Clinical Study Protocol	
Study Intervention	Datopotamab deruxtecan (Dato-DXd, DS-1062a)
Study Code	D9266C00001
Version	4.0
Date	29 May 2023

Phase 1/2, 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

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Regulatory Agency Identifier Number(s): NCT Number: NCT05460273

This CSP has been subject to a peer review according to AstraZeneca Standard procedures. The CSP is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: D9266C00001

Amendment Number: 3

Study Intervention: Datopotamab deruxtecan (Dato-DXd, DS-1062a)

Study Phase: Phase 1/Phase 2

Short Title: Dato-DXd in Patients with Advanced Solid Tumours

Acronym: TROPION-PanTumor02

Study Physician Name and Contact Information will be provided separately.

VERSION HISTORY

DOCUMENT HISTORY	
Document	**Date**
Amendment 3 (Version 4.0)	29 May 2023
Amendment 2 (Version 3.0)	31 March 2022
Amendment 1 (Version 2.0)	17 November 2021
Original Protocol (Version 1.0)	20 October 2021

Amendment 3 (Version 4.0; 29 May 2023)

The overall rationale for this amendment is to accomplish the following:

- Update the protocol language to reflect new clinical data and external guidance and to provide clarification
- Make minor adjustments to the text.

List of Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis; 1.3 Schedule of Activities; 4.1.1 Study Overview; 7.1.2 Follow-up for Survival; 8.2.4 Overall Survival	Updated the time windows for study activities and clarified the recording requirements for additional assessments during survival follow-up.	To provide a wider window for data collection of subsequent progression status and overall survival
1.1 Synopsis; 3 Objectives and Endpoints; 8.6.2 Immunogenicity Assessments; 9.4.4.4 Immunogenicity Data	Clarified that neutralising antibodies may be tested when ADA is positive, as Dato-DXd is at low-risk of immunogenicity and the nAb evaluation could be optional for early studies.	To reflect that neutralising ADA may be determined when ADA is positive.
1.3 Schedule of Activities; 8.3.5.5 Ophthalmologic Assessments; 8.4.11 Adverse Events of Special Interest	Clarified that an Ophthalmologic Assessment Manual will be used instead of the previous form provided in the Appendices. Updated instructions for the use of artificial tears. Removed Appendix K Ophthalmologic Assessment Form.	To align with the latest recommendations from the external advisory board (ie, that artificial tears be used 4-8 times per day as opposed to “daily”) and clarify that the Ophthalmologic Assessment form is now included in the Dato-DXd Site Ophthalmologic Assessment Manual
1.3 Schedule of Activities; 6.5 Concomitant Therapy; 7.1.1 Follow-up of	Sections 1.3, 8.4.1, and 8.4.7; Appendix B2. Updated to specify the collection timeframe for AEs, SAEs,	To clarify instructions and collect extra information on AESIs

Section Number and Name	Description of Change	Brief Rationale
Participants Post Discontinuation of Study Intervention; 8.4.1 Time Period and Frequency for Collecting AE and SAE Information; 8.4.7 Disease Progression; 8.4.11 Adverse Events of Special Interest; Appendix B2 Definitions of Serious Adverse Event	all AESIs and AESIs of ILD/pneumonitis, and to clarify the types of events to be reported within 24 hours of investigator awareness. Clarification that pre-existing medical conditions identified through mandatory screening procedures are to be recorded as medical history. Removed text about distinguishing between serious and severe AEs.	
	Sections 6.5, 7.1.1, and 8.4.11. Text added to state that all AESIs and concomitant medications administered as treatment for drug-related AESIs should be followed until either event resolution, end of study, including any post-treatment follow-up, trial termination, withdrawal of consent, or participant death. ILD/Pneumonitis: • Added text to state that all ILD/pneumonitis events should be reported beyond the specified safety follow-up period. Infusion-related Reaction: • Amended text regarding collection of ≥Grade 3 AEs via a targeted questionnaire of IRR.	To collect extra information on AESIs and ensure that any AESIs are followed until resolution
1.3 Schedule of Activities; 8.3.2 Vital Signs; 8.3.3 Electrocardiograms; 8.3.5.2 Pulmonary Assessments; 8.3.5.3 ILD/Pneumonitis Investigation	Simplified the instructions for handling ECG readings, vital signs, and pulmonary assessments. Removed Appendix J Guidance for Management of Participants with Drug-Induced ILD/pneumonitis. Updated the evaluation procedures for ILD. All references to Appendix J were removed and replaced with references to the TMGs in the CSP Annex.	To simplify the instructions for assessments and remove redundant instructions for management of ILD/pneumonitis
1.3 Schedule of Activities	Removed the ECG assessment during the EoT visit.	To clarify that the requirements for ECG are reduced due to no cardiac safety signal noted for Dato-DXd
2.2.1 Dato-DXd; 2.3.1 Risk Assessment; 2.3.2 Benefit	Updated the description of prior data, the description of risks and benefits,	To reflect clinical data for Dato-DXd up to the DCO of 16Nov2022 (in

Section Number and Name	Description of Change	Brief Rationale
Assessment; 2.3.3 Overall Benefit/Risk Conclusion; 4.3 Justification for Dose	and the dose justification. Removed Sections 8.3.5.5 CCI [redacted].	alignment with Dato-DXd IB Edition 7.0)
	In Table 2 and Section 2.3.3, CCI was downgraded from an important identified risk to an identified risk and CCI was removed from the description of the risk.	CCI [redacted]
	In Table 2, CCI [redacted] risk.	The change to CCI was to make it an important risk, in line with non-clinical data and class effect information.
5.1 Inclusion Criteria; 5.2 Exclusion Criteria; 8.3.4 Clinical Safety Laboratory Assessments; Appendix F Contraception Requirements	Updated instructions for sex and contraception. Inclusion criteria 9-11 and Appendix F: Added further details of contraception requirements for female and male participants and instructions for donating or using ova or freezing or donating sperm, respectively.	Clarification
	Exclusion criterion 26 clarified that females should refrain from breastfeeding from screening throughout the study and for CCI after the last dose of Dato-DXd.	To follow FDA guidance on how long participants should refrain from breastfeeding in clinical studies (5 half-lives of study intervention + 6 months)
	Section 8.3.4 revised pregnancy wording to clarify that repeat pregnancy tests (urine or serum test per institutional guidelines) must be performed within 72 hours before the first dose of study intervention and clarify the steps to be taken if the result is positive or abnormal.	Changed in line with a program-wide decision to add clarification for the timing for collection of the screening serum pregnancy test
5.2 Exclusion Criteria; 8.3.4 Clinical Safety Laboratory Assessments	Clarified criteria for HBV and HCV in criterion 7.	To align with FDA guidance to broaden eligibility criteria for

Section Number and Name	Description of Change	Brief Rationale
		participants infected with HBV and HCV
6.2.2.1 Administration of Dato-DXd; Appendix G2 Restricted, Prohibited, and Permitted Concomitant Medications/Therapies (Table 18)	Revised advice that participants receive CCI [redacted] agents prior to infusion of Dato-DXd and on subsequent days as needed from "recommended" to "highly recommended" and clarified that they should remain on site for at least 1 hour post-infusion of every dose of Dato-DXd.	To ensure an adequate duration of monitoring for IRR after Dato-DXd infusions and to clarify the recommendations for pre-medication
6.6 Dose Modification; 6.6.1 Dose Delays; 6.6.2 Dose Delays for Reasons other than Treatment-related Toxicity; 6.6.3 Dose Reductions; 8.4.5 Adverse Events Based on Examinations and Tests; 8.4.11 Adverse Events of Special Interest	Text amended to say that 2 consecutive doses of Dato-DXd must be administered at least 18 days apart (rather than 19 days apart).	To match the new visit window (±3 days).
	Text amended to: "A dose of Dato-DXd can be delayed CCI [redacted] from the planned date of administration (ie, CCI [redacted] from the last infusion date). [redacted]	To allow more time for any adverse event to resolve before requiring permanent discontinuation of Dato-DXd
	New subsections added to clarify the procedures for dose modifications, including adding Figure 3, outlining the procedure if treatment with Dato-DXd is delayed for conditions other than toxicity resolution, and clarifying the procedure in the event that a dose delay occurs prior to completion of PK blood sampling. Also, "dose interruption" was changed to "dose delay" to clarify that the whole dose would be delayed.	To clarify and ensure consistency with TMGs
6.7 Continued Access to Study Intervention After the End of the Study	Clarified the strategy for providing Dato-DXd after the study	Upon completion of data collection in a trial, participants may still be benefitting from treatment in the opinion of the investigator. This language has been added for transparency to health authorities,

Section Number and Name	Description of Change	Brief Rationale
		regulators and ethics boards on how these participants may continue to receive that treatment.
6.8 Treatment of Overdose; 8.5 Overdose; Appendix B4 Medication Error, Drug Abuse, or Drug Misuse	Clarified the handling of drug misuse and overdose	Update required due to AstraZeneca safety
8 Study Assessments and Procedures; 8.3.4 Clinical Safety Laboratory Assessments; 8.6 Human Biological Samples	Clarified the instructions for laboratory assessments and for handling human biological samples, including the timing of procedures, how abnormal test results will be handled, and how long samples will be stored.	Clarification
8.4.8 Disease Under Study	Clarified that events unequivocally due to Disease Under Study should not be reported as AEs during the study unless they meet SAE criteria (not those leading to study intervention discontinuation).	To clarify the reporting of events due to Disease Under Study
8.7.1 Collection of Mandatory Samples for Biomarker Analysis	Revised the time for biomarker sample retention to one year after final CSR publication.	Update for consistency with a company-wide policy and local regulations
9.3 Populations for Analyses; 9.4.1 General Considerations; 9.4.2.1.1.3 Primary Endpoint: Confirmed ORR by ICR; 9.4.4.1 Pharmacokinetics	Added “enrolled” population, general statistical considerations, and additional description of ORR analysis. Expanded the description of PK analysis procedures.	To clarify the analysis procedures
Appendix A Regulatory, Ethical, and Study Oversight Considerations	Added text about investigator oversight and reporting requirements for serious breaches. Added text about informed consent, data protection, and data quality assurance. Updated the minimum duration of record retention.	Update required to comply with regulatory requirements and global company requirements
Appendix E Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)	Table E14: changed “Non-PD or NE” to “Non-PD or NE or NA” in the “Non-Target Lesions” column for NE target lesions. Updated the instructions in RECIST 1.1 TL assessment at follow-up to clarify the description of TLs.	Correction and clarification

Section Number and Name	Description of Change	Brief Rationale
Appendix G Concomitant Medications	Clarified that corticosteroids can be used as clinically indicated, clarified the restrictions on the use of palliative radiotherapy, and clarified that anti-resorptive/bone therapy is allowed for treatment of bone metastases and osteoporosis. Clarified the instructions for prohibition of chronic systemic corticosteroids/immunosuppressants. Clarified the instructions for supportive medications/therapies.	To clarify instructions
Throughout	Removed various references to COVID-19 protocols, including removing Appendix I Instructions Related to COVID-19. Updated 9.4.4.5 COVID-19 Impact (previously called COVID-19 Data)	To align with the current stage of the COVID-19 pandemic and because no adverse impacts have been identified between COVID-19 and the benefit/risk considerations for Dato-DXd

ADA, anti-drug antibody; AE, adverse event; AESI, adverse event of special interest; COVID-19, coronavirus 2019-nCoV; CSP, clinical study protocol; CSR, clinical study report; Dato-DXd, datopotamab deruxtecan; DCO, data cutoff; ECG, electrocardiogram; EoT, end of treatment; FDA, Food and Drug Administration; HBV, hepatitis B virus; HCV, hepatitis C virus; IB, Investigator's Brochure; ICR, independent central review; ILD, interstitial lung disease; IRR, infusion-related reaction; NA, not applicable; NE, not evaluable; ORR, objective response rate; PD, progression of disease; PK, pharmacokinetic; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; SAE; serious adverse event; TL, target lesion; TMG, toxicity management guideline.

List of Non-substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Title Page, 1.1 Synopsis	Added Clinicaltrials.gov number	Update with new registry information
1.1 Synopsis; 4.1 Overall Design	Clarified the meaning of "screened"	Minor clarification
1.3 Schedule of Activities	Simplified descriptions and moved the "Notes" column into the footnotes	Minor clarification
8.1 Administrative and General/Baseline Procedures	Added a section to clarify administrative and general/baseline procedures	To clarify the administrative/general procedures
Appendix A8 Source Documents	Revised the location of the definition of what constitutes source data.	Correction.
Appendix C3 International Air Transport Association	Updated the name of this section	Correction

Section Number and Name	Description of Change	Brief Rationale
Guidance Document (62nd Edition)		
Appendix E Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)	Updated the subheading numbers and added the word “alone” to “Special considerations regarding lesion measurability at baseline” to clarify that the indicated assessments alone are not considered adequate.	Minor clarification.
	Removed the section “Central Imaging” from “RECIST 1.1 evaluation of overall visit response at follow-up”.	Reduce redundancy
Throughout	Minor updates to wording	Clarification

RECIST, Response Evaluation Criteria in Solid Tumours.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: Phase 1/Phase 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.

Short Title: Dato-DXd in Patients With Advanced Solid Tumours.

Regulatory Agency Identifier Number(s):

Clinicaltrials.gov NCT05460273

Rationale:

Cancer is a major global health issue and the leading cause of death in China (Feng et al 2019, Zhang et al 2015, Zhou et al 2019) with 4.5 million new cases and 3 million deaths in 2020 (GLOBOCAN 2020). The situation in China has been alarming partly due to the aging and growing population, as well as socioeconomic development. It is essential to develop new therapies for Chinese cancer patients who are refractory or intolerant to standard therapies, or for whom no standard therapy exists.

The Phase 1 first-in-human Study DS1062-A-J101 is evaluating Dato-DXd in TROP2-unselected participants with advanced NSCLC who have relapsed from or are refractory to SoC therapy as well as in participants with advanced TNBC who have relapsed from or are refractory to SoC therapy or for whom no SoC therapy is available. An additional cohort of participants with hormone receptor-positive, HER2-negative breast cancer is currently recruiting as of March 2021. Other tumour types may also be explored in the future. Clinical data from Study DS1062-A-J101 show efficacy of Dato-DXd with a manageable toxicity profile. However, none of the participants in Study DS1062-A-J101 are from China, and there is an unmet need for more information about the safety and efficacy of Dato-DXd in the adult Chinese population.

Given these encouraging preliminary safety and efficacy data, the current study is designed to further assess the efficacy, safety, PK, and immunogenicity of Dato-DXd in adult Chinese patients with selected advanced or metastatic solid tumours. This single-arm study consists of multiple cohorts, divided by indication. Cohort 1, which includes participants with advanced or metastatic NSCLC with or without AGAs who have received immune-oncology therapies and platinum-based chemotherapy (for participants with NSCLC without AGAs) or one or two prior lines of applicable targeted therapy and platinum-based chemotherapy (for participants with NSCLC with AGAs), and Cohort 2, which includes participants with inoperable locally advanced or metastatic TNBC who have received at least 2 prior chemotherapy regimens for advanced breast cancer, counting the (neo)adjuvant therapy as a

prior chemotherapy regimen if progression occurred within 12 months after completion of the therapy, will be prioritised for enrolment. Additional cohorts will be added for future enrolment of participants with advanced or metastatic solid tumours and may include, but are not limited to, patients with advanced/unresectable or metastatic gastric or GEJ adenocarcinoma or urothelial carcinoma that is refractory or intolerant to SoC therapy or for which no SoC therapy is available.

Objectives and Endpoints:

The objectives and endpoints of this study for each cohort are shown below.

Objectives	Endpoints
Primary	
To estimate the effectiveness of Dato-DXd by assessment of confirmed ORR by ICR	Confirmed ORR is defined as the proportion of participants in each cohort who have a confirmed CR or confirmed PR, as assessed by ICR per RECIST 1.1. The measure of interest is the estimate of confirmed ORR.
Secondary	
To estimate the effectiveness of Dato-DXd by assessment of confirmed ORR by investigator assessment.	Confirmed ORR is defined as the proportion of participants in each cohort who have a confirmed CR or confirmed PR, as determined by investigator assessment per RECIST 1.1.
To estimate the effectiveness of Dato-DXd by assessment of DoR.	Duration of response is defined as the time from the date of first documented response (which is subsequently confirmed) until date of documented progression per RECIST 1.1, as assessed by ICR and by investigator, or death due to any cause.
To estimate the effectiveness of Dato-DXd by assessment of DCR.	Disease control rate is defined as the percentage of participants who have a confirmed CR or PR or who have SD per RECIST 1.1, as assessed by ICR and by investigator.
To estimate the effectiveness of Dato-DXd by assessment of BOR.	Best overall response is defined as participant's best confirmed response during their participation in the study, but prior to starting any subsequent anticancer therapy, up until RECIST 1.1-defined progression or the last evaluable assessment in the absence of RECIST 1.1-defined progression. Best overall response will be assessed by ICR and by investigator per RECIST 1.1.

Objectives	Endpoints
To estimate the effectiveness of Dato-DXd by assessment of TTR.	Time to response is defined as the time from date of first dose of study intervention until the date of first documented objective response, which is subsequently confirmed per RECIST 1.1, as assessed by ICR and by investigator.
To estimate the effectiveness of Dato-DXd by assessment of PFS.	Progression-free survival is defined as time from date of first dose of study intervention until PD per RECIST 1.1, as assessed by ICR and by investigator, or death due to any cause.
To estimate the effectiveness of Dato-DXd by assessment of OS.	Overall survival is defined as the time from the date of the first dose of study intervention to the date of death due to any cause.
To assess the safety and tolerability of Dato-DXd.	Safety and tolerability are evaluated in terms of TEAEs, AESIs including ILD evaluated by an independent adjudication committee, vital signs, clinical laboratory, ECG, ECHO/MUGA parameters, and ophthalmologic findings.
To evaluate the PK of Dato-DXd.	Plasma concentrations and appropriate PK parameters of Dato-DXd, total anti-TROP2 antibody, and MAAA-1181a (DXd) will be calculated for participants with PK samples if data permit.
To investigate the immunogenicity of Dato-DXd.	The presence of ADAs against Dato-DXd will be evaluated. Titre will be determined when ADA is positive.

For the exploratory objectives and endpoints, see Section 3 of the protocol.

Overall Design

Disclosure Statement: This is a Phase 1/Phase 2, multicentre, open-label, multiple-cohort study, which is designed to evaluate the efficacy, safety, PK, and immunogenicity of Dato-DXd in adult Chinese participants with advanced or metastatic solid tumours.

Participant Population:

This study is divided into cohorts of participants with the same tumour type. The starting cohorts are Cohort 1 (NSCLC) and Cohort 2 (TNBC). Future cohorts will consist of other advanced or metastatic solid tumour types, including, but not limited to, advanced/unresectable or metastatic gastric or GEJ adenocarcinoma or urothelial carcinoma that is refractory or intolerant to SoC therapy or for which no SoC therapy is available. Cohort 1 and Cohort 2 will be prioritised for immediate enrolment, and the CSP will be amended as needed for the future cohorts.

Cohort 1: The target population of Cohort 1 is adult Chinese participants with advanced or metastatic NSCLC with orwithout AGAs (ie, alterations in genes with approved therapies, such as *EGFR, ALK,* or other known AGAs). Eligible participants without AGAs will have been previously treated with platinum-based chemotherapy and anti-PD-1/anti-PD-L1 monoclonal antibody, either in combination or sequentially. Participants without AGAs who received anti-PD-1/anti-PD-L1 monoclonal antibody as frontline therapy may have received the combination of platinum-based chemotherapy and anti-PD-1/anti-PD-L1 monoclonal antibody in the second-line setting. Eligible participants with AGAs will have been previously treated with one or two prior lines of applicable targeted therapy that is approved for the participant's genomic alteration and platinum-based chemotherapy as the only prior line of cytotoxic therapy. Participants with AGAs may have received up to one anti-PD-1/anti-PD-L1 monoclonal antibody treatment alone or in combination with chemotherapy.

Cohort 2: The target population of Cohort 2 is adult Chinese participants with inoperable locally advanced or metastatic TNBC who have received at least 2 prior chemotherapy regimens for advanced breast cancer, counting the (neo)adjuvant therapy as a prior chemotherapy regimen if progression occurred within 12 months after completion of the therapy.

Number of Participants:

Cohort 1: Approximately 40 eligible NSCLC participants in China will be enrolled.

Cohort 2: Approximately 78 eligible TNBC participants in China will be enrolled.

For Cohort 1, approximately 6 participants with AGAs will be enrolled.

An enrolment cap will be placed on Cohort 2: at most around 20% (approximately N=15) of enrolled participants with a DFI ≤ 12 months.

Note: 'Screened' means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. 'Enrolled' means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process and the participant is confirmed as eligible. Potential participants who are screened for the purpose of determining eligibility for the study, but are not enrolled, are considered 'screen failures.'

Study Periods:

Screening Period: The Screening Period will start on the day of signing the ICF and have a maximum duration of 28 days. Rescreening is permitted one time. During the 28-day Screening Period, participants' eligibility will be confirmed.

The study start date is the date when the first participant has signed an ICF. A participant is eligible to be enrolled into the study when the investigator or designee has obtained written informed consent, has confirmed all inclusion and exclusion criteria have been met by the participant, and all Screening procedures have been completed.

Intervention Period: Eligible participants will enter the Intervention Period. The Intervention Period starts on Cycle 1 Day 1 and continues until a participant permanently discontinues Dato-DXd.

During the Intervention Period, participants will receive Dato-DXd. Participants will be treated with Dato-DXd at 6.0 mg/kg via an intravenous infusion on Day 1, Q3W until they meet one of the discontinuation criteria.

Up to 2 dose reductions will be permitted for participants receiving Dato-DXd. Once the dose of Dato-DXd has been reduced because of toxicity, all subsequent cycles should be administered at that lower dose level, unless further dose reduction is required. Once the dose of Dato-DXd is reduced, no dose re-escalation will be permitted. One additional dose reduction may be possible on a case-by-case basis after discussion and agreement between the investigator and sponsor. A dose can be delayed for CCI from the planned date of administration (ie, CCI from the last infusion date).

Participants will undergo radiographic assessment of tumour response based on RECIST 1.1 every 6 weeks (± 7 days) from the date of the first dose of study intervention until radiographic PD as assessed by investigator. The assessment must continue until PD as defined per RECIST 1.1, whether or not the participant is still on treatment. Following PD assessed by investigator, one additional follow-up tumour assessment should be performed at the next scheduled imaging visit and no less than 4 weeks after the prior assessment of PD. The intent of this additional follow-up assessment is to minimise the discordance between investigator and ICR assessments. The scans from all assessments of tumour response, including the follow-up assessment, will be sent for ICR review.

Post-intervention Follow-up Period: After study intervention discontinuation, all participants will undergo an end-of-treatment visit (within 7 days of the decision to stop treatment) and will be followed up for safety assessments CCI after their last dose of study intervention (ie, the Safety Follow-up Visit). If the day on which the investigator determines that the patient should discontinue study intervention is over CCI after the last dose of study intervention received by the patient, an additional safety follow-up assessment is not needed.

Participants who have discontinued study intervention prior to objective RECIST 1.1-defined radiological progression confirmed by investigator assessment, regardless of whether or not they have commenced subsequent anticancer therapy, will be followed up with tumour

assessments according to the SoA until RECIST 1.1-defined PD, regardless of whether or not the participant started a subsequent anticancer therapy, unless they have withdrawn all consent to study-related assessments.

After discontinuation of study intervention, participants will then be followed up every 3 months (± 14 days) for collection of information on survival, including the cause and date of death, and subsequent anticancer therapy. The Post-intervention Follow-up Period will continue until death, withdrawal of consent, or the end of the study.

Statistical Methods:

The primary endpoint of the study is confirmed ORR by ICR, defined as the proportion of participants in each cohort with confirmed CR or PR as assessed by ICR based on RECIST 1.1. Objective response rate by ICR will be estimated with a 2-sided 95% exact CI using the Clopper-Pearson method based primarily on the RES population, who received at least one dose of study intervention and had measurable disease at baseline by ICR. The primary analysis and final analysis will be performed separately for each cohort.

The DCO for the primary analysis of ORR by ICR will occur approximately 6 months after the last participant for that cohort has initiated study intervention. Duration of response, DCR, BOR, TTR, PFS, OS, and available safety, immunogenicity, and PK data will also be summarised at this time.

