		
• Definition of DCR and ORR estimand updated to remove confirmation	DCR and ORR are analysed for both confirmed and unconfirmed responses	Yes (Edition 2)
• Clarified in estimand that PFS2 is based on radiological or clinical progression	Clarification	Yes (Edition 2)
• Added Mouth and Throat Symptoms Diary to exploratory PRO estimand	Clarification	Yes (Edition 2)
• Added biomarker assay correlation and comparison and clarified the definition of relevant participant population for analyses to estimand assessing correlation between biomarkers and clinical response endpoints.	Clarification	Yes (Edition 2)
• Increase of target screening number from 800 to 1100 participants	To reflect screen failure rate	Yes (Edition 2)
• Specified follow-up scan after initial determination of RECIST 1.1-defined progression by the investigator should be ≥ 4 weeks later, but no later than the next scheduled visit per the imaging schedule	Clarification	Yes (Edition 2)
• Addition of PD-L1 status as a stratification factor and subgroup analysis in analysis of time-to-event endpoints	To align with addition of PD-L1 status as a stratification factor	Yes (Edition 2)

- Updated PFS sensitivity analyses: - Sensitivity analysis 1 - Evaluation-time bias: updated Table 13 and clarified the midpoint between the time of progression and the previous evaluable RECIST assessment was used as the event time; clarified death date was used for the death in absence of progression event time; and removed the censoring for participants who progressed or died immediately after 2 or more consecutive missed visits - Added sensitivity analysis 5 – Stratification according to eCRF - Added sensitivity analysis 6 – No censoring to events for participants who progressed or died after >1 missed visits - Added sensitivity analysis 7 – Subsequent anti-cancer therapy being an event - Added sensitivity analysis 8 – Evaluation-time bias using interval censoring analysis - Added summary of duration of follow-up for all participants - Removed summary of the participants who miss 2 or more consecutive visits	To align with AstraZeneca oncology standard for Dato-DXd studies	Yes (Edition 2)
- Removed the estimates of 25th and 75th percentiles of OS - Added the OS rate estimate at 3, 6, 9, 12 months, and every 6 months thereafter) and the 95% CI	To align with AstraZeneca oncology standard	Yes (Edition 2)
- Added the OS sensitivity analysis 2 – Stratification according to eCRF - Added the OS sensitivity analysis 3 – IPCW analysis - Added forest plot for primary and sensitivity analyses of OS	To align with AstraZeneca oncology standard	Yes (Edition 2)
- Added unconfirmed ORR analysis - Updated the ORR analysis to NOT require measurable disease at baseline to align with ITT principle	To align with AstraZeneca oncology standard	Yes (Edition 2)
Updated potential Hy's law criteria to ALT or AST $\geq 3 \times \text{ULN}$ and total bilirubin $\geq 2 \times \text{ULN}$ rather than ALT or AST $> 3 \times \text{ULN}$ and total bilirubin $> 2 \times \text{ULN}$; clarified potential Hy's law required that the onset date of ALT or AST elevation should have occurred ≤ 28 days prior to the total bilirubin elevation; changed total bilirubin $> 1.5 \times \text{ULN}$ to total bilirubin $\geq 1.5 \times \text{ULN}$.	To align with AstraZeneca oncology standard	Yes (Edition 2)

Protocol deviations:

Table 29 Important Protocol Deviations (FAS)

	Dato-DXd N = 323 n (%)	ICC N = 321 n (%)	Total N = 644 n (%)
Participants with at least one important protocol deviation	38 (11.8)	25 (7.8)	63 (9.8)
Related to			
Inclusion criteria deviations	17 (5.3)	9 (2.8)	26 (4.0)
Exclusion criteria deviations	1 (0.3)	4 (1.2)	5 (0.8)
Discontinuation criteria for study product met but participant not withdrawn from study treatment	4 (1.2)	2 (0.6)	6 (0.9)
Investigational product deviation	5 (1.5)	2 (0.6)	7 (1.1)
Excluded medications taken	0	2 (0.6)	2 (0.3)
Deviations to study procedure	11 (3.4)	7 (2.2)	18 (2.8)

The same participant may have more than one important protocol deviation.

Baseline data

Table 30 Demographic and Key Baseline Characteristics (FAS)

	Statistics	Dato-DXd N = 323	ICC N = 321	Total N = 644
Age (years) ^a				
	n	323	321	644
	Mean (StDev)	55.3 (12.24)	56.4 (11.78)	55.9 (12.02)
	Median (range)	56.0 (27 – 85)	57.0 (23 – 83)	56.0 (23 – 85)
Age group (years) ^a				
< 65	n (%)	245 (75.9)	239 (74.5)	484 (75.2)
≥ 65	n (%)	78 (24.1)	82 (25.5)	160 (24.8)
Sex				
Male	n (%)	0	2 (0.6)	2 (0.3)
Female	n (%)	323 (100)	319 (99.4)	642 (99.7)
Race				
Black or African American	n (%)	13 (4.0)	14 (4.4)	27 (4.2)
Native Hawaiian or other Pacific Islander	n (%)	0	0	0

American Indian or Alaska Native	n (%)	0	0	0
Asian	n (%)	151 (46.7)	131 (40.8)	282 (43.8)
White	n (%)	131 (40.6)	153 (47.7)	284 (44.1)
Multiple	n (%)	2 (0.6)	0	2 (0.3)
Native Hawaiian or Other Pacific Islander + Asian	n (%)	1 (0.3)	0	1 (0.2)
White + Brown		1 (0.3)	0	1 (0.2)
Other	n (%)	5 (1.5)	6 (1.9)	11 (1.7)
Not Reported	n (%)	21 (6.5)	17 (5.3)	38 (5.9)
Ethnicity				
Hispanic or Latino	n (%)	45 (13.9)	52 (16.2)	97 (15.1)
Not Hispanic or Latino	n (%)	271 (83.9)	265 (82.6)	536 (83.2)
Missing	n (%)	7 (2.2)	4 (1.2)	11 (1.7)
Weight (kg)				
	n	322	321	643
	Mean (StDev)	64.1 (15.44)	66.3 (14.99)	65.2 (15.24)
	Median (range)	60.2 (36 – 150)	64.0 (39 – 141)	62.0 (36 – 150)
BMI (kg/m²)^b				
	n	322	321	643
	Mean (StDev)	25.3 (5.73)	26.0 (5.33)	25.7 (5.54)
	Median (range)	24.3 (15 – 66)	24.8 (16 – 46)	24.6 (15 – 66)
ECOG PS, n (%)				
(0) Normal activity	n (%)	195 (60.4)	182 (56.7)	377 (58.5)
(1) Restricted activity	n (%)	128 (39.6)	139 (43.3)	267 (41.5)
Region (eCRF data)				
US, Canada, Europe	n (%)	120 (37.2)	120 (37.4)	240 (37.3)
Rest of World	n (%)	203 (62.8)	201 (62.6)	404 (62.7)

^a Age is calculated at last birthday in whole years using the date of randomisation and date of birth.

^b BMI = weight (kg)/[height (m)]².

Table 31 Disease Characteristics at Study Entry/Randomisation (FAS)

	Statistics	Dato-DXd N = 323	ICC N = 321	Total N = 644
DFI history (eCRF data)				
De novo	n (%)	109 (33.7)	110 (34.3)	219 (34.0)
Prior DFI ≤ 12 months	n (%)	67 (20.7)	66 (20.6)	133 (20.7)
Prior DFI > 12 months	n (%)	147 (45.5)	145 (45.2)	292 (45.3)
DFI (months) ^a				
	n	214	211	425
	Mean (StDev)	30.76 (36.730)	36.54 (49.438)	33.63 (43.550)
	Median (range)	19.94 (-0.2 – 238.2)	18.37 (-2.2 – 295.5)	18.96 (-2.2 – 295.5)
DFI group (months) ^a				
≤ 0 ^b	n (%)	1 (0.3)	7 (2.2)	8 (1.2)
> 0 - ≤ 6	n (%)	46 (14.2)	44 (13.7)	90 (14.0)
> 6 - ≤ 12	n (%)	20 (6.2)	15 (4.7)	35 (5.4)
> 12 - ≤ 24	n (%)	53 (16.4)	56 (17.4)	109 (16.9)
> 24 - ≤ 60	n (%)	66 (20.4)	52 (16.2)	118 (18.3)
> 60	n (%)	28 (8.7)	37 (11.5)	65 (10.1)
Time from original TNBC diagnosis to randomisation (years) ^c				
	n	323	321	644
	Mean (StDev)	2.17 (3.037)	2.11 (3.704)	2.14 (3.383)
	Median (range)	1.09 (0.0 – 21.9)	1.08 (0.0 – 34.4)	1.08 (0.0 – 34.4)
Time from first documented recurrence of locally recurrent inoperable or distant metastatic disease to randomisation (days) ^d				
	n	323	321	644
	Mean (StDev)	58.7 (75.34)	61.1 (51.48)	59.9 (64.52)
	Median (range)	45.0 (1 – 1188)	50.0 (2 – 483)	48.0 (1 – 1188)
Overall disease classification				
Locally recurrent inoperable	n (%)	9 (2.8)	9 (2.8)	18 (2.8)
Metastatic, recurrent	n (%)	205 (63.5)	202 (62.9)	407 (63.2)
Locally recurrent + Metastatic recurrent	n (%)	82 (25.4)	74 (23.1)	156 (24.2)
Metastatic recurrent only	n (%)	123 (38.1)	128 (39.9)	251 (39.0)
Metastatic, de novo	n (%)	109 (33.7)	110 (34.3)	219 (34.0)
Visceral metastases	n (%)	253 (78.3)	233 (72.6)	486 (75.5)
Liver metastases	n (%)	93 (28.8)	98 (30.5)	191 (29.7)
Brain metastases	n (%)	36 (11.1)	28 (8.7)	64 (9.9)
Number of metastatic sites				
0	n (%)	10 (3.1)	10 (3.1)	20 (3.1)
1	n (%)	101 (31.3)	110 (34.3)	211 (32.8)
2	n (%)	96 (29.7)	95 (29.6)	191 (29.7)
3	n (%)	66 (20.4)	65 (20.2)	131 (20.3)

> 3	n (%)	50 (15.5)	41 (12.8)	91 (14.1)
PD-L1 status by central laboratory (eCRF data)				
Positive (CPS $\geq$ 10)	n (%)	34 (10.5)	29 (9.0)	63 (9.8)
Negative (CPS < 10)	n (%)	287 (88.9)	291 (90.7)	578 (89.8)
NA	n (%)	1 (0.3)	1 (0.3)	2 (0.3)
Missing	n (%)	1 (0.3)	0	1 (0.2)
PD-L1 positive – reason for inclusion (IRT data)				
Prior (neo) adjuvant PD-1/PD-L1 inhibitor therapy	n (%)	4 (1.2)	5 (1.6)	9 (1.4)
Comorbidities that preclude PD-1/PD-L1 inhibitor therapy	n (%)	3 (0.9)	4 (1.2)	7 (1.1)
No regulatory access to PD-1/PD-L1 inhibitor therapy	n (%)	27 (8.4)	20 (6.2)	47 (7.3)

^a DFI in months is defined as (date of first documented local or distant disease recurrence – date of completion of treatment with curative intent +1)/30.4375. The participants with DFI de novo are excluded from the presentation.

^b Diagnosis of recurrence occurred while on adjuvant therapy.

^c Time from diagnosis to randomisation (years) is defined as (date of randomisation – original TNBC diagnosis date + 1)/365.25.

^d Time from first documented recurrence of locally recurrent inoperable or distant metastatic disease to randomisation (days) is defined as (Date of randomisation - date of first documented recurrence of locally recurrent inoperable or distant metastatic disease + 1).

Table 32 Previous Disease-related Treatment Modalities (FAS)

Previous treatment modalities	Dato-DXd N = 323 n (%)	ICC N = 321 n (%)	Total N = 644 n (%)
Treatment status	215 (66.6)	207 (64.5)	422 (65.5)
Neo-adjuvant	125 (38.7)	125 (38.9)	250 (38.8)
Adjuvant	170 (52.6)	153 (47.7)	323 (50.2)
First-line	1 (0.3)	2 (0.6)	3 (0.5)
Second line	0	1 (0.3)	1 (0.2)
Taxanes	186 (57.6)	179 (55.8)	365 (56.7)
Neo-adjuvant	119 (36.8)	112 (34.9)	231 (35.9)
Adjuvant	70 (21.7)	71 (22.1)	141 (21.9)
Nitrogen mustard analogues	185 (57.3)	183 (57.0)	368 (57.1)
Neo-adjuvant	108 (33.4)	109 (34.0)	217 (33.7)
Adjuvant	80 (24.8)	77 (24.0)	157 (24.4)
Anthracyclines and related substances	182 (56.3)	178 (55.5)	360 (55.9)
Neo-adjuvant	109 (33.7)	112 (34.9)	221 (34.3)
Adjuvant	74 (22.9)	67 (20.9)	141 (21.9)
Pyrimidine analogues	87 (26.9)	84 (26.2)	171 (26.6)
Neo-adjuvant	13 (4.0)	9 (2.8)	22 (3.4)
Adjuvant	79 (24.5)	78 (24.3)	157 (24.4)
Platinum compounds	51 (15.8)	52 (16.2)	103 (16.0)
Neo-adjuvant	42 (13.0)	47 (14.6)	89 (13.8)
Adjuvant	10 (3.1)	8 (2.5)	18 (2.8)
Aromatase inhibitors	30 (9.3)	34 (10.6)	64 (9.9)
Neo-adjuvant	2 (0.6)	2 (0.6)	4 (0.6)
Adjuvant	28 (8.7)	32 (10.0)	60 (9.3)
First-line	1 (0.3)	2 (0.6)	3 (0.5)
Second line	0	1 (0.3)	1 (0.2)
Anti-oestrogens	19 (5.9)	18 (5.6)	37 (5.7)
Neo-adjuvant	0	2 (0.6)	2 (0.3)
Adjuvant	19 (5.9)	16 (5.0)	35 (5.4)
PD-1/PD-L1 inhibitors	15 (4.6)	18 (5.6)	33 (5.1)
Neo-adjuvant	10 (3.1)	13 (4.0)	23 (3.6)
Adjuvant	9 (2.8)	10 (3.1)	19 (3.0)

HER2 inhibitors	6 (1.9)	1 (0.3)	7 (1.1)
Neo-adjuvant	2 (0.6)	1 (0.3)	3 (0.5)
Adjuvant	5 (1.5)	0	5 (0.8)
CDK inhibitors	2 (0.6)	2 (0.6)	4 (0.6)
Neo-adjuvant	1 (0.3)	0	1 (0.2)
Adjuvant	0	1 (0.3)	1 (0.2)
First-line	1 (0.3)	1 (0.3)	2 (0.3)
Second line	0	1 (0.3)	1 (0.2)

Previous treatment modality is any treatment that stopped prior to start of treatment with IP. For treatment non-starters, cancer therapies stopped prior to randomisation are included.

Previous disease-related systemic anticancer therapies are listed based on ATC classification.

The table includes treatment modalities related to disease under investigation.

Participants with therapies in more than one category are counted once in each category.

Table 33 Patient Demographics and Baseline Disease Characteristics (Full Analysis Set)

		Global population N = 644		Region 1 population N = 240		EU population N = 187	
		Dato-DXd (N = 323)	ICC (N = 321)	Dato-DXd (N = 120)	ICC (N = 120)	Dato-DXd (N = 93)	ICC (N = 94)
Age (years) ^a							
	Mean	55.3	56.4	56.9	58.0	56.3	58.0
	StDev	12.24	11.78	12.50	11.87	12.46	12.45
	Median	56.0	57.0	57.0	57.0	55.0	56.0
	Min	27	23	31	33	31	33
	Max	85	83	84	83	81	83
Age group (years) n (%)							
< 65	n (%)	245 (75.9)	239 (74.5)	82 (68.3)	84 (70.0)	63 (67.7)	67 (71.3)
≥ 65	n (%)	78 (24.1)	82 (25.5)	38 (31.7)	36 (30.0)	30 (32.3)	27 (28.7)
DFI (months) ^b							
	n	214	211	83	82	65	62
	Mean	30.76	36.54	29.91	40.52	30.33	39.82
	StDev	36.730	49.438	31.553	51.249	31.765	50.324
	Median	19.94	18.37	22.05	18.43	22.08	18.97
	Min	-0.2	-2.2	-0.2	-2.2	0.1	-2.2
	Max	238.2	295.5	126.6	243.9	126.6	243.9
DFI group (months) ^b							
≤ 0 ^c	n (%)	1 (0.3)	7 (2.2)	1 (0.8)	3 (2.5)	0	2 (2.1)
> 0 - ≤ 6	n (%)	46 (14.2)	44 (13.7)	21 (17.5)	21 (17.5)	16 (17.2)	14 (14.9)
> 6 - ≤ 12	n (%)	20 (6.2)	15 (4.7)	11 (9.2)	8 (6.7)	8 (8.6)	7 (7.4)
> 12 - ≤ 24	n (%)	53 (16.4)	56 (17.4)	12 (10.0)	12 (10.0)	11 (11.8)	10 (10.6)
> 24 - ≤ 60	n (%)	66 (20.4)	52 (16.2)	25 (20.8)	20 (16.7)	21 (22.6)	16 (17.0)
> 60	n (%)	28 (8.7)	37 (11.5)	13 (10.8)	18 (15.0)	9 (9.7)	13 (13.8)

Time from original TNBC diagnosis to randomization (years) ^d							
	n	323	321	120	120	93	94
	Mean	2.17	2.11	2.33	2.38	2.43	2.38
	StDev	3.037	3.704	2.664	4.153	2.750	4.264
	Median	1.09	1.08	1.56	1.21	1.63	1.11
	Min	0.0	0.0	0.1	0.1	0.1	0.1
	Max	21.9	34.4	12.5	34.4	12.5	34.4
Time from first documented recurrence of locally recurrent inoperable or distant metastatic disease to randomization (days) ^e							
	n	323	321	120	120	93	94
	Mean	58.7	61.1	55.9	64.2	56.3	58.7
	StDev	75.34	51.48	36.11	55.07	37.16	36.72
	Median	45.0	50.0	49.5	53.0	54.0	50.5
	Min	1	2	1	11	1	12
	Max	1188	483	224	483	224	235
Overall disease classification							
Locally recurrent inoperable	n (%)	9 (2.8)	9 (2.8)	3 (2.5)	2 (1.7)	3 (3.2)	2 (2.1)
Metastatic, recurrent	n (%)	205 (63.5)	202 (62.9)	80 (66.7)	80 (66.7)	62 (66.7)	60 (63.8)
Locally recurrent + Metastatic recurrent	n (%)	82 (25.4)	74 (23.1)	33 (27.5)	28 (23.3)	28 (30.1)	23 (24.5)
Metastatic recurrent only	n (%)	123 (38.1)	128 (39.9)	47 (39.2)	52 (43.3)	34 (36.6)	37 (39.4)
Metastatic, de novo	n (%)	109 (33.7)	110 (34.3)	37 (30.8)	38 (31.7)	28 (30.1)	32 (34.0)
Visceral metastases	n (%)	253 (78.3)	233 (72.6)	96 (80.0)	91 (75.8)	76 (81.7)	69 (73.4)
Liver metastases	n (%)	93 (28.8)	98 (30.5)	37 (30.8)	34 (28.3)	31 (33.3)	26 (27.7)
Brain metastases	n (%)	36 (11.1)	28 (8.7)	12 (10.0)	7 (5.8)	8 (8.6)	6 (6.4)
Number of metastatic sites							
0	n (%)	10 (3.1)	10 (3.1)	3 (2.5)	2 (1.7)	3 (3.2)	2 (2.1)
1	n (%)	101 (31.3)	110 (34.3)	37 (30.8)	44 (36.7)	25 (26.9)	33 (35.1)
2	n (%)	96 (29.7)	95 (29.6)	38 (31.7)	46 (38.3)	30 (32.3)	36 (38.3)
3	n (%)	66 (20.4)	65 (20.2)	27 (22.5)	18 (15.0)	24 (25.8)	16 (17.0)
> 3	n (%)	50 (15.5)	41 (12.8)	15 (12.5)	10 (8.3)	11 (11.8)	7 (7.4)
Pre-selected choice of chemotherapy							
Paclitaxel	n (%)	82 (25.4)	92 (28.7)	41 (34.2)	34 (28.3)	32 (34.4)	26 (27.7)
Nab-paclitaxel	n (%)	180 (55.7)	172 (53.6)	49 (40.8)	56 (46.7)	38 (40.9)	47 (50.0)
Capecitabine	n (%)	7 (2.2)	8 (2.5)	5 (4.2)	4 (3.3)	5 (5.4)	3 (3.2)
Carboplatin	n (%)	11 (3.4)	14 (4.4)	6 (5.0)	9 (7.5)	5 (5.4)	7 (7.4)
Eribulin mesylate/Eribulin	n (%)	43 (13.3)	35 (10.9)	19 (15.8)	17 (14.2)	13 (14.0)	11 (11.7)

^a Age is calculated at last birthday in whole years using the date of randomization and date of birth.

^b DFI in months is defined as (date of first documented local or distant disease recurrence – date of completion of treatment with curative intent + 1)/30.4375. The participants with DFI de novo were excluded from the presentation.

^c Diagnosis of recurrence occurred while on adjuvant therapy.

^d Time from diagnosis to randomization (years) is defined as (date of randomization – original TNBC diagnosis date)/365.25.

^e Time from first documented recurrence of locally recurrent inoperable or distant metastatic disease to randomization (days) is defined as (Date of randomization - date of first documented recurrence of locally recurrent inoperable or distant metastatic disease + 1).

Numbers analysed

Table 34 Analyses Sets (All Participants)

	Dato-DXd N = 323	ICC N = 321	Total N = 644
Enrolled set ^a			1277
FAS ^b	323	321	644
SAF ^c	319	309	628
Excluded from SAF	4	12	16
Did not receive treatment	4	12	16
PROAS ^d	318	319	637
Excluded from PROAS	5	2	7
ePRO data were not collected per protocol	5	2	7
PK analysis set ^e	319	NA	319
Excluded from PK analysis set	4	NA	4
Did not receive treatment	4	NA	4
ADA evaluable set ^f	319	NA	319
Excluded from ADA evaluable set	4	NA	4
Did not receive treatment	4	NA	4

^a Participants enrolled are those who signed informed consent.

^b The FAS includes all randomised participants.

^c The SAF consists of all participants who received at least one dose of study treatment.

^d The PROAS includes all randomised participants who had their PRO data collected per protocol.

^e The PK analysis set includes all participants randomly assigned to study intervention who took at least one dose of study intervention (Dato-DXd) for whom any post-dose PK data are available.

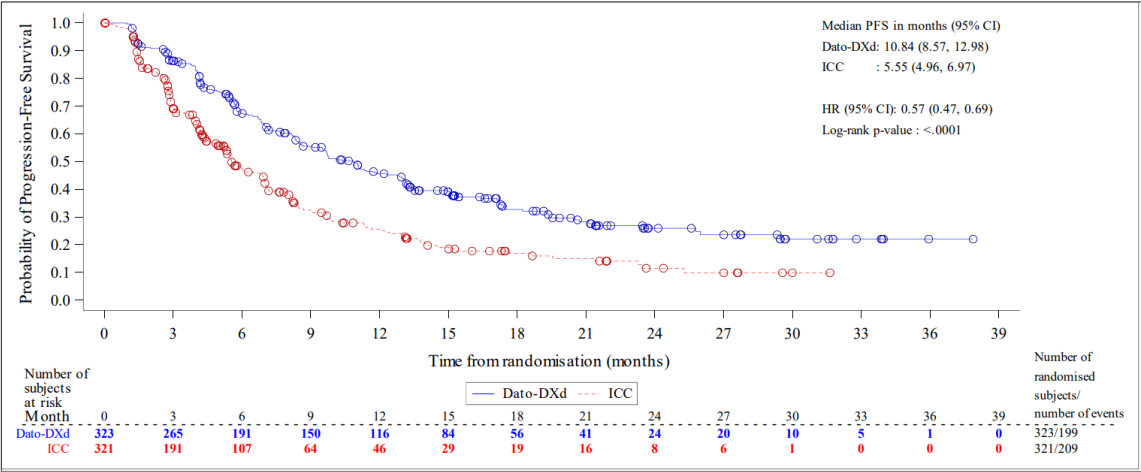
^f The ADA evaluable set consists of participants in the SAF who received at least one dose of Dato-DXd and with a non-missing ADA Dato-DXd result at any time.

The same participant could have been excluded from an analysis set for more than one reason.

Outcomes and estimation

Dual primary outcome, PFS by BICR

Figure 22 PFS, Kaplan-Meier Plot, BICR Data (FAS)



Circle indicates a censored observation. RECIST version 1.1. 2-sided p-value.
Source: Figure 14.2.1.2

Table 35 PFS, Primary Analysis, BICR Data (FAS)

	Dato-DXd N = 323	ICC N = 321
Total events ^a , n (%)	199 (61.6)	209 (65.1)
RECIST progression	188 (58.2)	189 (58.9)
Death in the absence of progression	11 (3.4)	20 (6.2)
Censored participants, n (%)	124 (38.4)	112 (34.9)
Censored RECIST progression ^b	2 (0.6)	3 (0.9)
Censored death ^c	39 (12.1)	33 (10.3)
Censored at Day 1	5 (1.5)	14 (4.4)
Progression-free at time of analysis	75 (23.2)	53 (16.5)
Early study discontinuation	3 (0.9)	9 (2.8)
Lost to follow-up	2 (0.6)	4 (1.2)
Withdrawn consent	1 (0.3)	5 (1.6)
Median PFS (months) ^d	10.84	5.55
95% CI for median PFS ^d	8.57 - 12.98	4.96 - 6.97
PFS rate at 3 months (%) ^d	86.34	69.06
95% CI for PFS rate at 3 months ^d	82.03 - 89.69	63.38 - 74.04
PFS rate at 6 months (%) ^d	67.38	47.57
95% CI for PFS rate at 6 months ^d	61.76 - 72.36	41.42 - 53.46
PFS rate at 9 months (%) ^d	55.50	32.53
95% CI for PFS rate at 9 months ^d	49.60 - 61.00	26.63 - 38.55
PFS rate at 12 months (%) ^d	45.59	25.62
95% CI for PFS rate at 12 months ^d	39.68 - 51.30	20.05 - 31.54
PFS rate at 18 months (%) ^d	32.71	16.81
95% CI for PFS rate at 18 months ^d	26.91 - 38.63	11.83 - 22.55
HR ^e	0.57	

	Dato-DXd N = 323	ICC N = 321
95% CI for HR ^e	0.47 - 0.69	
99% CI for HR ^{e,f}	0.44 - 0.73	
2-sided p-value ^g	< 0.0001	
Median (range) duration of follow-up in censored participants (months)	14.98 (0.0 - 37.9)	4.45 (0.0 - 31.6)
Median (range) duration of follow-up in all participants (months)	8.31 (0.0 - 37.9)	4.17 (0.0 - 31.6)

^a Only includes progression events that occur within 2 assessments of the last evaluable assessment.

^b RECIST progression event occurred ≥ 2 visits after last evaluable RECIST assessment (or randomisation).

^c Death occurred ≥ 2 visits after last evaluable RECIST assessment (or randomisation).

^d Calculated using the Kaplan-Meier technique.

^e The analysis was performed using a stratified Cox Proportional Hazards model with stratification variables DFI history and PD-L1 status. A HR < 1 favours Dato-DXd to be associated with a longer PFS than ICC.

^f The nominal p-value boundary for declaring statistical significance is 0.01 for a 5% overall alpha.

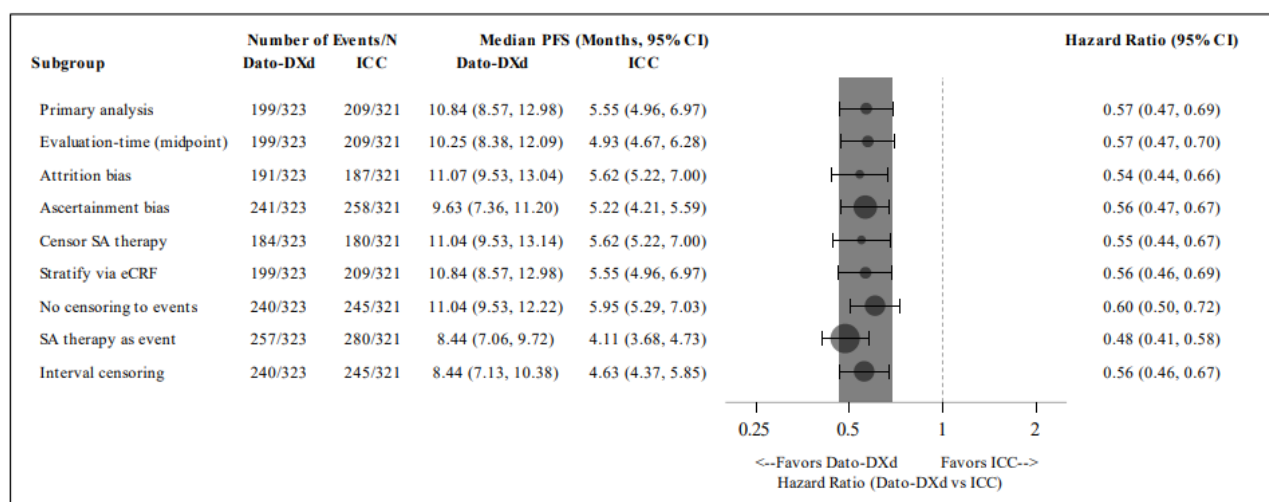
^g Calculated using a stratified log-rank test adjusting for the stratification factors of DFI history and PD-L1 status.