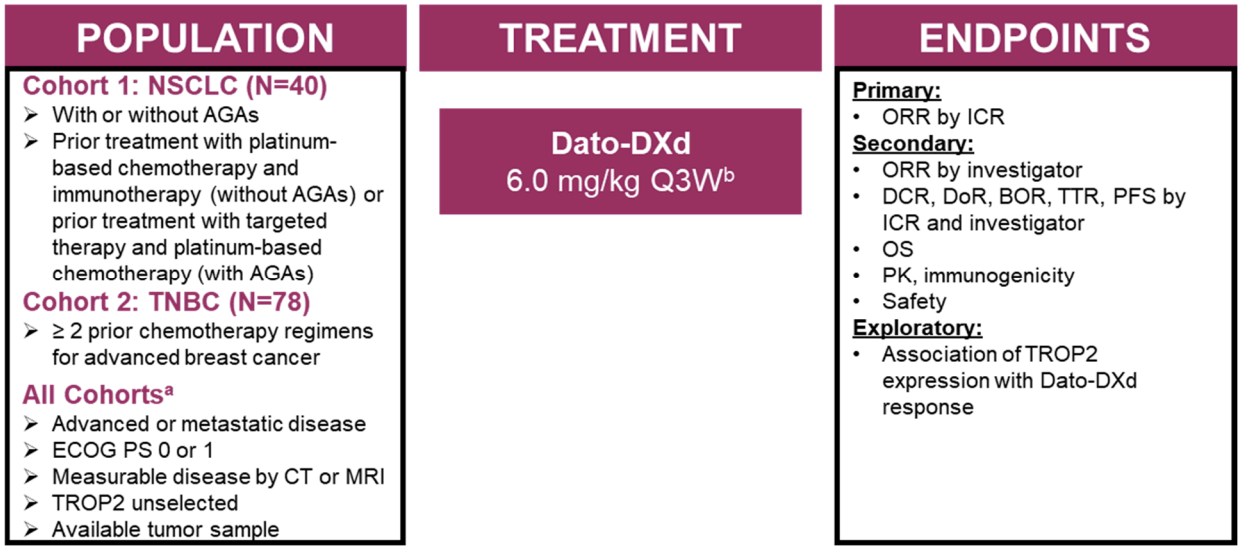
The DCO for the full final analysis of ORR by ICR will occur approximately 12 months after the last participant for that cohort has initiated study intervention. The full final analysis will report the analyses of all primary and secondary endpoints, including updated ORR and DoR, DCR, BOR, TTR, PFS, OS, PK, immunogenicity, and safety.

Safety data will be summarised descriptively.

Pharmacokinetic parameters of each participant with intensive PK samples will be estimated using non-compartmental analysis methods. Descriptive statistics will be provided for all plasma concentration data at each time point and PK parameters. The plasma concentration data will also be presented graphically as appropriate. The PK data generated in this study will be used for PopPK and E-R analyses, if data permit, to characterise the relationships of dose, exposure, efficacy, and safety endpoints. The results of the PopPK and E-R analyses will be reported separately from the clinical study report. Immunogenicity will be assessed through characterisation of incidence and titre of ADA.

1.2 Schema

Figure 1 Study Design



[a] Additional cohorts may include, but are not limited to, advanced/unresectable or metastatic gastric or gastrointestinal junction adenocarcinoma or urothelial carcinoma that is refractory or intolerant to SoC therapy or for which no SoC therapy is available.
[b] Study intervention will be delivered via intravenous infusion and continue until one of the criteria for discontinuation is met.

AGA, actionable genomic alteration; BOR, best overall response; CT, computed tomography; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ICR, independent central review; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; TNBC, triple-negative breast cancer; TROP2, tumour-associated calcium signal transducer 2; TTR, time to response.

1.3 Schedule of Activities

The procedures for this study are presented in the SoA (Table 1). Procedures and/or assessments are required from screening until data collection ends (inclusive of follow-up periods). Following the final DCO date, participants will be managed per SoC assessments at Investigator discretion.

Table 1 Schedule of Activities

Procedure	Screening [a]	Intervention period (days ±visit window)						Post-intervention period			Details in CSP section or appendix
		C1			C2	C3	C4 + until PD	EoT or E/D[b]	Follow-up		
									Safety [c]	Survival [d]	
Day	Day -28 to -1	Day 1	Day 8	Day 15	Day 1	Day 1	Day 1				
Visit window (± days)	N/A	±3	±3	±3	±3	±3	±3	-3,+7	+7	±14	
Informed consent: main study [e]	X										Section 5.1
Informed consent: intensive PK sampling (optional) [e]	X										Section 5.1
Study Procedures and Safety Assessments											
Inclusion and exclusion criteria	X	X[f]									Sections 5.1 and 5.2
Treatment assignment in IRT		X[g]									Section 6.2.2
Demography	X										Section 5.1 and 8.1
Medical history	X	X[f]									Sections 5.1, 5.2 and 8.1
Current medical conditions	X	X[f]									Sections 5.1 and 5.2
Full physical examination	X										Section 8.3.1
Targeted physical examination		X			X[h]	X[h]	X[h]	X	X		Section 8.3.1
Height	X										Section 8.3.1
Weight	X	X[f]			X[h]	X[h]	X[h]	X	X		Section 8.3.1
ECOG performance status	X	X[f]			X[h]	X[h]	X[h]	X	X		Section 8.3.5.4
12-lead ECG	X	As clinically indicated									Section 8.3.3
ECHO/MUGA (LVEF)	X	As clinically indicated									Section 8.3.5.1
Vital signs	X	X[f,h,j]			X[h,j]	X[h,j]	X[h,j]	X	X		Section 8.3.2
CCI [i]	X	X[f,h,j]			X[h,j]	X[h,j]	X[h,j]	X	X		Section 8.3.5.2
Pulmonary function tests		If ILD/pneumonitis is suspected									Section 8.3.5.2 and 8.3.5.3
ILD/pneumonitis investigation		If ILD/pneumonitis is suspected									Section 8.3.5.3

Procedure	Screening [a]	Intervention period (days ±visit window)						Post-intervention period			Details in CSP section or appendix
		C1			C2	C3	C4 + until PD	EoT or E/D[b]	Follow-up		
									Safety [c]	Survival [d]	
Day	**Day -28 to -1**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**Day 1**				
Visit window (± days)	**N/A**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-3,+7**	**+7**	**±14**	
Chest CT (HRCT preferred if feasible)		If ILD/pneumonitis is suspected									Section 8.3.5.2 and 8.3.5.3
Ophthalmologic assessments [k]	X	As clinically indicated						X			Section 8.3.5.5
Oral care plan [l]		Daily before dosing, throughout treatment, and up to the safety follow-up visit									Section 8.3.5.6
AE review	X	At every visit and may be conducted via phone if not tied to a visit						X	X	X (SAEs)	Sections 6.6 and 8.4
Prior and concomitant medication review	X	At every visit and may be conducted by phone if not tied to a visit						X	X		Sections 5.2 and 6.5
Subsequent anticancer therapy [m]									X	X	Section 7.1.2
Laboratory Assessments											
Serum or urine pregnancy test (FOCBP only)	X [n]	X [n]			X [n]	X [n]	X [n]	X [n]	X [n]		Sections 5.1, 5.2, and 8.4.14
Hepatitis B and C and HIV [o]	X										Sections 5.2 and 8.3.4
Clinical safety laboratory assessments (clinical chemistry, haematology)	X	X [f]			X [h]	X [h]	X [h]	X	X		Sections 5.1 and 8.3.4
Coagulation	X	As clinically indicated.									Section 8.3.4
Urinalysis	X	As clinically indicated									Section 8.3.4
Biomarker Assessments											
Tumour sample collection (archived or newly acquired biopsy) subject to all required approvals. [p]	X										Section 8.7.1
PK Testing											

Procedure	Screening [a]	Intervention period (days ±visit window)						Post-intervention period			Details in CSP section or appendix
		C1			C2	C3	C4 + until PD	EoT or E/D[b]	Follow-up		
									Safety [c]	Survival [d]	
Day	**Day -28 to -1**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**Day 1**				
Visit window (± days)	**N/A**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-3,+7**	**+7**	**±14**	
Pre-dose blood sample for Dato-DXd, total anti-TROP2 antibody, and DXd (MAAA-1181a) sparse PK testing (within 8 hours)		X			X		X (C4 and C8)				Section 8.6.1
Post-dose blood sample for Dato-DXd, total anti-TROP2 antibody, and DXd sparse PK testing		X [q]					X (C4 and C8) [r]				Section 8.6.1
Additional post-dose blood sample for Dato-DXd PK testing (only required for participants in the intensive PK cohort) [s]		X [t]	X	X							Section 8.6.1
Additional blood sample for Dato-DXd PK testing (if feasible)		As soon as ILD/pneumonitis is suspected									Sections 8.3.5.3 and 8.6.1
Immunogenicity Testing											
Pre-dose blood sample for immunogenicity testing (within 8 hours)		X			X		X (C4, C8, and every 4 cycles thereafter)				Section 8.6.2
Post-dose blood sample for immunogenicity testing								X	X		Section 8.6.2
Imaging and Efficacy Assessments											

Procedure	Screening [a]	Intervention period (days ±visit window)						Post-intervention period			Details in CSP section or appendix
		C1			C2	C3	C4 + until PD	EoT or E/D[b]	Follow-up		
									Safety [c]	Survival [d]	
Day	**Day -28 to -1**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**Day 1**				
Visit window (± days)	**N/A**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-3,+7**	**+7**	**±14**	
Tumour imaging (RECIST 1.1) [u]	X	Every 6 weeks (±7 days) from the date of the first dose of study intervention until RECIST 1.1-defined radiological PD by investigator assessment, whether or not the participant is still on treatment. CCI									Sections 8.2.1 and 8.2.2
Brain scan [v]	X	Participants CCI must have the lesions recorded as part of the RECIST assessment and must have a brain scan CCI									Sections 8.2.1 and 8.2.2
Bone imaging [w]	X	CCI									Sections 8.2.1 and 8.2.2
Survival status										X	Sections 7.1.2 and 8.2.4
Study Intervention Administration											
Study intervention administered (IV infusion)		X Dato-DXd at 6.0 mg/kg will be administered via IV infusion on Day 1 of each 3-week cycle									Section 6

[a] Up to 28 days before the first dose of study intervention. It is strongly recommended that screening assessments be conducted as close as possible to Day 1.

[b] Within 7 days after the decision to stop treatment. A -3, + 7-day window is allowable. If the reason for discontinuation is PD, then both "EoT/discontinuation" and "PD" visits can be conducted at the same visit.

[c] The Safety Follow-up Visit will be performed CCI after the last study intervention administration. If the day on which the investigator determines that the patient should discontinue study intervention is over CCI after the last dose of study intervention received by the patient, an additional safety follow-up assessment is not needed.

[d] Every 3 months ± 14 days.

[e] Written informed consent and any locally required privacy act document authorisation must be obtained prior to performing any CSP-specific procedures, including screening/baseline evaluations.

[f] If screening assessments have been performed within 72 hours prior to starting study intervention, they do not have to be repeated at C1 Day 1 if the participant's condition has not changed.

[g] Every effort should be made to minimise the time between treatment assignment in IRT and starting treatment (ie, within 3 business days of treatment assignment).

[h] Within 72 hours prior to infusion.

[i] If CCI is measured on the day of infusion, it should be measured CCI

[j] Assessment should also be conducted at the end of infusion.

[k] Ophthalmologic assessments including but not limited to visual acuity testing, slit lamp examination, intraocular pressure measurement, fundoscopy, and fluorescein staining will be performed at screening, as clinically indicated, and at the EoT visit by an ophthalmologist, or if unavailable, another licensed eye care provider. Please refer to the Dato-DXd Site Ophthalmologic Assessment Manual for further details.

[l] Participants will be provided an OCP prior to and during study treatment. Daily before dosing, throughout treatment, and up to the safety follow-up visit.

[m] Subsequent anti-cancer drug treatment may commence following discontinuation of study intervention, including at PD.

[n] A negative serum pregnancy test must be documented during screening for all FOCBP. If a serum pregnancy test is collected greater than 72 hours prior to the first dose of study intervention, perform a repeat pregnancy test (urine or serum per institutional guideline) within 72 hours before the first dose of study intervention. Perform repeat pregnancy tests (urine or serum per institutional guideline) within 72 hours before each infusion at each cycle, at EoT, and the first follow-up visit. A positive urine pregnancy test result must immediately be confirmed using a serum test.

[o] As required by local regulations or IRB/EC. Prior HBV surface antigen, HCV antibody test, and HIV antibody test results can be used if performed within 120 days before screening. If an HIV infection meets the criteria outlined in Section 5.2, monitoring of viral RNA load and CD4+ cell count is recommended and should be performed per local SoC (eg, every 3 months).

[p] Tumour samples collected from the primary tumour or from a metastatic site before treatment with Dato-DXd should be provided for all enrolled participants in this study based on local regulatory approval. A fresh tumour sample collected during screening is preferred if clinically feasible in the form of an FFPE tissue. For the FFPE tissues, a minimum of 5 slides of freshly prepared, unstained, 4- to 5-micron sections are required. If such a de novo collection is not feasible, an archival tumour sample collected as close to screening as possible must be provided, in the form of a minimum of 5 slides of freshly prepared, unstained, 4 to 5-micron sections from the archival FFPE tumour block. As uncontrolled oxidation processes affect tumour sections, tumour tissue blocks are preferred, if local regulation permits.

[q] Within 30 minutes after end of infusion. One additional sample at 5 hours (± 15 minutes) after start of infusion for C1 will be collected.

[r] Within one hour after end of infusion.

[s] Additional samples will be collected only for participants enrolled in selected sites.

[t] Collect samples at 7 (± 15 minutes) and 24 (± 2 hours) hours after start of infusion for C1.

[u] The baseline tumour assessment must be performed within 28 days before the start of study intervention and as close as possible to the start of study intervention.

[v] A brain scan must be performed at baseline within 28 days before the start of study intervention and as close as possible to the start of study intervention. Participants with brain metastases at baseline must have the lesions recorded as part of the RECIST assessment and must have a brain scan performed every 6 weeks (±7 days) from the date of the first dose of study intervention until radiological progression per RECIST. Otherwise, follow-up brain imaging is required only if new brain metastases are suspected.

[w] All participants should have a baseline bone scan or skeletal survey performed no more than 12 weeks before, and as close as possible to, the start of study intervention.

Note: All assessments on treatment days are to be performed prior to study intervention administration, unless otherwise indicated. Data collection following study analysis until the end of the study is described in Section 8.

AE, adverse event; HBV, hepatitis B virus; HCV, hepatitis C virus; C, cycle; CD, cluster of differentiation; CSP, Clinical Study Protocol; Dato-DXd, datopotamab deruxtecan; EC, Ethics Committee; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; E/D, Early Study Intervention/Discontinuation; EoT, end of treatment; FFPE, formalin fixed and paraffin embedded; FOCBP, female of child-bearing potential; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRCT, high-resolution computed tomography; ICF, informed consent form; ILD, interstitial lung disease; IRB, Institutional Review Board; IRT, interactive response technology; IV, intravenous; LVEF, left ventricular ejection fraction; MUGA, multigated acquisition; OCP, oral care plan; PD, progression of disease; PK, pharmacokinetic; QXW, every X weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, Version 1.1; SAE, serious adverse event; SoC, standard of care; SpO_2, peripheral capillary oxygen saturation

2 INTRODUCTION

Datopotamab deruxtecan (Dato-DXd, DS-1062a) is an ADC that binds to trophoblast cell surface protein 2 (TROP2), also known as tumour-associated calcium signal transducer 2. Dato-DXd is in development as a candidate therapy for cancer.

2.1 Study Rationale

Cancer is a major global health issue and the leading cause of death in China (Feng et al 2019, Zhang et al 2015, Zhou et al 2019) with 4.5 million new cases and 3 million deaths in 2020 (GLOBOCAN 2020). The situation in China has been alarming partly due to the aging and growing population, as well as socioeconomic development. It is essential to develop new therapies for Chinese cancer patients who are refractory or intolerant to standard therapies, or for whom no standard therapy exists.

The Phase 1 first-in-human Study DS1062-A-J101 is evaluating Dato-DXd in TROP2-unselected participants with advanced NSCLC who have relapsed from or are refractory to SoC therapy as well as in participants with advanced TNBC who have relapsed from or are refractory to SoC therapy or for whom no SoC therapy is available. An additional cohort of participants with hormone receptor-positive, HER2-negative breast cancer is currently recruiting as of March 2021. Other tumour types may also be explored in the future. Clinical data from Study DS1062-A-J101 show efficacy of Dato-DXd with a manageable toxicity profile. However, none of the patients in Study DS1062-A-J101 are from China, and there is an unmet need for more information about the safety and efficacy of Dato-DXd in the adult Chinese population.

Given these encouraging preliminary safety and efficacy data, the current study is designed to further assess the efficacy, safety, PK, and immunogenicity of Dato-DXd in adult Chinese patients with selected advanced or metastatic solid tumours. This single-arm study consists of multiple cohorts divided by indication. Cohort 1, which includes participants with advanced or metastatic NSCLC with or without AGAs who have received immune-oncology therapies and platinum-based chemotherapy (for participants with NSCLC without AGAs), or one or two prior lines of applicable targeted therapy and platinum-based chemotherapy (for participants with NSCLC with AGAs), and Cohort 2, which includes participants with inoperable locally advanced or metastatic TNBC who have received at least 2 prior chemotherapy regimens for advanced breast cancer, counting the (neo)adjuvant therapy as a prior chemotherapy regimen if progression occurred within 12 months after completion of the therapy, will be prioritised for enrolment. Future cohorts may include, but are not limited to, participants with advanced/unresectable or metastatic gastric or GEJ adenocarcinoma or urothelial carcinoma that is refractory or intolerant to SoC therapy or for which no SoC therapy is available.

2.2 Background

2.2.1 Dato-DXd

Antibody-drug conjugates are payload delivery systems that have been developed to overcome the challenges of delivering cytotoxics and cytostatics specifically into cancer cells by targeting cells that express the preferred marker.

As of 27 July 2020, AstraZeneca and Daiichi Sankyo Company, Limited (Daiichi Sankyo) entered into a joint global development and collaboration agreement for Dato-DXd, a TROP2 targeting ADC that is being developed as a therapeutic candidate for cancer.

Dato-DXd is an ADC comprising a recombinant humanised anti-TROP2 immunoglobulin G1 monoclonal antibody, MAAP-9001a, which is covalently conjugated via a cleavable drug-linker, MAAA-1162a (the complex of MAAA-1181a, hereafter referred to as DXd, and a maleimide tetrapeptide linker), using thioether bonds to the topoisomerase I inhibitor DXd. This tumour-selective cleavable drug-linker is stable in the systemic circulation. Dato-DXd binds to the transmembrane glycoprotein TROP2, which is highly expressed on the cell surface of epithelial tumours and is internalised. The drug component of Dato-DXd, DXd (a DNA topoisomerase I inhibitor), is released by enzymatic processes after internalisation, leading to inhibition of tumour growth and apoptosis of the target tumour cells and neighbouring tumour cells via the inhibition of DNA topoisomerase I.

TROP2 is highly expressed in various epithelial tumours, including oesophageal squamous cell carcinoma (Nakashima et al 2004), breast cancer (Lin et al 2013), and NSCLC (Kobayashi et al 2010). Its expression correlates with aggressive tumour behaviour and has been used as a prognostic marker in several types of cancer (Fong et al 2008, Kobayashi et al 2010, Lin et al 2013, Mühlmann et al 2009).
In vitro studies indicate that Dato-DXd exhibits TROP2 expression-dependent cell growth inhibitory activity, and in vivo studies using a tumour-bearing mouse model indicate that administration of Dato-DXd results in the regression of TROP2-positive tumours. The biodistribution and antitumour activity of the ADC are expected to depend on the expression level of the target antigen in tumour tissue. The targeted indications of the Dato-DXd programme have high expression of TROP2 (Cubas et al 2009, Shvartsur et al 2015).

There are currently no TROP2-directed therapies approved for the treatment of NSCLC. A detailed description of the chemistry, pharmacology, mechanism of action, efficacy, and safety of Dato-DXd is provided in the IB.

2.2.2 Non-small-cell Lung Cancer

As of 2020, lung cancer was the most common cause of death worldwide, accounting for 1.8 million annual deaths (https://www.who.int/news-room/fact-sheets/detail/cancer). In China, lung cancer is also the malignant tumour with the highest incidence rate and mortality

rate (Sung et al 2021, Chen et al 2016). Advances in early detection of lung cancer have been slow, and more than half of lung cancers are still diagnosed at an advanced stage (Siegel et al 2019). Only 18.6% of all patients with lung cancer are alive 5 years or more after diagnosis (Howlader et al 2017). Non-small-cell lung cancer accounts for 80% to 85% of all lung cancers (American Cancer Society 2020). The introduction of targeted therapies and checkpoint inhibitors in recent years has improved the treatment landscape, and patients with metastatic NSCLC are now surviving longer (Paz-Ares et al 2018, Ricciardi et al 2014, NCCN Practice Guidelines in Oncology 2021). A number of genomic alterations that have an impact on therapy selection have been identified in NSCLC, and molecular testing is part of the SoC in the evaluation of NSCLC (NCCN Practice Guidelines in Oncology 2021). These include, but not limited to, *EGFR* gene mutations, *ALK* gene rearrangements, *ROS1* rearrangements, *NTRK* gene fusions, *BRAF* point mutations, *RET* gene rearrangements, and *METex14* skipping variants. For the subset of patients with NSCLC whose tumours have AGAs, targeted therapies (eg, EGFR, ALK, ROS1, *METex14* skipping, or RET kinase inhibitors) are recommended during the course of treatment as systemic treatments. However, once patients have developed acquired resistance to the various targeted therapies and progressed after platinum-based chemotherapy, therapeutic options are generally limited to cytotoxic agents deployed as monotherapy, and median survival times are less than one year.

For patients with metastatic NSCLC and negative test results for AGAs, the NCCN and CSCO guidelines recommend an immune checkpoint inhibitor with or without chemotherapy as first-line therapy. The expression of PD-L1 is often assessed to select patients for immune checkpoint inhibitors. For patients with PD-L1 levels of 1% or more, especially with 50% or more, immune checkpoint inhibitor monotherapy is recommended based on the results from the KEYNOTE 042 study (Cho et al 2021). Platinum-based chemotherapy with or without immune checkpoint inhibitors is recommended for patients with metastatic NSCLC and negative test results for AGAs regardless of PD-L1 status, based on the results from the KEYNOTE-189 (Gray et al 2020), KEYNOTE 407 (Paz-Ares et al 2018), CameL (Zhou et al 2021), ORIENT-11 (Yang et al 2020), ORIENT-12 (Zhou et al 2020a), RATIONALE 304 (Lu et al 2020), RATIONALE 307 (Wang et al 2020), and GEMSTONE 302 study (Zhou et al 2020b).

Among patients relapsing or progressing after frontline platinum-containing doublet chemotherapy, the Checkmate-017 and Checkmate-057 studies demonstrated superior OS of nivolumab over docetaxel monotherapy in patients with squamous and non-squamous NSCLC, respectively (Brahmer et al 2015, Borghaei et al 2015). For patients relapsing or progressing after frontline immune checkpoint inhibitor monotherapy, chemotherapy is recommended by NCCN and CSCO guidelines.

As a result of these and similar studies, patients with NSCLC and without AGAs generally receive platinum doublets and immune checkpoint inhibitors, either in combination or in

sequence, as the first one or two lines of therapy. None of these therapies, however, are considered curative in the advanced setting, and once patients have progressed after them, therapeutic options are generally limited to cytotoxic agents deployed as monotherapy, and median survival times are less than one year.

Docetaxel monotherapy remains perhaps the most widely used treatment for patients whose NSCLC has progressed after platinum-based chemotherapy and immune checkpoint inhibitors (for patients with NSCLC without AGAs) or target therapies (for patients with NSCLC with AGAs), consistent with NCCN and CSCO guidelines. The INTEREST (Kim et al 2008), Checkmate 078 (Wu et al 2019), KEYNOTE-010 (Herbst et al 2016), and OAK (Rittmeyer et al 2017) studies suggest that the NSCLC patients who received docetaxel as second-line therapy have median PFS of 2.0 months to 4 months and median survival of 8.0 months to 9.6 months. Consequently, novel treatments for patients who have advanced or metastatic NSCLC after receiving platinum-based chemotherapy and immune-oncology therapies (for patients with NSCLC without AGAs), or targeted therapies (for patients with NSCLC with AGAs), are still needed to improve prognosis, control disease, and prevent symptoms while minimising toxicity; this represents an area of considerable unmet medical need. A new class of therapy with better efficacy and fewer side effects would therefore be a preferred option in this treatment setting.

2.2.3 Triple-negative Breast Cancer

Triple-negative breast cancer accounts for approximately 15% of invasive breast cancers (Li et al 2018, Si et al 2015) and is a subgroup that is not amenable to hormonal-based therapeutics available for the larger group of breast cancer that express oestrogen and/or progesterone, or anti-HER2 therapeutics for those that have elevated HER2 production. Compared with other subtypes of breast cancer, the survival time of TNBC patients is shorter, and the mortality rate is 40% within the first 5 years after diagnosis (Dent et al 2007). Triple-negative breast cancer is highly invasive, and approximately 46% of TNBC patients will have distant metastasis. The median survival time after metastasis is only 13.3 months, and the recurrence rate after surgery is as high as 25%. Metastasis often involves the brain and visceral organs. Distant metastasis mostly occurs in the third year after diagnosis (Lin et al 2008). The average time to relapse in non-TNBC patients is 35 to 67 months, while that in TNBC patients is only 19 to 40 months. The mortality rate of TNBC patients within 3 months after recurrence is as high as 75% (Gluz et al 2009, Zhang et al 2015). In China, therapeutic options are currently limited to sequential chemotherapies. Sequential single chemotherapy agents (given until PD or unacceptable toxicity) are recommended in preference to chemotherapy combinations except in patients with a need for rapid symptom and/or disease control. The most commonly used agents in the metastatic setting are taxanes, anthracyclines, platinum agents, vinorelbine, capecitabine, and eribulin. Although chemotherapy significantly improves clinical outcomes for TNBC patients, recurrence rates remain relatively high and TNBC tumours often develop resistance to chemotherapeutic agents (Carey et al 2007,

Foulkes et al 2010). The limited treatment options and aggressive phenotypes of TNBC highlight the need for advances in more effective therapeutic treatment options for TNBC patients, especially in treated patients who are refractory to chemotherapy or who relapse to multiple lines of chemotherapy agents.

A TROP2 ADC sacituzumab govitecan-hziy (IMMU-132; Trodelvy™), was recently approved by the US FDA, but is not currently approved in China, for the treatment of adult patients with unresectable locally advanced or metastatic TNBC who have received 2 or more prior systemic therapies, with at least one of them for metastatic disease based on the results from the Phase 3 IMMU-132-05 study (Bardia et al 2021a). Thus, there remains an unmet medical need for treatment options for Chinese patients with advanced TNBC.

Dato-DXd has shown promising preliminary efficacy in TNBC patients in Study DS1062-A-J101, but this study did not include participants from China (Bardia 2021). The current study intends to fill a crucial knowledge gap by evaluating Dato-DXd in Chinese participants with advanced TNBC.

2.2.4 Other Solid Tumours

2.2.4.1 Gastric or Gastroesophageal Junction Adenocarcinoma

Gastric adenocarcinoma is the fifth most common cancer worldwide. In 2020, there were over one million newly diagnosed cases and 768 thousand deaths annually worldwide, making gastric cancer the fourth leading cause of cancer-related deaths in the world (GLOBOCAN 2020b, Torre et al 2015). Globally, the highest incidence of GC is reported in East Asian countries, particularly China (with nearly half of global cases), Japan, and South Korea. In China, gastric adenocarcinoma is now the second most commonly diagnosed cancer and is the second leading cause of cancer-related death (Chen et al 2016). GLOBOCAN statistics estimate that there were over 478 thousand new cases of gastric adenocarcinoma and over 373 thousand deaths caused by gastric adenocarcinoma in China in 2018 (GLOBOCAN 2020). Worldwide, approximately 65% of gastric adenocarcinoma patients present with locally advanced or metastatic disease with a poor outcome (Meza-Junco and Sawyer 2012). In China, this figure is higher, with approximately 80% of patients presenting with advanced disease and likely to have a poor outcome: the 5-year relative survival rate was 35.9% in patients with GC in the period from 2010 to 2014 (Yang et al 2018). In patients with GC who are refractory to standard therapies, the median life expectancy is approximately 6 months, underlining the high unmet medical need.

2.2.4.2 Urothelial Carcinoma

Urothelial cancer is the ninth most common cancer worldwide (Torre et al 2015). The SoC in patients with advanced bladder cancer has been platinum-based combination therapy regimens. Despite initial high response rates, most patients inevitably progress; in the second

line setting, immunotherapy with checkpoint inhibitors is utilised with ORRs approximately in the 20% range (Balar et al 2017).

Sacituzumab govitecan-hziy is approved by the US FDA, but not in China, for use in patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and either a PD-1 or PD-L1 inhibitor based on the Phase 2 TROPHY study (Tagawa et al 2021).

2.2.5 Other TROP2-directed Antibody-Drug Conjugate Therapies

Sacituzumab govitecan-hziy, a TROP2-directed ADC, is approved by the US FDA to use in certain patients with metastatic TNBC or locally advanced or metastatic urothelial cancer (see Section 2.2.3 and Section 2.2.4.2).

There are no approved TROP2-directed ADC therapies for other tumour types. However, sacituzumab govitecan-hziy has demonstrated antitumour efficacy and acceptable tolerability in a Phase 1/Phase 2 multicentre Study (IMMU-132-01) in patients with advanced epithelial cancers (Bardia et al 2021b). This basket trial showed that ORR was 31.5% (17 of 54 participants) for hormone receptor-positive metastatic breast cancer, 16.7% (9 of 54 participants) for NSCLC, 17.7% (11 of 62 participants) for SCLC, 5.3% (1 of 19 participants) for oesophageal carcinoma, 3.2% (1 of 31 participants) for colorectal cancer, 22.2% (4 of 18 participants) for endometrial cancer, and 9.1% (1 of 11 participants) for castrate-resistant prostate cancer.

2.3 Benefit/Risk Assessment

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP and applicable regulatory requirements.

More detailed information about the known and expected benefits and potential risks of Dato-DXd may be found in the IB. A risk assessment is included in Table 2.

2.3.1 Risk Assessment

A risk assessment is included in Table 2.

Table 2 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study intervention: Dato-DXd		
CCI [redacted] is considered an important	Based on data from ongoing Study DS1062-A-J101 (TROPION-PanTumor01) in	These identified and potential risks are generally manageable through dose

identified risk associated with administration of Dato-DXd. Other identified risks for Dato-DXd are CCI [redacted] CCI [redacted] are considered potential risks for Dato-DXd. CCI [redacted] is considered an important potential risk. CCI [redacted] impairment. Information on AEs is presented in Section 8.4.	participants with NSCLC (N = CCI) as of CCI [redacted] participants were noted to have potential ILD/pneumonitis events. Of the CCI participants with potential ILD/pneumonitis events, CCI [redacted] had ILD/pneumonitis events adjudicated as drug-related, including CCI participants CCI [redacted] in the 6 mg/kg dose group. Three cases of Dato-DXd-related ILD/pneumonitis with a fatal outcome have been reported, all in the 8 mg/kg dose group. No fatal cases of ILD/pneumonitis were observed in the 6 mg/kg dose group. As of the DCO date of CCI [redacted] for all indications, CCI [redacted] of CCI participants treated with Dato-DXd experienced serious IRR events. All CCI events were reported as CCI [redacted] and related to Dato-DXd. Based on a cumulative review of safety data, including available nonclinical, clinical, and epidemiologic information and scientific literature (published and unpublished), reported toxicities for the same class of agents of the mAb and payload as Dato-DXd, and taking into consideration biological plausibility, the important identified risk is CCI [redacted] is considered an important potential risk. No confirmed cases of Hy's Law or DILI have been observed. Please see the current version of the IB for a detailed and up-to-date summary of data including AEs, SAEs, and CTCAE Grade 3 to 5 events reported across the Dato-DXd programme.	modification (Section 6.6) and routine clinical practice. CCI [redacted] Specific inclusion/exclusion criteria (Section 5) and TMGs (see the TMG Annex) are currently in place to mitigate the risks and AESIs.

AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; Dato-DXd, datopotamab deruxtecan; DCO, data cutoff; DILI, drug-induced liver injury; IB, investigator's brochure; ILD, interstitial lung disease; IRR, infusion-related reaction; mAb, monoclonal antibody; NSCLC, non-small-cell lung cancer; SAE, serious adverse event; TMG, toxicity management guidelines

2.3.2 Benefit Assessment

Dato-DXd is under development for the treatment of lung and breast tumours. In vitro studies indicate that Dato-DXd exhibits TROP2 expression-dependent cell growth inhibitory activity, and in vivo studies using a tumour-bearing mouse model indicate that administration of Dato-DXd results in the regression of TROP2-positive tumours.

Supportive preliminary clinical data on Dato-DXd monotherapy are available from ongoing Phase I first-in-human study, DS1062-A-J101 (TROPION-PanTumor01), evaluating escalating doses of Dato-DXd (0.27 mg/kg to 10 mg/kg) in participants with heavily pre-treated advanced NSCLC and TNBC, relapsed or refractory to SoC therapy. These data have demonstrated efficacy across dose groups, with tumour responses observed at doses of 4, 6, and 8 mg/kg and an acceptable and manageable toxicity profile (see Section 4.3). The patient populations tested to date include TROP2-unselected patients with advanced NSCLC with or without AGAs who have relapsed from or are refractory to SoC therapy and patients with advanced TNBC who have relapsed from or are refractory to SoC therapy or for whom no SoC therapy is available. As of the DCO date of 06 April 2021, 34 NSCLC participants with AGA were treated with Dato-DXd at doses of 4.0, 6.0, or 8.0 mg/kg and were evaluable for response assessment. The ORR by ICR was 35.3% (12/34 [95% CI, 19.7-53.5]). The overall DCR was 82.4%, and the median DoR was 9.5 mo (95% CI, 3.3-NE). The efficacy and safety profile of Dato-DXd as a late-line treatment in advanced NSCLC patients with or without AGA was comparable. These results from Study DS1062-A-J101, which has sites in the US and Japan, support the evaluation of benefit for patients in China in the present study.

TROP2, the molecular target of Dato-DXd, is associated with increased tumour growth and enhanced proliferation, cell migration, and anchorage-independent growth. TROP2 is overexpressed in the majority of human epithelial cancers (including oral, head-and-neck, thyroid, lung, oesophageal, gastric, colorectal, pancreatic, breast, renal, uterine, cervical, ovarian cancers, and glioma) (Goldenberg et al 2018) but with lower expression in certain normal tissues. Thus, a TROP2-directed ADC strategy is likely to benefit patients with multiple cancer types, including those not yet tested in Study DS1062-A-J101.

2.3.3 Overall Benefit/Risk Conclusion

There is an unmet medical need for efficacious and safe therapies in treatment of patients with advanced or metastatic solid tumours, especially tumours that are relapsed or refractory to SoC therapy. Preliminary results from Study DS1062-A-J101 have shown promising efficacy of Dato-DXd at a dose of 6.0 mg/kg Q3W and support further evaluation of Dato-DXd in the Chinese population and for Chinese patients with other advanced solid tumours. In this cohort, the most frequent TEAEs were nausea/vomiting, stomatitis, fatigue, alopecia, decreased appetite, and constipation. The toxicity profile of the 6.0 mg/kg dose regimen of Dato-DXd was acceptable and manageable.

The 2 most relevant risks considered for the benefit/risk assessment are the important identified risk of CCI and the identified risk of CCI, both of which can be CCI. To specifically mitigate these risks, strict inclusion/exclusion criteria have been included in this CSP. Participants will also be monitored closely throughout the study and clinical and laboratory assessments will be performed before every cycle. Toxicity management guidelines will assist with the management of the most commonly seen AEs (see the TMG Annex).

Overall, Dato-DXd is a potent anticancer therapy with the potential to provide an improved meaningful clinical benefit and a more favourable safety profile compared with the current SoC for patients with advanced or metastatic solid tumours. It is therefore of key importance to evaluate the role of Dato-DXd in Chinese patients with advanced or metastatic solid tumours. Furthermore, Dato-DXd may provide benefit to Chinese patients with other advanced or metastatic solid tumours who are refractory or intolerant to SoC therapy, or for whom no SoC therapy is available, and those patients will be part of future cohorts of this study. Considering the measures to minimise risks to participants, the risks identified in association with Dato-DXd are justified by the anticipated benefits that may be afforded to participants with advanced or metastatic solid tumours. The benefit/risk assessment supports the proposed study.

3 OBJECTIVES AND ENDPOINTS

The objectives and endpoints of this study for each cohort are shown in Table 3.

Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
To estimate the effectiveness of Dato-DXd by assessment of confirmed ORR by ICR.	Confirmed ORR is defined as the proportion of participants in each cohort who have a confirmed CR or confirmed PR, as assessed by ICR per RECIST 1.1. The measure of interest is the estimate of confirmed ORR.
Secondary	
To estimate the effectiveness of Dato-DXd by assessment of confirmed ORR by investigator assessment.	Confirmed ORR is defined as the proportion of participants in each cohort who have a confirmed CR or confirmed PR, as determined by investigator assessment per RECIST 1.1.
To estimate the effectiveness of Dato-DXd by assessment of DoR.	Duration of response is defined as the time from the date of first documented response (which is subsequently confirmed) until date of documented progression per RECIST 1.1, as assessed by ICR and by investigator, or death due to any cause.
To estimate the effectiveness of Dato-DXd by assessment of DCR.	Disease control rate is defined as the percentage of participants who have a confirmed CR or PR or who have SD per RECIST 1.1, as assessed by ICR and by investigator.
To estimate the effectiveness of Dato-DXd by assessment of BOR.	Best overall response is defined as participant's best confirmed response during their participation in the study, but prior to starting any subsequent anticancer therapy, up until RECIST 1.1-defined PD or the last evaluable assessment in the absence of RECIST 1.1-defined progression. Best overall response will be assessed by ICR and by investigator per RECIST 1.1.
To estimate the effectiveness of Dato-DXd by assessment of TTR.	Time to response is defined as the time from the date of the first dose of study intervention until the date of first documented objective response, which is subsequently confirmed per RECIST 1.1, as assessed by ICR and by investigator.
To estimate the effectiveness of Dato-DXd by assessment of PFS.	Progression-free survival is defined as time from the date of the first dose of study intervention until progression per RECIST 1.1, as assessed by ICR and by investigator, or death due to any cause.

Objectives	Endpoints
To estimate the effectiveness of Dato-DXd by assessment of OS.	Overall survival is defined as the time from the date of the first dose of study intervention to the date of death due to any cause.
To assess the safety and tolerability of Dato-DXd.	Safety and tolerability are evaluated in terms of TEAEs, AESIs including ILD evaluated by an independent adjudication committee, vital signs, and clinical laboratory, ECG, ECHO/MUGA parameters, and ophthalmologic findings.
To evaluate the PK of Dato-DXd.	Plasma concentrations and appropriate PK parameters of Dato-DXd, total anti-TROP2 antibody, and DXd will be calculated for participants with PK samples if data permit.
To investigate the immunogenicity of Dato-DXd.	The presence of ADAs against Dato-DXd will be evaluated. Titre will be determined when ADA is positive.
Exploratory	
To investigate the association of a biomarker (TROP2) with response (ORR, PFS, and OS) to Dato-DXd.	Expression of TROP2 will be measured in tumour samples.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 1/Phase 2, multicentre, open-label, multiple-cohort study, which is designed to evaluate the efficacy, safety, PK, and immunogenicity of Dato-DXd in adult Chinese participants with advanced or metastatic solid tumours. It is a single-arm study with no blinding.

This study is divided into cohorts of participants with the same tumour type. The starting cohorts are Cohort 1 (NSCLC) and Cohort 2 (TNBC). Future cohorts will consist of other advanced or metastatic solid tumour types, including, but not limited to, advanced/unresectable or metastatic gastric or GEJ adenocarcinoma or urothelial carcinoma that is refractory or intolerant to SoC therapy or for which no SoC therapy is available. Cohort 1 and Cohort 2 will be prioritised for immediate enrolment and the CSP will be amended as needed for the future cohorts.

Cohort 1: The target population of Cohort 1 is adult Chinese participants with advanced or metastatic NSCLC with or without AGAs (ie, alterations in genes with approved therapies, such as *EGFR, ALK,* or other known AGAs). Eligible participants without AGAs will have been previously treated with platinum-based chemotherapy and anti-PD-1/anti-PD-L1 monoclonal antibody either in combination or sequentially. Participants without AGAs who received anti-PD-1/anti-PD-L1 monoclonal antibody as frontline therapy may have received

the combination of platinum-based chemotherapy and anti-PD-1/anti-PD-L1 monoclonal antibody in the second-line setting. Eligible participants with AGAs will have been previously treated with one or two prior lines of an applicable targeted therapy that is approved for the participant's genomic alteration and platinum-based chemotherapy as the only prior line of cytotoxic therapy. Participants with AGAs may have received up to one anti-PD-1/anti-PD-L1 monoclonal antibody treatment alone or in combination with chemotherapy. A total of approximately 40 eligible participants in China will be enrolled in this cohort. Cohort 1 will enrol approximately [redacted] participants with AGAs.

Cohort 2: The target population of Cohort 2 is adult Chinese participants with inoperable locally advanced or metastatic TNBC who have received at least 2 prior chemotherapy regimens for advanced breast cancer, counting the (neo)adjuvant therapy as a prior chemotherapy regimen if progression occurred within 12 months after completion of the therapy (DFI $\leq$ 12 months). A total of approximately 78 eligible participants in China will be enrolled in this cohort. Cohort 2 will enrol at most around 20% (approximately N=15) of enrolled participants with a DFI $\leq$ 12 months.

Enrolled participants will be treated with Dato-DXd at 6.0 mg/kg via an IV infusion on Day 1, Q3W.

Note: 'Screened' means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. 'Enrolled' means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process and the participant is confirmed as eligible. Potential participants who are screened for the purpose of determining eligibility for the study, but are not enrolled, are considered 'screen failures.'

The primary objective of the study is to estimate the effectiveness of Dato-DXd by assessment of confirmed ORR by ICR.

A study-level flow diagram is presented in Section 1.2.

4.1.1 Study Overview

The study will be divided into 3 periods: the Screening Period, Intervention Period, and Post-intervention Follow-up Period.

Screening Period: The Screening Period will start on the day of signing the ICF and have a maximum duration of 28 days. Rescreening is permitted one time. During the 28-day Screening Period, participants' eligibility will be confirmed. Participants will undergo the assessments described in the SoA (see Section 1.3).

The study start date is the date when the first participant has signed an ICF. A participant is eligible to be enrolled into the study when the investigator or designee has obtained written informed consent, has confirmed all eligibility criteria have been met by the participant, and all Screening procedures have been completed.

Intervention Period: Eligible participants will enter the Intervention Period. The Intervention Period starts on Cycle 1 Day 1 and continues, as described in the SoA (see Section 1.3), until a participant permanently discontinues Dato-DXd. During the Intervention Period, participants will receive Dato-DXd at 6.0 mg/kg via an IV infusion Q3W until they meet one of the discontinuation criteria (see Section 6.2.2.1 and Section 7.1). See Section 6.6 for the dose modification criteria.

Participants will undergo radiographic assessment of tumour response based on RECIST 1.1 every 6 weeks (±7 days) from the date of the first dose of study intervention until radiographic PD as assessed by investigator. Following PD assessed by investigator, one additional follow-up tumour assessment should be performed at the next scheduled imaging visit and no less than 4 weeks after the prior assessment of PD. The intent of this additional follow-up assessment is to minimise the discordance between investigator and ICR assessments.

Post-intervention Follow-up Period: The Post-intervention Follow-up Period will start upon permanent discontinuation of Dato-DXd. After study intervention discontinuation, all participants will undergo an end-of-treatment visit (within 7 days of the decision to stop treatment) and will be followed up for safety assessments CCI after their last dose of study intervention (ie, the Safety Follow-up Visit), as described in the SoA (see Section 1.3). If the day on which the investigator determines that the patient should discontinue study intervention is over CCI after the last dose of study intervention received by the patient, an additional follow-up assessment is not needed.

Participants who have discontinued treatment without objective RECIST 1.1-defined radiological progression confirmed by investigator assessment, regardless of whether or not they have commenced subsequent anticancer therapy, will be followed up with tumour assessments as indicated in the SoA (see Section 1.3) until RECIST 1.1-defined PD regardless of whether or not the participant started a subsequent anticancer therapy, unless they have withdrawn all consent to study-related assessments.

After discontinuation of study intervention, participants will then be followed up every 3 months (±14 days) for collection of information on survival, including the cause and date of death, and subsequent anticancer therapy. The Post-intervention Follow-up Period will continue until death, withdrawal of consent, or the end of the study (ie, progression/survival follow-up), as per the SoA (see Section 1.3).

The DCO for the primary analysis of ORR by ICR will occur approximately 6 months after the last participant for that cohort has initiated study intervention, and the DCO for the full final analysis of ORR by ICR will occur approximately 12 months after the last participant for that cohort has initiated study intervention.

4.1.2 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with COVID-19 or a similar pandemic infection), which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The investigator or designee should contact the study sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with GCP, and minimise risks to study integrity.

Where allowable by local health authorities, ECs, health care provider guidelines (eg, hospital policies), or local government, these changes may include the following options:

- Obtaining reconsent for the mitigation procedures (note: in the case of verbal reconsent, the ICF should be signed at the participant's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated study physician.
- Home or remote visit: Performed by a site qualified HCP or HCP provided by a TPV.
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix H.

4.2 Scientific Rationale for Study Design

This is a Phase 1/Phase 2, multicentre, open-label, multiple-cohort study of Dato-DXd, which is designed to evaluate the efficacy, safety, PK, and immunogenicity of Dato-DXd in adult Chinese participants with advanced NSCLC, TNBC, gastric or GEJ cancer, urothelial cancer, and other solid tumours. It is a single-arm study with no blinding.

There is an unmet need for treatments for many patients with advanced or metastatic solid tumours. Thus, the Phase 1 first-in-human Study DS1062-A-J101 is evaluating Dato-DXd in TROP2-unselected participants with advanced NSCLC who have relapsed from or are refractory to SoC therapy as well as in participants with inoperable locally advanced or metastatic TNBC. An additional cohort of participants with hormone receptor-positive, HER2-negative breast cancer is currently recruiting as of March 2021. Other tumour types may also be explored in the future. Clinical data from Study DS1062-A-J101 show efficacy of Dato-DXd with a manageable toxicity profile. However, none of the participants in Study DS1062-A-J101 are from China and there is an unmet need for more information about the safety and efficacy of Dato-DXd in the adult Chinese population.

Given these encouraging preliminary safety and efficacy data for patients with advanced NSCLC and TNBC, the current study will prioritise these patient groups to further assess the efficacy, safety, PK, and immunogenicity of Dato-DXd in adult Chinese participants. Thus, the study will immediately enrol participants in Cohort 1 (NSCLC) and Cohort 2 (TNBC).

The single-arm study design will provide new efficacy and safety information on an important patient population and will support the global therapeutic development for Dato-DXd.

4.2.1 Rationale for Study Endpoints

The primary endpoint is confirmed ORR assessed by ICR, defined as the proportion of participants in each cohort with confirmed CR or confirmed PR, as assessed by ICR based on RECIST 1.1. Confirmed ORR by ICR represents the percentage of participants in each cohort whose disease decreases in size or disappears and provides an early signal for clinical benefit since it is a direct measure of the drug's antitumour activity. It is an appropriate and reasonable efficacy endpoint for single-arm studies considering the unmet medical needs and the encouraging efficacy data in terms of ORR by ICR observed in Study DS1062-A-J101, in accordance with the requirements of the National Medical Products Administration's Center for Drug Evaluation.

Additional secondary efficacy endpoints for each cohort (ORR assessed by investigator; DoR, DCR, BOR, TTR, and PFS by investigator assessment and ICR; and OS) will be used to further evaluate efficacy and to corroborate the benefits of antitumour effects demonstrated by confirmed ORR as assessed by ICR.

As part of the secondary endpoint assessment, blood samples will be taken to allow for research into the PK and immunogenicity of Dato-DXd. The safety and tolerability of Dato-DXd will be assessed by the standard safety endpoints. Careful consideration has been given to the mitigation of risks related to the mode of action and the nature of the target, which will be closely monitored during the study.

4.2.2 Rationale for Study Design in TNBC Cohort

The efficacy of sacituzumab govitecan-hziy was relatively poorer in TNBC patients with brain metastasis based on the published data from IMMU-132-05 study, with an ORR of 3.1% and clinical benefit rate of 9.4% (Bardia et al 2021a). Dato-DXd has demonstrated promising antitumour efficacy in Study DS1062-A-J101 in patients with advanced/metastatic NSCLC regardless of brain metastasis. However, because there is only limited data from the Study DS1062-A-J101 TNBC cohort to assess the efficacy and safety of Dato-DXd in TNBC patients with brain metastasis, the TNBC cohort will exclude participants with brain metastases.

The DFI from the completion of (neo)adjuvant chemotherapy is considered to be one of the key factors with prognostic impact in TNBC (Deluche et al 2020). DFI plays an important role in the prognosis for patients with relapsed breast cancer, as longer DFI is associated with superior prognostic outcome compared with shorter DFI (Dawood et al 2010). Participants with inoperable locally advanced or metastatic breast cancer with a DFI $\leq$ 12 months will be capped at around 20%. This distribution of participants is supported by the real-world prevalence and the KEYNOTE-355 study (Cortes et al 2020).

4.3 Justification for Dose

The 6 mg/kg IV dose of Dato-DXd was selected based on results from the ongoing Phase I, 2-part (dose escalation and dose expansion), multicentre, nonrandomised, open-label, multiple dose, first-in-human study (Study DS1062-A-J101 [TROPION-PanTumor01]) in participants with advanced solid tumours. In this study, Dato-DXd showed a generally tolerable safety profile in participants with NSCLC across a dose range of 0.27 mg/kg to 8 mg/kg. During the dose escalation phase, the non-tolerated dose for Dato-DXd was 10.0 mg/kg and the maximum tolerated dose (8 mg/kg) was determined.

As of CCI , data are available for 210 participants with NSCLC who were treated with Dato-DXd in the 0.27 mg/kg to 10.0 mg/kg Q3W cohorts.

Out of 180 response-evaluable participants (treated with Dato-DXd at doses of 4 mg/kg [50 participants], 6 mg/kg [50 participants], and 8 mg/kg [80 participants]), the ORR by blinded independent central review was 22.0% (11 PRs in 50 participants) in the 4 mg/kg dose group, 26.0% (13 PRs in 50 participants) in the 6 mg/kg dose group and 23.8% (18 PRs and 1 CR in 80 participants) in the 8 mg/kg dose group. The DCR was 76.0% (11 PRs and 26 SDs in 50 participants) in the 4 mg/kg dose group, 70.0% (13 PRs and 20 SDs in 50 participants) in the 6 mg/kg dose group, and 78.8% (1 CR, 18 PRs and 42 SDs in 80 participants) in the 8 mg/kg dose group.

Dato-DXd has an important identified CCI that can have a life threatening or fatal outcome. As of CCI , CCI

CCI have been reported in participants with NSCLC in Study DS1062-A-J101; (TROPION-PanTumor01), all in the 8 mg/kg dose group. CCI of ILD/pneumonitis were observed in the 6 mg/kg dose group (see Table 2). Toxicity management guidelines are in place to address toxicity (see the Annex document to this CSP for Dato-DXd). Dose-dependent effects and trends were observed with a larger proportion of participants in the higher dose groups experiencing TEAEs that were severe, serious, and which resulted in dose delay, reduction, and discontinuation, compared with participants in lower dose groups.