Progression was determined by BICR assessment, RECIST 1.1.

n = number of participants per category; N = number of participants per treatment group

Source: Table 14.2.1.1

Figure 23 PFS, Forest Plot, by Sensitivity Analysis, BICR Data (FAS)



The sensitivity analyses are described in SAP Section 4.2.3.1.

A HR < 1 favours Dato-DXd to be associated with a longer PFS than ICC.

Size of circle is proportional to the number of events.

Grey band represents the 95% CI for the HR in the primary analysis.

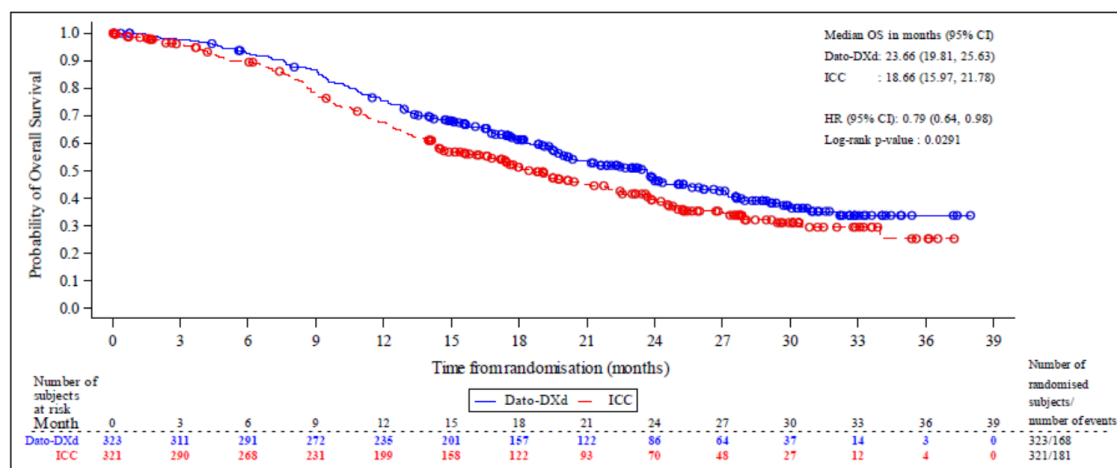
RECIST version 1.1

N = number of participants per treatment group

Source: Figure 14.2.1.8.1

Dual primary outcome, OS

Figure 24 OS, Kaplan Meier Plot (FAS)



Circle indicates a censored observation. 2-sided p-value. A p-value < 0.0499 is significant.

Source: Figure 14.2.2.2

Table 36 OS, Primary Analysis (FAS)

	Dato-DXd N = 323	ICC N = 321
Death, n (%)	168 (52.0)	181 (56.4)
Censored participants, n (%)	155 (48.0)	140 (43.6)
Still in survival follow-up ^a	142 (44.0)	106 (33.0)
Early study discontinuation	13 (4.0)	34 (10.6)
Lost to follow-up	4 (1.2)	7 (2.2)
Withdrew consent	6 (1.9)	27 (8.4)
Other	3 (0.9)	0
Median OS (months) ^b	23.66	18.66
95% CI for median OS ^b	19.81 - 25.63	15.97 - 21.78
Survival rate at 12 months (%) ^b	75.23	67.81
95% CI for survival rate at 12 months ^b	70.07 - 79.63	62.18 - 72.80
Survival rate at 18 months (%) ^b	61.24	51.27
95% CI for survival rate at 18 months ^b	55.49 - 66.47	45.33 - 56.90
Survival rate at 24 months (%) ^b	46.73	39.36
95% CI for survival rate at 24 months ^b	40.51 - 52.70	33.28 - 45.37
Survival rate at 36 months (%) ^b	33.70	25.21
95% CI for survival rate at 36 months ^b	26.63 - 40.90	16.23 - 35.19
HR ^c	0.79	
95% CI for HR ^c	0.64 - 0.98	
95.01% CI for HR ^{c,d}	0.64 - 0.98	
2-sided p-value ^e	0.0291	
Median (range) duration of follow-up in censored participants (months)	23.03 (0.1 - 38.0)	20.16 (0.0 - 37.3)
Median (range) duration of follow-up in all participants by treatment arm (months)	17.68 (0.1 - 38.0)	14.69 (0.0 - 37.3)
Median (range) duration of follow-up in all participants (months)	16.61 (0.0 - 38.0)	

^a Includes participants known to be alive at DCO date.

^b Calculated using the Kaplan-Meier technique.

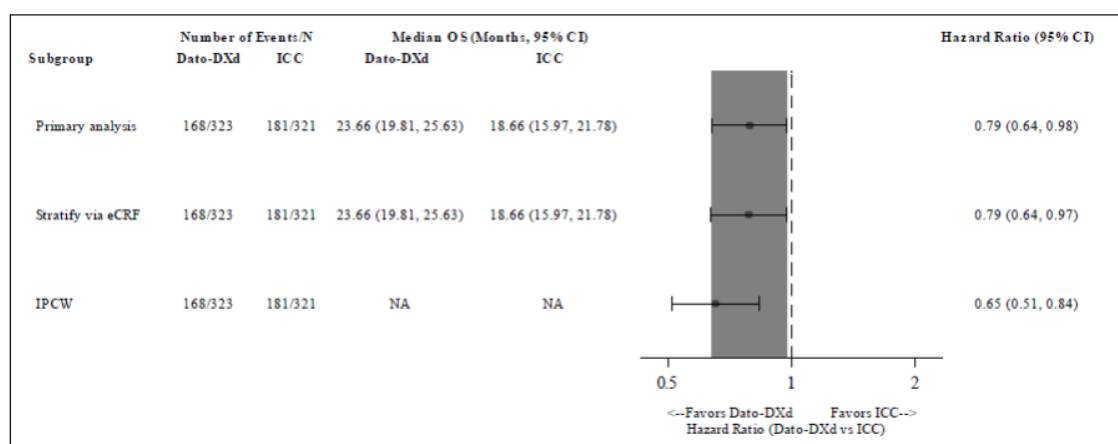
^c The analysis was performed using a stratified Cox Proportional Hazards model with stratification variable DFI history. A HR < 1 favours Dato-DXd to be associated with a longer OS than ICC.

^d Primary PFS by BICR is significant, the nominal p-value boundary for declaring statistical significance in the final OS analysis is 0.0499 for a 5% overall alpha. Corresponding 95.01% CI are shown.

^e Calculated using a stratified log-rank test adjusting for the stratification factor of DFI history.

n = number of participants per category; N = number of participants per treatment group

Figure 25 OS, Forest Plot, by Sensitivity Analysis (FAS)



The sensitivity analyses are described in SAP Section 4.2.4.1.

A HR <1 favours Dato-DXd to be associated with a longer OS than ICC.

Size of circle is proportional to the number of events.

Grey band represents the 95% CI for the HR in the primary analysis.

N = number of participants per treatment group

Table 37 OS, Sensitivity analysis (FAS)

Group	N	Number (%) of participants with events	Median (months) (95% CI)	Comparison between groups		
				HR	95% CI	2-sided p-value
Stratification according to eCRF						
Dato-DXd	323	168 (52.0)	23.66 (19.81, 25.63)	0.79	0.64, 0.97	0.0253
ICC	321	181 (56.4)	18.66 (15.97, 21.78)			
IPCW analysis						
Dato-DXd	323	168 (52.0)	NA	0.65	0.51, 0.84	0.0007 ^a
ICC	321	181 (56.4)	NA			

^a The p-value was calculated using a stratified Cox Proportional Hazards model from the IPCW analysis.

Sensitivity analyses are described in SAP Section 4.2.4.1.

The HR and CI were calculated using a stratified Cox Proportional Hazards model, adjusting for the stratification variables and ties handled by Efron approach. The p-value was calculated using a stratified log-rank test, adjusting for the stratification variables. The stratification variable(s) includes DFI history unless otherwise specified.

A HR < 1 favours Dato-DXd to be associated with a longer OS than ICC.

N = number of participants per treatment group

Secondary outcomes

PFS by investigator

Table 38 Progression-free survival, Primary Analysis, Investigator Data (FAS) ^a

	Dato-DXd N = 323	ICC N = 321
Total events ^a , n (%)	241 (74.6)	258 (80.4)
RECIST progression	235 (72.8)	239 (74.5)
Death in the absence of progression	6 (1.9)	19 (5.9)
Censored participants, n (%)	82 (25.4)	63 (19.6)
Censored RECIST progression ^b	2 (0.6)	4 (1.2)
Censored death ^c	10 (3.1)	14 (4.4)
Censored at Day 1	5 (1.5)	13 (4.0)
Progression-free at time of analysis	64 (19.8)	25 (7.8)
Early study discontinuation	1 (0.3)	7 (2.2)
Lost to follow-up	0	2 (0.6)
Withdrawn consent	1 (0.3)	5 (1.6)
Median PFS (months) ^d	9.63	5.22
95% CI for median PFS ^d	7.36 - 11.20	4.21 - 5.59
PFS rate at 3 months (%) ^d	82.90	67.30
95% CI for PFS rate at 3 months ^d	78.27 - 86.63	61.63 - 72.32
PFS rate at 6 months (%) ^d	60.48	41.36
95% CI for PFS rate at 6 months ^d	54.80 - 65.67	35.61 - 47.00
PFS rate at 9 months (%) ^d	51.12	29.28
95% CI for PFS rate at 9 months ^d	45.38 - 56.55	24.03 - 34.72
PFS rate at 12 months (%) ^d	40.73	18.49
95% CI for PFS rate at 12 months ^d	35.14 - 46.23	14.07 - 23.40
PFS rate at 18 months (%) ^d	27.48	9.22
95% CI for PFS rate at 18 months ^d	22.34 - 32.84	5.97 - 13.32
HR ^e	0.56	
95% CI for HR ^e	0.47 - 0.67	
Median (range) duration of follow-up in censored participants (months)	15.36 (0.0 - 37.9)	3.02 (0.0 - 30.0)
Median (range) duration of follow-up in all participants (months)	8.31 (0.0 - 37.9)	4.17 (0.0 - 31.6)

^a Only includes progression events that occur within 2 assessments of the last evaluable assessment.

^b RECIST progression event occurred ≥ 2 visits after last evaluable RECIST assessment (or randomisation).

^c Death occurred ≥ 2 visits after last evaluable RECIST assessment (or randomisation).

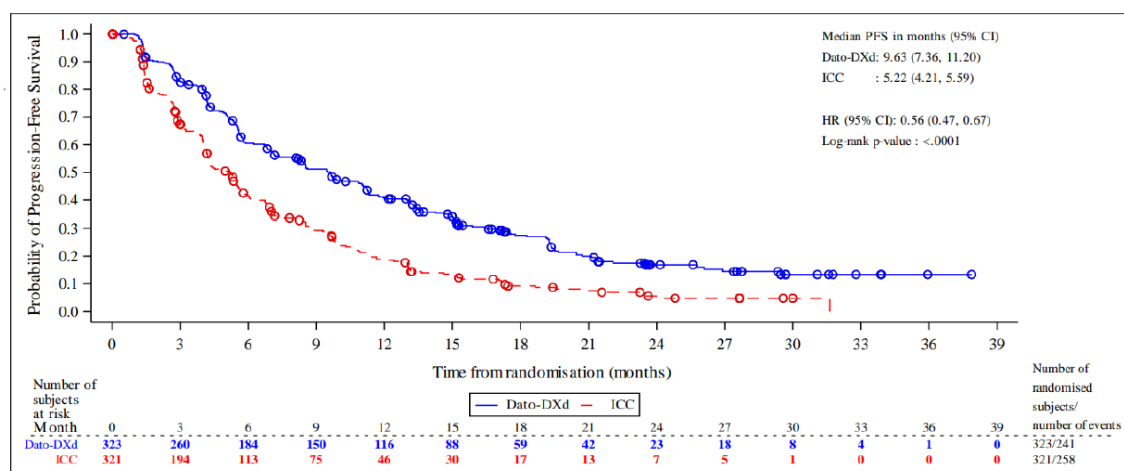
^d Calculated using the Kaplan-Meier technique.

^e The analysis was performed using a stratified Cox Proportional Hazards model with stratification variables DFI history and PD-L1 status. A HR < 1 favours Dato-DXd to be associated with a longer progression-free survival than ICC.

Progression in months is determined by investigator assessment, RECIST 1.1.

n, number of participants per category; N, number of participants per treatment group

Figure 26 PFS, Kaplan-Meier Plot, Investigator Data (FAS)



Circle indicates a censored observation. RECIST version 1.1. 2-sided p-value.

Source: Figure 14.2.6.2

ORR by BICR

Table 39 ORR, Confirmed Based on BICR Data, Logistic Regression (FAS – Participants with Measurable Disease at Baseline)

Group	N	Number (%) of participants with response ^a	Adjusted response rate (%)	95% CI for adjusted response rate	Comparison between groups		
					Odds ratio	95% CI	2-sided p-value
Dato-DXd	323	202 (62.5)	62.8	57.3, 68.0	4.24	3.03, 5.95	< 0.0001
ICC	321	94 (29.3)	28.5	23.7, 33.7			

^a Responses exclude unconfirmed responses.

The analysis was performed using a logistic regression model with factors for treatment, DFI history, and PD-L1 status.

An odds ratio > 1 favours Dato-DXd.

RECIST version 1.1.

N = number of participants per treatment group

Source: Table 14.2.3.1

Best objective response (BOR) by BICR

Table 20 BOR, Confirmed Response, BICR Data (FAS)

Response status	BOR	Dato-DXd N = 323 n (%)	ICC N = 321 n (%)
Response (confirmed)	Total	202 (62.5)	94 (29.3)
	CR ^a	29 (9.0)	8 (2.5)
	PR ^a	173 (53.6)	86 (26.8)
Non-response	Total	121 (37.5)	227 (70.7)
	SD	87 (26.9)	151 (47.0)
	Unconfirmed CR ^b	0	1 (0.3)
	Unconfirmed PR ^b	15 (4.6)	25 (7.8)
	SD $\geq$ 5 weeks	72 (22.3)	125 (38.9)
	Progression	27 (8.4)	52 (16.2)
	RECIST progression	26 (8.0)	43 (13.4)
	Death	1 (0.3)	9 (2.8)
	Not evaluable	7 (2.2)	24 (7.5)
	SD < 5 weeks	0	1 (0.3)
	No baseline or post-baseline assessments	5 (1.5)	16 (5.0)
	No evidence of disease	1 (0.3)	3 (0.9)
	NA	1 (0.3)	4 (1.2)

^a Response requires confirmation.

^b PR or CR achieved but either no confirmation assessment performed or a confirmation assessment performed but response not confirmed.

RECIST version 1.1.

n = number of participants per category; N = number of participants per treatment group

Source: Table 14.2.4.1

DOR by BICR

Table 21 **Duration and Onset of Objective Response in Participants with Confirmed Objective Response, BICR Data (FAS)**

	Dato-DXd N = 323	ICC N = 321
Number of responders who subsequently progressed or died	112	59
DoR from onset of response (months) ^{a,b}		
25th percentile	5.91	4.21
Median	12.32	7.10
95% CI	9.07, 15.87	5.55, 8.87
75th percentile	NC	13.57
Percentage remaining in response ^{b,c}		
6 Months	74.93	55.97
9 Months	58.71	38.32
12 Months	50.11	29.73
Time to onset of response from randomisation (months)		
25th percentile	1.3	1.5
Median	1.4	1.6
75th percentile	2.8	2.9

^c DoR is the time from the first documentation of confirmed response of CR or PR until the date of progression or death, or the last evaluable RECIST assessment for participants that do not progress (or die) or do not progress (or die) within 2 missed visits of the last evaluable assessment (or randomisation).

^d Calculated using Kaplan-Meier technique.

^e Percentage is based on the number of responders.

RECIST version 1.1.

N = number of participants per treatment group

Source: Table 14.2.5.1

Time to first subsequent therapy (TFST)

Table 23 TFST, Primary Analysis (FAS)

	Dato-DXd N = 323	ICC N = 321
Total events, n (%)	249 (77.1)	279 (86.9)
Initial therapy	0	3 (0.9)
First subsequent anticancer therapy	209 (64.7)	228 (71.0)
Death	40 (12.4)	48 (15.0)
Censored participants, n (%)	74 (22.9)	42 (13.1)
No first subsequent anticancer therapy prior to latest assessment date ^a	13 (4.0)	7 (2.2)
No subsequent anticancer therapy ^b	51 (15.8)	10 (3.1)
Lost to follow-up	2 (0.6)	3 (0.9)
Withdrawn consent	5 (1.5)	22 (6.9)
Discontinued study (any other specified reason for discontinuing study)	3 (0.9)	0
Median TFST (months) ^c	10.91	5.62
95% CI for median TFST ^c	9.46 - 12.09	4.93 - 6.31
HR ^d	0.49	
95% CI for HR ^d	0.41 - 0.59	

^a Participants who had at least one record in TTSCAPRX but no subsequent anticancer therapy record.

^b Participants who didn't have record in TTSCAPRX.

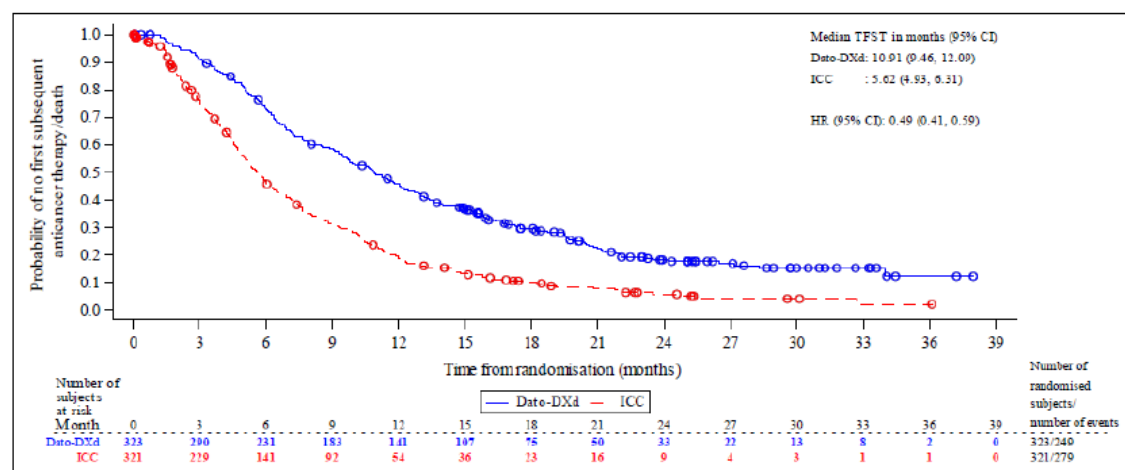
^c Calculated using the Kaplan-Meier technique.

^d The analysis was performed using a stratified Cox Proportional Hazards model with stratification variables DFI history and PD-L1 status. A HR < 1 favours Dato-DXd.

TFST is the time from the date of randomisation to the start date of the first subsequent anticancer therapy after discontinuation of randomised treatment, or death. For participants not receiving randomised treatment but remaining in the study the first alternative anticancer therapy they receive is the initial therapy. In this situation, TFST is time from randomisation to the start date of the initial therapy or death.

n = number of participants per category; N = number of participants per treatment group

Source: Table 14.2.8.1

Figure 12 TFST, Kaplan-Meier Plot (FAS)

Circle indicates a censored observation.

Source: Figure 14.2.8.2

PFS2

Table 25 PFS2, Primary Analysis (FAS)

	Dato-DXd (N = 323)	ICC (N = 321)
Total events ^a , n (%)	197 (61.0)	226 (70.4)
Second progression	113 (35.0)	129 (40.2)
Objective radiological progression	101 (31.3)	110 (34.3)
Symptomatic progression in absence of objective radiological progression	11 (3.4)	13 (4.0)
Other	1 (0.3)	6 (1.9)

	Dato-DXd (N = 323)	ICC (N = 321)
Death in the absence of progression	84 (26.0)	97 (30.2)
Censored participants, n (%)	126 (39.0)	95 (29.6)
No first progression in absence of death	70 (21.7)	45 (14.0)
No subsequent anticancer therapy after first progression in absence of death	16 (5.0)	12 (3.7)
PFS2 event-free at time of analysis	19 (5.9)	11 (3.4)
PFS2 assessment has not occurred and no PFS2 event	21 (6.5)	27 (8.4)
Median PFS2 (months) ^b	15.61	11.76
95% CI for median PFS2 ^b	13.27 - 17.38	10.94 - 12.75
HR ^c	0.61	
95% CI for HR ^c	0.50 - 0.74	

^a Only includes progression events that occurred within 2 missed assessments of the last evaluable assessment.

^b Calculated using the Kaplan-Meier technique.

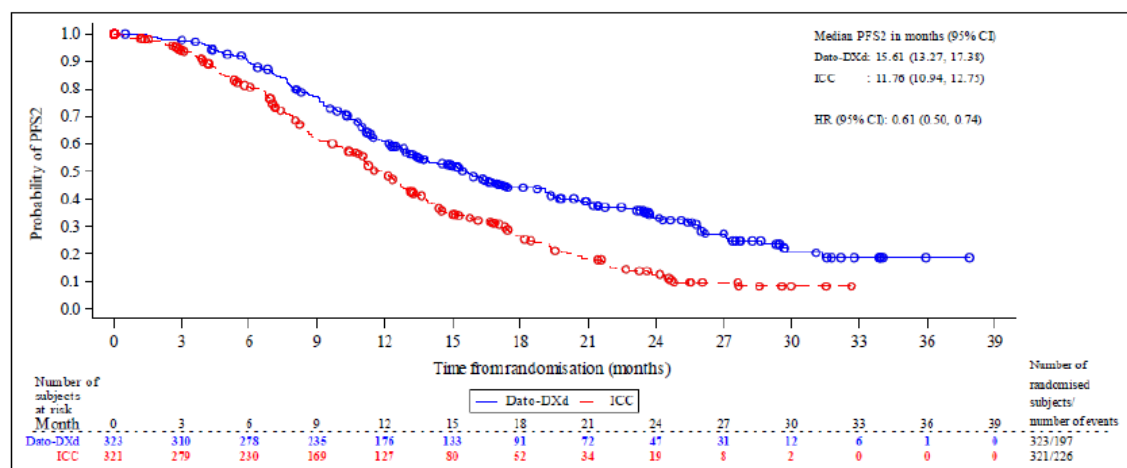
^c The analysis was performed using a stratified Cox Proportional Hazards model with stratification variables DFI history, and PD-L1 status. A HR < 1 favours Dato-DXd to be associated with a longer PFS2 than ICC.

Progression is determined by investigator assessment.

n = number of participants per category; N = number of participants per treatment group

Source: Table 14.2.10.1

Figure 14 PFS2, Kaplan-Meier Plot (FAS)



Circle indicates a censored observation.

RECIST version 1.1.

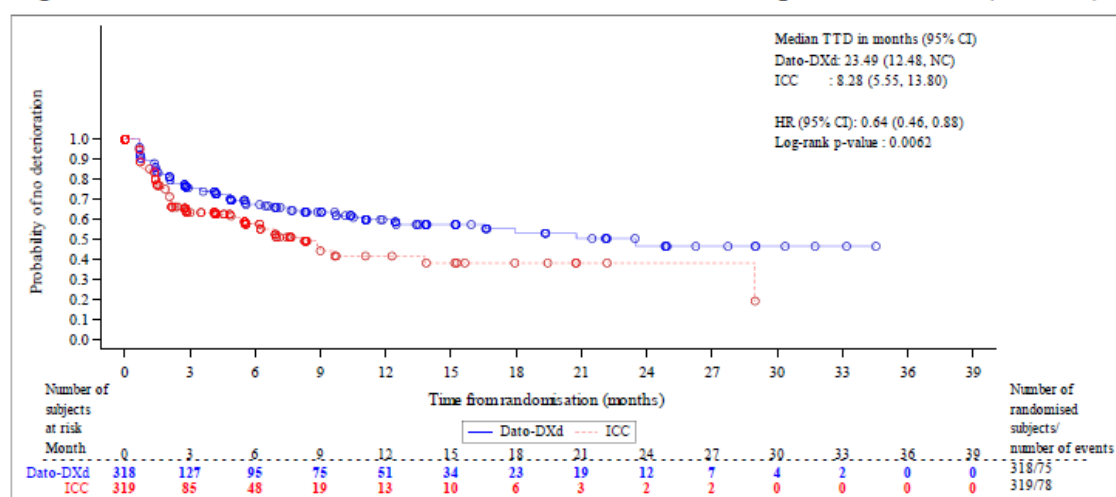
Source: Figure 14.2.10.2

Patient reported outcomes

Table 28 Time to First and Confirmed Deterioration in GHS/QoL (PROAS)

	Time to first deterioration		Time to confirmed deterioration	
	Dato-DXd N = 318	ICC N = 319	Dato-DXd N = 318	ICC N = 319
Total events ^a , n (%)	75 (23.6)	78 (24.5)	50 (15.7)	54 (16.9)
Deterioration	75 (23.6)	78 (24.5)	50 (15.7)	54 (16.9)
Censored participants, n (%)	243 (76.4)	241 (75.5)	268 (84.3)	265 (83.1)
Censored deterioration ^b	3 (0.9)	2 (0.6)	2 (0.6)	2 (0.6)
No deterioration at time of analysis	61 (19.2)	39 (12.2)	71 (22.3)	53 (16.6)
No baseline data recorded at time of analysis	103 (32.4)	116 (36.4)	103 (32.4)	116 (36.4)
Impossible to deteriorate ^c	11 (3.5)	7 (2.2)	11 (3.5)	7 (2.2)
No post-baseline data recorded at time of analysis	3 (0.9)	18 (5.6)	3 (0.9)	18 (5.6)
Lost to follow-up	2 (0.6)	0	2 (0.6)	0
Withdrawn consent	3 (0.9)	5 (1.6)	3 (0.9)	6 (1.9)

Figure 19 Time to First Deterioration in GHS/QoL, Kaplan-Meier Plot (PROAS)



Circle indicates a censored observation. 2-sided p-value.

Time to first deterioration is defined as time from the date of randomisation to the date of first deterioration, regardless of whether the participant discontinues the IP or receives another anticancer therapy prior to deterioration.

Per ITT principle to avoid bias, the analysis included the data from 14 participants who completed questionnaires under incorrect languages or locales.

Source: Figure 14.2.11.2

Table 31 Time to First and Confirmed Deterioration in Pain, Physical Functioning, GHS/QoL, Fatigue, Other Symptoms, and Functioning Scales by EORTC IL146 (PROAS)

Subscale	Time to first deterioration						Time to confirmed deterioration					
	Total events ^a , n (%)		Median TTD ^b , (months)		Comparison between groups		Total events ^a , n (%)		Median TTD ^b , (months)		Comparison between groups	
	Dato-DXd N = 318	ICC N = 319	Dato-DXd N = 318	ICC N = 319	HR (95% CI) ^c	2-sided p-value ^d	Dato-DXd N = 318	ICC N = 319	Dato-DXd N = 318	ICC N = 319	HR (95% CI) ^c	2-sided p-value ^d
Functioning												
Role	93 (29.2)	85 (26.6)	11.07	5.55	0.71 (0.53 - 0.96)	0.0262	56 (17.6)	63 (19.7)	NC	15.21	0.56 (0.39 - 0.81)	0.0019
Emotional	50 (15.7)	54 (16.9)	NC	NC	0.61 (0.41 - 0.90)	0.0129	31 (9.7)	34 (10.7)	NC	NC	0.57 (0.35 - 0.94)	0.0263
Cognitive	63 (19.8)	49 (15.4)	30.39	NC	0.82 (0.57 - 1.21)	0.3176	45 (14.2)	35 (11.0)	NC	NC	0.82 (0.52 - 1.28)	0.3699
Social	87 (27.4)	83 (26.0)	17.97	5.55	0.72 (0.53 - 0.98)	0.0360	62 (19.5)	59 (18.5)	NC	17.97	0.71 (0.50 - 1.02)	0.0667
Symptoms												
Fatigue	107 (33.6)	110 (34.5)	8.28	3.45	0.65 (0.49 - 0.85)	0.0018	80 (25.2)	83 (26.0)	19.42	6.21	0.63 (0.46 - 0.86)	0.0041
Nausea/ Vomiting	135 (42.5)	90 (28.2)	3.55	5.59	1.27 (0.97 - 1.66)	0.0856	88 (27.7)	60 (18.8)	15.21	24.87	1.06 (0.76 - 1.48)	0.7479
Dyspnoea	93 (29.2)	75 (23.5)	15.21	8.97	0.87 (0.64 - 1.19)	0.4024	68 (21.4)	55 (17.2)	20.76	NC	0.82 (0.58 - 1.18)	0.2947
Insomnia	102 (32.1)	84 (26.3)	7.66	4.86	0.87 (0.65 - 1.17)	0.3481	67 (21.1)	51 (16.0)	NC	NC	0.92 (0.64 - 1.33)	0.6501
Appetite loss	130 (40.9)	89 (27.9)	4.17	4.17	1.16 (0.89 - 1.53)	0.2789	104 (32.7)	65 (20.4)	6.31	17.94	1.22 (0.90 - 1.68)	0.2048
Constipation	149 (46.9)	97 (30.4)	2.76	3.48	1.33 (1.03 - 1.72)	0.0353	108 (34.0)	71 (22.3)	5.55	12.45	1.21 (0.90 - 1.63)	0.2267
Diarrhoea	89 (28.0)	80 (25.1)	15.21	6.97	0.75 (0.55 - 1.02)	0.0647	43 (13.5)	42 (13.2)	NC	NC	0.66 (0.43 - 1.02)	0.0593

^a Only includes deterioration that occurred within 2 assessments of the previous evaluable PRO assessment.

^b Calculated using the Kaplan-Meier technique.

^c The analysis was performed using a stratified Cox Proportional Hazards model. A HR < 1 favours Dato-DXd to be associated with a longer time to deterioration than ICC.

^d Calculated using a stratified log-rank test adjusting for the stratification factors.

Time to first deterioration is defined as time from the date of randomisation to the date of first deterioration, regardless of whether the participant discontinues the IP or receives another anticancer therapy prior to deterioration. Time to confirmed deterioration is defined as the time from randomisation until the date of the first deterioration that is confirmed at a subsequent timepoint (except if the first deterioration is at the participant's last available assessment), regardless of whether the participant discontinues the IP or receives another anticancer therapy prior to deterioration.

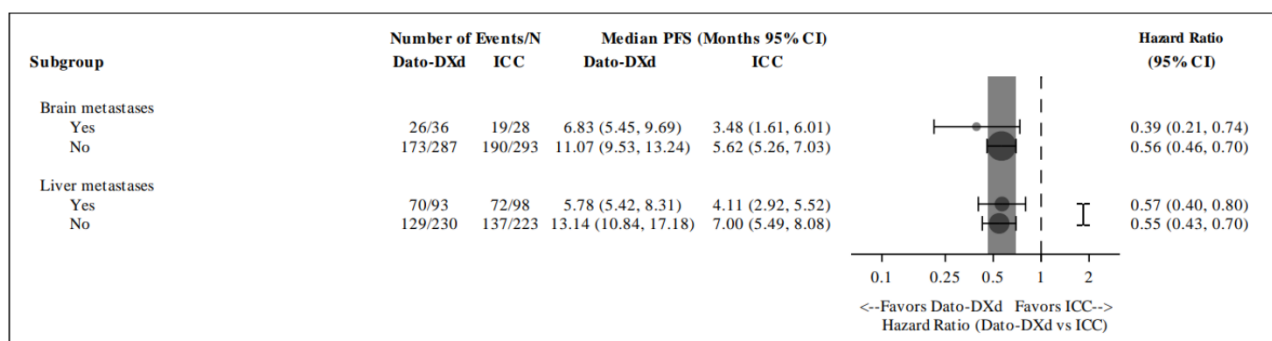
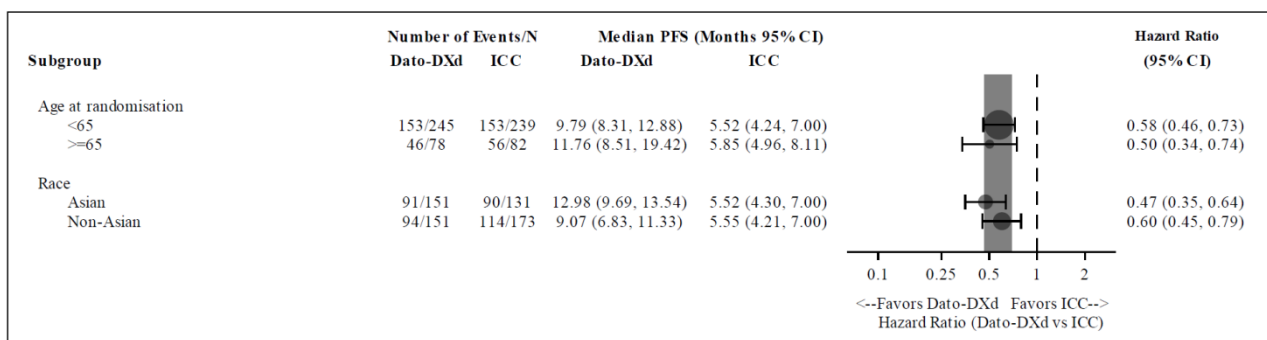
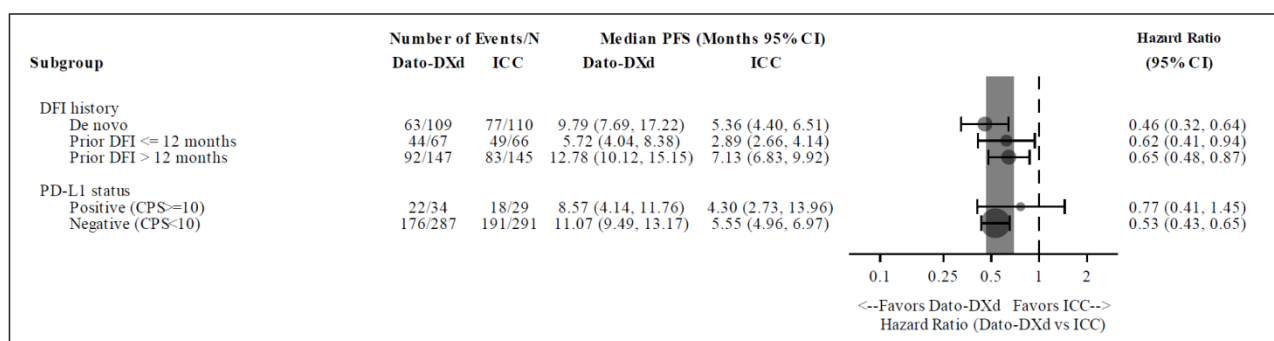
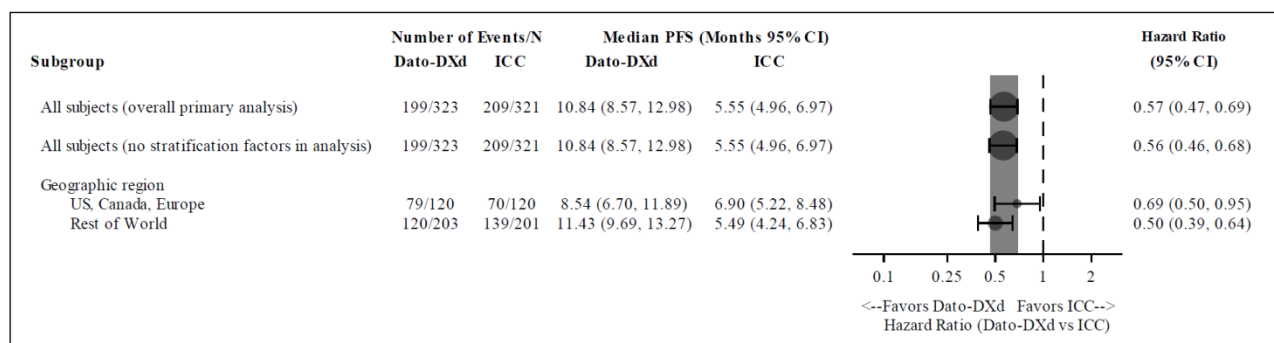
* There are less than 10 events in total for a unique stratum or less than 2 events in either treatment group for a unique stratum, therefore unstratified Cox proportional hazards model and log-rank test are performed.

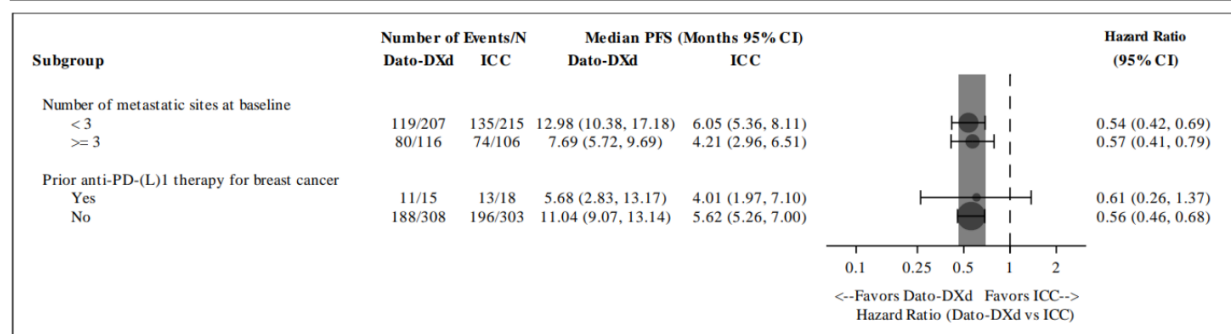
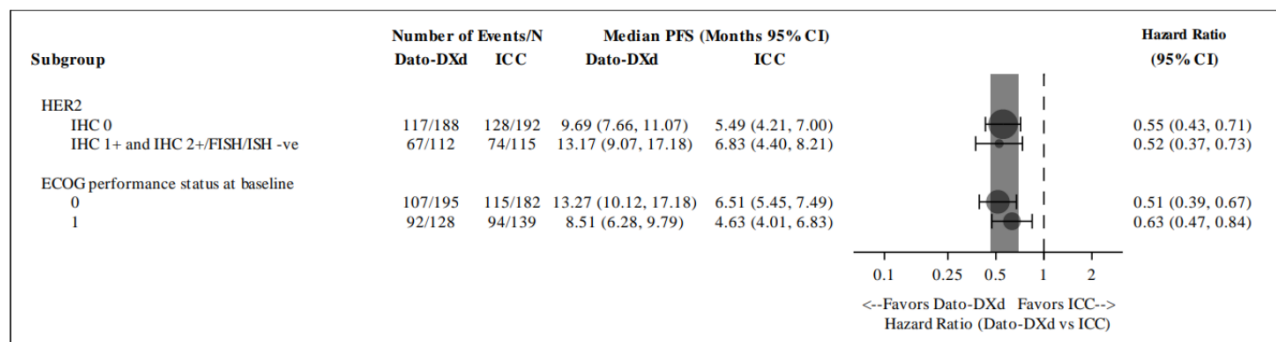
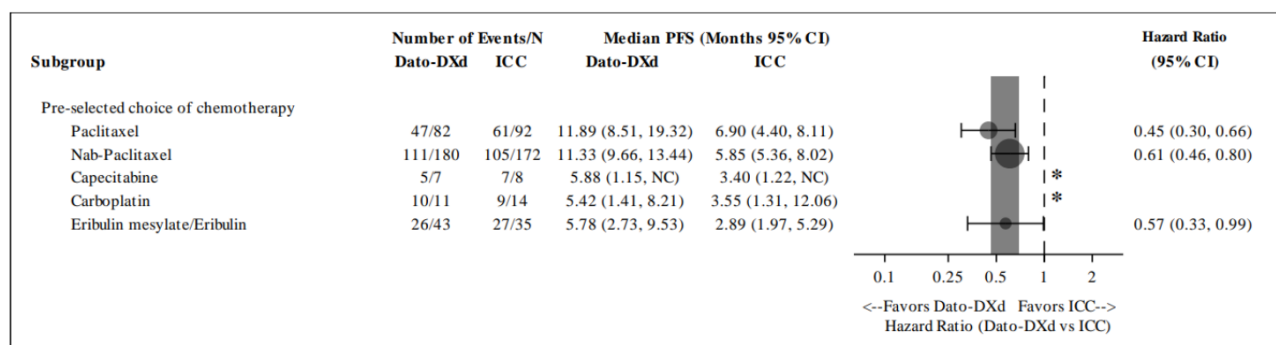
Source: Table 14.2.11.1, Table 14.2.11.3

Ancillary analyses

PFS by BICR subgroup analyses

Figure 27 PFS, Forest Plot, by Subgroup, BICR Data (FAS)





A HR < 1 favours Dato-DXd to be associated with a longer PFS than ICC.

The overall primary analysis was performed using a stratified Cox Proportional Hazards model with stratification variables DFI history and PD-L1 status from IRT system.

Cox Proportional Hazards model containing a term for treatment (without stratification factors) was performed.

The subgroup analysis was performed using a Cox Proportional Hazards model with treatment as the only covariate. Subgroup variables are based on eCRF data, except that PD-L1 status is based on central laboratory 22C3 testing, and the pre-selected ICC are from the IRT system.

Size of circle is proportional to the number of events.

Grey band represents the 95% CI for the HR for the overall (all participants primary) analysis.

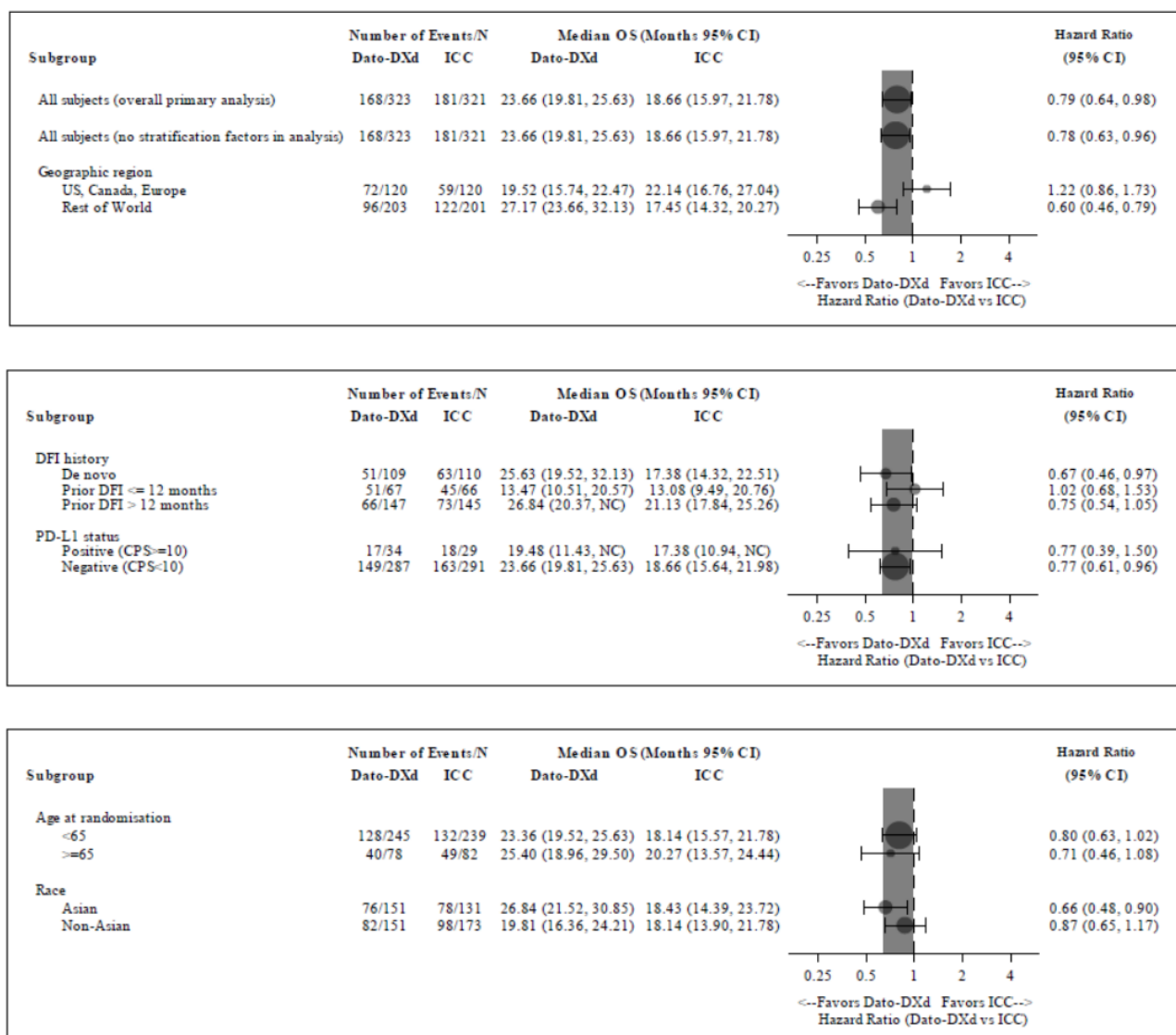
Progression includes deaths in the absence of RECIST progression. Progression events that do not occur within 2 assessments of the last evaluable assessment (or randomisation) are censored. RECIST version 1.1.

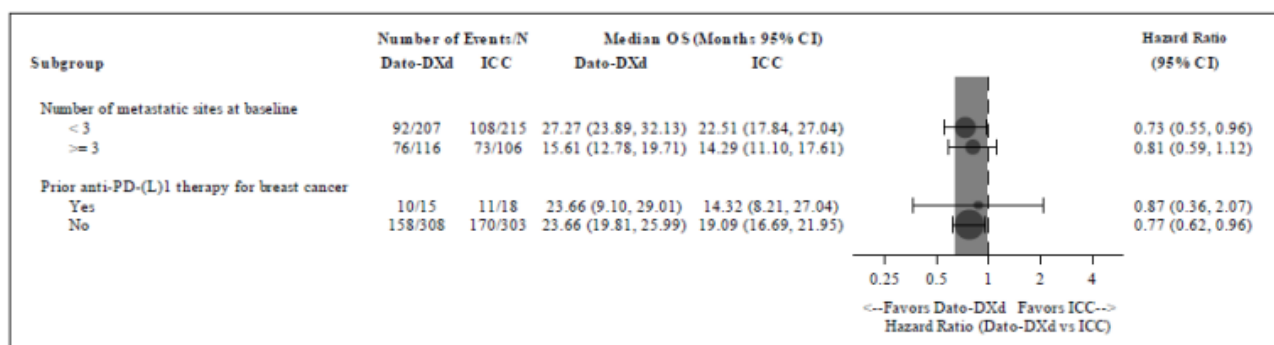
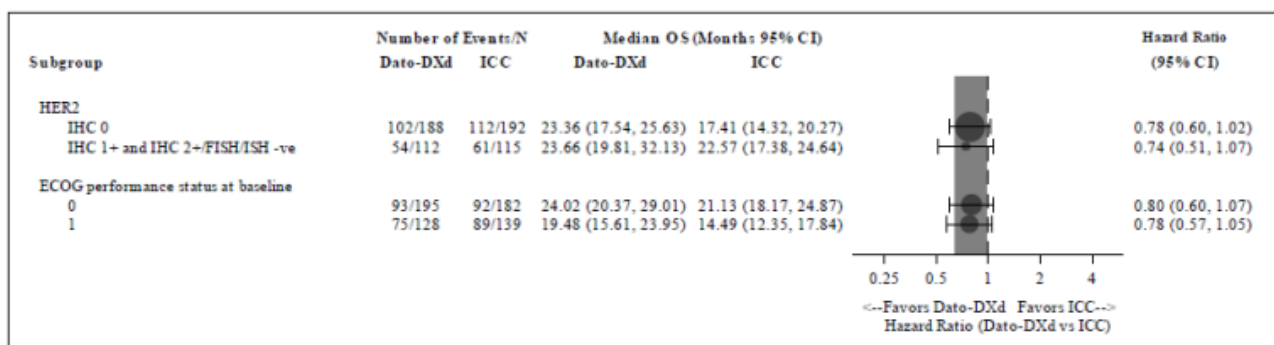
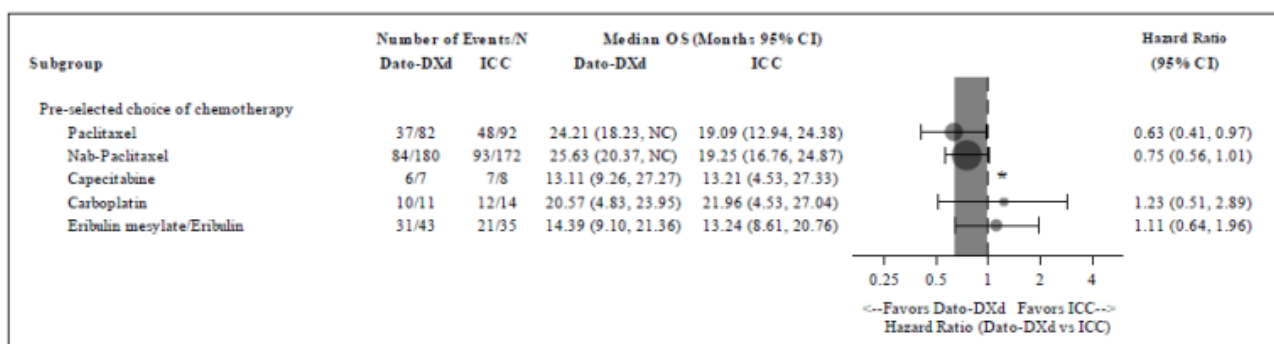
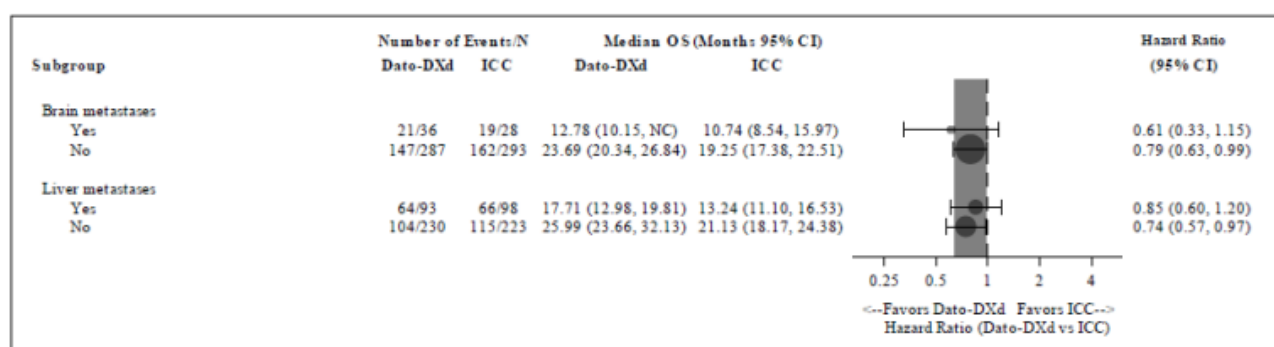
* There are less than 20 events across both treatment groups in a subgroup and thus HR (95% CI) for the treatment comparison is not displayed.

N = number of participants per treatment group

OS subgroup analyses

Figure 28 OS, Forest Plot, by Subgroup (FAS)





A HR < 1 favours Dato-DXd to be associated with a longer OS than ICC.

The overall primary analysis was performed using a stratified Cox Proportional Hazards model with stratification variable DFI history.

A Cox Proportional Hazards model containing a term for treatment (without stratification factors) was performed.

The subgroup analysis was performed using a Cox Proportional Hazards model with treatment as the only covariate. Subgroup variables are based on eCRF data, except that PD-L1 status is based on central laboratory 22C3 testing, and the pre-selected ICC are from the IRT system.

Size of circle is proportional to the number of events.

Grey band represents the 95% CI for the HR in the overall (all participants primary) analysis.

* There are less than 20 events across both treatment groups in a subgroup and thus HR (95% CI) for the treatment comparison is not displayed.

N = number of participants per treatment group

Table 40 Subsequent Cancer Therapy by Therapy Class (FAS)

Therapy class	Global population N = 644		Region 1 population N = 240		EU population N = 187	
	Dato-DXd N = 323 n (%)	ICC N = 321 n (%)	Dato-DXd N = 120 n (%)	ICC N = 120 n (%)	Dato-DXd N = 93 n (%)	ICC N = 94 n (%)
Any post-study treatment cancer therapy	210 (65.0)	232 (72.3)	81 (67.5)	87 (72.5)	67 (72.0)	70 (74.5)
Pyrimidine analogues	116 (35.9)	133 (41.4)	40 (33.3)	38 (31.7)	34 (36.6)	32 (34.0)
Taxanes	99 (30.7)	38 (11.8)	24 (20.0)	15 (12.5)	20 (21.5)	13 (13.8)
Platinum compounds	86 (26.6)	85 (26.5)	31 (25.8)	27 (22.5)	28 (30.1)	23 (24.5)
Other antineoplastic agents	50 (15.5)	46 (14.3)	19 (15.8)	16 (13.3)	15 (16.1)	14 (14.9)
Other monoclonal antibodies and antibody drug conjugates	42 (13.0)	84 (26.2)	30 (25.0)	54 (45.0)	25 (26.9)	43 (45.7)
Sacituzumab govitecan	33 (10.2)	71 (22.1)	24 (20.0)	50 (41.7)	19 (20.4)	43 (45.7)
Sacituzumab govitecan hziy	0	5 (1.6)	0	4 (3.3)	0	0
Sacituzumab tirumotecan	0	1 (0.3)	0	0	0	0
Anthracyclines and related substances	32 (9.9)	36 (11.2)	14 (11.7)	16 (13.3)	12 (12.9)	14 (14.9)
PD-1/PD-L1 inhibitors	19 (5.9)	23 (7.2)	3 (2.5)	7 (5.8)	1 (1.1)	4 (4.3)
HER2 inhibitors	18 (5.6)	39 (12.1)	4 (3.3)	18 (15.0)	3 (3.2)	14 (14.9)
Trastuzumab deruxtecan	15 (4.6)	34 (10.6)	3 (2.5)	17 (14.2)	3 (3.2)	13 (13.8)
Trastuzumab deruxtecan nxki	1 (0.3)	0	1 (0.8)	0	0	0

Post-study treatment cancer therapy is any cancer therapy that started after the last dose date of IP. For treatment non-starters, cancer therapies initiated after randomization are included.

Radiotherapy is excluded.

Participants are counted once per ATC Classification and generic term regardless of the frequency of medication usage.

Table is sorted by descending frequency for ATC classification and generic term

n, number of participants per category; N, number of participants per treatment group

TROP2 in TNBC, biomarker report

The TB02 study included an objective to explore whether TROP2 protein expression level may correlate with clinical response from Dato-DXd in TNBC. TROP2 expression was measured by the

exploratory IHC Ventana FLA EPR20043 assay in tumour samples obtained as close as possible to the time of diagnosis of metastatic or inoperable disease.

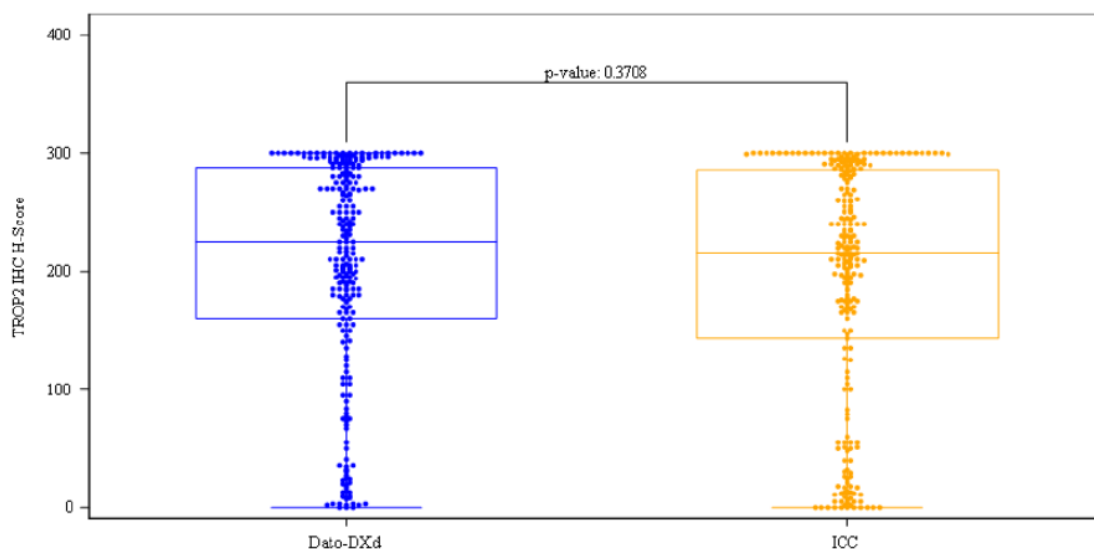
TROP2 cell membrane IHC expression was assessed by pathologists by membrane H-score and then assigned to one of 3 subgroups. Samples that were not evaluable (NE) or missing were included in a missing/NE category.