An E-R analysis of the Study DS1062-A-J101 (TROPION-PanTumor01) study data, including response, sum of diameters, PFS, and key AE (eg, stomatitis/mucosal inflammation) endpoints, suggested that the 6 mg/kg Q3W dose had better efficacy than the 4 mg/kg q3w dose of Dato-DXd and the 8 mg/kg Q3W dose (maximum tolerated dose) had additional safety liability with no significant improvement in efficacy relative to the 6 mg/kg q3w dose of Dato-DXd. Hence, the 6 mg/kg dose is the optimal monotherapy dose for further development of Dato-DXd in clinical studies.

The proposed dose should also be appropriate for the Chinese patients in this study since no clinically relevant ethnic difference in Dato-DXd exposure is expected with the treatment of Dato-DXd in Chinese patients based on the preliminary data from the DS1062-A-J101 study. No notable differences were observed in exposure of Dato-DXd, total anti-TROP2 antibody, and DXd (AUC_{tau} and C_{max}) between Japanese and non-Japanese populations.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit shown in the SoA (Section 1.3) and undergone determination of OS.

The study may be stopped if, in the judgment of AstraZeneca, study participants are placed at undue risk because of clinically significant findings.

The end of the study is defined as the time of the DCO for the final analysis. The final analysis will be performed approximately 12 months after the last participant has initiated study intervention. Participants may be withdrawn from the study at this time; however, participants may remain on study intervention beyond closure of the database if, in the opinion of the investigator, they continue to receive benefit from study intervention and have no evidence of PD.

See Section 6.7 for details on participant management following the final DCO as well as following study completion.

5 STUDY POPULATION

This study is divided into cohorts of participants with the same tumour type. The starting cohorts are Cohort 1 (NSCLC) and Cohort 2 (TNBC). Future cohorts will consist of other advanced or metastatic solid tumour types, including, but not limited to, gastric or GEJ cancer, urothelial cancer, and other solid tumours. Cohort 1 and Cohort 2 will be prioritised for immediate enrolment and the CSP will be amended as needed for the future cohorts.

Cohort 1: The target population of Cohort 1 is adult Chinese participants with advanced or metastatic NSCLC with or without AGAs (ie, alterations in genes with approved therapies, such as *EGFR, ALK,* or other known AGAs). Eligible participants without AGAs will have been previously treated with platinum-based chemotherapy and anti-PD-1/anti-PD-L1 monoclonal antibody, either in combination or sequentially. Participants without AGAs who received anti-PD-1/anti-PD-L1 monoclonal antibody as frontline therapy may have received the combination of platinum-based chemotherapy and anti-PD-1/anti-PD-L1 monoclonal antibody in the second-line setting. Eligible participants with AGAs will have been previously treated with one or two prior lines of applicable targeted therapy that is approved for the participant's genomic alteration and platinum-based chemotherapy as the only prior line of cytotoxic therapy. Participants with AGAs may have received up to one anti-PD-1/anti-PD-L1 monoclonal antibody treatment alone or in combination with chemotherapy.

Cohort 2: The target population of Cohort 2 is adult Chinese participants with inoperable locally advanced or metastatic TNBC who have received at least 2 prior chemotherapy regimens for advanced breast cancer, counting the (neo)adjuvant therapy as a prior chemotherapy regimen if progression occurred within 12 months after completion of the therapy.

Future cohorts are anticipated to enrol other target populations of adult Chinese participants with advanced or metastatic solid tumours, including, but not limited to, advanced/unresectable or metastatic gastric or GEJ adenocarcinoma, or urothelial carcinoma that is refractory or intolerant to SoC therapy or for which no SoC therapy is available.

Prospective approval of CSP deviations to recruitment and enrolment criteria, also known as CSP waivers or exemptions, is not permitted.

Participants who do not meet the eligibility criteria requirements are screen failures; refer to Section 5.4.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Inclusion Criteria for All Participants

Age

1 Participant must be ≥ 18 years at the time of screening.

Participant and Disease Characteristics

2 Eastern Cooperative Oncology Group performance status of 0 or 1.

3 The enrolled participants should make available an archival FFPE tumour sample or newly acquired FFPE tumour sample for immunohistochemistry staining to centrally determine TROP2 expression, based on local regulatory approval.

4 At least one lesion not previously irradiated that qualifies as a RECIST 1.1 target lesion at baseline and can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes, which must have short axis ≥ 15 mm) with CT or MRI and is suitable for accurate repeated measurements.

Note: Participants with bone only metastases in the absence of other measurable disease are not permitted.

5 Has LVEF ≥ CCI by either an ECHO or MUGA scan within 28 days before enrolment.

6 Adequate bone marrow reserve and organ function within 7 days before enrolment defined as follows:

- Haemoglobin ≥ 9.0 g/dL (red blood cell/plasma transfusion is not allowed within one week prior to Screening assessment).
- Absolute neutrophil count ≥ 1.5×10^9/L (granulocyte colony stimulating factor administration is not allowed within one week prior to Screening assessment).
- Platelet count ≥ 100×10^9/L (platelet transfusion is not allowed within one week prior to Screening assessment).
- International normalised ratio/prothrombin time and either partial thromboplastin time or activated partial thromboplastin time ≤ 1.5 × the ULN.
- Total bilirubin ≤ 1.5 × ULN if no liver metastases or < 3 × ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline.
- Aspartate aminotransferase/ALT ≤ 3 × ULN or AST/ALT < 5.0 × ULN in the presence of liver metastases at baseline.
- Calculated creatinine clearance ≥ CCI mL/min as determined by the Cockcroft-Gault equation (using actual body weight).
  - Males:

$$\text{CrCL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age [years]})}{72 \times \text{serum creatinine (mg/dL)}}$$

  - Females:

$$\text{CrCL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age [years]})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

7 Has a minimum life expectancy of 12 weeks

Sex and Contraceptive/Barrier Requirements

8 Male and/or female

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies;

9 All FOCBP must have a negative serum pregnancy test documented during screening; see Appendix F for further details and for a definition of females not of child-bearing potential.

10 FOCBP must use one highly effective form of birth control or avoid intercourse from screening throughout study and for CCI after the last dose of Dato-DXd; see Appendix F for further details. Starting at the time of first dose of Dato-DXd, female participants must not donate, or retrieve for their own use, ova at any time during this study and for CCI after the last dose of Dato-DXd. Preservation of ova should be considered prior to enrolment in this study. Females receiving HRT and whose menopausal status is in doubt will be required to use one of the contraception methods outlined for FOCBP if they wish to continue using HRT during the study. Otherwise, HRT must be discontinued to allow confirmation of post-menopausal status prior to enrolment; see Appendix F for further details.

11 Male participants must use a condom plus an additional contraceptive method (see Appendix F), or avoid intercourse, from the time of screening throughout the total duration of the study and the drug washout period (CCI after the last dose of study intervention), in addition to the female partner using a highly effective contraceptive method. Male participants must not donate or bank sperm during this same time period. Preservation of sperm should be considered prior to enrolment in the study.

Informed Consent

12 Capable of giving signed informed consent as described in Appendix A, which includes compliance with the requirements and restrictions listed in the ICF and in this CSP.

Additional Inclusion Criteria for Cohort 1 (NSCLC)

Participant and Disease Characteristics

13 Histologically or cytologically documented Stage IIIB or IIIC NSCLC disease not amenable for surgical resection or definitive chemoradiation or Stage IV NSCLC disease at the beginning of study intervention (based on the American Joint Committee on Cancer, Eighth Edition).

For the subset of participants without AGAs:

- Documented negative test results for *EGFR* and *ALK* genomic alterations. If test results for *EGFR* and *ALK* are not available, participants are required to undergo testing performed locally for these genomic alterations.
- No known genomic alterations in *ROS1*, *RET*, *METex14 skipping*, or other AGAs with approved therapies.
  Note: Tests for AGAs other than *EGFR* and *ALK* are not mandatory. Known status for *ROS1*, *RET*, *METex14 skipping*, or other AGAs (except *EGFR* and *ALK*) is not required for enrolment and participants with unknown status for these genomic alterations will be classified as without AGAs for enrolment.

For the subset of participants with AGAs:

- Documented positive test results for one or more actionable genomic alteration: *EGFR, ALK, ROS1, METex14 skipping, RET* or other AGAs with approved therapies.

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

15 Participants must meet ONE of the following prior therapy requirements for advanced or metastatic NSCLC:

For the subset of participants without AGAs:

- Received platinum-based chemotherapy in combination with anti-PD-1/anti-PD-L1 monoclonal antibody as the only prior line of therapy.
- Received prior platinum-based chemoradiotherapy with maintenance anti-PD-1/ anti-PD-L1 monoclonal antibody for Stage III disease and relapsed/progressed within 6 months from the last dose of platinum-based chemotherapy.
- Received prior platinum-based chemoradiotherapy CCI [redacted] for Stage III disease and subsequently received anti-PD-1/ anti-PD-L1 monoclonal antibody therapy CCI [redacted] for recurrent disease.
- Received platinum-based chemotherapy and anti-PD-1/ anti-PD-L1 monoclonal antibody CCI [redacted] sequentially as the only 2 prior lines of therapy.
  NOTE:
  - Participants who received anti-PD-1/ anti-PD-L1 monoclonal antibody as first line therapy may have received the combination of platinum-based chemotherapy and anti-PD-1/anti-PD-L1 monoclonal antibody as second line therapy.
  - Participants with known CCI [redacted] mutation, in the absence of other AGA, who received CCI [redacted] as a separate line of therapy in addition to the prior therapy requirements described above, are not eligible.

For the subset of participants with AGAs:

- Received one or two prior lines of applicable targeted therapy for the participant's genomic alteration at the time of screening:
  - Participants who have tumours with EGFR L858R or Exon 19 deletion mutations must have received prior osimertinib.
  - Those who received a targeted agent as adjuvant therapy for early-stage disease must have relapsed or progressed while on the treatment or within [redacted] months of the last dose OR received at least one additional course of targeted therapy for the same genomic alteration CCI [redacted] for relapsed/progressive disease.
  - Participants who have been treated with a prior TKI must receive additional approved targeted therapy, if locally available and clinically appropriate, for the applicable genomic alteration, or the participant will not be allowed in the study.
- Received platinum-based chemotherapy as the only prior line of cytotoxic therapy:
  - One platinum-containing regimen for advanced disease.
  - Those who received a platinum-containing regimen as adjuvant therapy for early-stage disease must have relapsed or progressed while on the treatment or within [redacted] months of the last dose OR received one additional course of platinum-containing therapy CCI [redacted] for relapsed/progressive disease.
- May have received CCI [redacted] anti-PD-1/anti-PD-L1 monoclonal antibody treatment alone or in combination with chemotherapy.

Additional Inclusion Criteria for Cohort 2 (TNBC)

Participant and Disease Characteristics

16 Pathologically documented oestrogen and progesterone receptor-negative (< 1% of cells expressing hormonal receptors via immunohistochemical analysis) and HER2-negative expression according to the American Society of Clinical Oncology – College of American Pathologists guidelines. If a participant had multiple results, the most recent test result will be used to confirm eligibility.

17 Inoperable locally advanced or metastatic breast cancer.

18 Received at least 2 prior chemotherapy regimens for locally advanced or metastatic breast cancer and previously treated with a taxane in any setting. Participant must have documented progression on their most recent chemotherapy regimen.

- For participants with a documented germline BRCA1/BRCA2 mutation who received a PARP inhibitor recommended in China guidelines, the PARP inhibitor can be used to meet the criteria for one of 2 prior chemotherapies.

- For participants with disease progression during neoadjuvant treatment or relapse within 12 months after the completion of (neo)adjuvant therapy, the (neo)adjuvant therapy can be counted as a prior chemotherapy regimen.
- If a chemotherapy drug is changed within 28 days of use to another drug, the first drug is not counted as a prior chemotherapy regimen.
- Targeted agents (eg, PD-1/PD-L1 inhibitors) on their own do not contribute to the count of prior chemotherapy regimens; however, use of such agents in combination with chemotherapy should be classified as one prior chemotherapy regimen.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Exclusion Criteria for All Participants

Medical Conditions

1 As judged by the investigator, has any evidence of diseases (such as severe or uncontrolled systemic diseases, including history of allogeneic organ transplant and active bleeding diseases or significant cardiac or psychological conditions), which, in the investigator's opinion, makes it undesirable for the participant to participate in the study or that would jeopardise compliance with the CSP.

2 Has history of another primary malignancy, except for adequately resected basal cell carcinoma of the skin or squamous cell carcinoma of the skin, in situ disease that has undergone potentially curative therapy, or other solid malignancy treated with curative intent with no known active disease within CCI years before enrolment and of CCI [redacted]

3 Has persistent toxicities caused by previous anticancer therapy, excluding alopecia, not yet improved to Grade ≤ 1 or baseline. Note: participants may be enrolled with some chronic, stable Grade 2 toxicities (defined as no worsening to > Grade 2 for at least 3 months prior to enrolment and managed with SoC treatment), which the investigator deems related to previous anticancer therapy, including (but not limited to):
   - Chemotherapy-induced neuropathy
   - Fatigue
   - Residual toxicities from prior immunotherapy treatment: Grade 1 or Grade 2 endocrinopathies, which may include:
     - Hypothyroidism/hyperthyroidism
     - Type 1 diabetes
     - Hyperglycaemia
     - Adrenal insufficiency
     - Adrenalitis

- Skin hypopigmentation (vitiligo)

Participants with irreversible toxicity that is not reasonably expected to be exacerbated by study intervention may be included (eg, hearing loss) after consultation with the AstraZeneca study clinical lead.

4 Has leptomeningeal carcinomatosis or metastasis.

5 Has significant third-space fluid retention (eg, ascites or pleural effusion) and is not amenable to required repeated drainage.

6 Has clinically significant corneal disease.

7 Has known active hepatitis or uncontrolled hepatitis B or C virus infection or is positive for hepatitis B or C virus based on the evaluation of tests for hepatitis B (hepatitis B virus surface antigen, anti-hepatitis B virus surface antibody, anti-hepatitis B virus core antibody, or hepatitis B virus DNA) or hepatitis C (positive hepatitis C antibody or hepatitis C virus RNA). Participants are eligible if they:

a) Have been curatively treated for HCV infection as demonstrated clinically and by viral serologies.

b) Have received HBV vaccination with only anti-HBs positivity and no clinical signs of hepatitis

c) Are HBsAg- and anti-HBc+ (ie, those who have cleared HBV after infection) and meet conditions i-iii of criterion "d" below:

d) Are HBsAg+ with chronic HBV infection (lasting 6 months or longer) and meet conditions i-iii below:

i) HBV DNA viral load < CCI .

ii) Have normal transaminase values, or, if liver metastases are present, abnormal transaminases, with a result of AST/ALT < 3 × ULN, which are not attributable to HBV infection.

iii) Start or maintain antiviral treatment if clinically indicated as per the investigator

8 Has uncontrolled infection requiring IV antibiotics, antivirals, or antifungals; suspected infections (eg, prodromal symptoms); or inability to rule out infections (participants with localised fungal infections of skin or nails are eligible).

9 Has known HIV infection that is not well controlled. All of the following criteria are required to define an HIV infection that is well controlled: undetectable viral RNA load, CD4+ counts > 250 cells/mm^3, no history of AIDS-defining opportunistic infection within CCI , and stable for CCI on same anti-HIV medications. If an HIV infection meets the above criteria, monitoring of viral RNA load and CD4+ count is recommended.

10 Has known active tuberculosis infection (clinical evaluation that may include clinical history, physical examination and radiographic findings, or tuberculosis testing in line with local practice).

11 Any other medical conditions, including cardiac disease or psychological disorders, and/or substance abuse, that may, in the opinion of the investigator, interfere with the participant's participation in the clinical study or evaluation of the clinical study results.

12 Has a mean resting QTcF > 470 ms, regardless of sex, obtained from triplicate 12-lead ECGs performed at screening OR

- Investigator judgment of one or more of the following:
  - History of QT prolongation associated with other medications that required discontinuation of that medication, or any current concomitant medication known to prolong the QT interval and cause Torsades de Pointes.
  - Congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives.

13 Has uncontrolled or significant cardiac disease including any of the following:

- Myocardial infarction or uncontrolled/unstable angina within 6 months before enrolment.
- Congestive heart failure (New York Heart Association Class II to IV).
- Cardiac arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia), which is symptomatic or requires treatment (CTCAE 5.0 Grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Participants with atrial fibrillation controlled by medication or arrhythmias controlled by pacemakers may be permitted upon discussion with the study clinical lead.
- Uncontrolled hypertension (resting systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg)

14 Has a history of non-infectious ILD/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.

15 Clinically severe pulmonary function compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (eg, pulmonary emboli within 3 months of the study enrolment, severe asthma, severe COPD, restrictive lung disease, pleural effusion, etc) or any autoimmune, connective tissue, or inflammatory disorders (eg, rheumatoid arthritis, Sjögren's syndrome, sarcoidosis, etc).

Prior/Concomitant Therapy

16 Has prior exposure to any of the following:
- Chloroquine/hydroxychloroquine without an adequate treatment washout period of > 14 days prior to enrolment
- Any agent including an ADC-containing a chemotherapeutic agent targeting topoisomerase I.
- TROP2-targeted therapy.

17 Prior exposure to the following anti-cancer therapies without an adequate treatment washout period prior to enrolment:
- Chemotherapy, immunotherapy (non-antibody-based therapy), retinoid therapy: ≥ 2 weeks or 5 times the terminal elimination $t_{½}$ of the chemotherapeutic agent, whichever is longer; ≥ 6 weeks for nitrosoureas or mitomycin C.
- Antibody-based anti-cancer therapy: ≥ 4 weeks

18 Any concurrent anti-cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, HRT) is acceptable.

19 Palliative radiotherapy with a limited field of radiation within ≤ 2 weeks or with wide field of radiation to the chest or to more than 30% of the bone marrow within ≤ 4 weeks before the first dose of study intervention.

20 Major surgical procedure or significant traumatic injury within ≤ 3 weeks of the first dose of study intervention or an anticipated need for major surgery during the study.

Prior/Concurrent Clinical Study Experience

21 Previous treatment in the present study

22 Participation in another clinical study with a study intervention or investigational medicinal device, randomisation into a prior Dato-DXd study regardless of treatment assignment, or concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study

23 Has a history of severe hypersensitivity reactions to either the drug substance or inactive ingredients (including, but not limited to, polysorbate 80) of Dato-DXd or to other monoclonal antibodies.

Other Exclusions

24 Involved in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

25 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

26 For females only: is pregnant (confirmed with positive pregnancy test), breastfeeding, or planning to become pregnant. Female participants should refrain from breastfeeding from

screening throughout the study and for CCI after the last dose of study intervention.

Additional Exclusion Criteria for Cohort 1 (NSCLC)

Medical Conditions

27 Has mixed SCLC and NSCLC histology.

28 Prior exposure to the following anti-cancer therapy without an adequate treatment washout period prior to enrolment:

- ≥ 1 week for tyrosine kinase inhibitors approved for the treatment of NSCLC; baseline CT scan must be completed after discontinuation of tyrosine kinase inhibitors.

29 Has spinal cord compression or brain metastases unless treated, asymptomatic, stable, and not requiring steroids for CCI prior to the start of study intervention. Participants with treated brain metastases who are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants must have recovered from the acute toxic effect of radiotherapy. A minimum of CCI must have elapsed between the end of whole brain radiotherapy and study enrolment.

Additional Exclusion Criteria for Cohort 2 (TNBC)

Medical Conditions

30 Participants with a history of or current brain metastases.

5.3 Lifestyle Considerations

The following restrictions apply while the participant is receiving study intervention and for the specified times before and after:

1 Participants must follow the contraception requirements outlined in Appendix F.

2 Participants should not donate blood or blood components while participating in this study and through CCI days after the last dose of study intervention.

3 Preservation of ova and sperm should be considered prior to enrolment in this study.

Restrictions relating to concomitant therapies are described in Appendix G.

5.3.1 Meals and Dietary Restrictions

In general, there are no dietary restrictions for the study assessments or treatment with Dato-DXd. Concomitant use of dietary supplements, medications not prescribed by the investigator, and alternative/complementary treatments is discouraged but not prohibited.

5.3.2 Tobacco

Use of tobacco products, e-cigarettes, and vaping is strongly discouraged, but not prohibited. Any prior or current use of these products should be recorded in the eCRF.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE during the Screening Period.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened a single time. Rescreened participants should be assigned the same participant number (ie, E-code) as for the initial screening. However, rescreening should be documented so that its effect on study results, if any, can be assessed. All assessments must be repeated for rescreening unless they are within 28 days of the first dose of study intervention. Exceptions will be considered in consultation with the sponsor on a case-by-case basis. A screening/baseline bone scan does not need to be repeated if it is within 12 weeks of enrolment.

These participants should have the reason for study withdrawal recorded in the eCRF as 'eligibility criteria not fulfilled' (ie, participant does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (ie, participants who are not entered in the study).

Participant enrolment is described in Section 6.2.2.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the CSP.

6.1 Study Intervention(s) Administered

Dato-DXd will be supplied by AstraZeneca as a CCI mg/vial lyophilised powder for concentrate for solution for infusion. Following reconstitution with sterile water for injection, the solution contains CCI mg/mL Dato-DXd in CCI mM histidine/histidine HCl, CCI % (w/v) sucrose and CCI (w/v) polysorbate 80; it has a pH of CCI. The final volume of Dato-DXd is CCI mL when reconstituted. See Table 4.

The reconstituted drug product is a [redacted]

Table 4 Study Intervention

Intervention name	Dato-DXd
Type	ADC
Dosage form	Lyophilised powder for concentrate for solution for infusion in a single-use vial.
Unit dose strength(s)	[redacted] mg/vial ([redacted] mg/mL)
Dosage regimen	6.0 mg/kg Q3W
Route of administration	IV infusion
Use	Experimental
IMP and NIMP	IMP
Sourcing	Provided centrally by the sponsor
Packaging and labelling	Dato-DXd will be provided in [redacted] mg vials in carton. Each vial and carton will be labelled in accordance with GMP Annex 13 and per country requirements [a]
Current/Former name(s) or alias(es)	DS-1062a

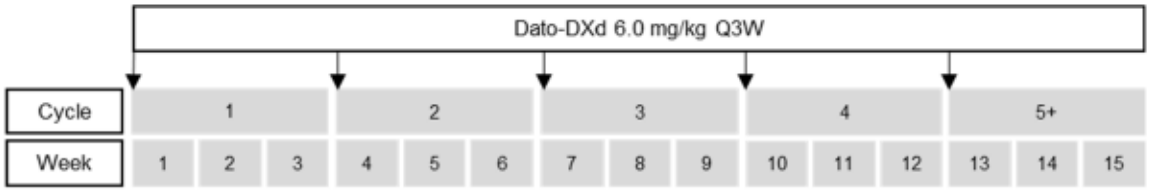
[a] Label text for Dato-DXd (DS-1062a) may show 'DS-1062' depending on the agreed product name used in the respective approved study master label document. All naming conventions for these compounds are correct during this transitional period.

ADC, antibody-drug conjugate; Dato-DXd, datopotamab deruxtecan; GMP, Good Manufacturing Practice; IMP, investigational medicinal product; IV, intravenous; NIMP, non-investigational medicinal product; Q3W, every 3 weeks.

All participants will receive a 6.0 mg/kg Dato-DXd as an IV infusion Q3W on Day 1 of each 21-day cycle. See Section 6.2.2.1 for detailed instructions about administration of Dato-DXd.

The drug formulation used in this study will be Lyo-DP.

Figure 2 Dosing Schedule



Dato-DXd, datopotamab deruxtecan; Q3W, every 3 weeks

Duration of Treatment

All participants in this study will receive 6.0 mg/kg Dato-DXd as an IV infusion Q3W on Day 1 of each 21-day cycle. Participants will continue to receive Dato-DXd until PD occurs as judged by investigator assessment or until any other discontinuation criterion is met, as defined in Section 7.1.

Intervention beyond RECIST 1.1-defined PD is not permitted in this study.

6.2 Preparation/Handling/Storage/Accountability of Interventions

The investigator or designee (eg, pharmacist) must confirm appropriate temperature conditions have been maintained during transit for all study intervention received at the site and throughout the entire study duration until authorisation is provided for on-site destruction or removal of the study intervention, reflecting completion of the study. In the event of a temperature excursion detected at any time during the study, sites will follow the reporting procedures for notifying the sponsor (or designated party); release of study intervention for clinical use can only occur once the event has been reviewed and approval is provided by the sponsor (or designated party).

Only authorised site staff may prepare, dispense and administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to authorised site staff (and investigator, where applicable).

The investigator is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records) reflecting destruction or return of all unused study intervention); this task may be delegated to study staff members identified on the site delegation log.

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.2.1 Storage of Dato-DXd

The investigator, or an appropriate delegate, will ensure that all study intervention is stored in a secure, limited access storage area, at appropriate temperatures and as specified on the label, and in accordance with applicable regulatory requirements. A calibrated temperature-monitoring device will be used to record the temperature conditions in the drug storage facility. A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging are to be reported to the study monitor upon detection. Storage conditions stated in the respective IBs may be superseded by the label storage instructions.

Dato-DXd vials are to be stored at [redacted]
Dato-DXd must be kept in original packaging until use to prevent prolonged light exposure.

6.2.2 Preparation of Dato-DXd

The dose of Dato-DXd must be prepared by the investigator's or site's designated study intervention manager using aseptic technique in compliance with local regulations and site requirements. [redacted]

Following preparation and during administration, the prepared IV bag [redacted].

6.2.2.1 Administration of Dato-DXd

Dato-DXd will be administered as a 6.0-mg/kg IV infusion Q3W on Day 1 of each 21-day cycle.

Premedication to mitigate the risk of IRRs is required prior to any dose of Dato-DXd and must include antihistamines and acetaminophen with or without glucocorticoids.