The following subgroups were assessed:

- Low H-score: 0 to 99 (< 100)
- Medium H-score: 100 to 199
- High H-score: 200 to 300 (≥ 200)
- Missing or NE

A total of 644 participants were included in the BFAS (biomarker full analysis set), of which 516 (80.1%) participants had an evaluable result with numerical value available for the H-score and were included in the IHC-EAS (IHC biomarker evaluable analysis set - primary analysis set evaluable). For 128 (19.9%) participants, IHC data were missing or non-evaluable due to lack of sample, low tumour content, local country restrictions (China and Brazil), or withdrawal of consent.

Figure 29 Boxplot of TROP2 IHC H-score by Treatment Arm (IHC-EAS)

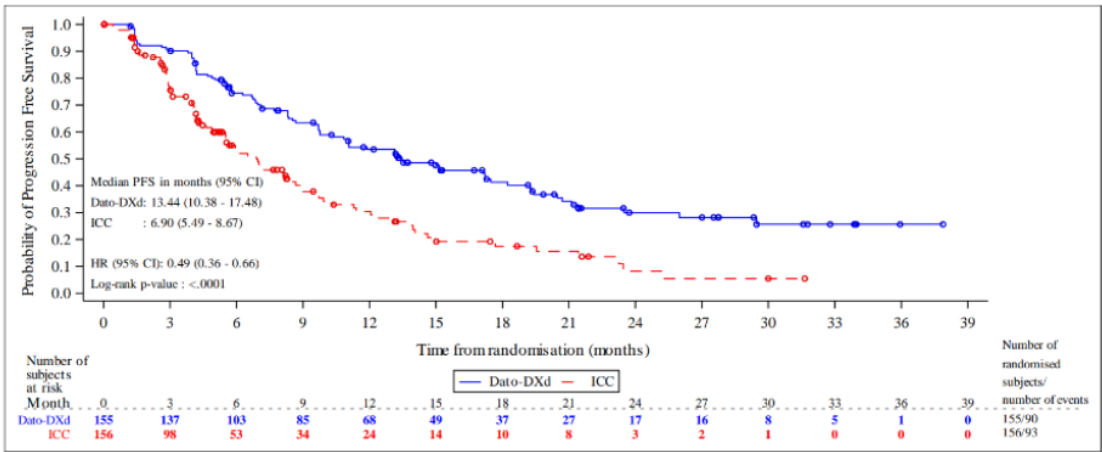


Nominal p-value derived from Wilcoxon Rank-Sum test.

DCO date: 25 Aug 2025.

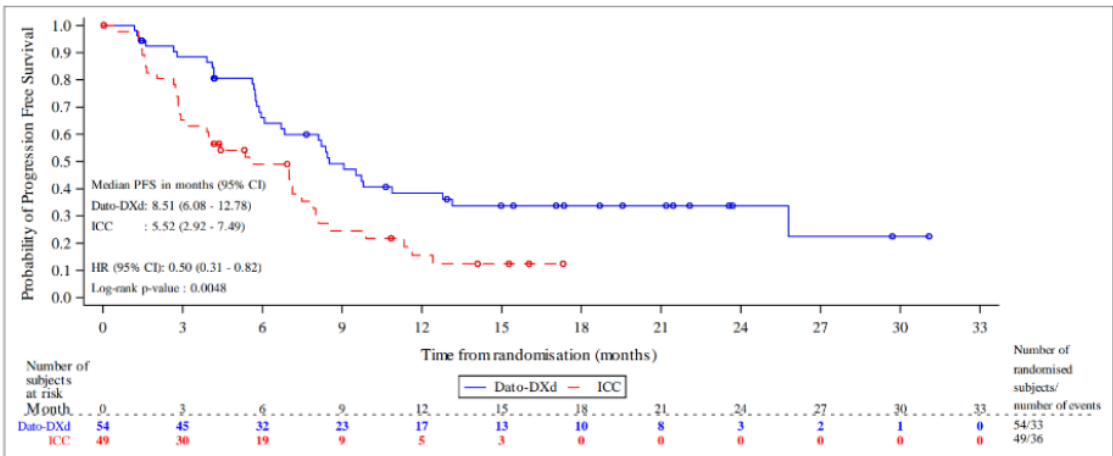
PFS by TROP2 level, High, Medium and Low

Figure 30 PFS, Kaplan-Meier Plot by TROP2 IHC H-Score (High) and Treatment Arm, BICR Data (BFAS)



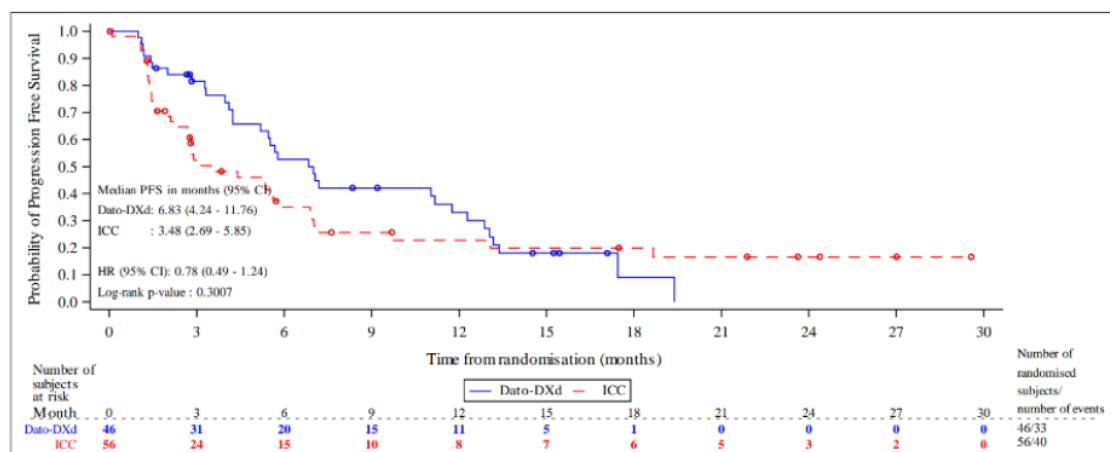
Circle indicates a censored observation. RECIST 1.1.
High TROP2 IHC H-score: 200-300.
DCO date: 25 Aug 2025.

Figure 31 PFS, Kaplan-Meier Plot by TROP2 IHC H-Score (Medium) and Treatment Arm, BICR Data (BFAS)



Circle indicates a censored observation. RECIST 1.1.
Medium TROP2 IHC H-score: 100-199.
DCO date: 25 Aug 2025.

Figure 32 PFS, Kaplan-Meier Plot by TROP2 IHC H-Score (Low) and Treatment Arm, BICR Data (BFAS)



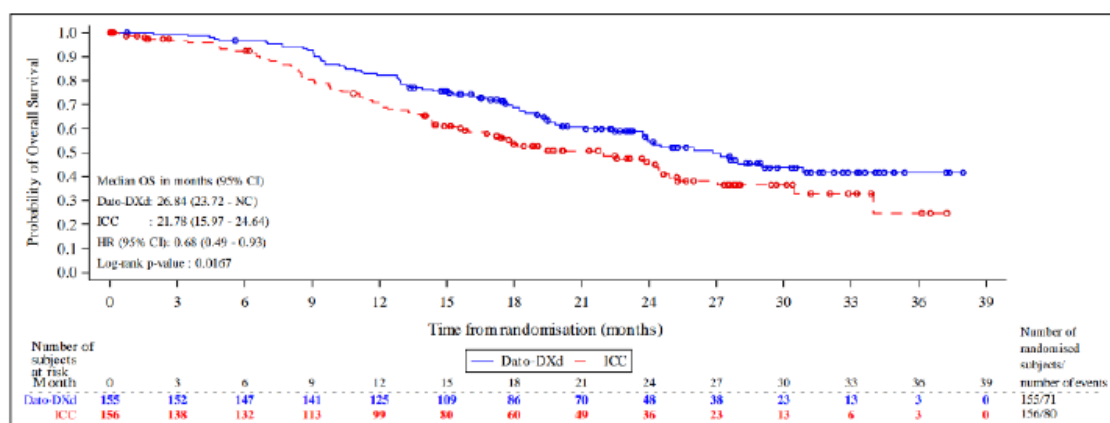
Circle indicates a censored observation. RECIST version 1.1.

Low TROP2 IHC H-score: 0-99.

DCO date: 25 Aug 2025.

OS by TROP2 scores, High, Medium and Low

Figure 33 OS, Kaplan-Meier Plot by TROP2 IHC H-Score (High) and Treatment Arm (BFAS)

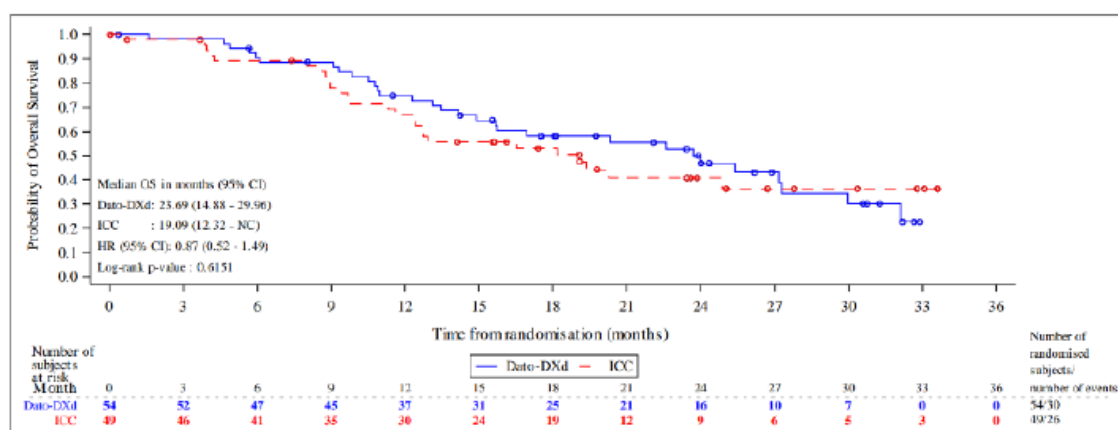


Circle indicates a censored observation.

High TROP2 IHC H-score: 200-300.

DCO date: 25 Aug 2025.

Figure 34 OS, Kaplan-Meier Plot by TROP2 IHC H-Score (Medium) and Treatment Arm (BFAS)

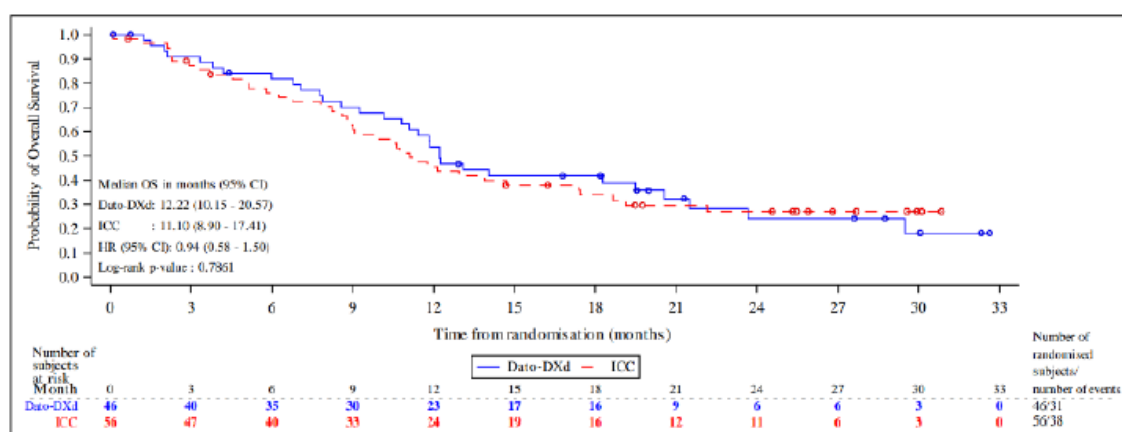


Circle indicates a censored observation.

Medium TROP2 IHC H-score: 100-199.

DCO date: 25 Aug 2025.

Figure 35 OS, Kaplan-Meier Plot by TROP2 IHC H-Score (Low) and Treatment Arm (BFAS)



Circle indicates a censored observation.

Low TROP2 IHC H-score: 0-99.

DCO date: 25 Aug 2025.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of efficacy for Study D926PC00001 (TROPION-Breast02)

Title: A Phase 3, Open-label, Randomised Study of datopotamab Deruxtecan (Dato-DXd) Versus Investigator's Choice of Chemotherapy in Patients who are not Candidates for PD-1/PD-L1 Inhibitor Therapy in First-line Locally Recurrent Inoperable or Metastatic Triple-negative Breast Cancer (TROPION-Breast02)

Study identifier D926PC00001

This was a Phase 3, randomised, multicentre, open label, sponsor blinded study of Dato-DXd versus investigator's choice of chemotherapy in participants who are not candidates for programmed death receptor-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitor therapy in first-line locally recurrent inoperable or metastatic triple-negative breast cancer (TROPION-Breast02)

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	39 Months (16-05-2022 to 25-08-2025) Not applicable Not applicable
Hypothesis	Superiority	
Treatments groups	Dato-DXd	Dato-DXd (6 mg/kg intravenous [IV] on Day 1, every 3 weeks [Q3W]) N=323
	Investigator's Choice of Chemotherapy (ICC)	<u>If no prior taxane, or prior taxane in the (neo)adjuvant setting and disease-free interval (DFI) > 12 months:</u> – Paclitaxel (80 mg/m² intravenous (IV) on Days 1, 8, and 15, Q3W) – Nab-paclitaxel (100 mg/m² IV on Days 1, 8, and 15, every 4 weeks [Q4W]) <u>If prior taxane and DFI ≤ 12 months:</u> – Capecitabine (1000 or 1250 mg/m² oral twice daily (BID) on Days 1 to 14 (Q3W); choice between the 2 doses will be determined by standard institutional practice. – Eribulin mesylate (1.4 mg/m² IV on Days 1 and 8, Q3W) – Carboplatin (area under the curve [AUC] 6 [using Calvert formula] IV Day 1, Q3W) N=321
Endpoints and definitions	Dual Primary endpoints	Progression-free survival (PFS) by blinded independent central review (BICR) PFS (Dato-DXd vs ICC). Time from the date of randomisation until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy, received another anticancer therapy, or clinically progressed prior to Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1 progression. Per RECIST Version 1.1, by BICR assessment.
		Overall survival (OS) OS (Dato-DXd vs ICC). Time from the date of randomisation until death due to any cause.
	Secondary	Objective response rate (ORR) ORR. The proportion of participants who had a confirmed complete response (CR) or partial response (PR), per RECIST 1.1 using BICR/investigator assessments. Confirmed responses required a confirmatory follow-up scan no sooner than 4 weeks after the initial determination of response. Best objective response (BOR) was a supportive endpoint for ORR.
		Duration of response (DoR) DoR. The time from the date of first documented confirmed response until the first date of documented progression or death due to any cause, per RECIST 1.1 using BICR/investigator

			assessments. Participants who were evaluable for the analysis of DoR were those who responded in the ORR.
		PFS by investigator assessment	Time from the date of randomisation until the date of disease progression or death (by any cause in the absence of progression) regardless of whether the participant withdrew from randomised therapy, received another anticancer therapy or clinically progressed prior to RECIST 1.1 progression. Per RECIST Version 1.1, by investigator assessment.
		Disease control rate (DCR)	DCR. DCR at 12 weeks was defined as the percentage of participants who had a confirmed CR or PR or who had stable disease (SD), per RECIST 1.1, as per BICR/investigator assessment and derived from the raw tumour data for at least 11 weeks after randomisation.
		Time from the date of randomisation to the date of deterioration (TTD)	TTD. Deterioration is defined as change from baseline that reaches a clinically meaningful deterioration threshold. This was done to assess pain, physical functioning, breast and arm symptoms, and global health status/quality of life in participants treated with Dato-DXd vs ICC.
		Time to first subsequent therapy or death (TFST)	TFST. Time from randomisation until the start date of the first subsequent anticancer therapy after discontinuation of randomised treatment, or death due to any cause.
		Time to second subsequent therapy or death (TSST)	TSST. Time from randomisation to until the start date of the second subsequent anticancer therapy after discontinuation of first subsequent treatment, or death due to any cause.
		Time to second progression or death (PFS2)	PFS2. Time from randomisation to the earliest of the progression events (following the initial progression), subsequent to first subsequent therapy, or death. The date of second progression was recorded by the investigator and defined according to local standard clinical practice.
Database lock	19 September 2025 (data cutoff [DCO] = 25 August 2025)		

Results and Analysis			
Analysis description	Final analysis of dual primary endpoints of PFS by BICR and OS		
Analysis population and time point description	Intent to treat (all randomised patients) The final analysis was performed based on a DCO date of 25 August 2025, when 408 PFS events (63.4% maturity) and 349 OS events (54.2% maturity) had occurred across the Dato-DXd and ICC treatment arms.		
Descriptive statistics and estimate variability	PFS by BICR, Primary Analysis (Full Analysis Set [FAS])		
	Treatment group	Dato-DXd	ICC
	Number of subjects	323	321
	PFS (months) ^a Median (95% confidence interval [CI])	10.84 (8.57, 12.98)	5.55 (4.96, 6.97)
	PFS rate at 3 months (%) ^a (95% CI)	86.34 (82.03, 89.69)	69.06 (63.38, 74.04)
	PFS rate at 6 months (%) ^a (95% CI)	67.38 (61.76, 72.36)	47.57 (41.42, 53.46)
	PFS rate at 9 months (%) ^a (95% CI)	55.50 (49.60, 61.00)	32.53 (26.63, 38.55)
	PFS rate at 12 months (%) ^a	45.59 (39.68, 51.30)	25.62 (20.05, 31.54)
	PFS rate at 18 months (%) ^a	32.71 (26.91, 38.63)	16.81 (11.83, 22.55)
	OS, Primary Analysis (FAS)		
	Treatment group	Dato-DXd	ICC
	Number of subjects	323	321
	OS (months) ^a Median (95% CI)	23.66 (19.81, 25.63)	18.66 (15.97, 21.78)
	OS rate at 12 months (%) ^a (95% CI)	75.23 (70.07, 79.63)	67.81 (62.18, 72.80)
	OS rate at 18 months (%) ^a	61.24 (55.49, 66.47)	51.27 (45.33, 56.90)
	OS rate at 24 months (%) ^a	46.73 (40.51, 52.70)	39.36 (33.28, 45.37)
	OS rate at 36 months (%) ^a	33.70 (26.63, 40.90)	25.21 (16.23, 35.19)

Descriptive statistics and estimate variability	Secondary efficacy endpoints		
	PFS by investigator assessment (months) ^a Median (95% CI)	9.63 (7.36, 11.20)	5.22 (4.21, 5.59)
	ORR, confirmed responses Patients with response/evaluable patients, n/N (%)	202/323 (62.5)	94/321 (29.3)
	DoR (months) ^a , Median (25 th , 75 th percentiles), by BICR	12.32 (5.91, not calculated [NC])	7.10 (4.21, 13.57)
	<u>BOR (% of participants)</u> CR = complete response ^b PR = partial response ^b SD = stable disease PD = progressive disease	CR (9.0) PR (53.6) SD ≥ 5 weeks (22.3) PD (8.4)	CR (2.5) PR (26.8) SD ≥ 5 weeks (38.9) PD (16.2)
	DCR, n/N (%)	270/323 (83.6)	192/321 (59.8)
	TFST (months) ^a Median (95% CI)	10.91 (9.46, 12.09)	5.62 (4.93, 6.31)
	TSST(months) ^a Median (95% CI)	16.66 (15.15, 19.48)	12.55 (11.30, 13.57)
	PFS2 (months) ^a Median (95% CI)	15.61 (13.27, 17.38)	11.76 (10.94, 12.75)
	<u>TTD (months) ^a</u> <u>Median (95% CI)</u> Pain Physical functioning Global health status/quality of life Breast and arm symptoms	Pain: NC (15.21, NC) Physical functioning: 10.38 (6.97, 20.76) Global health status/quality of life: 23.49 (12.48, NC) Breast and arm symptoms: NC (NC, NC); NC (16.66, NC)	Pain: 12.45 (9.66, NC) Physical functioning: 4.14 (2.83, 8.31) Global health status/quality of life: 8.28 (5.55, 13.80) Breast and arm symptoms: NC (18.04, NC); 12.45 (8.28, NC)

Effect estimate per comparison	Hazard ratio (HR), OR, and p-values for primary and secondary efficacy endpoints		
	Primary endpoint: PFS by BICR	Comparison groups	Dato-DXd vs ICC
		HR ^{c, d}	0.57
		95% CI ^c	0.47, 0.69
		Two-sided p-value (nominal) ^e	<0.0001
	Primary endpoint: OS	Comparison groups	Dato-DXd vs ICC
		HR ^{c, d}	0.79
		95% CI ^c	0.64, 0.98
		Two-sided p-value (nominal) ^e	0.0291
	Secondary endpoint: PFS by investigator assessment	Comparison groups	Dato-DXd vs ICC
		HR ^{c, d}	0.56
		95% CI ^c	0.47, 0.67
	Secondary endpoint: ORR, confirmed by Investigator	Comparison groups	Dato-DXd vs ICC
		Odds ratio ^{f, g}	4.24
		95% CI ^f	3.03, 5.95
		Two-sided p-value ^f	<0.0001
	Secondary endpoint: DCR	Comparison groups	Dato-DXd vs ICC
		Odds ratio ^{f, g}	3.71
		95% CI ^f	2.53, 5.46
		Two-sided p-value ^f	<0.0001
	Secondary endpoint: TFST	Comparison groups	Dato-DXd vs ICC
		HR ^c	0.49
		95% CI ^c	0.41, 0.59
	Secondary endpoint: TSST	Comparison groups	Dato-DXd vs ICC
		HR ^c	0.67
		95% CI ^c	0.55, 0.81
	Secondary endpoint: PFS2	Comparison groups	Dato-DXd vs ICC
		HR ^{c, d}	0.61
		95% CI ^c	0.50, 0.74
	Secondary endpoint: TTD, pain	Comparison groups	Dato-DXd vs ICC
		HR ^c	0.79
		95% CI ^c	0.55, 1.15
		Two-sided p-value ^f	0.2121
	Secondary endpoint: TTD, physical functioning	Comparison groups	Dato-DXd vs ICC
		HR ^c	0.67
		95% CI ^c	0.51, 0.90
		Two-sided p-value ^f	0.0068
	Secondary endpoint: TTD,	Comparison groups	Dato-DXd vs ICC

	global health status/quality of life	HR ^c	0.64
		95% CI ^c	0.46, 0.88
		Two-sided p-value ^f	0.0062
	Secondary endpoint: TTD, breast symptoms	Comparison groups	Dato-DXd vs ICC
		HR ^c	0.91
		95% CI ^c	0.57, 1.46
		Two-sided p-value ^f	0.6804
	Secondary endpoint: TTD, arm symptoms	Comparison groups	Dato-DXd vs ICC
		HR ^c	0.51
		95% CI ^c	0.35, 0.75
		Two-sided p-value ^f	0.0004
	Notes		
	^a Calculated using the Kaplan-Meier technique. ^b Response required confirmation. ^c The HR and CI were estimated from a stratified Cox Proportional Hazards model with the Efron method to control for ties, the stratification factors of DFI history and PD-L1 status, and the CI calculated using a profile likelihood approach. ^d An HR < 1 favoured Dato DXd, for example to be associated with a longer OS or PFS than ICC. ^e P-values were generated using the stratified log-rank test adjusting for stratification variables of DFI history and PD-L1 status for PFS and DFI history for OS. ^f The analysis was performed using logistic regression adjusting for factors of treatment, DFI history, and PD-L1 status with the CI calculated using a profile likelihood approach and the p-value calculated using a stratified log-rank test adjusting for stratification factors of geographic region, DFI history, and PD-L1 status. ^g An odds ratio > 1 favoured Dato-DXd compared to ICC.		

Supportive study(ies)

Design:

TP01 is a Phase I, 2-part, multicentre, multiple-dose, FIH study in participants with advanced solid tumours. The main objective of part 1 was to investigate the safety and tolerability and to determine the maximum tolerated dose (MTD) and the recommended dose for expansion (RDE) of Dato-DXd. The main objective of part 2 was to investigate the safety and tolerability of Dato-DXd.

Efficacy endpoints included ORR, DCR, CBR, DoR, TTR, PFS, and OS. The efficacy endpoints were evaluated by BICR and the investigator. Efficacy analyses of TP01 used the FAS, which included all participants who received at least one dose of Dato-DXd.

Results:

Table 41 Subject Disposition – All Screened Subjects

	TNBC 6.0 mg/kg N=42 n (%)	TNBC 8.0 mg/kg N=2 n (%)	HR+BC 6.0 mg/kg N=41 n (%)	Total TNBC N=44 n (%)	Total BC N=85 n (%)
No. of subjects screened ^a					119
No. of screen failures					34
Treatment status					
Ongoing study treatment	3 (7.1)	0	5 (12.2)	3 (6.8)	8 (9.4)
Discontinued from study treatment	39 (92.9)	2 (100)	36 (87.8)	41 (93.2)	77 (90.6)
Primary reason for study treatment discontinuation					
Progressive disease per RECIST	32 (76.2)	2 (100)	24 (58.5)	34 (77.3)	58 (68.2)
Clinical progression	4 (9.5)	0	5 (12.2)	4 (9.1)	9 (10.6)
Adverse event	1 (2.4)	0	5 (12.2)	1 (2.3)	6 (7.1)
Death	0	0	1 (2.4)	0	1 (1.2)
Withdrawal by subject	0	0	1 (2.4)	0	1 (1.2)
Other	2 (4.8)	0	0	2 (4.5)	2 (2.4)
Study duration (months)					
n	42	2	41	44	85
Mean	19.1	24.5	13.4	19.4	16.5
Standard deviation	2.10	0.37	1.47	2.34	3.56
Minimum	15	24	9	15	9
Median	19.1	24.5	13.7	19.3	16.0
Maximum	23	25	16	25	25

BC=breast cancer; HR+=hormone receptor-positive; RECIST=Response Evaluation Criteria in Solid Tumors; TNBC=triple-negative breast cancer.

^a Subjects who signed an informed consent form and were screened.

Table 42 Best Overall Response, Objective Response Rate, Disease Control Rate, and Clinical Benefit Rate by BICR per RECIST v1.1 (FAS)

	TNBC 6.0 mg/kg N=42 n (%)	TNBC 8.0 mg/kg N=2 n (%)	HR+BC 6.0 mg/kg N=41 n (%)	Total TNBC N=44 n (%)
Response with Confirmation of CR/PR				
BOR				
CR	1 (2.4)	0	0	1 (2.3)
PR	12 (28.6)	1 (50.0)	11 (26.8)	13 (29.5)
SD	17 (40.5)	1 (50.0)	23 (56.1)	18 (40.9)
Non-CR/non-PD	3 (7.1)	0	1 (2.4)	3 (6.8)
PD	8 (19.0)	0	5 (12.2)	8 (18.2)
NE	1 (2.4)	0	1 (2.4)	1 (2.3)
Reason for NE				
No adequate post-baseline tumor assessment	1 (2.4)	0	1 (2.4)	1 (2.3)
ORR (CR+PR)	13 (31.0)	1 (50.0)	11 (26.8)	14 (31.8)
95% Exact CI ^a	(17.6, 47.1)	(1.3, 98.7)	(14.2, 42.9)	(18.6, 47.6)
DCR (CR+PR+SD+non-CR/non-PD)	33 (78.6)	2 (100)	35 (85.4)	35 (79.5)
95% exact CI ^a	(63.2, 89.7)	(15.8, 100.0)	(70.8, 94.4)	(64.7, 90.2)
CBR (CR+PR+SD [non-CR/non-PD] for at least 6 months), n (%)	16 (38.1)	1 (50.0)	18 (43.9)	17 (38.6)
95% exact CI ^a	(23.6, 54.4)	(1.3, 98.7)	(28.5, 60.3)	(24.4, 54.5)

BC=breast cancer; BOR=best overall response; CBR=clinical benefit rate; CI=confidence interval; CR=complete response; DCR=disease control rate; HR+=hormone receptor-positive; NE=not evaluable; ORR=objective response rate; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease; TNBC=triple-negative breast cancer.

^a Using 2-sided exact (Clopper-Pearson) method.

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

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy assessment of the applied extension of indication is based on the pivotal trial Tropion-02 (TB02) trial. **The study was designed** as a phase III, randomized, open-label, 2-arm, multicentre, international study assessing the efficacy and safety of Dato-DXd compared with investigator's Choice of Chemotherapy (ICC) in participants with locally recurrent inoperable or metastatic TNBC in the first-line setting, who were not candidates for PD-1/PD-L1 inhibitor therapy.

The PD-L1 criteria consisted of several parts. Patients with PD-L1 negative tumours or patients whose tumours were positive but had relapsed after prior PD-1/PD-L1 inhibitor treatment in the early breast cancer (EBC) setting, comorbidities precluding PD-1/PD-L1 inhibitor treatment or no regulatory access to pembrolizumab. This represents a source of heterogeneity as these patients are not prognostically equal. However, this was alleviated to some degree by including PD-L1 status (CPS $\geq$ 10 vs CPS < 10) as a stratification factor.

The **choice of comparator** chemotherapy (ICC) was pre-defined prior to randomisation and consisted of the current SOC monotherapy chemotherapy options such as taxanes, eribulin and capecitabine with the exception of anthracyclines (as well as docetaxel and combination chemotherapy which are less used options in this context). During CHMP SA, inclusion either of anthracyclines as an option or of a criterion specifying prior use at inclusion was advised. Despite this, and the fact that this option is clinically relevant and included in the ESMO treatment guideline on TNBC, anthracyclines were not included as a treatment option in the ICC. However, it is acknowledged that there is no clear superiority of one monotherapy agent over others, when considering capecitabine, taxanes and anthracyclines, and there is no ideal sequence of treatments that can be applied to all patients. The TB02 trial recruited 1/3 of patients with *de novo* disease status, which due to the omission of anthracycline monotherapy could only receive part of the ESMO endorsed first-line treatment. The inclusion of "not considered the best treatment option in the opinion of the treating physician" is not successfully justified as 9-15% of study population received anthracyclines as a subsequent therapy. While this design choice limits external generalisability of the TB02 trial results, it does not preclude efficacy demonstration in this procedural setting, and it is considered acceptable given that the TROPION-02 trial is in line with the recent clinical trial context (i.e. IMpassion130 and IMpassion131 and KEYNOTE-355 studies). Additional information has been included in the SmPC section 5.1 specifying the omission of anthracyclines in the ICC.

The **inclusion criteria** of TB02 reflect the targeted population.

Several **changes to the study protocol** and procedures were made after study initiation from protocol version 2.0 to 3.0. These were mostly clarifications that did not change definitions of primary or secondary outcomes significantly. Regarding changes to PD-L1 testing, the Applicant has clarified that all participants were enrolled after the availability of central PD-L1 testing. The number of patients who discontinued from study treatment for "other reasons" were more than double for the ICC arm than for the Dato-DXd (21 (6.8%) patients compared to 10 (3.1%) patients). Reasons for early discontinuation were not recorded systematically. Demographic variables for patients with early study discontinuation were reasonably similar to each other prognostically and impact on study efficacy outcomes is considered limited.

The study screened 1277 patients in order to include 644 patients. With a patient representativeness of 644/1277 (~50%), the generalizability to the population of TNBC cancer patients may be limited, however this does not affect the internal validity and hypotheses of the

study. Also, a large extent of screen failures were due to the fact that many patients had not been PD-L1 tested at the initial diagnosis (44% (262/595 screen failures)).

The **statistical methodology** specified the full analysis set (FAS) as all randomised participants. Participants were analysed on the basis of randomised study treatment, regardless of the treatment actually received. This is aligned with the ITT principle and endorsed. Superiority of PFS (by BIRC) and OS were tested by stratified log-rank test. PFS was stratified by DFI history and PD-L1 status, and the dual primary endpoint of OS was stratified by DFI history. Selected stratification factors were removed from the stratified analysis in accordance with the pre-specified SAP rules because of the small number of events within certain strata. This pooling was implemented to ensure that the resulting strata contained sufficient number of events to support robust and reliable analyses. The HR was estimated from a stratified (same as above) Cox Proportional Hazards model, and the CI calculated using a profile likelihood approach, which presumably has better coverage than the Wald CI. This is endorsed.

The primary analysis of PFS specified the following intercurrent events: withdrawal from randomized therapy, receiving another anti-cancer therapy or clinically progressing prior to RECIST 1.1 progression. These ICE's are addressed by "treatment policy strategy". However, if the participant progresses or dies immediately after 2 or more consecutive missed visits, the participant will be censored. A number of sensitivity analyses were performed. Of particular interest were: no censoring to events regardless of two missed visits, initiation of new anti-cancer therapy deemed event and evaluation time bias all consistent with the primary analysis.

The dual primary endpoints, PFS and OS, were tested with a hierarchical structure allowing the initial 1% allocated to PFS to be recycled to OS, if PFS was significant. The multiplicity strategy (Burman et al 2009) is endorsed. This application is based on 408 PFS (BICR) events and 349 OS events, close to the original planned final analyses, i.e., 422 and 340 events. The final analyses of both PFS and OS were performed based on DCO 25 August 2025 (). No previous interim analysis was conducted.

Efficacy data and additional analyses

Baseline characteristics were well-balanced between arms and the minor differences observed are not expected to impact validity of the study results. The majority of patients were included in Rest of World n=404/644 (62.7%), with a large majority of patients in Region 1 (US/Canada/Europe) recruited in Europe (n=187/240)

Disease characteristics were also well-balanced in the ITT, no marked differences in distribution of major prognostics factors were observed between the Dato-DXd arm and the ICC, such as disease-free interval (DFI) below 1 year (20.7% vs 20.6%) and median time from TNBC diagnosis of 1.09 and 1.08 years, respectively. There were more patients discontinuing treatment in the ICC arm than in the Dato-DXd arm (97.4% compared to 84.9%) and at DCO 14.1% compared to 2.6% were still ongoing allocated treatment with Dato-DXd or ICC, respectively.

Results from the final analysis at DCO showed a total of 408 out of 644 participants (63.4% maturity) recorded to have had PFS events based on BICR, including 199 events out of 323 randomised participants (61.6%) in the Dato-DXd arm and 209 events out of 321 randomised participants (65.1%) in the ICC arm. The **median PFS by BICR** was 10.84 months (95% CI: 8.57, 12.98) in the Dato-DXd arm compared to 5.55 months (95% CI: 4.96, 6.97) in the ICC arm, representing a clinically relevant difference of 5.29 months in favour of Dato-DXd with a HR of 0.57 (95% CI: 0.47, 0.69). Sensitivity analyses of PFS were consistent with the main analysis with HRs ranging from 0.48 – 0.60. Censoring was balanced, with 124 (38.4%) censored in the Dato-DXd

arm and 112 (34.9%) in the ICC with a slightly higher percentage of patients being censored at day 1 in the ICC compared to the Dato-DXd arm (14 (4.4%) patients compared to 5 (1.5%) patients in the Dato-DXd arm).

At DCO, OS data had reached 54.2% maturity with 349 events observed out of a total of 644 randomised participants. The **median OS** was 23.66 months (95% CI: 19.81, 25.63) in the Dato-DXd arm vs 18.66 months (95% CI: 15.97, 21.78) in the ICC arm with a HR of 0.79 (95% CI: 0.64, 0.98). Overall censoring was acceptable with 155 (48.0%) censored patients in the Dato-DXd arm compared to 140 (43.6%) in the ICC. No sensitivity analyses of OS are specified in the protocol or amendments, but appear in the original SAP 1.0 dated 10 August 2022, which changed markedly with the SAP 2.0 dated 7 February 2025 (~6 months before FA DCO). Here analyses were added to assess the impact of baseline covariates, time-dependant variables and subsequent anti-cancer therapies on OS via an IPCW model. Results showed marked improvement of OS HRs from 0.79 (95% CI: 0.64, 0.98) in the original analysis to 0.65 (95% CI: 0.51, 0.84). This difference might be driven by the impact of subsequent therapy rather than baseline factors and is expanded upon below.

Subgroup analyses of PFS and OS were pre-specified in the protocol SAP version 4.0. PFS subgroup analyses are consistent with the main result with HR CIs generally below the 1.00 threshold in sufficiently large subgroups. Most notably, a sufficiently large subgroup analyses of geographic region with 79 and 70 events in each arm shows that the benefit of Dato-DXd compared to ICC in patients from US, Canada and Europe is lower than what was observed for Rest of World (HR 0.69 (95% CI: 0.50, 0.95) compared to HR 0.50 (95% CI: 0.39, 0.64)). While this difference is acceptable in itself, it suggests that relevant regional differences could be present in the dataset.

Subgroup analyses of OS in patients treated with Dato-DXd compared to ICC in region 1 i.e. US, Canada, Europe showed an HR of 1.22 (95% CI: 0.86, 1.73) compared to an HR of 0.60 (95% CI: 0.46, 0.79) in Rest of World. This analysis was performed post-hoc for the European population only (n=187, 78% of region 1 population) and resulted in an HR of 1.34 (95% CI: 0.90, 1.99). Sensitivity analyses were provided looking into baseline characteristics and subsequent ADC use.

Regarding baseline characteristics, a post-hoc OS IPCW sensitivity analyses showed that OS HR improved when accounting for prognostic variables at baseline (HR 0.90 (95% CI: 0.54, 1.51)). Importantly, the proportion of patients with liver metastases in the Dato-DXd arm of region 1 was 2.5% higher than in the ICC arm (30.8% vs 28.3%). This is a small difference, but compared to Region 2, the between arm (Dato-arm vs ICC arm) difference was -4.2% (27.6% vs 31.8%), which highlights that, not only was the proportional difference of patients with liver metastases numerically higher in the ICC arm in Region 2 compared to the ICC arm of Region 1, the difference in itself also favoured the ICC in Region 1 whereas in Region 2, this baseline prognostic factor numerically favoured Dato-DXd arm (4.2% less patients with liver metastases compared with the ICC). A similar shift in favourable/unfavourable position of baseline prognostic factors were seen for ECOG PS 0, Brain metastases and number of metastatic sites (3 and >3). Furthermore, in the European population only, the between baseline prognostic factors such as liver metastases and number of metastatic sites >3 were even more unbalanced in favour of the ICC arm (5.6% and 8.8% arm differences respectively). In an additional requested multivariate Cox proportional hazards model OS sensitivity analysis adjusting for imbalanced prognostic characteristics, it is noted that the adjusted OS HR in Region 1 was 1.02 (95% CI: 0.71, 1.48) from an unadjusted OS HR of 1.22 (0.86, 1.73) and the adjusted OS HR in European population was 1.11 (0.73, 1.69) compared to 1.34 (0.90, 1.99) in the unadjusted analysis.

The potential differential OS results in Region 1 and the European population could also arise because of an unbalance of subsequent therapies received between arms. Indeed, a significantly higher proportion of ICC patients received subsequent ADC use compared to the Dato-DXd arm (45.7% vs 20.4% for sacituzumab govitecan and 13.8% vs 3.2% trastuzumab deruxtecan). In Region 1, 45.0% in the ICC arm received a subsequent ADC, while this was only 20.0% in the Dato-DXd arm. This was markedly different from Region 2, where 20.9% in the ICC arm received a subsequent ADC, while 11.8% did so in the Dato-DXd arm. A two-stage OS sensitivity analysis adjusting for ADC use only, demonstrated OS HRs of 0.83 (95% CI: 0.59, 1.18) and 0.79 (0.53, 1.18) for Region 1 and the European population, respectively.

Although there are limitations on the interpretation of these adjusted analyses, the results of the additional analyses reasonably support the claim that the above-mentioned descriptive imbalances in poor prognostic baseline variables likely partly account for the differential OS result in Region 1 and the European population and the adjusted OS HRs are not considered detrimental. In addition, the variability seen in the OS measures between regions suggest that the extent of the overall impact of Dato-DXd on overall survival in breast cancer may depend on the other treatments available and the evolving treatment paradigm.

Almost half of the OS events are unaccounted for in TB02; however, OS updates are not possible as the Applicant did not collect OS data beyond the DCO of the primary outcome. Given the maturity of the currently available OS data (54.2% maturity), the trajectory is expected to remain stable even with more maturity and no further updates are required.

Secondary outcomes were all consistent with the primary outcomes showing clinically relevant benefit of Dato-DXd on PFS by investigator, ORR, BOR, DOR, TFST and PFS2 compared to ICC. Median PFS by investigator was 9.63 months (95% CI: 7.36, 11.20) in the Dato-DXd arm compared to 5.22 months (95% CI: 4.21, 5.59) in the ICC arm with a corresponding HR of 0.56 (95% CI: 0.47, 0.67), which is somewhat lower than PFS by BICR where median PFS was 10.84 months in the Dato-DXd arm compared to 5.55 months in the ICC. However, this analysis was also based on more events than the BICR analysis with 74.6% and 80.4% total events compared 61.6% and 65.1% in the BICR analysis for Dato-DXd and ICC arms, respectively. This is considered acceptable as between arm discordance rate between analyses is 13% for the Dato-DXd arm and 15.3% for the ICC arm. Confirmed ORR was 62.5% for the Dato-DXd arm and 29.3% for the ICC with more CR in the Dato-DXd arm than in the ICC (9.0% compared to 2.5%). Subgroup analyses of ORR odds ratios showed consistent response across all subgroups.

Patient-reported outcomes suffered from a high rate of missing-at-baseline (32.4% in the Dato-DXd arm and 36.4% in the ICC). Overall, a positive development in GHS/QoL favouring the Dato-DXd arm was indicated by time to first deterioration (TTD) on GHS/QoL (HR 0.64; 95% CI: 0.46, 0.88) with a median TTD of 23.49 months Dato-DXd compared to 8.28 months in the ICC. Focusing on specific subscales of the EORTC-IL146 (comparable to the QLQ-C30), Dato-DXd seems to postpone TTD in diarrhoea and fatigue, but not in nausea/vomiting, appetite loss and constipation, which is somewhat contradicting the major benefit seen on GHS/QoL. The open-label design and lack of multiplicity control significantly hamper the interpretability of PRO data, which should not be reflected in the SmPC.

Exploratory endpoints displaying **PFS and OS by TROP2 levels** show that efficacy is most likely preserved across different levels of TROP2, although a clear beneficial effect on OS results for the medium and low groups is less convincing. Of note, in the low TROP-2 expression group, OS HR was 0.94 (95% CI 0.58-1.50) with nearly overlapping OS KM curves and for PFS the benefit was only marginal (HR 0.78, 95% CI 0.49-1.24). This is compared to TROP2 high, where OS HR was 0.68 (95% CI 0.49-0.93) and PFS HR was 0.49 (0.36-0.66). However, the at-risk population was

markedly lower for TROP2 low analyses than for TROP2 high (102 compared to 311, respectively) resulting in very wide confidence intervals. With this uncertainty, it is considered difficult to conclude upon the impact of TROP2 expression and this is not pursued further.

2.4.3. Conclusions on the clinical efficacy

The pivotal study TB02 demonstrated a clinically relevant and superior efficacy of datopotamab deruxtecan (Dato-DXd) compared to standard of care (single-agent chemotherapy) regarding PFS in the ITT. The results in terms of OS were also statistically significant.

2.5. Clinical safety

Introduction

The safety profile of datopotamab deruxtecan (Dato-DXd) was previously assessed in the TROPION-Breast01 Study, the pivotal study which led to the approval of Dato-DXd in patients with advanced and metastatic breast cancer as later line therapy. In this study, the safety profile of Dato-DXd was found to be characterized by gastrointestinal toxicity, stomatitis, ILD, eye disorders, and to a lesser degree haematological toxicity and neurotoxicity. Adverse events of special interest are known to be ILD/pneumonitis, infusion-related reactions, oral mucositis/stomatitis, mucosal inflammation other than oral mucositis/stomatitis and ocular surface events.

Safety data pooling strategy

The safety assessment of this application is based on the ongoing pivotal Study TROPION-Breast02 (TB02). Supportive safety data are provided from Studies TROPION-Breast01 (TB01), TROPION-PanTumor02 (TP02), TROPION-PanTumor01 (TP01).

For the purpose of this submission, safety data from pivotal Study TB02 and the breast cancer population from the supportive Studies TB01, TP02 and TP01 were pooled.

Table 43 Safety Data Pooling Strategy: Clinical Studies and Number of Participants Included in Datasets

Pivotal Study TB02 (TNBC) Dato-DXd 6 mg/kg N = 319	Pooled BC ^a Dato-DXd 6 mg/kg N = 841
TB02 Dato-DXd 6 mg/kg	TB02 (n = 319) TB01 (n = 360) TP02 BC (n = 79) TP01 BC (n = 83)

^a Pooled BC populations consist of participants with TNBC and HR-positive/HER2-negative BC.

Patient exposure

Table 44 Study Treatment Exposure and Treatment Compliance in the Pivotal Study and Pooled Studies (Safety Analysis Set)

Parameter	Pivotal Study TB02		Pooled Studies ^a
	Dato-DXd 6 mg/kg N = 319	ICC N = 309	BC Dato-DXd 6 mg/kg N = 841
Treatment duration (months) ^b			
Mean (SD)	10.7 (8.09)	5.67 (5.247)	8.8 (6.99)
Median	8.5	4.14	6.4
Min, Max	0.7, 38.0	0.1, 32.0	0.7, 38.0
Total amount of dose taken (mg/kg)			
Mean (SD)	81.2 (59.21)	NA	66.5 (52.03)
Median	63.1	NA	49.1
Min, Max	5.9, 324.0	NA	5.9, 324.0
Actual dose intensity (mg/kg/cycle)			
Mean (SD)	5.4 (0.76)	NA	5.3 (0.81)
Median	5.8	NA	5.7
Min, Max	3.0, 6.4	NA	2.3, 6.5
Relative dose intensity (%)			
Mean (SD)	92.1 (12.43)	90.75 (11.290)	89.5 (13.54)
Median	98.6	95.42	96.0
Min, Max	50.3, 116.7	39.7, 105.6	37.9, 116.7
Total number of cycles initiated			
Mean (SD)	14.8 (11.07)	6.9 (NC)	12.0 (9.60)
Median	12.0	5.0	9.0
Min, Max	1, 54	NC	1, 54
Treatment duration category, n (%)			
> 0 to ≤ 3 months	53 (16.6)	NA	185 (22.0)
> 3 to ≤ 6 months	73 (22.9)	NA	206 (24.5)
> 6 months	193 (60.5)	103 (33.3)	450 (53.5)
> 6 to ≤ 9 months	43 (13.5)	NA	144 (17.1)
> 9 to ≤ 12 months	38 (11.9)	NA	88 (10.5)
> 12 months	112 (35.1)	29 (9.4)	218 (25.9)
> 12 to ≤ 18 months	51 (16.0)	NA	114 (13.6)
> 18 to ≤ 24 months	37 (11.6)	NA	71 (8.4)
> 24 months	24 (7.5)	NA	33 (3.9)

Relative dose intensity, by category, n (%)			
≥ 95%	205 (64.3)	NA	439 (52.2)
< 95% to ≥ 90%	21 (6.6)	NA	77 (9.2)
< 90% to ≥ 80%	38 (11.9)	NA	135 (16.1)
< 80% to ≥ 60%	43 (13.5)	NA	157 (18.7)
< 60%	12 (3.8)	NA	33 (3.9)

^a See Table 2 for an overview of studies included in the pooled analyses.

^b Total exposure of Dato-DXd (months) is calculated as (min (last date where dose > 0 + 20, date of death, date of DCO) – first dose date + 1) / (365.25 / 12).
 Total exposure of Paclitaxel (months) is calculated as (min (last paclitaxel dose date where dose > 0 + 6, date of death, date of DCO) – first Paclitaxel dose date + 1) / (365.25 / 12).
 Total exposure of Nab-paclitaxel (months) is calculated as (min (last Nab-paclitaxel dose date where dose > 0 + W, date of death, date of DCO) – first Nab-paclitaxel dose date + 1) / (365.25 / 12), where W = 6 if the last Nab-paclitaxel dose was scheduled on Day 1 or Day 8, and W = 13 if the last Nab-paclitaxel dose was scheduled on Day 15.
 Total exposure of Capecitabine (months) is calculated as (min (last Capecitabine dose date where dose > 0 + W, date of death, date of DCO) – first Capecitabine dose date + 1) / (365.25 / 12), where W = 0 if the last Capecitabine dose was scheduled on Day 1 to Day 13 of the cycle, and W=7 if the last Capecitabine dose was scheduled on Day 14.
 Total exposure of Carboplatin (months) is calculated as (min (last Carboplatin dose date where dose > 0 + 20, date of death, date of DCO) – first Carboplatin dose date + 1) / (365.25 / 12).
 Total exposure of Eribulin mesylate/Eribulin (months) is calculated as (min (last Eribulin mesylate/Eribulin dose date where dose > 0 + W, date of death, date of DCO) – first Eribulin mesylate/Eribulin dose date + 1) / (365.25 / 12), where W = 6 if the last Eribulin mesylate/Eribulin dose was scheduled on Day 1 and W = 13 if the last Eribulin mesylate/Eribulin dose was scheduled on Day 8.

Table 45 Drug Interruptions, Cycle Delay and Dose Reductions (SAF)

	Number (%) of participants	
	Dato-DXd N = 319	ICC N = 309
No drug interruption	306 (95.9)	302 (97.7)
Number of participants with an interruption		
Any	13 (4.1)	7 (2.3)
1 interruption	13 (4.1)	6 (1.9)
> 2 interruptions	0	1 (0.3)
Reason for drug interruption ^a		
AE	9 (2.8)	4 (1.3)
Other	4 (1.3)	3 (1.0)
No cycle delay	146 (45.8)	184 (59.5)
Number of participants with a cycle delay		
Any	173 (54.2)	125 (40.5)
1 cycle delay	78 (24.5)	61 (19.7)
2 cycle delays	33 (10.3)	29 (9.4)
> 2 cycle delays	62 (19.4)	35 (11.3)
Reason for cycle delay ^b		
AE	140 (43.9)	96 (31.1)
Participant decision	30 (9.4)	16 (5.2)
Other	62 (19.4)	49 (15.9)
No dose reduction	227 (71.2)	244 (79.0)
Number of participants with a dose reduction		
Any	92 (28.8)	65 (21.0)
1 reduction	71 (22.3)	53 (17.2)
2 reductions	21 (6.6)	9 (2.9)
> 2 reductions	0	3 (1.0)

Reason for dose reduction ^c		
AE	91 (28.5)	63 (20.4)
Technical issue	0	1 (0.3)
Other	2 (0.6)	2 (0.6)
Number of participants with both drug interruption and cycle delay	9 (2.8)	5 (1.6)
Number of participants with both drug interruption and dose reduction	6 (1.9)	1 (0.3)
Number of participants with both cycle delay and dose reduction	85 (26.6)	49 (15.9)
Number of participants with drug interruption, cycle delay, and dose reduction	6 (1.9)	1 (0.3)
Number of participants with drug interruption or cycle delay	177 (55.5)	127 (41.1)
Number of participants with drug interruption or dose reduction	99 (31.0)	71 (23.0)
Number of participants with cycle delay or dose reduction	180 (56.4)	141 (45.6)

^a Reasons for interruption are not mutually exclusive for participants with multiple interruptions although will be counted only once per category. Drug interruption is collected from eCRF exposure (EX) page.

^b Reasons for cycle delay are not mutually exclusive for participants with multiple cycle delays although will be counted only once per category.

^c Reasons for dose reductions are not mutually exclusive for participants with multiple reductions although will be counted only once per category.

Table 46 Summary of Demographics in the Pivotal Study and Pooled Studies (Safety Analysis Set)

Parameter	Pivotal Study TB02		Pooled Studies ^a
	Dato-DXd 6 mg/kg N = 319	ICC N = 309	BC Dato-DXd 6 mg/kg N = 841
Age (years), n ^b	319	309	841
Mean (SD)	55.4 (12.19)	56.2 (11.81)	54.8 (11.75)
Median (min, max)	56.0 (26, 85)	56.0 (23, 83)	55.0 (26, 86)
Age group (years), n (%)			
< 65	241 (75.5)	231 (74.8)	651 (77.4)
≥ 65	78 (24.5)	78 (25.2)	190 (22.6)
Sex, n (%)			
Female	319 (100)	307 (99.4)	835 (99.3)

Male	0	2 (0.6)	6 (0.7)
Race, n (%)			
Caucasian or White	128 (40.1)	147 (47.6)	358 (42.6)
Asian	150 (47.0)	126 (40.8)	393 (46.7)
Black or African American	13 (4.1)	14 (4.5)	20 (2.4)
Other	7 (2.2)	6 (1.9)	17 (2.0)
Missing ^c	21 (6.6)	16 (5.2)	53 (6.3)
Ethnicity, n (%)			
Hispanic or Latino	44 (13.8)	52 (16.8)	96 (11.4)
Not Hispanic or Latino	268 (84.0)	254 (82.2)	733 (87.2)
Missing ^c	7 (2.2)	3 (1.0)	12 (1.4)
Region, n (%)			
US, Canada, Europe	118 (37.0)	113 (36.6)	367 (43.6)
Rest of World	201 (63.0)	196 (63.4)	474 (56.4)
Height (cm), n			
Mean (SD)	158.8 (7.02)	159.6 (7.40)	159.8 (7.27)
Median (min, max)	158.7 (137, 180)	160.0 (138, 178)	160.0 (130, 185)
Baseline Weight (kg), n			
Mean (SD)	64.1 (15.42)	66.4 (14.92)	64.8 (15.30)
Median (min, max)	60.0 (36, 150)	64.0 (39, 141)	61.0 (36, 150)
BMI (kg/m²), n			
Mean (SD)	25.4 (5.73)	26.1 (5.33)	25.3 (5.44)
Median (min, max)	24.3 (16, 66)	25.0 (16, 46)	24.3 (15, 66)
ECOG PS, n (%)			
(0) Normal activity	185 (58.0)	173 (56.0)	455 (54.1)
(1) Restricted activity	134 (42.0)	136 (44.0)	382 (45.4)
(2) In bed less than or equal to 50% of the time	0	0	4 (0.5)

Baseline Brain Metastasis, n (%)			
Yes	36 (11.3)	26 (8.4)	83 (9.9)
No	283 (88.7)	283 (91.6)	758 (90.1)
Renal function status at baseline, n (%) ^d			
Normal	174 (54.5)	166 (53.7)	464 (55.2)
Mild	120 (37.6)	119 (38.5)	303 (36.0)
Moderate	24 (7.5)	24 (7.8)	73 (8.7)
Severe	1 (0.3)	0	1 (0.1)
Hepatic function at baseline, n (%) ^e			
Normal	246 (77.1)	234 (75.7)	533 (63.4)
Mild	73 (22.9)	73 (23.6)	300 (35.7)
Moderate	0	1 (0.3)	7 (0.8)
Severe	0	0	1 (0.1)
Missing	0	1 (0.3)	0

^a See Table 2 for an overview of studies included in the pooled analyses.

^b Age informed in years is calculated using the main study consent date and the birth date.

^c Missing row includes both Missing and Not Reported/Unknown.

^d Renal function: Normal = creatinine clearance (CrCl) $\geq$ 90 mL/min; mild = CrCl $\geq$ 60 and $<$ 90 mL/min; moderate = CrCl $\geq$ 30 and $<$ 60 mL/min. severe = CrCl $<$ 30 mL/min

^e Hepatic function: Normal = (TBL $\leq$ ULN and AST $\leq$ ULN); Mild = (TBL $\leq$ ULN and AST $>$ ULN) or (TBL $>$ ULN and $\leq$ 1.5 $\times$ ULN and any AST); Moderate = TBL $>$ 1.5 $\times$ ULN and $\leq$ 3.0 $\times$ ULN and any AST; Severe = TBL $>$ 3.0 $\times$ ULN and any AST.

Adverse events

AEs presented in the safety evaluation are treatment emergent. The following AEs were considered treatment emergent:

- AEs with an onset date on or after the first dose of study intervention and within 28 (+ 7) days after the last dose of study intervention or up to the day prior to the start of subsequent therapy, whichever occurred first.
- Worsening of pre-existing events on or after the first dose of study intervention and within 28 (+ 7) days after the last dose of study intervention or up to the day prior to the start of subsequent therapy, whichever occurred first.

Per protocol, all ILD/pneumonitis events regardless of severity were to be reported beyond the 28 (+ 7)-day safety follow-up period.

Table 47 Overall Summary of Treatment-emergent Adverse Events in the Pivotal Study and Pooled Studies (Safety Analysis Set)

AE Category	Number (%) of Participants		
	Pivotal Study TB02		Pooled Studies ^a
	Dato-DXd 6 mg/kg N = 319	ICC N = 309	BC Dato-DXd 6 mg/kg N = 841
Any TEAE	315 (98.7)	293 (94.8)	828 (98.5)
Any TEAE of CTCAE Grade ≥ 3	138 (43.3)	116 (37.5)	333 (39.6)
Any treatment-related TEAE	296 (92.8)	257 (83.2)	794 (94.4)
Any treatment-related TEAE of CTCAE Grade ≥ 3	105 (32.9)	89 (28.8)	230 (27.3)
Any serious TEAE	54 (16.9)	48 (15.5)	142 (16.9)
Any serious TEAE CTCAE of Grade ≥ 3	43 (13.5)	43 (13.9)	114 (13.6)
Any treatment-related serious TEAE	29 (9.1)	26 (8.4)	61 (7.3)
Any treatment-related serious TEAE Grade ≥ 3	25 (7.8)	24 (7.8)	49 (5.8)
Any TEAE associated with death	1 (0.3)	5 (1.6)	3 (0.4)
Any treatment-related TEAE associated with death	0	0	0
Any TEAE associated with dose reduction	90 (28.2)	57 (18.4)	210 (25.0)
Any treatment-related TEAE associated with dose reduction	85 (26.6)	56 (18.1)	194 (23.1)
Any serious TEAE associated with dose reduction	12 (3.8)	5 (1.6)	19 (2.3)
Any treatment-related serious TEAE associated with dose reduction	9 (2.8)	5 (1.6)	14 (1.7)
Any TEAE associated with drug interruption	113 (35.4)	98 (31.7)	261 (31.0)
Any treatment-related TEAE associated with drug interruption	76 (23.8)	60 (19.4)	165 (19.6)
Any serious TEAE associated with drug interruption	15 (4.7)	16 (5.2)	39 (4.6)
Any treatment-related serious TEAE associated with drug interruption	6 (1.9)	4 (1.3)	14 (1.7)
Any TEAE associated with drug withdrawn	15 (4.7)	24 (7.8)	38 (4.5)
Any treatment-related TEAE associated with drug withdrawn	14 (4.4)	23 (7.4)	33 (3.9)
Any serious TEAE associated with drug withdrawn	4 (1.3)	6 (1.9)	11 (1.3)
Any treatment-related serious TEAE associated with drug withdrawn	3 (0.9)	5 (1.6)	7 (0.8)

^a See Table 2 for an overview of studies included in the pooled analyses.