Based on the currently available clinical safety data, it is highly recommended that participants receive [redacted] agents prior to infusion of Dato-DXd and on subsequent days as needed. [redacted] and [redacted] should be considered and administered in accordance with the prescribing information or institutional guidelines. [redacted] can be used, if needed.

Dato-DXd will be administered using an IV bag containing [redacted] and delivered through an IV administration set with a [redacted]. The standard infusion time for Dato-DXd is approximately [redacted] for the first infusion. If the [redacted] infusion is well tolerated and the participant does not experience an IRR, then the minimum infusion time for subsequent cycles is [redacted]. However, if there are interruptions during the infusion, [redacted].

The IV line will be flushed with 5% dextrose for injection according to local practices to ensure the full dose is administered. Infusion time does not include the final flush time.

Refer to the Pharmacy Manual for detailed information about preparation and administration of Dato-DXd.

The participant should remain at the site for at least CCI post-infusion of every dose of Dato-DXd for close observation for possible allergic reactions and IRRs at each treatment cycle.

The participant's weight at screening (baseline) will be used to calculate the initial dose. If, during the course of treatment, the participant's weight changes by CCI, the participant's dose will be recalculated based on the participant's updated weight. After the recalculation, the updated participant's weight will be used as the new baseline weight. The site may follow local institutional policy for re-calculating dose based on weight changes CCI

6.2.2.2 Safety Monitoring

Participants will be monitored during and after infusion of Dato-DXd. Vital signs will be measured according to the SoA.

Management of study intervention-related toxicities are described in the TMGs for Dato-DXd, (see the TMG Annex). As with any biologic product, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognise and treat anaphylaxis.

6.3 Measures to Minimise Bias

6.3.1 Participant Enrolment

All participants will be centrally assigned to the open-label study intervention using an IRT. Participants should begin treatment on the day of treatment assignment in IRT.

Before the study is initiated at a site, the call/log-in directions and user guides for the IRT will be provided to the site. The IRT will provide the kit identification number to be allocated to the participant at each dispensing visit. Study intervention will be dispensed at the study visits summarised in the SoA (see Section 1.3).

Returned study intervention should not be re-dispensed to the participants.

If a participant withdraws from the study, then his/her E-code cannot be reused. Withdrawn participants will not be replaced.

Investigators should keep a record (ie, the participant screening log) of participants who entered screening.

At screening/baseline (Days -28 to -1), the investigators or suitably trained delegate will perform the following:

- Obtain signed informed consent before any study-specific procedures are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the participant. However, all screening laboratory and imaging results must have been obtained within 28 days of the first dose of study intervention Except for virus antibody test results, which can be used if performed within 120 days before screening.
- Obtain a unique CCI E-code, through the IRT in the following format CCI [redacted] This number is the participant's unique identifier and is used to identify the participant on the eCRFs.
- Determine participant eligibility (see Sections 5.1 and 5.2).
- Enrol eligible participant into the study and obtain treatment assignment. Treatment assignment should be obtained from the IRT on the same day the participant's eligibility is confirmed and they are enrolled in the study. The date of enrolment is defined as the date the participant is confirmed as eligible in the IRT.

If the participant is ineligible, the IRT will be accessed to terminate the participant in the system.

Participants will begin treatment on Cycle 1 Day 1. Participants must not be enrolled and treated unless all eligibility criteria have been met.

6.3.2 Procedures for Handling Incorrectly Enrolled Participants

Participants who fail to meet all of the eligibility criteria should not, under any circumstances, be enrolled or receive study intervention. There can be no exceptions to this rule. Participants who are enrolled but subsequently found not to meet all the eligibility criteria must not be started on study intervention and must be withdrawn from the study.

When a participant does not meet all the eligibility criteria but is enrolled in error, or incorrectly started on treatment, the investigator should inform the AstraZeneca study clinical lead immediately, and a discussion should occur between the AstraZeneca study clinical lead and the investigator regarding whether to continue or discontinue the participant from treatment. The AstraZeneca study clinical lead must ensure all decisions are appropriately documented and that the potential benefit/risk profile remains positive for the participant.

6.3.3 Methods for Assigning Treatment Groups

Not applicable.

6.3.4 Methods for Ensuring Blinding

Not applicable.

6.4 Study Intervention Compliance

Sites will follow local practices for verification of study intervention doses prepared and administered to study participants.

When participants are dosed at the site, they will have study intervention prepared, dispensed, and administered by the investigator or designee under medical supervision. The date, and time if applicable, of the administered study intervention will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing in accordance with local treatment verification practices.

Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

6.5 Concomitant Therapy

Any concomitant treatment, procedure, or other medication considered necessary by the investigator for the participant's safety and wellbeing, or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, or other specific categories of interest) that the participant is receiving from the time of screening or receives during the study, including the CCI follow-up period following the last dose of study intervention, must be recorded in the eCRF along with the following:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Concomitant medications administered as treatment for drug-related AESIs should be recorded until either event resolution, end of study, trial termination, withdrawal of consent, or participant death.

The study physician should be contacted if there are any questions regarding concomitant or prior therapy.

If any concomitant therapy is administered due to new or unresolved AE, it should be recorded.

Participants must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

Restricted, prohibited, and permitted concomitant medications/therapies are described in more detail in Appendix G 2.

Guidance regarding potential interactions with concomitant medications is provided in Appendix G.

6.5.1 Drug-Drug Interactions

In vitro DDI studies indicated that DXd, the drug component of Dato-DXd, is a substrate of P-gp, MATE2-K, OATP1B1, OATP1B3, BCRP, MRP1, and CYP3A4. No human DDI study of Dato-DXd has been conducted. Since DDI is primarily driven by DXd, DDI study results for fam-trastuzumab deruxtecan-nxki (ENHERTU®), which has the same DXd payload, are relevant and described below:

- Coadministration of itraconazole, a strong CYP3A inhibitor, with multiple doses of fam-trastuzumab deruxtecan-nxki increased steady state AUC from 0 to 17 days ($AUC_{0\text{-}17d}$) of fam-trastuzumab deruxtecan-nxki by 11% and DXd by 18%. The impact of these changes is not clinically meaningful.
- Coadministration of ritonavir, a dual inhibitor of OATP1B/CYP3A, with multiple doses of fam-trastuzumab deruxtecan-nxki increased steady state $AUC_{0\text{-}17d}$ of fam-trastuzumab deruxtecan-nxki by 19% and DXd by 22%. The impact of these changes is not clinically meaningful.

Based on the information above, the effect of CYP3A/OATP1B on DXd is not considered to be clinically meaningful, and as a result, concomitant use of CYP3A/OATP1B inhibitors with Dato-DXd is permitted. However, participants should be closely monitored when Dato-DXd is concomitantly used with drugs that inhibit CYP3A, OATP 1B1, and OATP1B3.

Concomitant use of drugs that inhibit MATE2-K, P-gp, BCRP, and MRP1 is permitted, although participants should be closely monitored for adverse reactions. As urinary excretion of DXd is expected to be low, MATE2-K, which is involved in the excretion of substrates into urine, is expected to have minimal impact on the exposure of DXd. In addition, multiple efflux transporters such as P-gp and BCRP are involved in the excretion of DXd; therefore, the risk of interactions with these inhibitors is also expected to be low. Likewise, because the expression of MRP1 in the liver is low, the inhibition of MRP1 is expected to have little impact on the exposure of DXd.

Concomitant use of drugs that are substrates of OAT1 and OATP1B1 is permitted. As the exposure of DXd is expected to be low with Dato-DXd at doses administered in clinical studies, the inhibition of OAT1 and OATP1B1 by DXd is expected to have little impact on drugs that are substrates of OAT1 and OATP1B1.

There is a hypothetical interaction between Dato-DXd and hydroxychloroquine and/or chloroquine; therefore, concomitant treatment with hydroxychloroquine or chloroquine is not

allowed whilst a participant is on Dato-DXd, and > 14 days of washout is required before starting Dato-DXd administration. If treatment with chloroquine or hydroxychloroquine treatment is absolutely required, study intervention must be interrupted. If chloroquine or hydroxychloroquine is administered for any reason, the study intervention must be interrupted, and a washout period of at least 14 days is required before restarting study intervention.

Guidance regarding potential interactions with concomitant medications is provided in Appendix G.

6.6 Dose Modification

Dosing modification guidelines and TMGs are in the TMG Annex.

Dose delays are permitted for Dato-DXd treatment.

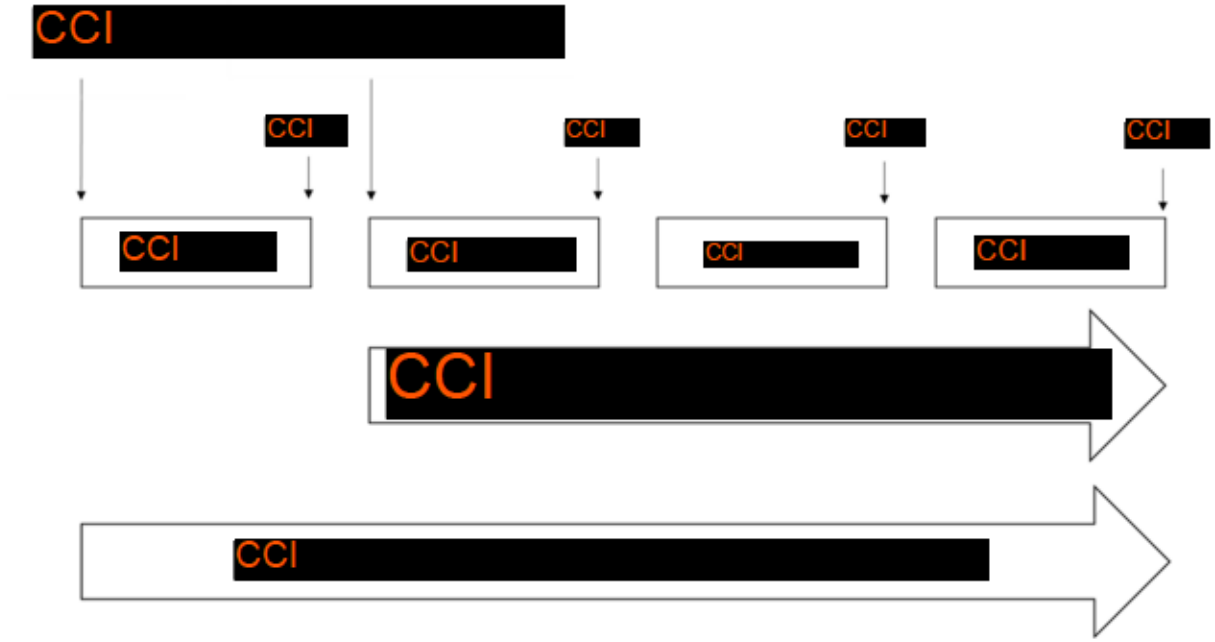
All dose reductions and delays (including any missed doses), and the reasons for the reductions/delays are to be recorded in the eCRF.

6.6.1 Dose Delays

The dosing interval for the next Dato-DXd cycle may be shortened, as clinically feasible, to gradually align with the schedule of tumour efficacy assessment. Two consecutive doses must be administered at least 18 days apart.

A dose of Dato-DXd can be delayed for up to CCI from the planned date of administration (ie, CCI from the last infusion date). CCI [redacted].

Figure 3 Dose Delay Schema for Dato-DXd



In the event of a dose delay occurring prior to completion of PK blood sampling in the study, investigators should contact the study clinical lead for guidance regarding scheduling of these procedures.

6.6.2 Dose Delays for Reasons other than Treatment-related Toxicity

Study treatment dose delay for conditions other than toxicity resolution should be kept as short as possible. CCI

Treatment cycles for a participant for whom Dato-DXd dosing is temporarily withheld for any reason may have future cycles scheduled based on the date of the last Dato-DXd dose.

6.6.3 Dose Reductions

In case a dose reduction is necessary, Dato-DXd will be modified as follows. Up to CCI dose reductions will be permitted for participants receiving Dato-DXd. Once the dose of Dato-DXd has been reduced because of toxicity, all subsequent cycles should be administered at that lower dose level unless further dose reduction is required (Table 5). Once the dose of DatoDXd is reduced, no dose re-escalation will be permitted. CCI dose reduction may be possible CCI after discussion and agreement between the investigator and sponsor.

Table 5 Dose Reduction Levels of Dato-DXd

Starting dose	Dose level -1	Dose level -2
6.0 mg/kg	CCI mg/kg	CCI mg/kg

Dato-DXd, datopotamab deruxtecan.

Investigators should consider dose reductions or discontinuations of Dato-DXd according to the participant's condition and after discussion with the study physician or designee (see the TMG Annex). For management of dose delays due to Dato-DXd-related events, the TMGs (see the TMG Annex) should be followed, as applicable.

6.6.4 Dose Modification for Toxicity Management

Full TMGs for Dato-DXd are included in the TMG Annex. The most current version of the TMGs for Dato-DXd is provided to the investigative site as an Annex document to the CSP and is maintained within the Site Master File.

Specific criteria for delay, interruption, re-initiation, dose reduction and/or discontinuation of Dato-DXd are listed in the Annex document to this CSP, which is applicable only to TEAEs that are assessed as related to use of Dato-DXd by the investigator(s). For non-drug-related TEAEs, follow standard clinical practice. Appropriate clinical experts should be consulted as deemed necessary.

The investigator may consider dose delays or discontinuations of Dato-DXd based on other events not listed in the TMGs (see the Annex document to this CSP) according to the participant's condition and after discussion with the study clinical lead or designee.

On improvement of an AE for which Dato-DXd was temporarily delayed, Dato-DXd may be restarted at the same dose at the discretion of the investigator. If a further episode of the same AE subsequently requires dose delay, or if a different AE subsequently requires dose delay, Dato-DXd may be restarted at a one-dose-level reduction on improvement of the AE or discontinued if the participant is receiving the lowest CSP-specified dose level.

Appropriate and optimal treatment of the toxicity should be attempted prior to considering dose modifications. Prior to discontinuation of study intervention due to toxicities, please consult with the study clinical lead.

If a participant experiences a clinically significant and/or unacceptable toxicity, dosing will be delayed or permanently discontinued in accordance with the TMGs and supportive therapy administered as required.

All dose modifications (delay, interruption, reduction, and/or discontinuation) should be based on the worst preceding toxicity (CTCAE version 5.0).

6.7 Continued Access to Study Intervention After the End of the Study

As described in Section 4.4, the study will remain open until the final DCO.

At the time of final analysis completion for each cohort, a number of participants can still be on study drug within the current study. These participants are to continue treatment CCI [redacted].

Participants should be followed according to the institution's SoC assessments. No further data collection is required, except for CCI [redacted]

AstraZeneca will continue to supply Dato-DXd after completion of this study while, in the opinion of the investigator, the participant is benefitting.

In the event that product development reaches a point where alternative product supply options become available, then these alternative product supply options will be discussed by AstraZeneca with the investigator. AstraZeneca will work with the investigator to transition the participant(s) to alternative supply, where possible.

In the event that CCI [redacted] is available at the time of the final DCO and database closure, participant(s) currently receiving treatment with Dato-DXd may then be transitioned to such a study, and the current study may reach its end. The CCI [redacted] would ensure treatment continuation with visit assessments per its protocol, as applicable. Any participant who would be eligible to move to such a study would be given a new informed consent, as applicable.

6.8 Treatment of Overdose

Use of Dato-DXd in doses exceeding that specified in the CSP is considered to be an overdose. There is currently no specific treatment in the event of overdose of Dato-DXd, and possible symptoms of overdose are not established.

In the event of an overdose, the investigator should:

- Evaluate the participant to determine, in consultation with the study clinical lead, if possible, whether study intervention should be interrupted/delayed or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up. Refer to Section 8.5 for details of AE/SAE reporting related to overdose.
- Document the quantity of the excess dose as well as the duration of the overdose.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety, subsequent anticancer therapy, and survival. The investigator should instruct the participant to contact the site before or at the time if study intervention is stopped. A participant that decides to discontinue study intervention will always be asked about the reason(s) and the presence of any AEs. The reason for discontinuation should be documented in the source document and the appropriate section of the eCRF.

Participants who have permanently discontinued from further receipt of study intervention will need to be discontinued from the IRT.

Participants may be discontinued from study intervention in the following situations:

- RECIST 1.1-defined radiological progression as assessed by the investigator (refer to Section 8.2.1 and Appendix E).
- Investigator determination that the participant is no longer benefiting from study intervention.
- An AE that, in the opinion of the investigator or AstraZeneca, contraindicates further dosing.
- Any AE that meets criteria for discontinuation defined in the dose modification guidelines for management of study intervention-related toxicities (see the TMG Annex).
- Participant decision. The participant is at any time free to discontinue treatment without prejudice to further treatment. A participant who discontinues treatment is normally expected to continue to participate in the study (eg, for safety and survival follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.2)
- Severe non-compliance with the CSP as judged by the investigator or AstraZeneca.
- Pregnancy or intent to become pregnant (see Appendix F and Section 8.4.14).
- Initiation of subsequent anticancer therapy.
- Initiation of treatment with another investigational agent.
- Subjective disease progression (global deterioration of health status) without objective evidence of PD according to RECIST 1.1.

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

See the SoA (Section 1.3) for data to be collected at the time of study intervention discontinuation (ie, the End-of-Treatment Visit) and follow-up and for any further evaluations that need to be completed.

7.1.1 Follow-up of Participants Post Discontinuation of Study Intervention

All participants who discontinue the study intervention will be followed up for safety assessments CCI after their last dose of study intervention. If the day on which the investigator determines that the patient should discontinue study intervention is over CCI after the last dose of study intervention received by the patient, an additional safety follow-up assessment is not needed. Additional assessments to be performed at the time of the CCI Safety Follow-up Visit are detailed in the SoA (see Section 1.3). For ILD/pneumonitis, safety follow-up will continue until the resolution of ILD/pneumonitis. All AESIs, regardless of severity or seriousness, must be followed until either event resolution, end of study, including any post-treatment follow-up, trial termination, withdrawal of consent, or participant death (see Section 8.4.11).

Participants who have discontinued study intervention prior to objective RECIST 1.1-defined radiological progression, regardless of whether or not they have commenced subsequent anticancer therapy, will be followed up with tumour assessments as indicated in the SoA (see Section 1.3) until RECIST 1.1-defined PD or death regardless of whether or not the participant started a subsequent anticancer therapy, unless they have withdrawn all consent to study-related assessments.

Subsequent anticancer drug treatments administered since the end of treatment with study intervention must be monitored and recorded in the eCRF until the end of the study. Best response and the date of PD on subsequent therapies, as assessed by local standard clinical practice, will be recorded in the eCRF. Subsequent anticancer drug treatments may commence following discontinuation of study intervention, including at PD.

7.1.2 Follow-up for Survival

Participants will be followed up for survival status and subsequent anticancer therapy as indicated in the SoA (see Section 1.3) until death, withdrawal of consent, or the end of the study. Survival information may be obtained via telephone contact with the participant or the participant's family, or by contact with the participant's current physician, or local death registries. Additional assessments including subsequent anti-cancer therapy, are to be recorded at the time of survival follow-up and are detailed in the SoA. See Section 8.2.4 for additional information..

7.2 Participant Discontinuation/Withdrawal From the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options to ensure the collection of endpoints and safety information including new AEs and follow-up on any ongoing AEs and concomitant medications (eg, telephone contact at CCI after study intervention is discontinued, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an Early Study Intervention Discontinuation visit should be conducted, as shown in the SoA (see Section 1.3). See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the study team.

7.3 Loss to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and no contact has been established by the time the study is completed (see Section 4.4), such that there is insufficient information to determine the participant's status at that time.

Participants who decline to continue participation in the study, including telephone contact, should be documented as 'withdrawal of consent' rather than 'lost to follow-up.' Investigators should document attempts to re-establish contact with missing participants throughout the study period. If contact with a missing participant is re-established, the participant should not be considered lost to follow-up and evaluations should resume according to the CSP.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit

schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, texts or emails, and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have been lost to follow-up from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant during survival follow-up within legal and ethical boundaries for all participants enrolled. Public sources may be searched for vital status information in accordance with applicable local laws. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

In order to support secondary efficacy endpoints of PFS, and OS analyses, the survival status of all participants in the Full Analysis Set should be re-checked; this includes those participants who withdrew consent or are classified as 'lost to follow-up.'

- Lost to follow-up: Site personnel should check hospital records and a publicly available death registry (if available), as well as checking with the participants' current physician, to obtain a current survival status (the applicable eCRF modules will be updated), in accordance with applicable local laws.
- In the event that the participant has actively withdrawn consent to the processing of their personal data, the survival status of the participant can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (see Section 1.3). Data collection following study analysis until the end of the study is described below.

- Clinical Study Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to

record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the CSP-specified criteria and were performed within the time frame defined in the SoA.

Instructions for the collection and handling of human biological samples will be provided in the study-specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on handling of human biological samples, see Appendix C.

Data Collection Following Study Analysis until the End of the Study

For SAE and AE reporting and laboratory assessment collection after final analysis, see Section 8.4.12. After the final DCO and database closure, only SAEs will be reported for the purposes of this study (see Section 8.4.12).

In addition, any AEs of ILD/pneumonitis will be followed up until resolution. For other safety reporting collection after final analysis, see Section 8.4.12.

8.1 Administrative and General/Baseline Procedures

Demographic data to be collected includes age at screening, sex, race, and ethnicity.

Medical history includes substance usage, smoking history, type and frequency of tobacco use, e-cigarette use, vaping, and family history of premature cardiovascular disease.

8.2 Efficacy Assessments

8.2.1 Imaging Tumour Assessments

Tumour assessments will use images from CT (preferred) or MRI, with IV contrast, of the chest and abdomen (including the entire liver and both adrenal glands) collected during screening/baseline and at regular (follow-up) intervals during study intervention. Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Any other areas of disease involvement should be additionally imaged at screening/baseline and regular intervals based on known metastasis sites or by the signs and symptoms of individual participants. The imaging modality used for baseline tumour assessment, CT/MRI for chest, abdomen and pelvis, MRI for brain, and bone image for bone should be kept the same consistently at each subsequent follow-up assessment throughout the study if possible. It is important to follow the tumour assessment schedule as closely as possible (see Section 1.3) relative to the date of the first dose of study intervention. Screening/baseline imaging should be performed no more than 28 days before the date of the first dose of study intervention and ideally should be performed as close as possible to and

prior to the date of the first dose of study intervention. An existing scan will be acceptable as baseline if performed within 28 days prior to date of enrolment and is consistent with the required modalities.

Treatment continues Q3W and scanning/tumour assessments will be performed every 6 weeks (± 7 days) from the date of the first dose of study intervention until RECIST 1.1-defined radiological PD by investigator assessment, even if the participant discontinues or delays study intervention or initiates new anticancer therapy unless they have withdrawn all consent to study related assessments. CCI [redacted] The intent of this CCI [redacted] is to minimise CCI [redacted]. The scans from all assessments of tumour response, including the follow-up assessment, will be sent for ICR review. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the participant has not progressed, every attempt should be made to perform the subsequent assessments at the next scheduled visit.

The RECIST 1.1 assessments of baseline images identify TLs (defined as measurable) and NTLs. On-study images are evaluated for TLs and NTLs chosen at baseline, and for NLs when they appear. This allows determination of follow-up TL response, NTL lesion response, the presence of unequivocal NLs, and overall time point responses (CR, PR, SD, PD, or NE).

When tumour assessments at a visit are performed over multiple days, the date of response (CR, PR, SD, non-CR/PD [participants with NTLs only], or NE) should be recorded as the date of the last radiographic evaluation included in the series for that assessment, and the date of progression should be recorded as the date of the earliest radiographic evaluation included in the series for that assessment.

For all participants, a CCI [redacted] must be performed CCI [redacted]. Participants CCI [redacted] at baseline must CCI [redacted] and must CCI [redacted] until radiological progression per RECIST 1.1 by investigator assessment. CCI [redacted]. Otherwise, CCI [redacted] is required only if CCI [redacted]. When CCI [redacted] is suspected, brain MRI or CT scan should be used to determine CCI [redacted] per RECIST 1.1.

8.2.2 Central Reading of Scans

All participants' radiographic imaging scans, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed iCRO for quality control, storage, and for ICR. Digital copies of all original scans should be stored at the investigator site as source documents. Electronic image transfer from the sites to the iCRO is strongly encouraged. ICR of images will be performed at the discretion of AstraZeneca. Results of these independent reviews will not be communicated to investigators, and results of investigator tumour assessments will not be shared with the central reviewers.

Further details of the ICR will be documented in an Independent Review Charter.

8.2.3 Bone Scan or Skeletal Survey

CCI bone scan or skeletal survey performed CCI , and CCI .

Bone scintigraphy is the preferred modality. If a participant had a choline PET/CT, or diffusion-weighted MRI as part of the routine clinical management performed within 28 days of start of study intervention, it may be utilised as a screening scan to document bone disease. However, if fluoro-deoxyglucose-PET/CT is used, a dedicated high quality structural CT or MRI of the relevant part of the skeleton is recommended to ensure that any changes represent a true bone metastasis and not a non-malignant lesion (eg, an inflammatory lesion).

Additional on-study bone scans or skeletal surveys may be performed, if clinically indicated.

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X -ray should be recorded as NTLs and followed by the same method (CT, MRI, or X-ray), as indicated in the SoA (see Section 1.3).

8.2.4 Overall Survival

Assessments for survival will be conducted every 3 months ± 14 days following objective PD or discontinuation of study intervention until death, withdrawal of consent, or the end of the study. Survival information may be obtained via telephone contact with the participant, participant's family, by contact with the participant's current physician, or local death registries, where applicable according to local laws, as described in Section 7.2.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (see Section 1.3).

8.3.1 Physical Examinations

A full physical examination will be performed at screening/baseline and include assessments of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and

neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), urogenital, dermatological, gastrointestinal, endocrine, haematologic/lymphatic, and neurological systems. Targeted physical examinations are to be used by the investigator on the basis of clinical observations and symptomatology.

A targeted physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Physical examination, as well as assessment of height and weight, will be performed at timelines as specified in the SoA (see Section 1.3). Investigators should pay special attention to clinical signs related to previous serious illnesses, as new or worsening abnormalities may qualify as AEs. See Section 8.4.5 for details.

8.3.2 Vital Signs

Vital signs will be assessed at timelines as specified in the SoA (see Section 1.3) and as clinically indicated. If measured on the day of infusion, CCI should be measured CCI (see Section 8.3.5.2). Participants should remain at the site for at least CCI post infusion of every dose of Dato-DXd for close observation for possible allergic reactions and IRRs.

Body temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed in the seated or supine/semi-recumbent position with a completely automated device. Manual techniques will be used only if an automated device is not available. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television and cell phones).

One reading of pulse rate and blood pressure will be taken.

Situations in which vital signs results should be reported as AEs are described in Section 8.4.5.

For any AEs of infusion reactions, the vital signs values should be entered into the eCRF.

8.3.3 Electrocardiograms

Triplicate 12-lead ECGs will be performed at screening within 7 days before enrolment.

Electrocardiograms will be performed after the participant has been resting in a supine/semi-recumbent position for at least 5 minutes (± 2 minutes) and recorded, while the participant remains in that position using an ECG machine that automatically calculates the heart rate and measures PR, RR, QRS, QT, and QTcF intervals, as possible. Refer to Section 7

for QTcF withdrawal criteria and any additional QTcF readings that may be necessary. Manual calculation of QTcF is acceptable.

All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal. Any clinically significant abnormalities detected require triplicate ECG results. At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should be completed within 5 minutes. Subsequent ECGs will only be taken in triplicate if abnormalities were noted at screening. At any visit during which a participant exhibits a heart rate ≤ 50 bpm or other clinical symptoms suggesting a need for an ECG investigation, the ECG will be repeated.

Situations in which ECG results should be reported as AEs are described in Section 8.4.5.

8.3.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the visits indicated in the SoA (see Section 1.3).

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry, haematology, coagulation, and urinalysis will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. Every effort should be made to obtain and provide the corresponding laboratory reference ranges.

Other safety laboratory tests include assessment for pregnancy (serum at screening or serum/urine at other time points), hepatitis B and C serology, and HIV antibody test. Prior HIV serology (anti-HIV with or without HIV RNA, as appropriate), hepatitis B serology (HBsAg, anti-HBs, and anti-HBc with or without HBV DNA, as appropriate), and hepatitis C serology (anti-HCV antibody with or without HCV RNA, as appropriate) testing results can be used if performed within 120 days before screening. In this case, there is no need for a repeat test during the 28 day screening period. If an HIV infection meets the criteria outlined in Section 5.2, monitoring of viral RNA load and CD4+ count is recommended. Participants must be tested for HIV if acceptable by local regulations or an IRB/EC.

Pregnancy tests may be performed at the site using a licensed test (urine beta-human chorionic gonadotropin pregnancy or serum test per institutional guideline) for all FOCBP. A negative serum pregnancy test (test must have a sensitivity of at least 25 mIU/mL) must be documented during screening for all FOCBP. If a serum pregnancy test is collected greater than 72 hours prior to the first dose of study intervention, perform a repeat pregnancy test (urine or serum

per institutional guideline) within 72 hours before the first dose of study intervention. Perform repeat pregnancy tests (urine or serum per institutional guideline) within 72 hours before each infusion at each cycle, at EoT, and the first follow-up visit. A positive urine pregnancy test result must immediately be confirmed using a serum test. If a positive urine pregnancy test result is confirmed using a serum test, then the participant should not be treated.

Laboratory assessments that yield abnormal, clinically significant results should be repeated as clinically indicated (preferably within 72 hours) and recorded in the eCRF.

The laboratory variables to be measured are listed in Table 6.

Table 6 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
Differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)	Albumin
Haematocrit	Alkaline phosphatase
Haemoglobin	ALT
Platelet count	AST
Red blood cell count	Bilirubin, total
White blood cell count	Calcium, total/ionized
	Chloride
Urinalysis	Creatinine (serum)
Glucose	Lactate dehydrogenase
Haemoglobin/Erythrocytes/Blood	Magnesium
Protein/Albumin	Potassium
	Protein, total
Coagulation	Sodium
Coagulation variables (aPTT or PTT and prothrombin time/INR)	Urea nitrogen/blood urea nitrogen/urea

ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; INR, international normalised ratio; PTT, partial thromboplastin time.

The investigator should assess the available results with regard to clinically relevant abnormalities in documentation. Situations in which laboratory safety results should be reported as AEs are described in Section 8.4.5.

All participants with CTCAE Grade 3 or Grade 4 laboratory values at the time of completion or discontinuation from study intervention must be followed and have further tests performed until the laboratory values have returned to Grade 1 or Grade 2, unless these values are not likely to improve because of the underlying disease.

Note: In case a participant shows an AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN please refer to Appendix D 'Actions required in cases of increases in liver biochemistry and evaluation of HL,' for further instructions.

8.3.5 Other Safety Assessments

8.3.5.1 Echocardiogram/Multigated Acquisition Scan

An ECHO or MUGA scan to assess LVEF will be performed at the visits as shown in the SoA (see Section 1.3). The modality of the cardiac function assessments must be consistent for a given participant (ie, if ECHO is used for the screening assessment for a given participant, then ECHO should also be used for subsequent scans for that participant). The participants should also be examined using the same machine and operator whenever possible, and quantitative measurements should be taken (ie, accurate to 1% and not estimated to 5%). All ECHOs/MUGAs will be evaluated by the investigator or delegated physician for monitoring cardiac function. If a MUGA scan is clinically indicated at the time of Dato-DXd infusion, it should be performed, and its results should be evaluated before infusion with Dato-DXd.

If a participant has had an ECHO or MUGA performed within 4 weeks prior to discontinuation of study intervention, the discontinuation visit ECHO/MUGA scan is not required unless clinically indicated. If a participant has any clinically significant decrease in LVEF (greater than CCI points to below CCI), there should be follow-up within 4 weeks until resolution.

Situations in which ECHO or MUGA results should be reported as AEs are described in Section 8.4.5.

8.3.5.2 Pulmonary Assessments

CCI should be evaluated by the investigator or the delegate physician at the time points outlined in the SoA (see Section 1.3) and as clinically indicated. If CCI is measured on the day of infusion, it should be measured CCI (see the SoA and Section 8.3.2). CCI and CCI may be performed CCI and should include basic spirometry at a minimum with optional additional components as mentioned in Table 7.

Table 7 Spirometry Component

Required spirometry components	Optional spirometry components
FVC (L)	PEF
FVC % predicted	CCI
FEV_1 (L)	FEV_6
FEV_1 % predicted	TLC
FEV_1/FVC %	RV

CCI; FEV, forced expiratory volume; FEV_1, FEV in one second; FEV_6, FEV in 6 seconds; FVC, forced vital capacity; PEF, peak expiratory flow; RV, residual volume; TLC, total lung capacity

CCI will be performed/encouraged if feasible, but for participants with prior severe and/or prior clinically significant pulmonary disorders, it is a requirement. In event of suspected ILD/pneumonitis, refer to Section 8.3.5.3 additional pulmonary assessments.

High-resolution CT of the chest will be performed/encouraged if feasible (otherwise non-contrast chest CT is acceptable; 1 to 2 mm slice thickness recommended) and if ILD/pneumonitis is suspected. Chest CT and/or chest HRCT scans will be reviewed separately for safety for the presence of ILD/pneumonitis prior to administration of the next scheduled dose of Dato-DXd.

8.3.5.3 ILD/Pneumonitis Investigation

For suspected ILD/pneumonitis (ie, if new or worsening pulmonary symptoms [eg, dyspnoea, cough, or fever] or radiological abnormality suggestive of ILD/pneumonitis is observed), treatment with Dato-DXd should be delayed, and a full investigation is required as described in the Dato-DXd TMGs (see the TMG Annex).

Evaluations should include the following:

- CCI

- CCI [redacted]

[redacted]

The results of the full diagnostic workup (including CCI [redacted], etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup to exclude alternative causes, such as CCI [redacted]. In the presence of CCI [redacted]

The following assessments should be performed, if feasible, to enhance the investigation and diagnosis of potential cases of ILD/pneumonitis. The results of the assessment will be collected.

- Other items:
  - When ILD/pneumonitis is suspected during treatment with study intervention, the CCI [redacted] should be measured where possible:
    - ILD/pneumonitis CCI [redacted]
    - CCI [redacted]
      - Additional clinical chemistry: CCI [redacted]

8.3.5.4 Eastern Cooperative Oncology Group Performance Status

The ECOG performance status will be assessed at the times specified in the SoA based on the following:

0 Fully active; able to carry out all usual activities without restrictions.

1 Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (eg, light housework or office work).

2 Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours.

3 Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.

4 Completely disabled; unable to carry out any self-care and totally confined to bed or chair.

5 Dead.

Any significant change from baseline or screening must be reported as an AE.

8.3.5.5 Ophthalmologic Assessments

Ophthalmologic assessments including but not limited to visual acuity testing, slit lamp examination, intraocular pressure measurement, fundoscopy, and fluorescein staining will be performed as specified in the SoA (see Section 1.3) and as clinically indicated by an ophthalmologist, or if unavailable, another licensed eye care provider. A suitable alternative to fluorescein staining of the cornea may be used in exceptional circumstances where fluorescein is not available. An ophthalmologic assessment should be considered for any ocular symptoms including, but not limited to, dry eye, decreased or blurred vision, foreign-body sensation, photophobia, tearing, pain, and eye redness. All OAs (baseline, as clinically indicated, EOT) should be documented on worksheets in the eCRF, and copies of all consultation reports should be filed in the source notes. Please refer to the Dato-DXd Site Ophthalmologic Assessment Manual for further details.

Participants who are receiving Dato-DXd should be advised to use artificial tears (preservative-free if possible) 4 times daily as a preventative measure and up to 8 times daily as clinically needed and to avoid the use of contact lenses. The use of other eye medications (eg, topical corticosteroids) for prophylaxis should be at the discretion of an ophthalmologist, or if unavailable, another licensed eye care provider.

Further recommendations for preventing and treating ocular surface toxicity are available in the SoA and the TMGs (see the Annex document to this CSP).Any significant change from baseline must be reported as an AE (see Section 8.4.5).

8.3.5.6 CCI

CCI will be started CCI as specified in the SoA. CCI will be provided CCI , which will include CCI . An CCI will also be provided to each enrolled participant before study drug initiation.

Participants should adhere to the following guidance:

- CCI
  - is highly recommended.

  - Note: Participants are allowed to CCI based on institutional/local guidelines.
- In the absence of CCI is recommended.
- CCI should also be considered.

The following algorithm, to be followed from steps 1 to 4, may be used as a guidance to select CCI:

1 CCI. If not available, then use→
2 CCI. If not available, then use→
3 CCI. If not available, then use→
4 CCI.

CCI should also include educating participants on the importance of CCI

As per investigator judgment, a professional CCI

For further information, refer to the Dato-DXd TMGs (see the Annex document to this CSP).

8.4 Adverse Events and Serious Adverse Events

The principal investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The investigator and any designees are responsible for detecting, documenting, recording, and reporting events that meet the definition of an AE.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events and SAEs will be collected from the time of signature of the ICF, throughout the Intervention Period and (other than ILD/pneumonitis) including the safety follow-up period (which is 28 days [+ 7 days] after the discontinuation of all study interventions). All

ILD/pneumonitis events regardless of severity should be reported beyond the CCI safety follow-up period. All AESIs, regardless of severity or seriousness, must be followed until either event resolution, end of study, including any post-treatment follow-up, trial termination, withdrawal of consent, or participant death. If an event that starts or worsens post the defined safety follow-up period noted above is considered to be due to a late onset toxicity to study intervention, then it should be reported as an SAE as applicable. Collection and reporting of AEs and SAEs after the final DCO is described in Section 8.4.12.

Pre-existing medical conditions that may have been identified by mandatory screening procedures (eg, cataract CCI , benign cyst on baseline imaging, etc.) should be recorded as medical history in the eCRF.

If the investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

The following types of events should be reported by the investigator in the EDC within 24 hours of awareness:

- Serious adverse events (see Section 8.4.13)
- All potential CCI cases should be reported within 24 hours, including both serious and non-serious potential CCI cases CCI .
- Hepatic events (both serious and non-serious) which meet the PHL criteria defined as an elevated ALT or AST ≥ 3 × ULN and an elevated TBL ≥ 2 × ULN regardless if it is due to disease progression per investigator assessment, that may occur at different time points during the study conduct, should always be reported to the sponsor. These events must be reported in the eCRF, with the investigator's assessment of seriousness, severity, causality, and a detailed narrative. A CCI is built within the eCRF to collect relevant additional information for these potential cases. If the participant discontinues study intervention due to liver enzyme abnormalities, the participant will have additional clinical and laboratory evaluations as described in Appendix D in order to determine the nature and severity of the potential liver injury.
- CCI (see Section 8.4.11).
- CCI (see Section 8.4.11).
- CCI
- Overdose (see Section 8.5).

Additional relevant information regarding the AESIs, regardless of seriousness, will be collected through CCI within the clinical study database (see Section 8.4.11).

8.4.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the investigator for as long as medically indicated but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse Event Variables

The following variables will be collected for each AE:

- Adverse event (verbatim)
- Date (and time, if applicable) when the AE started and stopped
- Initial CTCAE 5.0 grade, plus any changes in CTCAE 5.0 grade
- Whether the AE is serious or not (Appendix B)
- Investigator causality rating against the study intervention(s) (yes or no)
- Action taken with regard to study intervention(s)
- Adverse event caused participant's withdrawal from study (yes or no)
- Administration of treatment for the AE
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- Seriousness criteria
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

The grading scales found in the CTCAE 5.0 will be utilised for all events with an assigned CTCAE 5.0 grading. For those events without assigned CTCAE 5.0 grades, the recommendation in the CTCAE 5.0 criteria that converts mild, moderate, and severe events into CTCAE 5.0 grades should be used. A copy of the CTCAE 5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.4.3 Causality Collection

The investigator should assess causal relationship between study intervention and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the study intervention?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

8.4.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.4.5 Adverse Events Based on Examinations and Tests

The results from the CSP-mandated laboratory tests, vital signs, physical examinations, ECGs, and ECHO/MUGA scans, ECOG performance status, and ophthalmologic assessments will be summarised in the CSR.

Deterioration as compared with baseline in CSP-mandated laboratory values, vital signs, ECGs, and ECHO/MUGA scans should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention or are considered to be clinically relevant as judged by the investigator (which may include, but are not limited to, consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or study intervention delay).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE, and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value that is unequivocally due to PD should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.4.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of HL.

8.4.7 Disease Progression

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the study intervention is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing, metastasis to the primary cancer under study should be considered as PD and not an AE. Events that are unequivocally due to PD should not be reported as AEs during the study, with the exception of hepatic events that meet PHL criteria as defined in Section 8.4.1.

8.4.8 Disease Under Study

Symptoms of disease under study are those that might be expected to occur as a direct result of NSCLC (Cohort 1), TNBC (Cohort 2), or other advanced or metastatic solid tumours in future cohorts, or procedures used to diagnose or treat the disease under study. Events that are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria.

8.4.9 New Cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New primary cancers are those that are not the primary reason for the administration of study intervention and are identified after the participant's inclusion in this study. They do not include metastases of the original cancer.

8.4.10 Deaths

All deaths that occur during the study Intervention Period, or within the CSP-defined Post-intervention Follow-up Period after the administration of the last dose of study intervention, must be reported as follows:

- Death clearly resulting from PD should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to PD under study, the AE causing the death must be reported as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign the main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE and documented in the Statement of Death page in the eCRF, but every effort should be made to determine a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual time frames.

Deaths occurring after the CSP-defined safety follow-up period after the administration of the last dose of study intervention should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined safety follow-up period and the event is considered to be due to a late-onset toxicity to study intervention, then it should also be reported as an SAE.

8.4.11 Adverse Events of Special Interest

Adverse events of special interest are events of scientific and medical interest specific to the further understanding of Dato-DXd safety profile and require close monitoring and rapid communication by the investigators to AstraZeneca. An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF using a recognised medical term or diagnosis that accurately reflects the event. Serious AESIs will be recorded and reported as per Section 8.4.13. AESIs are detailed in the IB, Section 5.5.1.3.

All AESIs, regardless of severity or seriousness, must be followed until either event resolution, end of study, including any post-treatment follow-up, trial termination, withdrawal of consent, or participant death.

Concomitant medications administered as treatment for drug-related AESIs should be recorded until either event resolution, end of study, trial termination, withdrawal of consent, or participant death.

For the Dato-DXd clinical programme, based on the available pre-clinical data, current clinical developmental program, review of the cumulative literature, reported toxicities for drugs with similar monoclonal antibody and payload of Dato-DXd and biological plausibility, the relevant PTs for ILD/pneumonitis, IRR, oral mucositis/stomatitis, mucosal inflammation other than oral mucositis/stomatitis, and ocular surface toxicity are considered to be AESIs.

Refer to the current IB for a summary of preliminary clinical study data.

ILD/Pneumonitis

ILD is considered CCI [redacted] based on a comprehensive cumulative review of the available safety data from the clinical development program, as well as the results of potential ILD/pneumonitis cases reviewed by the independent ILD Adjudication Committee, available data from recent epidemiology/literature, biological plausibility, and safety information from drugs with a similar monoclonal antibody and/or payload as Dato-DXd.

All potential ILD/pneumonitis cases should be reported within 24 hours, including both serious and non-serious potential ILD/pneumonitis cases (potential ILD/pneumonitis is described in the Event Adjudication Site Manual). A TQ is built within the eCRF to collect relevant additional information for these potential cases regardless of seriousness.

All ILD/pneumonitis events regardless of severity should be reported beyond the 28 + 7-daysafety follow-up period.

Recommendations for preventing and treating ILD/pneumonitis are available in the TMG Annex.

Interstitial lung disease/pneumonitis should be ruled out if a participant develops radiographic changes potentially consistent with ILD/pneumonitis or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnoea, cough, or fever. If the AE is confirmed to have an aetiology other than ILD/pneumonitis, follow the management guidance outlined in the TMG Annex.

If the AE is suspected to be ILD/pneumonitis, treatment with study intervention should be delayed pending further evaluations. Evaluations should include those outlined in Section 8.3.5.3. If the AE is confirmed to be ILD/pneumonitis, follow the management guidance outlined in the TMG Annex. All events of ILD/pneumonitis, regardless of severity or seriousness, will be followed until resolution including after DatoDXd- discontinuation. An autopsy in cases of Grade 5 ILD/pneumonitis is encouraged. An independent ILD Adjudication Committee is responsible for reviewing all cases of potential ILD/pneumonitis (see Section 9.6.1).

Infusion-related Reaction

Infusion-related reaction is CCI [redacted] associated with Dato-DXd treatment. Additional data for these ≥ Grade 3 AEs will be collected via TQs of IRR.

Recommendations for preventing and treating IRR are available in the TMG Annex.

Oral Mucositis/Stomatitis

Oral mucositis/stomatitis AEs are considered as CCI [redacted] and AESIs associated with Dato DXd treatment. Mucosal inflammation other than oral mucositis/stomatitis is also an

identified risk but is considered as a separate AESI. Additional data for these AEs regardless of CTCAE grading will be collected via TQs of oral mucositis/stomatitis.

Mucosal Inflammation Other than Oral Mucositis/Stomatitis

Mucosal inflammation AEs are considered as CCI associated with Dato-DXd treatment and as a separate AESI from oral mucositis/stomatitis. Additional data for these AEs regardless of CTCAE grading will be collected via TQs of mucosal inflammation.

Ocular Surface Toxicity

Ocular surface toxicity (eg, dry eye, keratitis) is considered an AESI associated with Dato-DXd treatment. Dry eye is considered as CCI and keratitis as CCI within this AESI. Additional data for these AEs regardless of CTCAE grading are collected via eCRF TQs for ocular surface toxicity. Recommendations for preventing and treating ocular surface toxicity are available in the SoA (see Section 1.3) and TMGs (see the TMG Annex), respectively.

Please refer to the Dato-DXd Site Ophthalmologic Assessment Manual for further details.

8.4.12 Safety Data to be Collected Following the Final Data Cut-off of the Study

For participants continuing to receive Dato-DXd after the final DCO and database closure, AEs and SAEs will be collected, but only SAEs will be reported. In addition, it is recommended that participants continue the scheduled site visits and investigators monitor the participant's safety laboratory results periodically during treatment with Dato-DXd in order to manage AEs, consistent with the dose modification guidelines for management of study intervention-related toxicities (see the TMG Annex). All data after the final DCO and database closure will be recorded in the participant notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

All SAEs that occur in participants still receiving Dato-DXd (or within the 28+7 days following the last dose of Dato-DXd) after the final DCO must be reported as detailed in Section 8.4.13.

8.4.13 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the study intervention, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate AstraZeneca representatives within one day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone followed by completion of a paper SAE form.

The AstraZeneca representative will advise the investigator/study site staff how to proceed.

For further guidance on the definition of a SAE, see Appendix B of the CSP.

The reference document for definition of expectedness/listedness is the IB for Dato-DXd.

8.4.14 Pregnancy

All pregnancies and outcomes of pregnancy with conception dates following the first date of study intervention, including pregnancy in the partner of male participants, should be reported to AstraZeneca.

8.4.14.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, study intervention should be discontinued immediately. The sponsor must be notified of any female participant or partner of a male participant who becomes pregnant while receiving or within 7 months of discontinuing Dato-DXd.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within one day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within one or 5 calendar days for SAEs (see Section 8.4.13) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP cohort in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

8.4.14.2 Paternal Exposure

Non-sterilised male participants who intend to be sexually active with a FOCBP should refrain from fathering a child or donating or banking sperm for the duration of the study (from the time of screening) and for 4 months after the last dose of Dato-DXd.

Pregnancy of the participant's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly) occurring from the date of the first dose of study intervention until 4 months after the last dose of study intervention should be followed up and documented in the medical record and provided to the AstraZeneca Patient Safety data entry site. Consent from the partner must be obtained before the information is collected and reported to AstraZeneca.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the investigator must obtain the consent of the participant's partner. The study team should adopt the Master Pregnant Partner Form in line with local procedures/requirements and submit it to the relevant Regulatory Authority/IRBs/IECs prior to use.

8.4.15 Special Situations of Medication Error, Drug Abuse, or Drug Misuse

8.4.15.1 Timelines

In the event of a medication error, drug abuse, or drug misuse in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within one day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within one (Initial Fatal/Life-threatening or follow-up Fatal/Life-threatening) or 5 (other serious initial and follow-up) calendar days if there is an

SAE associated with the event of medication error, drug abuse, or drug misuse and within 30 days for all other events.

8.4.15.2 Medication Error

For the purposes of this clinical study, a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication error can be found in Appendix B 4.

8.4.15.3 Drug Abuse

Drug abuse is the persistent or sporadic intentional, non-therapeutic excessive use of study intervention for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

8.4.15.4 Drug Misuse

Drug misuse is the intentional and inappropriate use of study intervention for medicinal purposes outside of the authorised product information, or for unauthorised study interventions, outside of the intended use as specified in the CSP and includes deliberate administration of a product by the wrong route.

The full definitions and examples of drug misuse can be found in Appendix B 4.

8.5 Overdose

Refer to Section 6.8 for definition and treatment of overdose.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE module in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within one or 5 calendar days for overdoses associated with an SAE (see Section 8.4.13) and within 30 days for all other overdoses.

8.6 Human Biological Samples

Instructions for the collection, handling, storage, and shipping of biological samples will be provided in the study-specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality.

Samples will be stored for a maximum of one year from the publication of the final CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed within six months of Bioanalytical Report finalisation.
- ADA samples will be disposed within one year of final CSR publication. ADA samples will only be used for ADA assay for this study.
- Samples collected in China will be stored and disposed of according to local laws and regulations.

For further details on Handling of Human Biological Samples, see Appendix C.

8.6.1 Pharmacokinetics

- Blood samples will be collected for measurement of plasma concentrations of Dato-DXd, total anti-TROP2 antibody, and DXd as specified in the SoA and Table 8. If CCI [redacted], additional blood samples for PK analyses may be collected if feasible.

Table 8 Pharmacokinetic Sampling Schedule

Cycles	Days	Intensive Sampling PK Cohort (at least 6 participants in each cohort)[a]	Sparse Sampling Pharmacokinetic Cohort (for the rest of the participants)
1	1	Pre-dose: Within 8 hours before infusion Post-dose: • Within 30 minutes after end of infusion • 5 hours (± 15 minutes) after infusion start • 7 hours (± 15 minutes) after infusion start	Pre-dose: Within 8 hours before infusion Post-dose: • Within 30 minutes after end of infusion • 5 hours (± 15 minutes) after infusion start
	2	24 hours (± 2 hours) after Day 1 infusion start	None
	8	7 days (± 1 day) after Day 1 infusion start	None
	15	14 days (± 1 day) after Day 1 infusion start	None
2	1 (± 2)	Pre-dose:	

Cycles	Days	Intensive Sampling PK Cohort (at least 6 participants in each cohort)[a]	Sparse Sampling Pharmacokinetic Cohort (for the rest of the participants)
		Within 8 hours before infusion	
4	1 (±3)	Pre-dose: Within 8 hours before infusion Post-dose: Within one hour after end of infusion	
8	1 (±3)	Pre-dose: Within 8 hours before infusion Post-dose: Within one hour after end of infusion	

[a] Participation in the intensive sampling PK cohort will be optional.