A TEAE is defined as an AE with a start or worsening date on or after the start of study treatment until 35 days since the last dose of study treatment (TP01), or earliest date between 35 days since the last dose of treatment and the start date of the first subsequent therapy (TB02, TB01, and TP02). Radiotherapy is not considered as a subsequent anti-cancer therapy in TB02, TB01, and TP02.

At each level of summarisation, a participant is counted once if the participant reported one or more AEs.

Table 48 Most Common Treatment-Emergent Adverse Events (Frequency of $\geq 5\%$ in Any Treatment Arm) by Decreasing Frequency and Preferred Term in the Pivotal Study and Pooled Studies (Safety Analysis Set)

Preferred Term	Number (%) of Participants		
	Pivotal Study TB02		Pooled Studies *
	Dato-DXd 6 mg/kg N = 319	ICC N = 309	BC Dato-DXd 6 mg/kg N = 841
Participants with any TEAE	315 (98.7)	293 (94.8)	828 (98.5)
Stomatitis	186 (58.3)	30 (9.7)	478 (56.8)
Nausea	154 (48.3)	69(22.3)	443 (52.7)
Alopecia	137 (42.9)	107 (34.6)	310 (36.9)
Constipation	127 (39.8)	52 (16.8)	292 (34.7)
Vomiting	72 (22.6)	34 (11.0)	210 (25.0)
Fatigue	56 (17.6)	48 (15.5)	203 (24.1)
Dry eye	84 (26.3)	15 (4.9)	201 (23.9)
Anaemia	66 (20.7)	88 (28.5)	162 (19.3)
Decreased appetite	61 (19.1)	26 (8.4)	148 (17.6)
Aspartate aminotransferase increased	40 (12.5)	34 (11.0)	132 (15.7)
Cough	59 (18.5)	39 (12.6)	128 (15.2)
Asthenia	49 (15.4)	40 (12.9)	114 (13.6)
COVID-19	27 (8.5)	19 (6.1)	104 (12.4)
Alanine aminotransferase increased	33 (10.3)	35 (11.3)	100 (11.9)
Rash	41 (12.9)	30 (9.7)	98 (11.7)

Neutrophil count decreased	28 (8.8)	58 (18.8)	90 (10.7)
Diarrhoea	27 (8.5)	59 (19.1)	86 (10.2)
Keratitis	44 (13.8)	3 (1.0)	86 (10.2)
Headache	25 (7.8)	25 (8.1)	79 (9.4)
White blood cell count decreased	24 (7.5)	45 (14.6)	77 (9.2)
Weight decreased	29 (9.1)	8 (2.6)	75 (8.9)
Pyrexia	20 (6.3)	9 (2.9)	65 (7.7)
Pruritus	19 (6.0)	14 (4.5)	64 (7.6)
Hypokalaemia	20 (6.3)	11 (3.6)	61 (7.3)
Oropharyngeal pain	20 (6.3)	4 (1.3)	60 (7.1)
Lacrimation increased	21 (6.6)	1 (0.3)	57 (6.8)
Punctate keratitis	13 (4.1)	2 (0.6)	56 (6.7)
Upper respiratory tract infection	25 (7.8)	14 (4.5)	56 (6.7)
Amylase increased	50 (15.7)	6 (1.9)	55 (6.5)
Abdominal pain	22 (6.9)	14 (4.5)	53 (6.3)
Urinary tract infection	17 (5.3)	16 (5.2)	53 (6.3)
Dry mouth	20 (6.3)	7 (2.3)	52 (6.2)
Blood alkaline phosphatase increased	13 (4.1)	12 (3.9)	50 (5.9)
Skin hyperpigmentation	26 (8.2)	1 (0.3)	50 (5.9)
Conjunctivitis	25 (7.8)	2 (0.6)	49 (5.8)
Hypoalbuminaemia	14 (4.4)	15 (4.9)	48 (5.7)
Dry skin	17 (5.3)	4 (1.3)	47 (5.6)
Pneumonia	24 (7.5)	16 (5.2)	46 (5.5)
Arthralgia	15 (4.7)	13 (4.2)	44 (5.2)
Dizziness	16 (5.0)	15 (4.9)	44 (5.2)
Dysgeusia	18 (5.6)	13 (4.2)	44 (5.2)
Hyponatraemia	14 (4.4)	9 (2.9)	43 (5.1)
Dyspepsia	20 (6.3)	11 (3.6)	42 (5.0)
Back pain	20 (6.3)	18 (5.8)	41 (4.9)

Insomnia	18 (5.6)	24 (7.8)	39 (4.6)
Neutropenia	16 (5.0)	42 (13.6)	39 (4.6)
Pain in extremity	14 (4.4)	16 (5.2)	38 (4.5)
Leukopenia	12 (3.8)	17 (5.5)	36 (4.3)
Malaise	18 (5.6)	14 (4.5)	35 (4.2)
Oedema peripheral	12 (3.8)	25 (8.1)	35 (4.2)
Abdominal pain upper	11 (3.4)	16 (5.2)	32 (3.8)
Nasopharyngitis	17 (5.3)	9 (2.9)	32 (3.8)
Weight increased	18 (5.6)	8 (2.6)	31 (3.7)
Myalgia	7 (2.2)	24 (7.8)	20 (2.4)
Neuropathy peripheral	8 (2.5)	46 (14.9)	19 (2.3)
Peripheral sensory neuropathy	7 (2.2)	31 (10.0)	17 (2.0)

^a See Table 2 for an overview of studies included in the pooled analyses.

At each level of summarisation, a participant is counted once if the participant reported one or more AEs.

Percentages are based on the number of participants in the Safety Analysis Set. TEAEs were coded using MedDRA version 28.0 and graded using NCI CTCAE version 5.0 for TB02, TB01, and TP02, and NCI CTCAE version 4.03 before protocol amendment version 5.0 and NCI CTCAE version 5.0 afterwards for TP01.

A TEAE is defined as an AE with a start or worsening date on or after the start of study treatment until 35 days since the last dose of study treatment (TP01), or earliest date between 35 days since the last dose of treatment and the start date of the first subsequent therapy (TB02, TB01, and TP02). Radiotherapy is not considered as a subsequent anti-cancer therapy.

Table is sorted by decreasing frequency of PT within SOC based on BC Dato-DXd 6 mg/kg column.

Table 49 Participants with TEAEs by Maximum CTCAE Grade in the Pivotal Study and Pooled Studies (Safety Analysis Set)

Maximum reported CTCAE Grade	Number (%) of Participants		
	Pivotal Study TB02		Pooled Studies ^a
	Dato-DXd 6 mg/kg N = 319	ICC N = 309	BC Dato-DXd 6 mg/kg N = 841
Total	315 (98.7)	293 (94.8)	828 (98.5)
Grade 1	25 (7.8)	43 (13.9)	94 (11.2)
Grade 2	152 (47.6)	134 (43.4)	401 (47.7)
Grade 3	126 (39.5)	93 (30.1)	304 (36.1)
Grade 4	11 (3.4)	18 (5.8)	26 (3.1)
Grade 5	1 (0.3)	5 (1.6)	3 (0.4)
Grade ≥ 3	138 (43.3)	116 (37.5)	333 (39.6)

^a See Table 2 for an overview of studies included in the pooled analyses.

A TEAE is defined as an AE with a start or worsening date on or after the start of study treatment until 35 days since the last dose of study treatment (TP01), or earliest date between 35 days since the last dose of treatment and the start date of the first subsequent therapy (TB02, TB01, and TP02). Radiotherapy is not considered as a subsequent anti-cancer therapy in TB02, TB01, and TP02.

Table 50 Treatment-emergent Adverse Events Leading to a Dose Reduction by Preferred Term Reported in $\geq 1\%$ of Participants in Any Treatment Arm in the Pivotal Study and Pooled Studies (Safety Analysis Set)

Preferred Term	Number (%) of Participants		
	Pivotal Study TB02		Pooled Studies ^a
	Dato-DXd 6 mg/kg N = 319	ICC N = 309	BC Dato-DXd 6 mg/kg N = 841
Participants with any TEAE leading to dose reduction	90 (28.2)	57 (18.4)	210 (25.0)
Stomatitis	36 (11.3)	2 (0.6)	90 (10.7)
Asthenia	6 (1.9)	1 (0.3)	13 (1.5)
Fatigue	4 (1.3)	4 (1.3)	13 (1.5)
Keratitis	8 (2.5)	0	12 (1.4)
Nausea	3 (0.9)	1 (0.3)	12 (1.4)
Amylase increased	9 (2.8)	0	10 (1.2)
Weight decreased	1 (0.3)	0	9 (1.1)
Pneumonia	4 (1.3)	0	4 (0.5)
Neutropenia	1 (0.3)	7 (2.3)	2 (0.2)
Peripheral sensory neuropathy	0	5 (1.6)	1 (0.1)
Neuropathy peripheral	0	13 (4.2)	0
Neutrophil count decreased	0	6 (1.9)	0

^a See Table 2 for an overview of studies included in the pooled analyses.

At each level of summarisation, a participant is counted once if the participant reported one or more AEs.

Percentages are based on the number of participants in the Safety Analysis Set. TEAEs were coded using MedDRA version 28.0 and graded using NCI CTCAE version 5.0 for TB02, TB01, and TP02, and NCI CTCAE version 4.03 before protocol amendment version 5.0 and NCI CTCAE version 5.0 afterwards for TP01.

A TEAE is defined as an AE with a start or worsening date on or after the start of study treatment until 35 days since the last dose of study treatment (TP01), or earliest date between 35 days since the last dose of treatment and the start date of the first subsequent therapy (TB02, TB01, and TP02). Radiotherapy is not considered as a subsequent anti-cancer therapy.

Table is sorted by decreasing frequency of PT within SOC based on BC Dato-DXd 6 mg/kg column.

Table 51 Summary of AEs Leading to Dose Modification of IP Reported in $\geq 1\%$ of Participants in either Treatment Arm by PT (SAF)

PT	Number (%) of participants	
	Dato-DXd N = 319	ICC N = 309
Any AE leading to dose modification of IP	153 (48.0)	127 (41.1)
Stomatitis	46 (14.4)	2 (0.6)
Amylase increased	22 (6.9)	0
Keratitis	12 (3.8)	0
COVID-19	9 (2.8)	11 (3.6)
Pneumonia	8 (2.5)	5 (1.6)
Asthenia	7 (2.2)	6 (1.9)
Nasopharyngitis	7 (2.2)	2 (0.6)
Neutrophil count decreased	6 (1.9)	19 (6.1)
Anaemia	6 (1.9)	5 (1.6)
Dry eye	6 (1.9)	1 (0.3)
Neutropenia	5 (1.6)	17 (5.5)
Upper respiratory tract infection	5 (1.6)	2 (0.6)
Pneumonitis	5 (1.6)	0
Fatigue	4 (1.3)	9 (2.9)
Infusion related reaction	4 (1.3)	2 (0.6)
Influenza	4 (1.3)	2 (0.6)
Nausea	4 (1.3)	1 (0.3)
Vomiting	4 (1.3)	0
Pyrexia	3 (0.9)	4 (1.3)
White blood cell count decreased	2 (0.6)	5 (1.6)
Hypoaesthesia	1 (0.3)	3 (1.0)
Paraesthesia	1 (0.3)	3 (1.0)
Neuropathy peripheral	0	15 (4.9)
Peripheral sensory neuropathy	0	6 (1.9)
Oedema peripheral	0	4 (1.3)
Palmar-plantar erythrodysesthesia syndrome	0	4 (1.3)
Febrile neutropenia	0	3 (1.0)
Myalgia	0	3 (1.0)
Platelet count decreased	0	3 (1.0)

Dose modification describes an AE where action taken is either dose reduced, or drug interrupted.

Includes AEs with an onset date or that worsen on or after the date of first dose of IP up to within 28 (+ 7) days after last dose of IP or up to the day prior to start of a subsequent anticancer therapy, whichever comes first.

Participants with multiple occurrences are counted once per SOC and PT regardless of the number of occurrences.

Table is sorted by decreasing frequency in the Dato-DXd arm, then decreasing frequency in the ICC arm, then alphabetically when the frequencies are the same.

Table 52 Summary of AEs Leading to Interruption of IP Reported in $\geq 1\%$ of Participants in Either Treatment Arm by PT (SAF)

PT	Number (%) of participants	
	Dato-DXd N = 319	ICC N = 309
Any AE leading to interruption of IP ^a	113 (35.4)	98 (31.7)
Amylase increased	13 (4.1)	0
Stomatitis	13 (4.1)	0
COVID-19	7 (2.2)	11 (3.6)
Nasopharyngitis	7 (2.2)	2 (0.6)
Neutrophil count decreased	6 (1.9)	16 (5.2)
Dry eye	6 (1.9)	1 (0.3)
Upper respiratory tract infection	5 (1.6)	2 (0.6)
Neutropenia	4 (1.3)	11 (3.6)
Pneumonia	4 (1.3)	5 (1.6)
Anaemia	4 (1.3)	4 (1.3)
Influenza	4 (1.3)	2 (0.6)
Infusion related reaction	4 (1.3)	2 (0.6)
Keratitis	4 (1.3)	0
Pyrexia	3 (0.9)	4 (1.3)
Urinary tract infection	2 (0.6)	3 (1.0)
White blood cell count decreased	2 (0.6)	3 (1.0)
Asthenia	1 (0.3)	5 (1.6)
Fatigue	0	5 (1.6)

^a For capecitabine, drug interruptions exclude any single (non-consecutive) missed doses.

Includes AEs with an onset date or that worsen on or after the date of first dose of IP up to within 28 (+ 7) days after last dose of IP or up to the day prior to start of a subsequent anticancer therapy, whichever comes first.

Participants with multiple occurrences are counted once per SOC and PT regardless of the number of occurrences.

Table is sorted by decreasing frequency in the Dato-DXd arm, then decreasing frequency in the ICC arm, then alphabetically when the frequencies are the same.

Table 53 Summary of AEs Leading to a Dose Reduction Reported in $\geq 1\%$ of Participants in Either Treatment Arm by PT (SAF)

PT	Number (%) of participants	
	Dato-DXd N = 319	ICC N = 309
Any AE leading to IP reduction	90 (28.2)	57 (18.4)
Stomatitis	36 (11.3)	2 (0.6)
Amylase increased	9 (2.8)	0
Keratitis	8 (2.5)	0
Asthenia	6 (1.9)	1 (0.3)
Fatigue	4 (1.3)	4 (1.3)
Pneumonia	4 (1.3)	0
Neutropenia	1 (0.3)	7 (2.3)
Neuropathy peripheral	0	13 (4.2)
Neutrophil count decreased	0	6 (1.9)
Peripheral sensory neuropathy	0	5 (1.6)

Includes AEs with an onset date or that worsen on or after the date of first dose of IP up to within 28 (+ 7) days after last dose of IP or up to the day prior to start of a subsequent anticancer therapy, whichever comes first.

Participants with multiple occurrences are counted once per SOC and PT regardless of the number of occurrences.

Table is sorted by decreasing frequency in the Dato-DXd arm, then decreasing frequency in the ICC arm, then alphabetically when the frequencies are the same.

Adverse Drug Reactions (ADR) in the SmPC

Following the FA of Study TB02, new ADRs for Dato-DXd were identified, including neutropenia (PTs: neutropenia, neutrophil count decreased), leukopenia (leukopenia, white blood cell count decreased), keratopathy (PTs: corneal epithelium defect, corneal lesion, injury corneal, keratopathy), increased amylase (amylase increased, hyperamylasaemia), and rhinorrhoea that have been added in the table of adverse reaction in SmPC section 4.8.

A summary of the frequency and severity of ADRs for Dato DXd based on the BC 6 mg/kg pool is provided below. ILD and keratitis are the 2 important identified risks for Dato DXd; ILD occurred in 2.82% participants in TB02 Dato-DXd arm and 2.97% participants in the BC 6 mg/kg pool, and keratitis occurred in 17.87% participants in the TB02 Dato-DXd arm and 16.65% participants in the BC 6 mg/kg pool.

Table 54 Adverse Drug Reactions in Pooled Data of TB02, TB01, TP02, TP01 (BC 6 mg/kg Pool), by Grouped/MedDRA SOC, Grouped Term/Preferred Term and Frequency (SAS)

MedDRA System Organ Class Preferred Term or Grouped Term	Number (%) of participants			
	Dato-DXd (N = 841)			
	CTCAE Grade			
	Frequency ^b	All Grades	Grade 3 or 4	Serious ADR
Participants with any adverse drug reaction	NA	809 (96.20)	253 (30.08)	76 (9.04)
Blood and lymphatic system disorders				
Anaemia	Very Common	162 (19.26)	25 (2.97)	6 (0.71)
Neutropenia ^a	Very Common	125 (14.86)	15 (1.78)	1 (0.12)
Leukopenia ^a	Very Common	105 (12.49)	6 (0.71)	0
Eye disorders				
Dry eye	Very Common	201 (23.90)	7 (0.83)	0
Keratitis ^a	Very Common	140 (16.65)	15 (1.78)	3 (0.36)
Conjunctivitis ^a	Common	71 (8.44)	2 (0.24)	0
Lacrimation increased	Common	57 (6.78)	0	0
Keratopathy ^a	Common	42 (4.99)	7 (0.83)	0
Blepharitis	Common	41 (4.88)	0	0
Meibomian gland dysfunction	Common	38 (4.52)	1 (0.12)	0
Vision blurred	Common	33 (3.92)	1 (0.12)	0
Photophobia	Common	10 (1.19)	0	0
Visual impairment ^a	Common	10 (1.19)	1 (0.12)	0
Gastrointestinal disorders				
Stomatitis ^a	Very Common	541 (64.33)	68 (8.09)	5 (0.59)
Nausea	Very Common	443 (52.68)	9 (1.07)	2 (0.24)
Constipation	Very Common	292 (34.72)	2 (0.24)	0
Vomiting	Very Common	210 (24.97)	14 (1.66)	9 (1.07)
Diarrhoea	Very Common	86 (10.23)	3 (0.36)	2 (0.24)
Dry mouth	Common	52 (6.18)	1 (0.12)	0
General disorders				
Fatigue ^a	Very Common	340 (40.43)	32 (3.80)	1 (0.12)
Immune system disorders				
Anaphylactic reaction	Uncommon	2 (0.24)	2 (0.24)	1 (0.12)
Infections and infestations				
COVID-19 ^a	Very Common	110 (13.08)	8 (0.95)	13 (1.55)
Pneumonia ^a	Common	53 (6.30)	16 (1.90)	16 (1.90)
Urinary tract infection	Common	53 (6.30)	9 (1.07)	7 (0.83)

MedDRA System Organ Class Preferred Term or Grouped Term	Number (%) of participants			
	Dato-DXd (N = 841)			
	CTCAE Grade			
	Frequency ^b	All Grades	Grade 3 or 4	Serious ADR
Sepsis	Uncommon	6 (0.71)	5 (0.59)	6 (0.71)
Injury, poisoning and procedural complications				
Infusion-related reaction ^a	Common	82 (9.75)	3 (0.36)	0
Investigations				
Aspartate aminotransferase increased	Very Common	132 (15.70)	16 (1.90)	0
Alanine aminotransferase increased	Very Common	100 (11.89)	11 (1.31)	1 (0.12)
Amylase increased ^a	Common	57 (6.78)	33 (3.92)	1 (0.12)
Metabolism and nutrition disorders				
Decreased appetite	Very Common	148 (17.60)	7 (0.83)	0
Nervous system disorders				
Dysgeusia	Common	44 (5.23)	0	0
Respiratory, thoracic and mediastinal disorders				
Potential interstitial lung disease ^{a,c}	Common	37 (4.40)	6 (0.71)	9 (1.07)
Dyspnoea	Common	36 (4.28)	2 (0.24)	3 (0.36)
Interstitial lung disease ^d	Common	25 (2.97)	3 (0.36)	7 (0.83)
Rhinorrhoea	Common	18 (2.14)	0	0
Skin and subcutaneous tissue disorders				
Alopecia	Very Common	310 (36.86)	0	0
Rash ^a	Very Common	128 (15.22)	2 (0.24)	0
Skin hyperpigmentation ^a	Common	66 (7.85)	0	0
Dry skin	Common	50 (5.95)	0	0
Pruritus	Common	49 (5.83)	1 (0.12)	0
Madarosis	Common	9 (1.07)	0	0

^a The PTs included in each of the grouped terms in this table are defined in Listing 2.7.4.8.1_bc_smpc.

^b Frequency: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$).

^c Investigator reported.

^d Adjudicated drug-related.

Percentages were calculated by using the number of participants in the Safety Analysis Set as the denominator. SOC's were sorted by alphabetic order. PT's/grouped terms were sorted by descending frequency in the "All Grades" column.

If a participant had multiple occurrences of the same ADR, the participant was counted once for that specific ADR. Sepsis was included regardless of investigator assessed seriousness.

MedDRA version 28.0.

CTCAE version 5.0.

Serious adverse event/deaths/other significant events

Table 55 SAEs Reported in $\geq 1\%$ of Participants in Either Treatment Group, by PT (SAF)

PT	Number (%) of participants	
	Dato-DXd N = 319	ICC N = 309
Any SAE	54 (16.9)	48 (15.5)
Pneumonia	7 (2.2)	6 (1.9)
Vomiting	6 (1.9)	2 (0.6)
Anaemia	4 (1.3)	3 (1.0)
COVID-19	4 (1.3)	0

Includes AEs with an onset date or that worsen on or after the date of first dose of IP up to within 28 (+7) days after last dose of IP or up to the day prior to start of a subsequent anticancer therapy, whichever comes first.

Participants with multiple occurrences are counted once per SOC and PT regardless of the number of occurrences.

Table is sorted by decreasing number of AEs for Dato-DXd then ICC.

Table 56 Treatment-emergent Adverse Events of CTCAE Grade ≥ 3 by Decreasing Frequency and Preferred Term Reported in $\geq 1\%$ of Participants in Any Treatment Arm in the Pivotal Study and Pooled Studies (Safety Analysis Set)

Preferred Term	Number (%) of Participants		
	Pivotal Study TB02		Pooled Studies ^a
	Dato-DXd 6 mg/kg N = 319	ICC N = 309	BC Dato-DXd 6 mg/kg N = 841
Participants with any TEAE Grade ≥ 3	138 (43.3)	116 (37.5)	333 (39.6)
Stomatitis	27 (8.5)	0	64 (7.6)
Amylase increased	31 (9.7)	0	32 (3.8)
Anaemia	9 (2.8)	16 (5.2)	25 (3.0)
Lymphocyte count decreased	4 (1.3)	2 (0.6)	18 (2.1)
Aspartate aminotransferase increased	2 (0.6)	2 (0.6)	16 (1.9)
Fatigue	3 (0.9)	3 (1.0)	16 (1.9)
Pneumonia	8 (2.5)	6 (1.9)	16 (1.9)
Vomiting	5 (1.6)	2 (0.6)	14 (1.7)
Asthenia	4 (1.3)	6 (1.9)	12 (1.4)
Alanine aminotransferase increased	2 (0.6)	2 (0.6)	11 (1.3)
Hypokalaemia	4 (1.3)	3 (1.0)	11 (1.3)
Keratitis	7 (2.2)	0	10 (1.2)
Nausea	2 (0.6)	2 (0.6)	9 (1.1)
Neutrophil count decreased	5 (1.6)	25 (8.1)	9 (1.1)
Urinary tract infection	2 (0.6)	4 (1.3)	9 (1.1)
Dry eye	4 (1.3)	0	7 (0.8)
Hypertension	1 (0.3)	5 (1.6)	6 (0.7)
Neutropenia	5 (1.6)	18 (5.8)	6 (0.7)
White blood cell count decreased	2 (0.6)	12 (3.9)	5 (0.6)
Diarrhoea	1 (0.3)	4 (1.3)	3 (0.4)
Thrombocytopenia	1 (0.3)	4 (1.3)	1 (0.1)
Febrile neutropenia	0	4 (1.3)	0

^a See Table 2 for an overview of studies included in the pooled analyses.

At each level of summarisation, a participant is counted once if the participant reported one or more AEs.

Percentages are based on the number of participants in the Safety Analysis Set. TEAEs were coded using MedDRA Version 28.0 and graded using NCI CTCAE version 5.0 for TB02, TB01, and TP02, and NCI CTCAE version 4.03 before protocol amendment version 5.0 and NCI CTCAE version 5.0 afterwards for TP01.

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 (TP01), or earliest date between 35 days since the last dose of treatment and the start date of the first subsequent therapy (TB02, TB01, and TP02). Radiotherapy is not considered as a subsequent anti-cancer therapy.

Table is sorted by decreasing frequency of PT within SOC based on BC Dato-DXd 6 mg/kg column.

AEs of special interest

ILD/Pneumonitis

Table 57 Overview of AESI ILD/Pneumonitis by Category (SAF)

AESI Category	Number (%) Of Participants	
	Dato-DXd N = 319	ICC N = 309
AESI-defined ILD/pneumonitis	16 (5.0)	4 (1.3)
Adjudicated ILD (all-causality) ^a	12 (3.8)	4 (1.3)
Adjudicated ILD (all-causality) ^a by CTCAE Grade ^b	12 (3.8)	4 (1.3)
Grade 1	1 (0.3)	2 (0.6)
Grade 2	8 (2.5)	2 (0.6)
Grade 3	2 (0.6)	0
Grade 4	0	0
Grade 5	1 (0.3)	0
Grade ≥ 3	3 (0.9)	0
Time to onset of first adjudicated ILD (all-causality) ^a (days) ^c		
n	12	4
Mean (StDev)	344.3 (199.67)	136.8 (169.91)
Median	264.5	61.5
Min, Max	142, 803	35, 389
Duration of adjudicated ILD (all-causality) ^a (days) ^d		
n	5	1
Mean (StDev)	85.0 (70.26)	71.0 (NC)
Median	66.0	71.0
Min, Max	13, 159	71, 71
Adjudicated ILD (all-causality) ^a outcome ^e	12 (100)	4 (100)
Recovered/resolved	5 (41.7)	1 (25.0)
Recovering/resolving	2 (16.7)	1 (25.0)
Recovered/resolved with sequelae	0	0
Not recovered/not resolved	5 (41.7)	2 (50.0)
Fatal	0	0
Adjudicated ILD (all-causality) ^a action taken ^f	12 (3.8)	4 (1.3)
Dose not changed	1 (0.3)	1 (0.3)
Drug interrupted	4 (1.3)	0

AESI Category	Number (%) Of Participants	
	Dato-DXd N = 319	ICC N = 309
Dose reduced	2 (0.6)	0
Drug permanently discontinued	4 (1.3)	1 (0.3)
NA	1 (0.3)	2 (0.6)
Adjudicated drug-related ILD ^a	9 (2.8)	2 (0.6)
Adjudicated drug-related ILD ^a by CTCAE Grade ^b		
Grade 1	1 (0.3)	1 (0.3)
Grade 2	7 (2.2)	1 (0.3)
Grade 3	0	0
Grade 4	0	0
Grade 5	1 (0.3)	0
Grade ≥ 3	1 (0.3)	0
Time to onset of first adjudicated drug-related ILD ^a (days) ^c		
n	9	2
Mean (StDev)	306.8 (144.93)	61.5 (36.06)
Median	259.0	61.5
Min, Max	161, 588	36, 87
Duration of adjudicated drug-related ILD ^a (days) ^d		
n	4	NA
Mean (StDev)	99.3 (72.31)	NA
Median	112.5	NA
Min, Max	13, 159	NA
Adjudicated drug-related ILD ^a outcome ^e		
Recovered/resolved	4 (44.4)	0
Recovering/resolving	2 (22.2)	1 (50.0)
Recovered/resolved with sequelae	0	0
Not recovered/not resolved	3 (33.3)	1 (50.0)
Fatal	0	0
Adjudicated drug-related ILD ^a action taken ^f		

AESI Category	Number (%) Of Participants	
	Dato-DXd N = 319	ICC N = 309
Dose not changed	0	0
Drug interrupted	3 (0.9)	0
Dose reduced	2 (0.6)	0
Drug permanently discontinued	3 (0.9)	1 (0.3)
NA	1 (0.3)	1 (0.3)

^a Based on adjudicated ILD/pneumonitis events from the ILD Adjudication Committee.