- Plasma samples will be used to analyse the PK of Dato-DXd, total anti-TROP2 antibody, and DXd. Samples collected for analyses of Dato-DXd, total anti-TROP2 antibody, and DXd plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Plasma concentrations of the 3 analytes (Dato-DXd, total anti-TROP2 antibody, and DXd) will be summarised for all evaluable participants in the PK analysis population using descriptive statistics at time points indicated in the SoA and Table 8.
- Non-compartment PK parameters that can be derived with sparse PK sampling may be reported as data allow. The non-compartment PK parameters to be obtained and reported in the intensive PK cohort may include, but are not limited to the C_{max}, the trough observed concentration, T_{max}, AUC, $t_{½}$, and CL, if the data allow. Details on the analysis of PK assessments will be provided in the SAP.
- Population PK and E-R analyses will be performed to characterise the relationships among dose, exposure, and the efficacy and safety endpoints, if applicable. The results of the popPK and E-R analyses will be reported separately from the CSR.

8.6.1.1 Determination of Drug Concentration

Samples for determination of drug concentration in plasma will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.6.2 Immunogenicity Assessments

Blood samples for determination of ADA in plasma will be collected per the SoA and assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report.

Anti-drug antibody samples may also be further tested for characterisation of the ADA response. Neutralising ADA may be determined when ADA is positive.

The effect of immunogenicity on PK, efficacy, and safety will be evaluated, if the data allow.

8.6.3 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Human Biological Sample Biomarkers

8.7.1 Collection of Mandatory Samples for Biomarker Analysis

Participant consent to the study includes participation in the mandatory biomarker assessment components of the study. Mandatory collection of tumour tissue for biomarker research is required as part of the study, once local regulatory approval is obtained.

Samples for biomarker assessment are required and will be collected from all enrolled participants in this study as specified in the SoA based on local regulatory approval.

Tumour samples collected for TROP2 testing from participants in China will be destroyed or repatriated within CCI of the final CSR publication. Human Genetic Resources approval will be followed for China sample collection and usage.

Tumour samples obtained from the primary tumour or from a metastatic site (excluding bone) before enrolment are mandatory for all enrolled participants in this study based on local regulatory approval. A fresh tumour sample collected during screening is preferred, if clinically feasible in the form of an FFPE tissue. For the FFPE tissues, a minimum of 5 slides of freshly prepared, unstained, 4- to 5-micron sections are required. If such a de novo collection is not feasible, an archival tumour sample collected as close to screening as possible must be provided, in the form of a minimum of 5 slides of freshly prepared, unstained, 4- to 5-micron sections from the archival FFPE tumour sample. As uncontrolled oxidation processes affect tumour sections, tumour tissue blocks are preferred.

Tumour lesions used for fresh biopsies should not be the same lesions used as RECIST 1.1 TLs, unless there are no other lesions suitable for biopsy and in this instance only core needle (not excisional/incisional) biopsy is allowed. Collection of tumour cells from fluid such as ascites or pleural effusion is not permitted. The tumour sample must not be taken from a previously irradiated lesion.

Samples will be tested for TROP2 protein measured by immunohistochemistry, to evaluate their association with the observed clinical responses to Dato-DXd (including but not limited to ORR, PFS, and OS, as well as key safety endpoints).

For further details on Handling of Human Biological Samples, including storage, re-use, and destruction, refer to Appendix B 4 and the Laboratory Manual.

8.7.2 Collection of Optional Biomarker Samples

Optional biomarker samples will not be collected in China.

8.8 Optional Genomics Initiative Sample

Not applicable

8.9 Health Economics

Not applicable

8.10 Study Participant Feedback Questionnaire

Not applicable

9 STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by AstraZeneca or its representatives.

A comprehensive SAP will be prepared prior to enrolment of the first participant in the study.

9.1 Statistical Hypotheses

The primary endpoint of the study is confirmed ORR by ICR, defined as the proportion of participants in each cohort with confirmed CR or confirmed PR, as assessed by ICR based on RECIST 1.1.

In view of the open-label, single-arm, multiple-cohort study design, no formal statistical hypothesis will be tested and, unless otherwise specified, study data will be presented using descriptive statistics. However, confirmed ORR by ICR per RECIST 1.1 is considered an early signal for clinical benefit.

9.2 Sample Size Determination

Sample size justification for Cohort 1 – NSCLC

Approximately 40 eligible NSCLC participants will be enrolled to have preliminary efficacy and safety data for Dato-DXd. If the observed ORR by ICR is CCI the 95% two-sided CI based on 40 participants is CCI If the observed ORR is CCI the two-sided 95% CI is CCI If the observed ORR is CCI the two-sided 95% CI is CCI The sample size will also provide reasonable utility for safety analyses. With a sample size of 40 participants, the probability of observing one or more instances of a

specific AE with a true incidence rate of 1%, 2%, and 5% is 33.1%, 55.4%, and 87.1%, respectively.

For CCI of the 40 eligible NSCLC participants without measurable disease at baseline by ICR, the information below shows the observed ORR (95% CI) based on the RES with CCI participants without measurable disease at baseline as assessed by ICR.

Number of participants in RES	Number of observed responders	Observed ORR (95% CI)
CCI of participants without measurable disease at baseline as assessed by ICR)	CCI	

Sample size justification for Cohort 2 – TNBC

Approximately 78 eligible TNBC participants will be enrolled to have preliminary efficacy and safety data for Dato-DXd. Seventy-eight participants will CCI The sample size will also provide reasonable utility for safety analyses. With a sample size of 78 participants, the probability of observing one or more instances of a specific AE with a true incidence rate of 1%, 2%, or 5% is 54.3%, 79.3%, 98.2%, respectively.

For CCI of the 78 eligible TNBC participants without measurable disease at baseline as assessed by ICR, the information below shows the observed ORR CCI based on the RES with CCI participants without measurable disease at baseline by ICR.

Number of participants in RES	Observed ORR % (n/N)	CCI
CCI of participants without measurable disease at baseline by ICR)	CCI	
CCI of participants without measurable disease at baseline by ICR)	CCI	

9.3 Populations for Analyses

The populations for analysis of each cohort are defined in Table 9. Each cohort will be treated as a separate study for analysis.

Table 9 Populations for Analysis

Population/Analysis Set	Description
Enrolled	All participants who provide informed consent and the participants are confirmed as eligible irrespective of whether they received the study treatment.
FAS	Enrolled participants who have received at least one dose of treatment. Participants who were enrolled but did not subsequently receive study intervention are not included in the analysis.
RES	Enrolled participants who received at least one dose of study intervention and had measurable disease at baseline by ICR.
PK analysis set	Enrolled participants who have received at least one dose of treatment and had measurable serum concentrations of Dato-DXd.
ADA evaluable set	Participants in the FAS with a non-missing baseline Dato-DXd ADA result and at least one post-baseline Dato-DXd ADA result.

ADA, anti-drug antibody; FAS, full analysis set; ICF, informed consent form; ICR, independent central review; PK, pharmacokinetic; RES, response evaluable set.

9.4 Statistical Analyses

The SAP will be finalised prior to enrolment of the first participant in the study, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and secondary endpoints. The statistical analysis will be performed separately for each cohort.

9.4.1 General Considerations

The DCO for the primary analysis of ORR by ICR will occur approximately 6 months after the last participant has initiated study intervention for that cohort. Duration of response, DCR,

BOR, TTR, PFS, OS, and available safety, immunogenicity, and PK data will also be summarised at this time.

The DCO for the full final analysis of ORR by ICR will occur approximately 12 months after the last participant has initiated study intervention for that cohort. The full final analysis will report the analyses of all primary and secondary endpoints, including updated ORR and DoR, DCR, BOR, TTR, PFS, OS, PK, immunogenicity, and safety.

The below general principles will be followed:

- Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, upper and lower quartiles minimum, and maximum. For log-transformed data, it is more appropriate to present geometric mean, coefficient of variation, median, minimum and maximum. Categorical variables will be summarised by frequency counts and percentages for each category.
- Unless otherwise stated, percentages will be calculated out of the population total.
- In general, for efficacy, the last observed measurement prior to the start of study intervention will be considered the baseline measurement. For RECIST 1.1 tumour assessments, baseline must be no more than 28 days before the date of the first dose of study intervention. If a baseline radiological tumour assessment is performed more than 28 days before the first dose of study intervention, then it will be reported as a protocol deviation, but the scan will still be included as baseline. For safety endpoints, the last observation before the first dose of study intervention will be considered the baseline measurement unless otherwise specified. Depending on the extent of any impact, summaries of data relating civil crisis, natural disaster, or public health crisis may be generated if appropriate. More details will be provided in the SAP.

Table 10 provides a summary of endpoints and corresponding analysis populations.

Table 10 Summary of Outcome Variables and Analysis Populations

Outcome Variable	Population(s)
Primary Efficacy Variable	
Confirmed ORR by ICR per RECIST 1.1	Primary analysis: RES Supplementary analyses: FAS
Secondary Efficacy Variables	
• Confirmed ORR by investigator assessment per RECIST 1.1 • DoR, DCR, BOR, and TTR by ICR and by investigator assessment per RECIST 1.1	Primary analysis: RES Supplementary analyses: FAS
• PFS by ICR and by investigator assessment per RECIST 1.1 • OS	Primary analysis: FAS

Outcome Variable	Population(s)
Baseline and Other Variables	
• Demography, baseline, and disease characteristics • Important deviations • Medical/surgical history • Previous and subsequent anticancer therapy • Concomitant medications/procedures	Primary analysis: FAS
Pharmacokinetics	
• Pharmacokinetics data	PK analysis set
Immunogenicity	
• Anti-drug antibodies	ADA Evaluable Set
Safety	
• Exposure to study intervention • Safety data	FAS

[a] DoR analysis will be based on the subset of participants in the RES who achieved confirmed response.
ADA, anti-drug antibody; AEs, adverse events BOR, best overall response; DCR, disease control rate; DoR, duration of response; FAS, full analysis set; ICR, independent central review; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; RECIST 1.1, Response Evaluation Criteria in Solid Tumours Version 1.1; RES, response evaluable set.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint

9.4.2.1.1 Calculation or Derivation of Tumour Response Variables

9.4.2.1.1.1 Investigator RECIST 1.1-based assessments

All RECIST 1.1 assessments, whether scheduled or unscheduled, will be included in the calculations regardless of whether a participant discontinues study intervention or receives another anticancer therapy.

At each visit, participants will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, PD, or NE depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within 28 days prior to enrolment. The tumour response endpoints (ORR, DoR, DCR, BOR, TTR, and PFS) will then be derived from the scan dates and overall visit responses.

9.4.2.1.1.2 Independent Central Review

An ICR of radiological scans will be performed on all participants to confirm the robustness of the investigator-assessed ORR, DoR, DCR, BOR, TTR, and PFS endpoints.

All images will be collected centrally. The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and will be adjudicated, if required. For each participant, the ICR will define the overall visit response data (CR, PR, SD, PD, or NE) and the relevant scan

dates for each time point (ie, for visits where response or progression is/is not identified). If a participant has had a tumour assessment that cannot be evaluated, then the participant will be assigned a visit response of NE (unless there is evidence of progression, in which case the response will be assigned as PD). Endpoints ORR, DoR, DCR, BOR, TTR, and PFS will then be derived from the scan dates and overall visit responses.

Further details of the ICR will be documented in an Independent Review Charter.

9.4.2.1.1.3 Primary Endpoint: Confirmed ORR by ICR

The primary endpoint of the study is confirmed ORR by ICR according to RECIST 1.1. Confirmed ORR (per RECIST 1.1 by ICR) is defined as the percentage of participants in each cohort with a confirmed response of CR or PR. Data obtained up until progression or the last evaluable assessment with the absence of progression will be included in the assessment of ORR. Participants who discontinue study intervention without progression, receive a subsequent anticancer therapy, and then respond will not be included as responders in the calculation of ORR (note that for this analysis palliative radiotherapy is not considered a subsequent anti-cancer therapy).

A confirmed response of CR or PR means that a response of CR or PR is recorded at one visit and confirmed by repeat imaging not less than 4 weeks after the response was first observed, with no evidence of progression between the initial and CR/PR confirmation visits.

ORR is based on the ICR data and using all scans regardless of whether they were scheduled or not.

Analyses of Primary Endpoint

The primary analysis of the primary endpoint will be based on the RES population. The ORR will be estimated with 2-sided 95% exact CI using the Clopper-Pearson method. Summaries will be produced presenting the number and percentage of participants with a confirmed tumour response.

Supplementary Analysis

Supplementary analysis of the primary endpoint will be performed in the FAS using the same methods as described above.

Sensitivity Analysis

Details of any sensitivity analyses to be conducted for the primary endpoint will be described in the SAP, as appropriate.

Subgroup Analysis

Details of any subgroup analyses to be conducted for the primary endpoint will be specified in the SAP, as appropriate.

9.4.2.2 Secondary Endpoint(s)

9.4.2.2.1 Confirmed Objective Response Rate by Investigator Assessment

The secondary efficacy endpoint of confirmed ORR is defined as the proportion of participants who have a confirmed CR or PR, as determined by the investigator at local site per RECIST 1.1.

Analysis Methods

Investigator-assessed ORR will be estimated using the same methods as those specified for ORR by ICR for the RES (see Section 9.4.2.1.1.3). Supplementary analysis will be performed using the FAS.

9.4.2.2.2 Duration of Response

Duration of Response by ICR

For participants who achieve a confirmed CR/PR per RECIST 1.1 by ICR, DoR is defined as the time from the date of first documented response (which is subsequently confirmed) until the date of documented progression (using RECIST 1.1 by ICR) or death in the absence of PD. The time of the initial response will be defined as the latest of the dates contributing towards the first documented response of CR or PR that is subsequently confirmed. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. If a participant does not progress following a response, then their DoR will be the PFS censoring time (ie, DoR = date of PFS event or censoring – date of first response + 1).

Duration of Response by Investigator Assessment

For participants who achieve a confirmed CR/PR per RECIST 1.1 by investigator assessment, DoR is defined as the time from the date of first documented response (which is subsequently confirmed) until the date of documented progression (using RECIST 1.1 by investigator assessment) or death in the absence of PD.

Data will be handled as described above for DoR by ICR.

Analysis Methods

The DoR will be analysed in the subset of participants in the RES who achieved confirmed response. Supplementary analysis will be performed using the FAS.

The survival distribution for DoR will be estimated by the Kaplan-Meier method, and the results will be presented graphically. The estimate of median DoR and corresponding 95% CI using the Brookmeyer-Crowley method with log-log transformation will be reported.

9.4.2.2.3 Disease Control Rate

Disease Control Rate by ICR

The DCR by ICR at the time of each DCO is defined as the percentage of participants who have a confirmed CR/PR or SD for at least 5 weeks (ie, 6 weeks – 1 week to allow for an early assessment within the assessment window) after the date of the first dose of study intervention (without subsequent anticancer therapy) per RECIST 1.1 by ICR.

Disease Control Rate by Investigator Assessment

The DCR by investigator assessment at the time of each DCO is defined as the percentage of participants who have a confirmed CR/PR or SD for at least 5 weeks (ie, 6 weeks – 1 week to allow for an early assessment within the assessment window) after the date of the first dose of study intervention (without subsequent anticancer therapy) per RECIST 1.1 by investigator assessment.

Analysis Methods

The DCR will be summarised descriptively with the number and percentage of participants with a confirmed CR/PR or SD for at least 5 weeks in the RES. Supplementary analysis will be performed using the FAS.

9.4.2.2.4 Best Overall Response

Confirmed Best Overall Response by ICR

The BOR is a participant's best response during their participation in the study, but prior to starting any subsequent anticancer therapy, up until RECIST 1.1-defined progression by ICR or the last evaluable assessment in the absence of RECIST 1.1-defined progression by ICR.

Categorisation of BOR will be based on RECIST 1.1 by ICR using the following response categories: (confirmed) CR, (confirmed) PR, SD, PD, and NE; unconfirmed CR/PR will be included in SD.

Confirmed Best Overall Response by Investigator Assessment

The BOR is calculated based on the overall visit responses per RECIST 1.1 using investigator assessments. The BOR is a participant's best response during their participation in the study, but prior to starting any subsequent anticancer therapy, up until RECIST 1.1 defined progression or the last evaluable assessment in the absence of RECIST 1.1 defined progression.

Categorisation of BOR will be based on RECIST 1.1 by investigator assessment using the following response categories: (confirmed) CR, (confirmed) PR, SD, PD, and NE; unconfirmed CR/PR will be included in SD.

For guidance on the evaluation of tumour response per RECIST 1.1, see Appendix E.

The BOR will be determined programmatically based on RECIST 1.1 using all investigator assessments up until the first progression event per RECIST 1.1 as determined by the investigator. For participants whose first progression event is death, BOR will be calculated based on all evaluable RECIST 1.1 assessments prior to death.

For participants who die with no evaluable RECIST 1.1 assessments, if death occurs ≤ 91 days (ie, 2 × [6 weeks] + 1 week) after the date of the first dose of study intervention, then BOR will be assigned to the PD category. For participants who die with no evaluable RECIST 1.1 assessments, if the death occurs > 91 days (ie, 2 × [6 weeks] + 1 week) after the date of the first dose of study intervention, BOR will be assigned to the NE category.

Analysis Methods

Confirmed BOR will be summarised descriptively by n (%) for each category (confirmed CR, confirmed PR, SD, PD, and NE) in the RES. Supplementary analysis will be performed using the FAS.

9.4.2.2.5 Time to Response

Time to Response by ICR

The TTR is defined as the time from the date of the first dose of study intervention until the date of first documented objective response, which is subsequently confirmed per RECIST 1.1 as assessed by ICR. The analysis will include participants who have a confirmed response. Data obtained from the date of the first dose of study intervention up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of TTR. Participants who go off treatment without a response or progression, receive a subsequent therapy, and then respond will not be included.

Time to Response by Investigator Assessment

The TTR is defined as the time from the date of the first dose of study intervention until the date of first documented objective response, which is subsequently confirmed per RECIST 1.1 as assessed by the investigator. Data will be handled as described above for TTR by ICR.

Analysis Methods

The TTR will be summarised descriptively among participants in the RES who have a confirmed response. Supplementary analysis will be performed using the FAS.

9.4.2.2.6 Progression-Free Survival

Progression-free Survival by ICR

The PFS will be defined as the time from the date of the first dose of study intervention until the date of objective PD per RECIST 1.1 as assessed by ICR or death (by any cause in the absence of progression) (ie, date of event or censoring – date of the first dose of study intervention + 1). The analysis will include all participants regardless of whether the participant withdraws from study intervention, receives another anti-cancer therapy or clinically progresses prior to RECIST 1.1 progression. Participants who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the participant progresses or dies after 2 or more consecutive missed visits, the participant will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits. (Note: NE visit is not considered as missed visit).

If the participant has no evaluable tumour assessment visits or does not have baseline data, they will be censored at Day 1, unless they die within 2 tumour assessment visits of baseline (< 91 days [2 × 6 weeks] + 1 week allowing for a late assessment within the visit window).

Progression-free Survival by Investigator Assessment

The PFS by investigator assessment is defined as the time from the date of the first dose of study intervention until the date of PD per RECIST 1.1 as assessed by the investigator or death (by any cause in the absence of progression) (ie, date of event or censoring – date of the first dose of study intervention + 1).

Data will be handled as described above for PFS by ICR.

Analysis Methods

The survival distribution for PFS will be estimated by the Kaplan-Meier method, and the results presented graphically. The estimate of median PFS and corresponding 95% CI using the Brookmeyer-Crowley method with log-log transformation will be reported. Summaries of the number and percentage of participants experiencing a PFS event and the type of event (RECIST 1.1 or death) will be provided along with median PFS for each treatment. The proportion of participants alive and progression-free at 3-monthly intervals from the date of the first dose of study intervention will be estimated. The analysis will be performed using the FAS.

9.4.2.2.7 Overall Survival

The OS is defined as the time from the date of the first dose of study intervention until death due to any cause. The analysis will include all participants, regardless of whether the participant withdraws from study intervention or receives another anti-cancer therapy. 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.

Note: Survival calls will be made at an increased frequency leading up to and after the DCO date for the analysis (these contacts will be made until the date of database lock). If participants are confirmed to be alive or if the death date is after the DCO date, then these participants will be censored at the date of DCO.

Analysis Methods

The survival distribution for OS will be estimated by the Kaplan-Meier method, and the results presented graphically. Summaries of the number and percentage of participants experiencing an OS event will be provided along with median OS and corresponding 95% CI using the Brookmeyer-Crowley method with log-log transformation. The proportion of participants alive at 3-monthly intervals from the date of the first dose of study intervention will be estimated. The analysis will be performed using the FAS.

9.4.2.3 Tertiary/Exploratory Endpoint(s)

Refer to the SAP for details on the analyses of tertiary/exploratory endpoints.

9.4.3 Safety

Safety analyses will be performed using the FAS. Safety data will be presented using descriptive statistics unless otherwise specified. Summary statistics for continuous variables will include number of participants, mean, standard deviation, minimum, median, and maximum. Frequency tables and shift tables will include number and percentage of participants in the respective category. Unless otherwise stated, percentages will be calculated out of the population total.

Baseline

In general, the baseline value for statistical analysis is the last non-missing value prior to administration of the first dose of study intervention. Details are described in the SAP.

Adverse Events

The AEs will be coded using the most recent version of MedDRA that will be released for execution at AstraZeneca and CTCAE 5.0.

Treatment-emergent Adverse Events: The following events are considered TEAEs:

- Adverse events with an onset date on or after the first dose of study intervention and within CCI after the last dose of study intervention or up to the day prior to the start of subsequent therapy, whichever comes first.

- Worsening of pre-existing events on or after the first dose of study intervention and within CCI after the last dose of study intervention or up to the day prior to the start of subsequent therapy, whichever comes first.

Only TEAEs will be presented.

The TEAEs will be presented by System Organ Class and/or PT covering number and percentage of participants reporting at least one event and number of events where appropriate.

An overview of TEAEs will be provided as follows: the number and percentage of participants with any TEAE, TEAEs with the outcome of death, serious TEAEs, and TEAEs leading to discontinuation of study intervention, as well as TEAEs leading to study intervention dose interruptions, and AEs leading to study intervention dose reduction.

Separate TEAE tables will be provided taking into consideration the relationship to study intervention as assessed by the investigator, the CTCAE 5.0 grade, seriousness, death, and events leading to discontinuation of study intervention, as well as other action taken related to study intervention, AESIs, and other significant TEAEs (if applicable).

An additional table will be presented for the number and percentage of participants with most common TEAEs. Most common TEAEs will be defined in the SAP.

All AEs will be listed including, but not limited to, verbatim term, PT, System Organ Class, CTCAE 5.0 grade, relationship to study drug, start and end dates, and outcome. Non-TEAEs will be flagged in the listing.

Vital Signs

For each scheduled post-baseline visit, descriptive statistics for all vital sign parameters will be presented for observed values and change from baseline.

Details of vital sign analyses will be provided in the SAP.

Electrocardiograms

For each scheduled post-baseline visit, descriptive statistics for all ECG parameters will be presented for observed values and change from baseline. The QTcF will be derived during creation of the reporting database using reported ECG values (RR and QT) using the following formula, where RR is in seconds:

$$QTcF = \frac{QT}{3\sqrt{RR}}$$

Details of ECG analyses will be provided in the SAP.

Laboratory Parameters

For each scheduled post-baseline visit, descriptive statistics for all clinical chemistry and haematology parameters will be presented for observed values and change from baseline.

Elevation in liver parameters for assessment of Hy's Law will be performed and reported appropriately if potential cases are identified during the course of the study.

Corrected calcium will be derived during creation of the reporting database using the following formula:

$$\text{Corrected calcium (mmol/L)} = \text{total calcium (mmol/L)} + ([40 - \text{albumin (g/L)}] \times 0.02)$$

A shift table for urinalysis will be presented with baseline assessment against the maximum on study intervention category.

Supportive laboratory listings will cover observed values and changes from baseline for each individual participant as well as abnormalities.

Details of laboratory analyses will be provided in the SAP.

Other Safety Analyses

All other safety endpoints, eg, physical examination findings, including WHO/ECOG performance status, ECHO/MUGA, and ophthalmologic findings, will be listed.

Appropriate summaries of all safety data will be produced as defined in the SAP.

Further details can be found in the SAP.

9.4.4 Other Analyses

9.4.4.1 Pharmacokinetics

Plasma concentrations of the 3 analytes (Dato-DXd, total anti-TROP2 antibody and DXd) will be summarised for all evaluable participants in the PK analysis population using descriptive statistics at time points indicated in the SoA by cohort.

Non-compartment PK parameters that can be derived with sparse PK sampling, such as peak and trough concentrations, may be reported as data allow. If full PK samples are collected in a subset of participants, the non-compartment PK parameters to be obtained and reported in the full PK cohort may include, but are not limited to the C_{max}, the trough observed concentration, T_{max}, AUC, $t_{1/2}$ and CL, if the data allow. Details on the analysis of PK assessments will be provided in the SAP. Population PK and E-R analyses will be performed to characterise the relationships of dose, exposure, efficacy and safety endpoints, if applicable. The results of the population PK and E-R analyses will be reported separately from the CSR.