^b Each participant has only been represented with the maximum reported CTCAE (version 5.0) grade reported by Adjudication Committee for each AESI category. CTCAE grade is based on adjudicated ILD/pneumonitis events from the ILD Adjudication Committee. Participants who have a maximum CTC Grade 5 event post the DCO date have been reset to unknown at the DCO date. This affects 0 participants in the Dato-DXd treatment group and 0 participants in the ICC treatment group.

^c Time to onset of first AESI = (investigator reported onset or worsening date of first AESI - date of IP first dose) + 1. Each participant is represented for the first occurrence of an AESI.

^d Duration of AESI = (stop date of AE – onset or worsening date of AE) + 1, dates reported by investigator. For participants with multiple AESIs within a category, the duration in days is summed for all resolved.

^e Each participant has been represented once with the worst outcome for each AESI category. The percentage for each outcome level is based on the total number of participants in the AESI category.

^f Each participant has been represented once with the worst action for each AESI category. The order (worst to less worse) is discontinued > reduced > interrupted > not changed > NA.

If a participant has multiple (PT level) events within a specific AE of interest, then the maximum CTCAE grade across those events is counted. Participants with multiple occurrences are counted once per AESI category regardless of the number of occurrences.

Includes all AEs reported by Adjudication Committee with an onset date on or prior to DCO.

Infusion-related reactions

Table 58 Overview of AESI Infusion-related Reaction by Category (SAF)

AESI Category	Number (%) of participants	
	Dato-DXd N = 319	ICC N = 309
Any AESI of infusion related reaction	28 (8.8)	29 (9.4)
By CTCAE Grade ^a		
Grade 1	14 (4.4)	15 (4.9)
Grade 2	13 (4.1)	13 (4.2)
Grade 3	1 (0.3)	1 (0.3)
Grade 4	0	0
Grade 5	0	0
Grade ≥ 3	1 (0.3)	1 (0.3)
Possibly related to study treatment ^b	17 (5.3)	23 (7.4)
SAE	1 (0.3)	1 (0.3)
Outcome ^c		
Recovered/resolved	25 (89.3)	26 (89.7)
Recovering/resolving	0	1 (3.4)
Recovered/resolved with sequelae	0	0
Not recovered/not resolved	3 (10.7)	2 (6.9)
Fatal	0	0
Action taken ^d		
Dose not changed	23 (7.2)	23 (7.4)
Drug interrupted	4 (1.3)	4 (1.3)
Dose reduced	0	1 (0.3)
Drug permanently discontinued	1 (0.3)	1 (0.3)
NA	0	0

^a Each participant has only been represented with the maximum reported CTCAE (version 5.0) grade for each AESI category and PT. Participants who have a maximum CTCAE Grade 5 event post the DCO, have been reset to unknown at the DCO date. This affects 0 participants in Dato-DXd treatment group and 0 in ICC treatment group.

^b As assessed by the investigator.

^c Each participant has been represented once with the worst outcome for each AESI category. The percentage for each outcome level is based on the total number of participants in the AESI category.

^d Each participant has been represented once with the worst action for each AESI category and PT. The order (worst to less worse) is discontinued > reduced > interrupted > not changed > NA.

CTCAE Grade: 1 Mild AE; 2 Moderate AE; 3 Severe AE; 4 Life-threatening; 5 Fatal.

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

Includes AEs with an onset date or that worsen on or after the date of first dose of IP up to within 28 (+ 7) days after last dose of IP or up to the day prior to start of a subsequent anticancer therapy, whichever comes first.

Includes IRR events within the IRR AESI medical concept that occurred on the same day of infusion.

Oral mucositis/stomatitis

Table 59 Overview of Oral Mucositis/Stomatitis AESI by Category (SAF)

AESI Category	Number (%) of participants	
	Dato-DXd N = 319	ICC N = 309
Any AESI of oral mucositis/stomatitis	201 (63.0)	40 (12.9)
By CTCAE Grade ^a		
Grade 1	86 (27.0)	30 (9.7)
Grade 2	88 (27.6)	10 (3.2)
Grade 3	27 (8.5)	0
Grade 4	0	0
Grade 5	0	0
Grade ≥ 3	27 (8.5)	0
Possibly related to study treatment ^b	192 (60.2)	30 (9.7)
SAE	3 (0.9)	0
Outcome ^c		
Recovered/resolved	145 (72.1)	35 (87.5)
Recovering/resolving	9 (4.5)	0
Recovered/resolved with sequelae	1 (0.5)	0
Not recovered/not resolved	46 (22.9)	5 (12.5)
Fatal	0	0
Action taken ^d		
Dose not changed	153 (48.0)	36 (11.7)
Drug interrupted	12 (3.8)	0
Dose reduced	36 (11.3)	2 (0.6)
Drug permanently discontinued	0	0
NA	0	2 (0.6)

^a Each participant has only been represented with the maximum reported CTCAE (version 5.0) grade for each AESI category and PT. Participants who have a maximum CTCAE Grade 5 event post the DCO, have been reset to unknown at the DCO date. This affects 0 participants in Dato-DXd treatment group and 0 in ICC treatment group.

^b As assessed by the investigator.

^c Each participant has been represented once with the worst outcome for each AESI category. The percentage for each outcome level is based on the total number of participants in the AESI category.

^d Each participant has been represented once with the worst action for each AESI category and PT. The order (worst to less worse) is discontinued > reduced > interrupted > not changed > NA.

CTCAE Grade: 1 Mild AE; 2 Moderate AE; 3 Severe AE; 4 Life-threatening; 5 Fatal.

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

Includes AEs with an onset date or that worsen on or after the date of first dose of IP up to within 28 (+ 7) days after last dose of IP or up to the day prior to start of a subsequent anticancer therapy, whichever comes first.

Mucosal Inflammation Other than Oral Mucositis/Stomatitis

Table 60 Overview of Mucosal Inflammation Other than Oral Mucositis/Stomatitis AESI by Category (SAF)

AESI Category	Number (%) of participants	
	Dato-DXd N = 319	ICC N = 309
Any AESI of mucosal inflammation other than oral mucositis/stomatitis	9 (2.8)	5 (1.6)
By CTCAE Grade ^a		
Grade 1	3 (0.9)	4 (1.3)
Grade 2	6 (1.9)	1 (0.3)
Grade 3	0	0
Grade 4	0	0
Grade 5	0	0
Grade ≥ 3	0	0
Possibly related to study treatment ^b	7 (2.2)	2 (0.6)
SAE	0	0
Outcome ^c		
Recovered/resolved	7 (77.8)	5 (100)
Recovering/resolving	0	0
Recovered/resolved with sequelae	0	0
Not recovered/not resolved	2 (22.2)	0
Fatal	0	0
Action taken ^d		
Dose not changed	7 (2.2)	3 (1.0)
Drug interrupted	0	2 (0.6)
Dose reduced	0	0
Drug permanently discontinued	1 (0.3)	0
NA	1 (0.3)	0

^a Each participant has only been represented with the maximum reported CTCAE (version 5.0) grade for each AESI category and PT. Participants who have a maximum CTCAE Grade 5 event post the DCO, have been reset to unknown at the DCO date. This affects 0 participants in Dato-DXd treatment group and 0 in ICC treatment group.

^b As assessed by the investigator.

^c Each participant has been represented once with the worst outcome for each AESI category. The percentage for each outcome level is based on the total number of participants in the AESI category.

^d Each participant has been represented once with the worst action for each AESI category and PT. The order (worst to less worse) is discontinued > reduced > interrupted > not changed > NA.

CTCAE Grade: 1 Mild AE; 2 Moderate AE; 3 Severe AE; 4 Life-threatening; 5 Fatal.

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

Includes AEs with an onset date or that worsen on or after the date of first dose of IP up to within 28 (+ 7) days after last dose of IP or up to the day prior to start of a subsequent anticancer therapy, whichever comes first.

Ocular Surface Events

Table 61 Overview of AESI Ocular Surface Events by Category (SAF)

AESI Category	Number (%) of participants	
	Dato-DXd N = 319	ICC N = 309
Any AESI of ocular surface events	163 (51.1)	29 (9.4)
By CTCAE Grade ^a		
Grade 1	83 (26.0)	19 (6.1)
Grade 2	56 (17.6)	9 (2.9)
Grade 3	21 (6.6)	1 (0.3)
Grade 4	3 (0.9)	0
Grade 5	0	0
Grade ≥ 3	24 (7.5)	1 (0.3)
Possibly related to study treatment ^b	149 (46.7)	15 (4.9)
SAE	2 (0.6)	0
Outcome ^c		
Recovered/resolved	67 (41.1)	16 (55.2)
Recovering/resolving	16 (9.8)	0
Recovered/resolved with sequelae	0	0
Not recovered/not resolved	80 (49.1)	13 (44.8)
Fatal	0	0
Action taken ^d		
Dose not changed	123 (38.6)	25 (8.1)
Drug interrupted	20 (6.3)	1 (0.3)
Dose reduced	15 (4.7)	0
Drug permanently discontinued	3 (0.9)	0
NA	2 (0.6)	3 (1.0)

^a Each participant has only been represented with the maximum reported CTCAE (version 5.0) grade for each AESI category and PT. Participants who have a maximum CTCAE Grade 5 event post the DCO, have been reset to unknown at the DCO date. This affects 0 participants in Dato-DXd treatment group and 0 in ICC treatment group.

^b As assessed by the investigator.

^c Each participant has been represented once with the worst outcome for each AESI category. The percentage for each outcome level is based on the total number of participants in the AESI category.

^d Each participant has been represented once with the worst action for each AESI category and PT. The order (worst to less worse) is discontinued > reduced > interrupted > not changed > NA.

CTCAE Grade: 1 Mild AE; 2 Moderate AE; 3 Severe AE; 4 Life-threatening; 5 Fatal

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

Includes AEs with an onset date or that worsen on or after the date of first dose of IP up to within 28 (+ 7) days after last dose of IP or up to the day prior to start of a subsequent anticancer therapy, whichever comes first.

Table 62 Resolution and Time to Resolution of Worst Ocular Surface Event AESIs for Dato-DXd, by Maximum CTCAE Grade, Participant Level (SAF)

Maximum CTCAE Grade ^a	Dato-DXd N = 319				
	Nobs (%)	Resolved to Grade ≤ 1 n (%)	Time to resolution to Grade ≤ 1 Median (min, max)	Fully resolved n (%)	Fully resolved Median (min, max)
Grade 2	56 (17.6)	34 (60.7)	65.5 (8, 547)	25 (44.6)	86.0 (18, 547)
Grade 3	21 (6.6)	16 (76.2)	28.5 (12, 323)	10 (47.6)	66.5 (15, 294)
Grade 4	3 (0.9)	1 (33.3)	43.0 (43, 43)	1 (33.3)	106.0 (106, 106)

^a Each participant has been represented once with the longest time of resolution for the maximum grade for any ocular surface AESI.

Resolved to CTCAE Grade ≤ 1 includes the ocular surface AESIs improving to Grade 1 as the most recent CTCAE grade or fully resolved or resolved with sequelae.

Includes AEs with an onset date, or that worsen, on or after the date of first dose of IP up to within 28 (+7) days after last dose of IP or up to the day prior to start of a subsequent anticancer therapy, whichever comes first.

Percentages of the Nobs are based on the number of participants per treatment group, N.

Percentages n (%) are based on Nobs.

Time to resolution is not calculated for AEs with partial start and end dates.

Nobs = Number of participants with the maximum CTCAE grade

Deaths

Table 63 Summary of Deaths (FAS)

Category	Number (%) of participants	
	Dato-DXd N = 323	ICC N = 321
Total number of deaths	168 (52.0)	181 (56.4)
Primary cause of death		
Any	168 (52.0)	181 (56.4)
Related to disease under investigation ^a	142 (44.4)	149 (46.4)
AE	1 (0.3)	6 (1.9)
On treatment ^b	1 (0.3)	4 (1.2)
Post treatment ^c	0	2 (0.6)
Other ^d	25 (7.7)	26 (8.1)
Secondary cause of death		
Any	17 (5.3)	27 (8.4)
Related to disease under investigation ^a	13 (4.0)	22 (6.9)
AE	0	1 (0.3)
On treatment ^b	0	1 (0.3)
Post treatment ^c	0	0
Other ^d	4 (1.2)	4 (1.2)
Related to disease under investigation and AE ^e	0	2 (0.6)

^a Death related to disease under investigation is as assessed by investigator.

^b On treatment includes deaths with the date of death on or after the date of first dose of IP up to within 28 (+ 7) days after last dose of IP or up to the day prior to start of a subsequent anticancer therapy, whichever comes first.

^c Post treatment includes deaths with the date of death more than 28 (+ 7) days after the last dose of IP or once subsequent anticancer therapy started, whichever comes first.

^d Participants who died and are not captured in the earlier categories.

^e Considers primary and secondary cause of death.

The table includes all deaths throughout the study. Categories are mutually exclusive.

Table 64 AEs with Outcome of Death (SAF)

PT	Number (%) participants	
	Dato-DXd N = 319	ICC N = 309
Any AE with outcome of death	1 (0.3)	5 (1.6)
Death	1 (0.3)	1 (0.3)
Cardiac failure	0	1 (0.3)
Septic shock	0	2 (0.6)
Streptococcal sepsis	0	1 (0.3)

Includes AEs with an onset date or that worsen on or after the date of first dose of IP up to within 28 (+ 7) days after last dose of IP or up to the day prior to start of a subsequent anticancer therapy, whichever comes first.

Participants with multiple occurrences are counted once per SOC and PT regardless of the number of occurrences.

Laboratory findings

Haematology

Table 65 Haematology, CTCAE grade change from baseline to maximum on treatment (SAS)

Parameter (unit)	Group	Baseline CTCAE grade [a]	Subject at baseline [b]	Maximum overall CTCAE grade during treatment (%) [c]				
				0	1	2	3	4
Hemoglobin (g/L)-low	Dato-DXd (N=319)	0	226 (100)	123 (54.4)	88 (38.9)	12 (5.3)	3 (1.3)	0
		1	79 (100)	2 (2.5)	47 (59.5)	24 (30.4)	6 (7.6)	0
		2	11 (100)	0	1 (9.1)	7 (63.6)	3 (27.3)	0
		3	1 (100)	0	0	1 (100)	0	0
		4	0	0	0	0	0	0
		Total evaluable	317 (100)	125 (39.4)	136 (42.9)	44 (13.9)	12 (3.8)	0
	ICC (N=309)	0	221 (100)	73 (33.0)	109 (49.3)	32 (14.5)	7 (3.2)	0
		1	70 (100)	2 (2.9)	28 (40.0)	32 (45.7)	8 (11.4)	0
		2	11 (100)	0	1 (9.1)	8 (72.7)	2 (18.2)	0
		3	0	0	0	0	0	0
		4	0	0	0	0	0	0
		Total evaluable	302 (100)	75 (24.8)	138 (45.7)	72 (23.8)	17 (5.6)	0
Lymphocytes (10 ⁹ /L)-low	Dato-DXd (N=319)	0	195 (100)	128 (65.6)	34 (17.4)	27 (13.8)	5 (2.6)	1 (0.5)
		1	46 (100)	9 (19.6)	16 (34.8)	17 (37.0)	4 (8.7)	0
		2	22 (100)	2 (9.1)	3 (13.6)	10 (45.5)	7 (31.8)	0
		3	3 (100)	0	0	1 (33.3)	2 (66.7)	0
		4	0	0	0	0	0	0
		Total evaluable	266 (100)	139 (52.3)	53 (19.9)	55 (20.7)	18 (6.8)	1 (0.4)
	ICC (N=309)	0	190 (100)	101 (53.2)	46 (24.2)	33 (17.4)	9 (4.7)	1 (0.5)
		1	46 (100)	3 (6.5)	17 (37.0)	21 (45.7)	4 (8.7)	1 (2.2)
		2	19 (100)	1 (5.3)	3 (15.8)	12 (63.2)	3 (15.8)	0
		3	2 (100)	0	0	0	1 (50.0)	1 (50.0)
		4	0	0	0	0	0	0
		Total evaluable	257 (100)	105 (40.9)	66 (25.7)	66 (25.7)	17 (6.6)	3 (1.2)

Neutrophils (10 ⁹ /L)	Dato-DXd 0	276 (100)	182 (65.9)	47 (17.0)	40 (14.5)	7 (2.5)	0
	(N=319)						
	1	7 (100)	0	2 (28.6)	2 (28.6)	3 (42.9)	0
	2	1 (100)	0	0	1 (100)	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total evaluable	284 (100)	182 (64.1)	49 (17.3)	43 (15.1)	10 (3.5)	0
	ICC						
	(N=309)						
	0	256 (100)	136 (53.1)	33 (12.9)	55 (21.5)	21 (8.2)	11 (4.3)
	1	6 (100)	0	0	1 (16.7)	3 (50.0)	2 (33.3)
	2	1 (100)	0	0	1 (100)	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total evaluable	263 (100)	136 (51.7)	33 (12.5)	57 (21.7)	24 (9.1)	13 (4.9)

Parameters are presented in alphabetical order.

[a] Baseline is the last non-missing value prior to administration of the first dose of investigational product.

[b] Subjects with a baseline value and at least one on-treatment value (used to calculate percentages).

[c] Derived from Lab assessments between the start of IP up to within 28 (+7) days after last dose of IP or up to the day

prior to start of a subsequent anticancer therapy, whichever comes first, and is the maximum CTCAE grade.

CTCAE Common Terminology Criteria for Adverse Events (version 5.0). ICC Investigator's choice chemotherapy. N Number of subjects per treatment group.

Liver function

Table 61 **Participants with Elevated Liver Test Based on Measured Laboratory Values (SAF)**

Parameter	Number (%) of Participants	
	Dato-DXd N = 319	ICC N = 309
Number of participants with measurements	317 (100)	299 (100)
Number of participants with at least one elevated liver test	165 (52.1)	158 (52.8)
Number of participants with elevated ALT, AST, and total bilirubin	10 (3.2)	13 (4.3)
AST elevation		
$\geq 3 \times \text{ULN}$	20 (6.3)	20 (6.7)
$\geq 5 \times \text{ULN}$	7 (2.2)	6 (2.0)
$\geq 10 \times \text{ULN}$	4 (1.3)	1 (0.3)
$\geq 20 \times \text{ULN}$	0	0
ALT elevation		
$\geq 3 \times \text{ULN}$	17 (5.4)	24 (8.0)
$\geq 5 \times \text{ULN}$	7 (2.2)	8 (2.7)
$\geq 10 \times \text{ULN}$	2 (0.6)	2 (0.7)
$\geq 20 \times \text{ULN}$	0	1 (0.3)
AST or ALT elevation		
$\geq 3 \times \text{ULN}$	26 (8.2)	33 (11.0)
$\geq 5 \times \text{ULN}$	10 (3.2)	11 (3.7)
$\geq 10 \times \text{ULN}$	4 (1.3)	2 (0.7)
$\geq 20 \times \text{ULN}$	0	1 (0.3)
Total bilirubin elevation		
$\geq 1.5 \times \text{ULN}$	6 (1.9)	4 (1.3)
$\geq 2 \times \text{ULN}$	1 (0.3)	4 (1.3)
AST or ALT elevation, and Total Bilirubin (BILI) elevation (ALT $\geq 3 \times \text{ULN}$ or AST $\geq 3 \times \text{ULN}$) and (BILI $\geq 2 \times \text{ULN}$ concomitantly or subsequently) ^a	1 (0.3)	3 (1.0)
ALP elevation		
$\geq 1.5 \times \text{ULN}$	55 (17.4)	53 (17.7)
$\geq 3 \times \text{ULN}$	12 (3.8)	12 (4.0)

^a Includes all participants who have ALT or AST $\geq 3 \times \text{ULN}$ and total bilirubin $\geq 2 \times \text{ULN}$, and in which the ALT or AST elevation occurring less or equal to 28 days prior to the total bilirubin elevation.

Percent is calculated based on the number of participants with measurements.

Includes measurements taken between the start of IP up to within 28 (+7) days after last dose of IP or up to the day prior to start of a subsequent anticancer therapy, whichever comes first.

Clinical chemistry

Table 66 Clinical chemistry, CTCAE grade change from baseline to maximum on treatment (SAS)

Parameter (unit)	Group	Baseline CTCAE grade [a]	Subject at baseline [b]	Maximum overall CTCAE grade during treatment (%) [c]				
				0	1	2	3	4
Amylase (ukat/L)	Dato-DXd (N=319)	0	225 (100)	106 (47.1)	19 (8.4)	16 (7.1)	46 (20.4)	38 (16.9)
		1	7 (100)	0	0	2 (28.6)	4 (57.1)	1 (14.3)
		2	2 (100)	0	0	1 (50.0)	0	1 (50.0)
		3	1 (100)	0	1 (100)	0	0	0
		4	1 (100)	0	0	0	0	1 (100)
		Total evaluable	236 (100)	106 (44.9)	20 (8.5)	19 (8.1)	50 (21.2)	41 (17.4)
	ICC (N=309)	0	227 (100)	211 (93.0)	11 (4.8)	5 (2.2)	0	0
		1	6 (100)	1 (16.7)	3 (50.0)	2 (33.3)	0	0
		2	0	0	0	0	0	0
		3	0	0	0	0	0	0
		4	1 (100)	0	1 (100)	0	0	0
		Total evaluable	234 (100)	212 (90.6)	15 (6.4)	7 (3.0)	0	0

Parameters are presented in alphabetical order.

[a] Baseline is the last non-missing value prior to administration of the first dose of investigational product.

[b] Subjects with a baseline value and at least one on-treatment value (used to calculate percentages).

[c] Derived from Lab assessments between the start of IP up to within 28 (+7) days after last dose of IP or up to the day prior to start of a subsequent anticancer therapy, whichever comes first, and is the maximum CTCAE grade.

CTCAE Common Terminology Criteria for Adverse Events (version 5.0). ICC Investigator's choice chemotherapy. N Number of subjects per treatment group.

Safety in special populations

Age, ECOG PS, Renal impairment, Hepatic impairment, brain metastases

Table 67 Subgroup Analysis of Overall Summary of TEAEs by Age (SAS)

TEAE Category	Number (%) Of Participants			
	Age (< 65 years)		Age (≥ 65 years)	
	Dato-DXd N = 241	ICC N = 231	Dato-DXd N = 78	ICC N = 78
Any TEAE of CTCAE Grade ≥3	101 (41.9)	81 (35.1)	37 (47.4)	35 (44.9)
Any serious TEAE	38 (15.8)	33 (14.3)	16 (20.5)	15 (19.2)
Any TEAE associated with drug withdrawn	12 (5.0)	13 (5.6)	3 (3.8)	11 (14.1)
Any TEAE associated with drug interruption	81 (33.6)	67 (29.0)	32 (41.0)	31 (39.7)
Any TEAE associated with dose reduction	66 (27.4)	37 (16.0)	24 (30.8)	20 (25.6)
Any TEAE associated with death	1 (0.4)	2 (0.9)	0	3 (3.8)

At each level of summarisation, a participant is counted once if the participant reported one or more AEs.

Percentages are based on the number of participants in the Safety Analysis Set.

Drug Interrupted includes both Infusion Interruption and Dose Delay.

Table 68 Subgroup Analysis of Overall Summary of TEAEs by Renal Function (SAS)

TEAE Category	Number (%) of Participants ^a					
	Renal function status at baseline (normal)		Renal function status at baseline (mild)		Renal function status at baseline (moderate)	
	Dato-DXd N = 174	ICC N = 166	Dato-DXd N = 120	ICC N = 119	Dato-DXd N = 24	ICC N = 24
Any TEAE of CTCAE Grade ≥ 3	77 (44.3)	64 (38.6)	48 (40.0)	40 (33.6)	13 (54.2)	12 (50.0)
Any serious TEAE	30 (17.2)	30 (18.1)	18 (15.0)	12 (10.1)	6 (25.0)	6 (25.0)
Any TEAE associated with drug withdrawn	9 (5.2)	12 (7.2)	5 (4.2)	9 (7.6)	1 (4.2)	3 (12.5)
Any TEAE associated with drug interruption	62 (35.6)	53 (31.9)	39 (32.5)	34 (28.6)	12 (50.0)	11 (45.8)
Any TEAE associated with dose reduction	53 (30.5)	27 (16.3)	29 (24.2)	25 (21.0)	8 (33.3)	5 (20.8)
Any TEAE associated with death	0	1 (0.6)	1 (0.8)	2 (1.7)	0	2 (8.3)

^a There was only one participant with severe renal impairment at baseline; data are not summarized for this subgroup and no meaningful inference could be drawn.

At each level of summarisation, a participant is counted once if the participant reported one or more AEs.

Percentages are based on the number of participants in the Safety Analysis Set.

Drug Interrupted includes both Infusion Interruption and Dose Delay.

Table 69 Subgroup Analysis of Overall Summary of TEAEs by ECOG PS (SAS)

TEAE Category	Number (%) of Participants			
	ECOG PS 0		ECOG PS 1	
	Dato-DXd N = 185	ICC N = 173	Dato-DXd N = 134	ICC N = 136
Any TEAE of CTCAE Grade ≥ 3	78 (42.2)	57 (32.9)	60 (44.8)	59 (43.4)
Any serious TEAE	24 (13.0)	20 (11.6)	30 (22.4)	28 (20.6)
Any TEAE associated with drug withdrawn	11 (5.9)	12 (6.9)	4 (3.0)	12 (8.8)
Any TEAE associated with drug interruption	71 (38.4)	59 (34.1)	42 (31.3)	39 (28.7)
Any TEAE associated with dose reduction	56 (30.3)	31 (17.9)	34 (25.4)	26 (19.1)
Any TEAE associated with death	0	3 (1.7)	1 (0.7)	2 (1.5)

At each level of summarisation, a participant is counted once if the participant reported one or more AEs.

Percentages are based on the number of participants in the Safety Analysis Set.

Drug Interrupted includes both Infusion Interruption and Dose Delay.

Table 70 Subgroup Analysis of Overall Summary of TEAEs by Hepatic Function (SAS)

TEAE Category	Number (%) of Participants ^a			
	Hepatic function at baseline (normal)		Hepatic function at baseline (mild)	
	Dato-DXd N = 246	ICC N = 234	Dato-DXd N = 73	ICC N = 73
Any TEAE of CTCAE Grade ≥ 3	111 (45.1)	83 (35.5)	27 (37.0)	32 (43.8)
Any serious TEAE	38 (15.4)	34 (14.5)	16 (21.9)	13 (17.8)
Any TEAE associated with drug withdrawn	12 (4.9)	21 (9.0)	3 (4.1)	3 (4.1)
Any TEAE associated with drug interruption	93 (37.8)	76 (32.5)	20 (27.4)	20 (27.4)
Any TEAE associated with dose reduction	73 (29.7)	43 (18.4)	17 (23.3)	14 (19.2)
Any TEAE associated with death	0	2 (0.9)	1 (1.4)	2 (2.7)

^b There was only one participant with moderate hepatic impairment and no participants with severe hepatic impairment at baseline; data are not summarized for these subgroups, and no meaningful inference could be drawn.

At each level of summarisation, a participant is counted once if the participant reported one or more AEs.

Percentages are based on the number of participants in the Safety Analysis Set.

Drug Interrupted includes both Infusion Interruption and Dose Delay.

Table 71 Subgroup Analysis of Overall Summary of TEAEs by Baseline Brain Metastases (SAS)

TEAE Category	Number (%) of Participants			
	Baseline Brain metastases (Yes)		Baseline Brain metastases (No)	
	Dato-DXd N = 36	ICC N = 26	Dato-DXd N = 283	ICC N = 283
Any TEAE of CTCAE Grade ≥ 3	19 (52.8)	1 (3.8)	119 (42.0)	115 (40.6)
Any serious TEAE	8 (22.2)	0	46 (16.3)	48 (17.0)
Any TEAE associated with drug withdrawn	2 (5.6)	0	13 (4.6)	24 (8.5)
Any TEAE associated with drug interruption	8 (22.2)	2 (7.7)	105 (37.1)	96 (33.9)
Any TEAE associated with dose reduction	13 (36.1)	4 (15.4)	77 (27.2)	53 (18.7)
Any TEAE associated with death	0	0	1 (0.4)	5 (1.8)

At each level of summarisation, a participant is counted once if the participant reported one or more AEs.

Percentages are based on the number of participants in the Safety Analysis Set.

Drug Interrupted includes both Infusion Interruption and Dose Delay.

Immunological events

There was no apparent effect of ADA on safety of Dato-DXd. See section 2.3 Immunogenicity.

Safety related to drug-drug interactions and other interactions

No new data regarding safety related to drug-drug interactions have been presented in this application.

Discontinuation due to adverse events

Table 72 Summary of AEs Leading to Discontinuation of IP, by PT (SAF)

PT	Number (%) of participants	
	Dato-DXd N = 319	ICC N = 309
Any AE leading to IP discontinuation	15 (4.7)	24 (7.8)
Pneumonitis	3 (0.9)	1 (0.3)
Interstitial lung disease	2 (0.6)	0
Keratitis	2 (0.6)	0
Pneumonia	1 (0.3)	1 (0.3)
Amylase increased	1 (0.3)	0
Anaphylactic reaction	1 (0.3)	0
Arthralgia	1 (0.3)	0
Corneal epithelium defect	1 (0.3)	0
Parotitis	1 (0.3)	0
Spinal cord compression	1 (0.3)	0
Vulvovaginal inflammation	1 (0.3)	0
Weight decreased	1 (0.3)	0
Neuropathy peripheral	0	7 (2.3)
Anaemia	0	2 (0.6)
Nausea	0	2 (0.6)
Paraesthesia	0	2 (0.6)
Alanine aminotransferase increased	0	1 (0.3)
Aspartate aminotransferase increased	0	1 (0.3)
Asthenia	0	1 (0.3)
Cystoid macular oedema	0	1 (0.3)
Decreased appetite	0	1 (0.3)
Diarrhoea	0	1 (0.3)
Ejection fraction decreased	0	1 (0.3)
Fatigue	0	1 (0.3)
Gait disturbance	0	1 (0.3)
Myelosuppression	0	1 (0.3)
Oedema peripheral	0	1 (0.3)
Peripheral motor neuropathy	0	1 (0.3)
Platelet count decreased	0	1 (0.3)
Pruritus	0	1 (0.3)
Rash	0	1 (0.3)
Thrombocytopenia	0	1 (0.3)

Includes AEs with an onset date or that worsen on or after the date of first dose of IP up to within 28 (+ 7) days after last dose of IP or up to the day prior to start of a subsequent anticancer therapy, whichever comes first.

Participants with multiple occurrences are counted once per SOC and PT regardless of the number of occurrences.

Table is sorted by decreasing frequency in the Dato-DXd arm, then decreasing frequency in the ICC arm, then alphabetically when the frequencies are the same.

Post marketing experience

Since the first approval of Dato-DXd on 04 April 2025 through 26 June 2025 (DCO for the latest periodic safety update report), the estimated cumulative patient exposure was 214.5 patient-years. No new safety concerns have been identified based on post-marketing reports.

2.5.1. Discussion on clinical safety

In study TB02, the safety profile of datopotamab deruxtecan (Dato-DXd) was compared to investigator's choice of chemotherapy (or ICC, being taxanes, capecitabine, eribulin or carboplatin) in the first line setting of unresectable or metastatic triple-negative breast cancer. Data for the evaluation of the safety of Dato-DXd treatment in the target population (HR/PR-negative/HER2-negative breast cancer) are derived from N = 319 from the pivotal phase III trial TROPION-Breast02 (TB02) with supportive data contributed by the TROPION-Breast01 (TB01), TROPION-PanTumor02 (TP02), TROPION-PanTumor01 (TP01), TROPION-Lung01 (TL01), and TROPION-Lung05 (TL05) studies. The pooled data from these supportive studies and the pivotal TB02 comprise data from 1365 patients, of which 841 are patients with breast cancer (BC). The magnitude of the datasets included for assessment of the safety profile of Dato-DXd are considered acceptable.

Exposure

At the time of the Final Analysis DCO (25 August 2025), 319 participants in the Dato-DXd arm and 309 in the investigator's choice of chemotherapy (ICC) arm had received study treatment in Study TB02. Median duration of exposure was 8.51 months in the Dato-DXd arm and 4.14 months in the ICC arm, respectively. The median relative dose intensity (RDI) was 98.64% in the Dato-DXd arm and 95.42% in the ICC arm. In the TB02 Study 60.5% had a treatment duration > 6 months and the median number of cycles initiated was 12.

Drug interruptions were reported for 13 (4.1%) participants in the Dato-DXd arm and 7 (2.3%) participants in the ICC arm. The primary reason for drug interruption in the Dato-DXd and ICC arms was AEs (9 [2.8%] and 4 [1.3%], respectively).

Similar proportions of participants in the TB02 Dato-DXd arm and the BC 6 mg/kg pool had drug interruption (4.1% and 2.6%, respectively) or dose reduction (28.8% and 26.5%). Cycle delay was required for a similar proportion of participants in the TB02 Dato-DXd arm compared with the BC 6 mg/kg pool (78.7% versus 75.9%).

The extent of exposure time is considered acceptable for safety evaluation.

Summary of Adverse Events

AEs were reported for 98.7% of participants in the Dato-DXd arm and 94.8% of participants in the ICC arm.

AEs of CTCAE Grade ≥ 3 were reported for 43.3% of participants in the Dato-DXd arm and 37.5% of participants in the ICC arm. SAEs occurred in 16.9% of participants in the Dato-DXd arm and 15.5% of participants in the ICC arm. Fatal AEs during study treatment or 28-day follow-up were reported for 1 (0.3%) participant in the Dato-DXd arm and 5 (1.6%) participants in the ICC arm.

AEs leading to discontinuation of study intervention were reported for 4.7% of participants in the Dato-DXd arm and 7.8% of participants in the ICC arm. The proportion of patients with AEs leading to dose interruption was similar in the treatment arms (35.4% of participants in the Dato-DXd and 31.7% of participants in the ICC arm), while the proportion of patients with AEs leading to dose

reduction was higher in the Dato-DXd arm (28.2% versus 18.4%).

Adverse Events

At the FA DCO (25 August 2025) similar proportions of patients experienced any TEAE in the Dato-DXd (98.7%) and ICC arm (94.8%). The system organ classes with the most frequently reported TEAEs in the Dato-DXd arm were gastrointestinal disorders (83.7% versus 55.0% in the ICC arm), skin and subcutaneous disorders (62.1% versus 51.1%), eye disorders (54.2% versus 13.3%), respiratory, thoracic and mediastinal disorders (37.0% versus 27.5%).

The most commonly reported TEAEs by Preferred Term for Dato-DXd were stomatitis (58.3% versus 9.7% in the ICC arm), nausea (48.3% versus 22.3%), alopecia (42.9% versus 34.6%), constipation (39.8% versus 16.8%) and dry eye (26.3% versus 4.9%), which were considerably more frequent in the Dato-DXd arm than in the ICC arm. All were reported in a higher proportion of patients in the Dato-DXd arm than in the ICC arm ($\geq 10\%$ difference, except for alopecia). Other frequently reported TEAEs for Dato-DXd were vomiting (22.6%), anaemia (20.7%), decreased appetite (19.1%), cough (18.5%), fatigue (17.6%), asthenia (15.4%), keratitis (13.8%) and rash (12.9%). TEAEs reported in at least 5% of subjects in either treatment arm at ≥ 2 -fold higher incidences in the Dato-DXd arm included keratitis, skin hyperpigmentation, conjunctivitis, lacrimation increased, pyrexia, dry mouth and oropharyngeal pain. Overall the types and reported frequencies of TEAEs were comparable to those of the BC Dato-DXd pooled studies.

Conversely, the most frequently reported TEAEs in the ICC arm included nausea and alopecia (but at a lower frequency than with Dato-DXd), anaemia, neutropenia, neutrophil count decrease, diarrhoea, fatigue (similar to the frequency with Dato-DXd), and white blood cell count decrease. Overall haematological toxicity was higher in the ICC arm. The TEAEs reported were in line with the known safety profiles of the chemotherapy options in the control arm.

Dose modifications

The proportion of patients with any TEAE leading to a dose reduction was highest in the Dato-DXd arm with 90 (28.2%) versus 57 (18.4%); however, when adjusted for exposure, the rates of AEs leading to dose reduction were 31.62 per 100 patient-years in the Dato-DXd arm and 39.02 per 100 patient-years in the ICC arm. The most common AE leading to dose reduction in the Dato-DXd arm was stomatitis (11.3%), followed by amylase increase (2.8%), keratitis (2.5%) and asthenia (1.9%). The most common AE leading to dose reduction in the ICC arm was peripheral neuropathy and neutropenia. Dose interruptions occurred slightly more often in the Dato-DXd arm (35.4% versus 31.7%), the main causes being amylase increase and stomatitis. Overall, dose modifications (either reduction or interruption) were more frequent in the Dato-DXd arm (in 48.0% versus 41.1%), with the dominating AEs being stomatitis, amylase increase, keratitis in the Dato-DXd arm and neuropathy and neutropenia in the ICC arm. The MAH took the opportunity to clarify in section 4.2 of the SmPC that treatment with Dato-DXd should discontinue in case there is a requirement for further dose reduction beyond the second one.

Serious Adverse Events

Overall the frequency of TEAEs with CTCAE grade 2 or 3 was slightly higher in the Dato-DXd arm (and aligned with the frequencies in the BC Dato-DXd Pool) than in the ICC arm, (47.6% vs. 43.4% and 39.5% vs. 30.1%, respectively) whereas grade 4 and 5 events were similar. The most common AEs of CTCAE Grade ≥ 3 were amylase increase (9.7%) and stomatitis (8.5%) in the Dato-DXd arm and neutropenia + neutrophil count decrease + white blood cell count decrease (overall 17.8%) and anaemia (5.2%) in the ICC arm.

Adverse Events of Special Interest (AESI)

ILD/pneumonitis

Interstitial lung disease (ILD), including pneumonitis, is an identified AE of special interest for Dato-DXd and fatal cases have been observed. Clinically, symptomatic ILD and pneumonitis are indistinguishable conditions and their treatment is identical (systemic corticosteroids). Therefore, ILD/pneumonitis should be grouped together when reporting their incidence. In TB02 the incidence of all-causality ILD/pneumonitis as reported by investigator was 16 (5.0%) in the Dato-DXd versus 4 (1.3%) in the ICC arm. In the TB02, all ILD/pneumonitis events assessed by investigator, were subsequently subject to adjudication by an independent ILD adjudication committee, which is an acceptable practice (EMA/CHMP/EWP/5872/03) to verify the presence or not of ILD or pneumonitis.

Discontinuation due to ILD/pneumonitis occurred in 5 patients (1.5%). One CTCAE grade 5 event of ILD/pneumonitis was reported in the TB02 trial. The risk of ILD/pneumonitis is appropriately reflected in the SmPC and the RMP.

Infusion-related reactions

As per FA, IRRs occurred in 8.8% of subjects in the Dato-DXd arm versus 9.4% in the ICC arm. Most events were grade 1 or 2, and only 1 grade 3 event was reported. Only a few patients required dose interruption (1.3%) and one patient discontinued study treatment.

Oral mucositis/ stomatitis

A significantly higher proportion of patients in the Dato-DXd arm had an AESI of oral mucositis/stomatitis in the Dato-DXd arm compared with in the ICC arm (63.0 % versus 12.9%, respectively). The most commonly reported preferred term contributing to oral mucositis/stomatitis AESIs in the Dato-DXd arm was stomatitis (58.3%). Most events were grade 1 or 2, while grade 3 events occurred in 8.5% of subjects in the Dato-DXd arm. Events were predominantly managed by dose reduction (11.3%). Few patients had a dose interruption (3.8%) and stomatitis did not lead to drug discontinuation. Preventive measures and supportive care options are appropriately described in the SmPC section 4.4.

Ocular surface events

Ocular surface events is a known risk of antibody-drug conjugates. In the TB02 trial ocular surface events (including keratitis) was reported in 51.1% of subjects in the Dato-DXd arm and in 9.4% the ICC arm. In the Dato-DXd arm most events were CTCAE grade 1 (56.0%) and grade 2 (17.6%), a minority were grade 3 (6.6%) and there were 3 (0.9%) grade 4 events. The most common PTs in the AESI of ocular surface events in the Dato-DXd arm were dry eye (26.3%), keratitis (13.8%), conjunctivitis (7.8%), lacrimation increased (6.6%) and punctate keratitis (4.1%). At DCO 41.1% of the events were resolved, 9.8% were resolving and 49.1% were not resolved. The median time to resolution for grade 2 ocular events was 86 days and for grade 3 the median time was 66.5 days. Among the resolved events, no sequelae were reported. Events resulted in dose interruption (n=20, 6.3%), or dose reduction (n=15, 4.7%), and three subjects (0.9%) discontinued from study treatment. At DCO, 58.9% of patients with ocular surface events (i.e. 96 of 149 patients with ocular surface events considered treatment related in the Dato-DXd arm) had unresolved ocular surface events. Since no follow-up data were collected after the final DCO, the median duration of ocular surface events cannot be established, nor whether a proportion of ocular surface events remains unresolved. Overall, the frequency and severity degree of ocular surface events is similar to what has already been described for Dato-DXd. Keratopathy was identified as a new ADR and has been added in the table of adverse reactions in SmPC section 4.8.

Deaths

The investigator reported the primary cause of death as related to the disease under investigation in the majority of cases in both treatment arms (Dato-DXd: 142 [44.4%]; ICC: 149 [46.4%] participants), with 'Other' primary causes of death in 25 (7.7%) participants in the Dato-DXd arm and 26 (8.1%) participants in the ICC arm (Table 55). AEs were reported as the primary cause of death for 1 (0.3%) participant in the Dato-DXd arm (CTCAE Grade 5 ILD/pneumonitis) and 6 (1.9%) participants in the ICC arm. The narratives presented for the category 'other' do not suggest the presence of any treatment-related deaths in this category. Further, no imbalance in the number of patients with 'other' causes of death is observed between the two treatment arms.

Laboratory findings

Haematology

Most subjects had normal or CTCAE grade 1 for haematology tests post-baseline. Grade 3 or 4 was reported in a limited number of subjects (< 5%). The majority of shifts from baseline were 1-grade or 2-grade. Anaemia was reported as TEAE in 20.7% and as an SAE in 1.3%. Dose interruption was seen in 1.3% due to neutropenia, in 1.9% due to neutrophil count decrease and in 0.6% due to white blood cell count decrease. There were no cases of febrile neutropenia in the Dato-DXd arm. Overall haematological toxicity was limited and manageable in the Dato-DXd arm.

Liver function

At least 1 elevated liver enzyme test was reported for 52.1% of participants in the Dato-DXd arm and 52.8% of participants in the ICC arm. Increases $\geq 3 \times$ ULN in AST or ALT were reported in 8.2% in the Dato-DXd arm and 11.0% in the ICC arm. The number of patients with concurrent ALT or AST $\geq 3 \times$ ULN and total bilirubin (BILI) ≥ 2 ULN was 1 in the Dato-DXd arm and 3 in the ICC arm. The one potential Hy's law case in the Dato-DXd arm was assessed as being due to the underlying cancer disease, which is agreed. The liver test elevations seen is similar to those reported earlier for Dato-DXd.

Amylase increase

Shifts in clinical chemistry values were mainly 1-grade shifts, with only a small percentage of participants in the Dato-DXd and ICC arms developing a 3-grade or 4-grade shift, with the exception of amylase. Of the 224 patients in the Dato-DXd arm, shifts in amylase to grade 3 were observed for 46 (20.4%) and shifts to grade 4 were seen for 38 (16.9%), but none in the ICC arm. Fifty (15.7%) participants in the Dato-DXd arm and 6 (1.9%) participants in the ICC arm had an AE of amylase increase. There were no SAEs due to amylase increase. Of note, 2 AEs relating to pancreatitis were reported, both in the Dato-DXd arm, neither of which was considered by the investigator to be related to study intervention: these were SAEs of Grade 4 pancreatitis and Grade 3 obstructive pancreatitis, both of which resolved. Amylase increase led to Dato-DXd discontinuation in 1 (0.3%) patient and dose reduction in 22 (6.9%). Amylase increase was identified as a new ADR for Dato-DXd and has been added in the table of adverse reactions in SmPC section 4.8.

Safety in special populations

Across the subgroups of age, renal and hepatic function, ECOG PS and baseline brain metastases, the safety profile of Dato-DXd was generally consistent with that of the rest of the Dato-DXd treated population. The subgroups were small, and the small differences in frequency of TEAEs are not considered significant. Importantly, there were no subgroups where interruptions, dose reductions or discontinuations were remarkably different from the rest of the Dato-DXd treated study population.

Discontinuations

AEs leading to discontinuation occurred in 4.7% in the Dato-DXd arm and 7.8% in the ICC arm. All AEs leading to discontinuation of study treatment in both treatment arms were reported in 1 participant each, except pneumonitis/ILD and keratitis in the Dato-DXd arm (5 [1.5%], and 2 [0.6%] participants, respectively) and neuropathy peripheral, anaemia, nausea, and paraesthesia in the ICC arm (7 [2.3%], 2 [0.6%], 2 [0.6%], and 2 [0.6%], respectively).

Overall, the data presented illustrate a toxicity profile of Dato-DXd, characterized by stomatitis, amylase increase and eye disorders, whereas the safety profile of the chemotherapy is mainly characterized by haematological toxicity.

2.5.2. Conclusions on clinical safety

In the pivotal study TB02, the safety profile of datopotamab deruxtecan (Dato-DXd) was compared to investigator's choice of chemotherapy (ICC), i.e. taxanes, capecitabine, eribulin or carboplatin, in the first line setting of unresectable or metastatic triple-negative breast cancer. Supportive safety data from 1365 patients, of which 841 are patients with breast cancer, was also provided, which showed no clinically significant changes of the known safety profile nor any new safety findings. While the frequency of AEs and SAEs was similar in the Dato-DXd arm and the ICC arm of the TB02 study, the nature of the safety profiles differed, with stomatitis and ocular surface events being characteristic for Dato-DXd and haematological events dominating the chemotherapy safety profile. Nausea and vomiting were seen in both arms, however twice as often in the Dato-DXd arm and appeared to be manageable. ILD/pneumonitis is still the greatest risk in the treatment with Dato-DXd and one grade 3 event as reported by investigator was adjudicated as a fatal ILD in the TB02 study. This risk is appropriately reflected in the SmPC and the RMP. In the targeted setting, the observed toxicities of Dato-DXd are considered acceptable and manageable.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted updated RMP version with this application.

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

The PRAC considered that the risk management plan version 2.0 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 2.0 with the following content:

Safety concerns

Table 73 **Summary of Safety Concerns**

Important identified risk	• Interstitial lung disease / pneumonitis • Keratitis
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Important potential risk	Embryo-foetal toxicity
Missing information	None

Pharmacovigilance plan

No additional pharmacovigilance activities.

Risk minimisation measures

Table 74 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	<u>Routine risk minimisation measures:</u> - SmPC Sections 4.2, 4.4, and 4.8 - PL Sections 2 and 4 - Legal status: Prescription-only medicine <u>Additional risk minimisation measures:</u> - None	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> - None <u>Additional pharmacovigilance activities:</u> - None
Keratitis	<u>Routine risk minimisation measures:</u> - SmPC Sections 4.2, 4.4, and 4.8 - PL Sections 2 and 4 - Legal status: Prescription-only medicine <u>Additional risk minimisation measures:</u> - None	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> - None <u>Additional pharmacovigilance activities:</u> - None
Important Potential Risks		
Embryo-foetal toxicity	<u>Routine risk minimisation measures:</u> - SmPC Sections 4.4 and 4.6 - PL Section 2 - Legal status: Prescription-only medicine <u>Additional risk minimisation measures:</u> - None	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> - None <u>Additional pharmacovigilance activities:</u> - None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Enhertu. The bridging report submitted by the MAH has been found acceptable.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Datroway (datopotamab deruxtecan) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This is an extension of indication for datopotamab deruxtecan (Dato-DXd) as monotherapy for the first-line treatment of adult patients with unresectable or metastatic triple-negative breast cancer (TNBC) who are not candidates for PD-1/PD-L1 inhibitor therapy.

3.1.2. Available therapies and unmet medical need

Metastatic hormone-receptor negative and HER2-negative breast cancer, commonly referred to as “triple-negative” breast cancer (TNBC) remains an incurable disease. Single-agent chemotherapy remains the mainstay of first-line treatment for these patients, with the addition of checkpoint inhibitors for patients with PD-L1 positive tumours, while PARP inhibitors may be considered for those patients with germline BRCA mutations (Gradishar et al 2024, Gennari et al 2021, Cardoso et al 2024).

For patients with TNBC who are ineligible for checkpoint inhibitors, which is the targeted patient population in this procedure, there are only chemotherapy options in the first line setting. The median PFS for patients treated with first-line chemotherapy for either recurrent or de novo metastatic TNBC is approximately 5.5 months, with median OS less than 2 years (Cortes et al 2020, Emens et al 2021, Miles et al 2021).

After first-line chemotherapy, these patients have the option of Sacituzumab govitecan, which is an anti-TROP2 ADC recommended for the treatment of adult patients with metastatic TNBC who have received 2 or more prior systemic therapies, at least one of them for advanced disease, but it is not recommended in the first-line setting (Gennari et al 2021, Gradishar et al 2024). Finally, patients with HER2-low or ultralow expressing tumours (IHC 1+ or IHC 2+/ISH-, or HER2-ultralow tumour status, described as IHC 0 with membrane staining (IHC >0<1+)) have the option of trastuzumab deruxtecan in the metastatic setting after having previously received chemotherapy after disease progression.

3.1.3. Main clinical studies

TROPION-Breast02 (TB02) is a phase III, randomized, open-label, 2-arm, multicentre, international study assessing the efficacy and safety of Dato-DXd compared with investigator's choice of chemotherapy (ICC) in participants with locally recurrent inoperable or metastatic TNBC who are not candidates for PD-1/PD-L1 inhibitor therapy.

The TB02 trial randomised 644 patients in a 1:1 design and the dual primary efficacy endpoints were PFS by BICR and OS.

3.2. Favourable effects

At the final analysis on DCO 25 august 2025, the median **PFS by BICR** was 10.84 months (95% CI: 8.57, 12.98) in the Dato-DXd arm compared to 5.55 months (95% CI: 4.96, 6.97) in the ICC arm with a HR of 0.57 (95% CI: 0.47, 0.69).

At the final analysis on DCO 25 august 2025, the median **OS** was 23.66 months (95% CI: 19.81, 25.63) in the Dato-DXd arm vs 18.66 months (95% CI: 15.97, 21.78) in the ICC arm with a HR of 0.79 (95% CI: 0.64, 0.98).

OS HRs for Region 1 (US/Canada/Europe) and European population were 1.22 (95% CI: 0.86, 1.73) and 1.34 (95% CI: 0.90, 1.99), respectively. A multivariate Cox proportional hazards model OS sensitivity analysis adjusting for imbalanced baseline prognostic characteristics demonstrated OS HRs of 1.02 (95% CI: 0.71, 1.48) and 1.11 (0.73, 1.69) for Region 1 and the European population, respectively. In Region 1, subsequent ADC use occurred in 50.8% compared to 20.9% in Region 2 (Rest of World). A two-stage OS sensitivity analysis adjusting for ADC use only, demonstrated OS HRs of 0.83 (95% CI: 0.59, 1.18) and 0.79 (0.53, 1.18) for Region 1 and the European population, respectively.

Median **PFS by investigator** was 9.63 months (95% CI: 7.36, 11.20) in the Dato-DXd arm compared to 5.22 months (95% CI: 4.21, 5.59) in the ICC arm with a corresponding HR of 0.56 (95% CI: 0.47, 0.67).

3.3. Uncertainties and limitations about favourable effects

Efficacy within Region 1 (US/Canada/Europe) and European population in terms of OS was not so pronounced compared to the ITT. Apart from imbalance of prognostic factors at baseline, there were regional imbalances in the use of subsequent ADC therapies control arm. Adjusted models of OS alleviated part of the uncertainties and reassured of a lack of detrimental effect.

3.4. Unfavourable effects

In the Dato-DXd treated subjects of the pivotal TB02 study:

- Any TEAE occurred in 98.7%
- Grade $\geq$ 3 TEAEs occurred in 43.3%
- SAEs occurred in 16.9%
- The most commonly observed ADRs were stomatitis (58.3%), nausea (48.3%), alopecia (42.9%), constipation (39.8%) and dry eye (26.3%), vomiting (22.6%), anaemia (20.7%), decreased appetite (19.1%), cough (18.5%), fatigue (17.6%), asthenia (15.4%), keratitis (13.8%) and rash (12.9%).

- AEsIs are stomatitis (58.3%), ocular surface events(51.1%) and ILD/pneumonitis (3.8%).
- ILD/pneumonitis is the main safety concern, as fatal outcomes have been observed.

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 75 Effects Table for Datroway (Dato-DXd) for unresectable or metastatic triple-negative breast cancer (TB02 trial - DCO: 25 august 2025)

Effect	Short description	Unit	Treatment Dato-DXd	Control Chemo-therapy	Uncertainties / Strength of evidence
Favourable Effects (FAS)					
			N = 323	N = 321	
PFS by BICR	Progression-free survival	Months (95%CI)	10.84 (8.57, 12.98)	5.55 (4.96, 6.97)	63.4% maturity (408 / 644 events) PFS by INV: 9.63 vs 5.22 months ORR by BICR: 62.5% vs 29.3%
			HR 0.57 (95% CI: 0.47, 0.69)		
OS	Overall survival	Months (95%CI)	23.66 (19.81, 25.63)	18.66 (15.97, 21.78)	54.2% maturity (349 / 644 events)
			HR 0.79 (95% CI: 0.64, 0.98)		
Unfavourable Effects (SAS)					
			n = 319	n = 309	
General					
TEAEs Grade ≥3 AEs		%	43.3	37.5	
SAEs		%	16.9	15.5	
TEAEs leading to death		% (n)	0.3 (1)	1.9 (6)	One patient (0.3%) died due to Dato-DXd associated ILD/pneumonitis as adjudicated by the ILD AC.
Discontinuations (any)		%	4.7	7.8	
Specific					
Stomatitis		%	58.3	9.7	
Keratitis		%	13.8	1.0	
ILD/pneumonitis		%	3.8	1.3	

Abbreviations: INV, Investigator; BICR, Blinded-Independent Review Committee; CR, Complete response; FAS, Full Analysis Set; SAS, Safety Analysis Set; TEAE: Treatment Emergent Adverse Event; ILD: interstitial lung disease; ILD AC: ILD adjudication committee; SAE: Serious Adverse Event.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy of Dato-DXd in metastatic TNBC is investigated in the pivotal randomised, open label TB02 trial, where Dato-DXd was compared to the current standard of care treatment of single-agent chemotherapy per clinician's choice (ICC). Primary dual endpoints of PFS by BICR and OS showed statistically and clinically relevant benefits of Dato-DXd over standard single-agent chemotherapy in the first-line treatment of unresectable and metastatic TNBC with compelling magnitudes of benefits in PFS (5.29 months longer, HR 0.57) and OS (5.00 months longer, HR 0.79). The data is considered mature with 63.4% maturity for PFS and 54.2% maturity for OS. The dual primary efficacy outcomes were supported by clinically relevant benefits in other secondary outcomes, such as PFS by investigator (4.11 months longer) and ORR/DoR.

The Applicant has clarified that no additional OS data was collected after the FA DCO. This is also stated in the end of study definitions from the initial study protocol dated 21. November 2021.

Uncertainties were identified regarding the OS outcomes in the Region 1 and the European population. The variability seen in the OS measures between regions suggest that the extent of the overall impact of Dato-DXd on overall survival in breast cancer may depend on the other treatments available and the evolving treatment paradigm. Although the benefit does not appear as pronounced as in the ITT population, adjusted models of OS alleviated part of the uncertainties and reassured of a lack of detrimental effect.

No clinically significant changes of the known safety profile, nor any new safety findings were detected. While the frequency of AEs and SAEs was similar in the Dato-DXd arm and the ICC arm of the TB02 study, the nature of the safety profile differed clinically significantly, with stomatitis and ocular surface events being characteristic for Dato-DXd and haematological events dominating the chemotherapy safety profile. Nausea and vomiting were seen in both arms, however twice as often in the Dato-DXd arm and appeared to be manageable. ILD/pneumonitis is still the greatest risk in the treatment with Dato-DXd and one fatal event was reported in the TB02 study. In the targeted setting of unresectable or metastatic TNBC, the observed toxicities of Dato-DXd are considered acceptable and manageable.

3.7.2. Balance of benefits and risks

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Datroway is positive.

4. Recommendations

Outcome

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

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	type II	I, II, and IIIB

Extension of indication to include, as monotherapy, the first-line treatment of adult patients with unresectable or metastatic triple-negative breast cancer (TNBC) who are not candidates for PD-1/PD-L1 inhibitor therapy for DATROWAY, based on final results from study D926PC00001 (TROPION-Breast02). This is a Phase 3, randomised, open-label, 2 arm, multicentre, international study assessing the efficacy and safety of Dato-DXd compared with investigator's choice chemotherapy in participants with locally recurrent inoperable or metastatic TNBC who are not candidates for PD-1/PD-L1 inhibitor therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the PI.

Amendments to the marketing authorisation

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

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

Risk management plan (RMP)

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

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

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

Additional market protection

The MAH withdrew the request for consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 for 'one year of market protection for a new indication' while the procedure was ongoing.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion EMA/VR/0000316654

Attachments

1. SmPC, Annex II, Labelling, Package Leaflet (changes highlighted) as adopted by the CHMP on 25 June 2026