CCI
CCI

[redacted]

9.4.4.3 Optional Exploratory Genetic Sample

Not applicable

9.4.4.4 Immunogenicity Data

Immunogenicity results will be listed by participant, and a summary will be provided by the number and percentage of participants who develop detectable anti-Dato-DXd antibodies. The immunogenicity titre and neutralising ADA data will be listed for samples confirmed positive for the presence of antiDatoDXd antibodies.

The effect of immunogenicity as well as the effect of its neutralising properties on PK, pharmacodynamics, efficacy, and safety will be evaluated, if the data allow.

9.4.4.5 COVID-19 Impact

Depending on the extent of any impact, summaries of data relating to participants diagnosed with COVID-19, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued study intervention, and other protocol deviations) may be generated if appropriate. Further detail will be provided in the SAP.

9.5 Interim Analyses

An interim analysis is not planned in this study.

9.6 Data Monitoring Committee

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the CSP and letters to investigators. An Independent Data Monitoring Committee is not considered necessary for this open-label, single-arm study.

9.6.1 ILD Adjudication Committee

CCI

[redacted]

To ensure adequate and relevant CCI

[redacted]

systematic additional data collection will be conducted [redacted]

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the CSP and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The CSP, CSP amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the CSP will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR 312.120, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilising medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after they become aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If European Union Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency Clinical Trials Information System. It is important to note that redacted versions of serious breach reports will be available to the public via the Clinical Trials Information System.
- The investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach.
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal

Regulations 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study centre.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorised designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

Participants who are rescreened are required to sign a new ICF.

A 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The participant must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.
- The participant must be informed that in some cases their data may be pseudonymised. The General Data Protection Regulation defines pseudonymisation as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to

ensure that the personal data are not attributed to an identified or identifiable natural person.

Unless previously specified, the biomarker data will have unknown clinical significance and AstraZeneca will not provide biomarker assessment results to participants, their family members, any insurance company, any employer, a clinical study investigator, a general physician, or any other third party, unless required to do so by law. However, AstraZeneca may share data and biosamples with research partners, for example Daiichi Sankyo.

The participant's samples will not be used for any purpose other than those described in the study CSP.

A 5 Committees Structure

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the CSP and letters to investigators.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov, as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.**Data Quality Assurance**

- All participant data relating to the study will be recorded on the CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory authority inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study, which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved CSP and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca GRAD Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the source data agreement form. All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first site opening is considered the first act of recruitment and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the CSP, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a co-ordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence (other than progression of the malignancy under evaluation) in a participant or clinical study participant administered a study intervention, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the study intervention.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definitions of Serious Adverse Event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up) that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above

AEs for **malignant tumours** reported during a study should generally be assessed as **serious** AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious** AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour event in question is a new malignant tumour (ie, it is *not* the tumour for which entry into the study is a criterion and that is being treated by the study intervention under study and is not the development of new or progression of existing metastasis to the tumour under study). Malignant tumours that—as part of normal, if rare, progression—undergo transformation (eg, Richter's transformation of B-cell chronic lymphocytic leukaemia into diffuse large B cell lymphoma) should not be considered a new malignant tumour.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form, it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability, or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity Rating Scale:

The grading scales found in the revised CTCAE 5.0 will be utilised for all events with an assigned CTCAE 5.0 grading. For those events without assigned CTCAE 5.0 grades, the recommendation in the CTCAE 5.0 criteria that converts mild, moderate and severe events into CTCAE 5.0 grades should be used. A copy of the CTCAE 5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality, consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug:

- Time course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, or other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered, such as the following:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related.'

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error, Drug Abuse, or Drug Misuse

For the purposes of this clinical study, a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human- or process-related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- occurred.
- was identified and intercepted before the participant received the drug.
- did not occur, but circumstances were recognised that could have led to an error.

Examples of events to be reported in clinical studies as medication errors are as follows:

- Drug name confusion.
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant.
- Drug not administered as indicated, for example, wrong route, dose (error greater than ± 10%), or wrong site of administration.
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet.
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature.
- Wrong participant received the medication (excluding IRT/RTSM errors).
- Wrong drug administered to participant (excluding IRT/RTSM errors).

Examples of events that **do not** require reporting as medication errors in clinical studies are as follows:

- Errors related to or resulting from IRT/RTSM - including those that lead to one of the above listed events that would otherwise have been a medication error.
- Participant accidentally missed drug dose(s) eg, forgot to take medication.
- Accidental overdose (will be captured as an overdose).
- Participant failed to return unused medication or empty packaging.

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of study intervention for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The study intervention is used by a person not enrolled in the study with the intent of getting a perceived reward.
- The study intervention in the form of a tablet is crushed and injected or snorted with the intent of getting high.

Drug Misuse

Drug misuse is the intentional and inappropriate use of the study intervention for medicinal purposes outside of the authorised product information, or for unauthorised study interventions, outside the intended use as specified in the CSP and includes deliberate administration of a product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The study intervention is used with the intention to cause an effect in another person.
- The study intervention is sold to other people for recreational purposes.
- The study intervention is used with the connotation to cause an effect or facilitate assault in another person.
- The study intervention is deliberately administered by the wrong route.
- The study intervention is split in half because it is easier to swallow, when it is stated in the protocol that it should be swallowed whole.

- Only half the dose of study intervention is taken because the participant feels that he/she is feeling better when not taking the whole dose.
- Someone who is not enrolled in the study takes the study intervention.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire lifecycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample lifecycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent specifically to the subsequent use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research. The participant will be presented with the option to opt out of the subsequent use of the donated samples during the withdrawal process. If the participant decides to opt out, then the donated samples will be disposed of. If the participant withdraws consent without opting out for the subsequent use of the donated samples, then the samples will be used as per CSP.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.

- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and that the action is documented and study site notified.

C 3 International Air Transport Association Guidance Document (62nd Edition)

Labelling and Shipment of Biohazard Samples

The IATA (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A infectious substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A pathogens are, for example, Ebola or Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B infectious substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, for example, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B

They are to be packed in accordance with UN3373 and IATA 650.

Exempt: Substances that do not contain infectious substances or substances that are unlikely to cause disease in humans or animals are not subject to these regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations.
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging. (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry-ice require additional dangerous goods specification for the dry-ice content.

Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

D 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

In studies where laboratory data are not routinely collected, the investigator should be vigilant for cases of PHL cases from ad hoc laboratory tests or AEs. Additional safety samples for example, liver chemistry tests to determine PHL cases, may be collected if clinically indicated at the discretion of the investigator.

Specific guidance on managing liver abnormalities can be found in the TMG Annex.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the study intervention.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

D 2 Definitions

PHL

Aspartate aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN at any point during the study following the start of study intervention irrespective of an increase in alkaline phosphatase.

HL

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the study intervention, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, or another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

D 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

Local laboratories being used

The investigator will, without delay, review each new laboratory report and, if the identification criteria are met, will:

- Notify the AstraZeneca representative.
- Determine whether the participant meets PHL criteria (see Section D 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

D 4 Follow-up

D 4.1 Potential Hy's Law Criteria Not Met

If the participant does not meet PHL criteria the investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

D 4.2 Potential Hy's Law Criteria Met

If the participant does meet PHL criteria the investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study intervention (See Section D 6).

- Notify the AstraZeneca representative who will then inform the study team.
- Within one day of PHL criteria being met, the investigator will report the case as an SAE of PHL; serious criterion 'Important medical event' and causality assessment 'yes/related' according to the CSP process for SAE reporting.
- For participants that met PHL criteria prior to starting study intervention, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- The study clinical lead contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact, the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the study clinical lead.
  - Complete the 3 Liver eCRF Modules as information becomes available.

#A 'significant' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the study clinical lead if there is any uncertainty.

D 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the study clinical lead contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the study intervention, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE, update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the study intervention:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to study intervention and seriousness criterion is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to the agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

D 6 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Intervention

This section is applicable to participants with liver metastases who meet PHL criteria on study intervention, having previously met PHL criteria at a study visit prior to starting study intervention.

At the first on-study intervention occurrence of PHL criteria being met the investigator will determine if there has been a **significant change** in the participant's condition compared with the last visit where the PHL criteria were met.

- If there is no significant change, no action is required.
- If there is a significant change, notify the AstraZeneca representative, who will inform the study team, then follow the subsequent process described in Section D 4.2.

D 7 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a participant meets PHL criteria on study intervention and has already met PHL criteria at a previous on study intervention visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study, eg, chronic or progressing malignant disease, severe infection or liver disease or did the participant meet PHL criteria prior to starting study intervention and at their first on-study intervention visit as described in Section D 6 of this Appendix?

If **No**: Follow the process described in Section D 4.2 for reporting PHL as an SAE.

If **Yes**: Determine if there has been a significant change in the participant's condition compared with when PHL criteria were previously met.

- If there is no significant change no action is required.
- If there is a significant change follow the process described in Section D 4.2 for reporting PHL as an SAE.

D 8 Laboratory Tests

The Hy's Law related laboratory tests will be performed at local laboratories in this study.

The list below represents the standard, comprehensive list of follow-up tests that are recommended but not mandatory to further evaluate increases in liver biochemistry and Hy's Law. This list may be modified according to clinical judgment. Any test result must be recorded.

Hy's Law lab tests

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc
	HBsAg HBV DNA[a] IgM and IgG anti-HCV HCV RNA[a] IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Autoimmune hepatitis	Antinuclear antibody Anti-liver/kidney microsomal antibody Anti-smooth muscle antibody
Metabolic diseases	Alpha-1-antitrypsin
	Ceruloplasmin
	Iron
	Ferritin
	Transferrin saturation

CMV, cytomegalovirus; DNA, deoxyribonucleic acid; EBV, Epstein-Barr virus; GGT, gamma glutamyl transferase; HAV, hepatitis A virus; HBc, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HSV, herpes simplex virus; IgG, immunoglobulin G; IgM, immunoglobulin M; INR, international normalised ratio; LDH, lactate dehydrogenase; RNA, ribonucleic acid.

[a] HCV RNA and HBV DNA are only tested when anti-HCV IgG/anti-HBc IgM or IgG is positive or inconclusive.

Appendix E Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

E 1 Introduction

This appendix details the implementation of RECIST 1.1 guidelines (Eisenhauer et al 2009). Investigator assessments will use the RECIST 1.1 guidelines described in this appendix.

E 2 Imaging modalities and acquisition specifications for RECIST 1.1

A summary of the imaging modalities that can be used for tumour assessment of TLs, NTLs and NLs is provided in Table E11.

Table E11 Summary of Imaging Modalities for Tumour Assessment

Target Lesions	Non-Target Lesions	New Lesions
CT	CT	CT
MRI	MRI	MRI
	Plain X-ray	Plain X-ray
	Chest X-ray	Chest X-ray
		Bone scan (Scintigraphy)
		^{18}F-fluoro-deoxyglucose-PET/CT

CT, computed tomography; PET/CT, positron emission tomography/CT; MRI, magnetic resonance imaging.

E 2.1 Computed Tomography and Magnetic Resonance Imaging

Computed tomography with IV contrast is the preferred imaging modality (although MRI with IV contrast is acceptable if CT is contraindicated) to generate reproducible anatomical images for tumour assessments (ie, for measurement of TLs, assessment of NTLs, and identification of NLs). It is essential that the same correct imaging modality, image acquisition parameters (eg, anatomic coverage, imaging sequences, etc), imaging facility, tumour assessor (eg, radiologist), and method of tumour assessment (eg, RECIST 1.1) are used consistently for each participant throughout the study. The use of the same scanner for serial scans is recommended, if possible. It is important to follow the image collection/tumour assessment schedule as closely as possible (refer to the SoA), and this on-study imaging schedule MUST be followed regardless of any delays in dosing or missed imaging visits. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the participant has not progressed, every attempt should be made to perform the subsequent scan acquisitions at the next scheduled imaging visit.

Due to its inherent rapid acquisition (seconds), CT is the imaging modality of choice. Body scans should be performed with breath-hold scanning techniques, if possible. Therefore, CT of the chest is recommended over MRI due to significant motion artefacts (eg, heart, major blood

vessels, breathing) associated with MRI. MRI has excellent contrast and spatial and temporal resolutions; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. In general, local oncology diagnostic imaging parameters are applied for scan acquisition. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases.

The most critical CT and MRI image acquisition parameters for optimal tumour evaluation are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

a. Anatomic coverage: Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual participants. Because a lesion later identified in a body part not scanned at baseline would be considered as a NL representing PD, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

Required anatomical regions to be imaged for assessment of tumour burden (TLs and/or NTLs) at baseline and follow-up visits vary according to the study, and these time points are specified in the SoA. Examples include the following:

- Intravenous contrast-enhanced CT of chest-abdomen (including the entire liver and both adrenal glands) (-pelvis).
- Non-contrast CT of chest and IV contrast-enhanced abdomen (including the entire liver and both adrenal glands) (-pelvis).
- Intravenous contrast-enhanced CT or MRI of the head and neck.
- Intravenous contrast-enhanced MRI (preferred) or CT of the brain.

For chest-abdomen (-pelvis) imaging, the following are scanning options in decreasing order of preference, with additional options (2 to 4) for consideration when participants have sensitivity to IV contrast or have compromised renal function:

1 Chest-abdomen (-pelvis) CT with IV CT contrast (most preferred).
2 Chest CT without IV-contrast + abdomen (-pelvis) MRI with IV MRI contrast, if CT IV contrast (iodine based) is medically contraindicated at any time during the study.
3 Chest-abdomen (-pelvis) CT without IV contrast, if both IV CT and MRI contrast are medically contraindicated or the participant has compromised renal function.

4 Chest-abdomen (-pelvis) MRI with IV MRI contrast, if CT cannot be performed at any time during the study.

b. Intravenous contrast administration: Optimal visualisation and measurement of metastases in solid tumours require consistent administration (dose and rate) of IV contrast as well as timing of scanning. An adequate volume of a suitable contrast agent should be given so that the tumour lesions are demonstrated to best effect and a consistent method is used on subsequent examinations for any given participant. Oral contrast is recommended to help visualise and differentiate structures in the abdomen and pelvis.

c. Slice thickness and reconstruction interval: It is recommended that CT or MRI scans be acquired/reconstructed as contiguous (no gap) slices with ≤ 5 mm thickness throughout the entire anatomic region of interest for optimal lesion measurements. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses > 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

For CT scans, all window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study.

E 2.2 Chest X-ray

Chest X-ray assessment will not be used for the assessment of TLs. Chest X-ray can, however, be used to assess NTLs and to identify the presence of NLs. However, there is preference that a higher resolution modality, such as CT, be used to confirm the presence of NLs.

E 2.3 Plain X-ray

Plain X-ray may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

E 2.4 Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray at baseline should be recorded as NTLs and followed by the same method per baseline assessment (CT, MRI, or X-ray).

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. NLs may be recorded in case positive hot-spots appear on a bone scan that were not present on a previous bone scan; however, a newly observed equivocal hot-spot on a bone scan that cannot be verified with correlative imaging (CT, MRI,

or X-ray) of the same anatomical region shall not be the only trigger for a PD assessment at that time point.

E 2.5 ^{18}F-Fluoro-deoxyglucose-PET/CT

^{18}F-fluoro-deoxyglucose PET/CT scans may be used as a method for identifying new extrahepatic lesions (but not intrahepatic lesions) for RECIST 1.1 assessments according to the following algorithm: NLs will be recorded where there is positive ^{18}F-fluoro-deoxyglucose uptake[1] not present at baseline or prior ^{18}F-fluoro-deoxyglucose-PET scan or in a location corresponding to a NL on a companion CT/MRI collected close in time to the ^{18}F-fluoro-deoxyglucose-PET scan. The PET portion of the PET/CT introduces additional data that may bias an investigator if it is not routinely or serially performed. Therefore, if there is no baseline or prior ^{18}F-fluoro-deoxyglucose-PET scan available for comparison, and no evidence of NLs on companion CT/MRI scans, then follow-up CT/MRI assessments should continue as per the regular imaging schedule to verify the unequivocal presence of NLs.

At present, low-dose or attenuation correction CT portions of a combined ^{18}F-fluoro-deoxyglucose-PET/CT scan are of limited use in anatomically based efficacy assessments, and it is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced CT scans for tumour measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed, as part of a PET/CT examination, is of identical diagnostic quality (with IV contrast) to a dedicated diagnostic CT scan, then the CT portion of the PET/CT can be used for RECIST 1.1 tumour assessments. Caution that this is not recommended because the PET portion of the CT introduces additional (PET) data that may bias an investigator if it is not routinely or serially performed.

E 2.6 Ultrasound

Ultrasound examination will not be used for RECIST 1.1 assessment of tumours as it is not a reproducible acquisition method (operator dependent), is subjective in interpretation, and may not provide an accurate assessment of the true tumour size. Tumours identified by ultrasound will need to be assessed by correlative CT or MRI anatomical scan.

E 2.7 Other tumour assessments

E 2.7.1 Clinical examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will not be used for RECIST 1.1 assessments. Tumours identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

[1] A positive ^{18}F-fluoro-deoxyglucose-PET scan lesion should be reported only when an uptake (eg, standard uptake value) greater than twice that of the surrounding tissue or liver is observed.

E 2.7.2 Endoscopy and laparoscopy

Endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

E 2.7.3 Histology and cytology

Histology or tumour markers on tumour biopsy samples will not be used as part of the tumour response assessment as per RECIST 1.1.

Results of cytological examination for the neoplastic origin of any effusion (eg, ascites, pericardial effusion, and pleural effusion) that appears or worsens during the study will not be used as part of the tumour response assessment as per RECIST 1.1.

Furthermore, an overall assessment of CR (all other disease disappears/reverts to normal) would be changed to PR if an effusion remains present radiologically.

E 3 Measurability of tumour lesions at baseline

E 3.1 RECIST 1.1 measurable lesions at baseline

A tumour lesion that can be accurately measured at baseline as ≥ 10 mm in the longest diameter for non-nodal lesions or ≥ 15 mm in short axis[2] diameter for lymph node lesions with IV contrast-enhanced CT or MRI and that is suitable for accurate repeated measurements. Please see additional RECIST 1.1 guidance below on measurability of intrahepatic hepatocellular carcinoma lesions and porta hepatis lymph nodes.

E 3.2 Non-measurable lesions at baseline

- Truly non-measurable lesions include the following:
  - Bone lesions (see exception below for soft tissue component)
  - Leptomeningeal disease
  - Ascites, pleural effusion, or pericardial effusion
  - Inflammatory breast disease
  - Lymphangitic involvement of skin or lung
- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis diameter at baseline)[3]
- Previously irradiated lesions[4]

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2 The short axis is defined as the longest in-plane axis perpendicular to the long axis.

3 Lymph nodes with < 10 mm short axis diameter are considered non-pathological and should not be recorded or followed as NTLs.

4 Localised post-radiation changes that affect lesion size may occur. Therefore, lesions that have been previously irradiated are typically considered non-measurable and as NTL at baseline and followed up as part of the NTL assessment.

- Brain metastasis

E 3.3 Special considerations regarding lesion measurability at baseline

- Bone lesions:
  - Bone scan, PET scan, or plain X-ray alone are not considered adequate imaging techniques to measure bone lesions; however, these techniques can be used to confirm the presence or disappearance of bone lesions.
  - Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability.
  - Blastic lesions are considered non-measurable.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same participant, these should be selected over cystic lesions as TLs.

E 3.4 RECIST 1.1 TL selection at baseline

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved should be identified as TLs at baseline. TLs should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis diameter for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes, in any location (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ (eg, adrenal glands), a segmented organ (eg, liver), or a multilobed organ (eg, lung) is each considered as a single organ.

The site and location of each TL should be documented, as well as the longest axis diameter for non-nodal lesions (or short axis diameter for lymph nodes). All measurements should be recorded in millimetres. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits, the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

E 3.4.1 Special cases for TL assessment at baseline

- For TLs measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis diameter.
- When lymph nodes are coalesced and no longer separable in a conglomerate mass, the vector of the longest diameter should be used to determine the perpendicular vector for the maximal short axis diameter of the coalesced mass. Non-nodal lesions that coalesce should similarly be assessed by the longest axis diameter.
- Tumour lesions selected for newly acquired screening biopsy should not be selected as TLs, unless imaging occurred at least approximately 2 weeks after biopsy, allowing time for healing.
- If the CT/MRI slice thickness used is > 5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as a NL.

E 3.5 RECIST 1.1 NTL selection at baseline

All other lesions, including non-measurable lesions and surplus measurable lesions, not recorded as TLs should be identified as NTLs at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

E 4 Evaluation of tumour response and progression

E 4.1 RECIST 1.1 TL assessment at follow-up

This section defines the criteria used to determine objective tumour visit response for RECIST 1.1-defined TLs (Table E12). These TLs will be the most reproducible lesions, not necessarily the largest lesions so as to prevent influence by imaging modality, technique, or biological functions. The imaging modality, location, and scan date of each TL identified previously at baseline should be documented at follow-up visits with the long axis diameter for non-nodal lesions or short axis diameter for lymph node lesions. All measurements should be recorded in millimetres. The sum of the diameters for all TLs at each follow-up visit will be compared with the baseline sum of diameters (for response or SD) or to the smallest prior (nadir) sum of diameters (for progression).

Special cases for TL assessment at follow-up:

- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as an NL.
- If a TL splits into 2 or more parts, the sum of the diameters of those parts should be recorded.
- If 2 or more TLs merge, then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s). If the merged

TLs are non-nodal lesions, record the long axis diameter of the merged lesion. If pathologic lymph nodes coalesce and are no longer individually separable within a conglomerate mass, the vector of the longest diameter of the coalesced mass should be used to determine the perpendicular vector for the maximal short axis diameter.

- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion. The choice of 'Too large to measure' in the CRF will trigger an overall visit response of PD.
- When a TL has had any intervention (eg, definitive radiotherapy, embolisation, surgery, transarterial chemo-embolisation, etc) during the study, the size of the TL should still be provided where possible and the intervention recorded in the RECIST 1.1 CRF for the current imaging visit and all subsequent visits. If a TL has been completely removed (surgery) or disappears, the longest diameter should be recorded as 0 mm.

Table E12 RECIST 1.1 Evaluation of Target Lesions

CR	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to < 10 mm.
PR	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.
SD	Neither sufficient decrease in the sum of diameters to qualify for PR nor sufficient increase to qualify for PD.
PD	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of diameters (nadir). This includes the baseline sum if that is the smallest on study. In addition to the relative increase of 20%, the sum must demonstrate an absolute increase of at least 5 mm from nadir.
NE	Only relevant if any of the TLs at follow-up were not assessed or NE (eg, missing anatomy) or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides NE as a TL response.
Not applicable	Only relevant if no TLs present at baseline.

CR, complete response; NE, not evaluable; PD, progression of disease; PR, partial response; SD, stable disease; TL, target lesion.

E 4.2 RECIST 1.1 NTL assessment at follow-up

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline (Table E13). Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the investigator.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in TLs, the overall tumour burden has increased sufficiently to merit unequivocal progression by

NTLs. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PD of target disease will therefore be extremely rare.

Table E13 RECIST 1.1 Evaluation of Non-Target Lesions

CR	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/non-PD	Persistence of one or more NTLs.
PD	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
NE	Only relevant when one or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For participants without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not applicable	Only relevant if no NTLs present at baseline.

CR, complete response; NE, not evaluable; NTL, non-target lesion; PD, progression of disease; TL, target lesion.

E 4.3 RECIST 1.1 NL identification at follow-up

Details, including the imaging modality, the date of scan, and the location of any NLs will also be recorded in the CRF. The presence of one or more NLs is assessed as progression. The finding of a NL should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumour. If a NL is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the previously (pre-existing) NL has been assessed as unequivocal at a follow-up visit, and then the progression date should be declared using the date of the initial scan when the NL first appeared.

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered an NL and will indicate PD.

E 4.4 RECIST 1.1 evaluation of overall visit response at follow-up

Derivation of overall visit response as a result of the combined assessment of TLs, NTLs, and NLs uses the algorithm shown in Table E14.

Table E14 RECIST 1.1 Overall Visit Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Visit Response
CR	CR	No	CR

Target Lesions	Non-Target Lesions	New Lesions	Overall Visit Response
CR	NA	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE or NA	No	PR
SD	Non-PD or NE or NA	No	SD
NE	Non-PD or NE or NA	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note: An overall assessment of CR (all other disease disappears/reverts to normal) would be changed to PR if ascites remains present radiologically.
CR, complete response; NA, not applicable (only relevant if there were NTLs at baseline), NE, not evaluable; NTL, non-target lesion; PD, progression of disease; PR, partial response; SD, stable disease; TL, target lesion.

The following overall visit responses are possible depending on the extent of tumour disease at baseline:

- For participants with TLs (at baseline): CR, PR, SD, PD, or NE.

E 5 References

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Appendix F Contraception Requirements

Contraception requirements for this study are as follows.

F 1 Female Participants

Females not of childbearing potential are defined as those who are either permanently sterilised (ie, hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or who are post-menopausal.

Females will be considered post-menopausal if they have been amenorrhoeic for 12 months prior to planned enrolment without an alternative medical cause. The following age-specific requirements apply:

- Females < 50 years old are considered post-menopausal if they have been amenorrhoeic for 12 months or more prior to the first dose of study intervention following cessation of exogenous hormonal treatment and follicle-stimulating hormone levels in the post-menopausal range.
- Females ≥ 50 years old are considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment, or had radiation-induced menopause with last menses > 1 year ago, or had chemotherapy-induced menopause with last menses > 1 year ago.
- In questionable cases, a blood sample with simultaneous follicle-stimulating hormone > 40 mIU/mL and oestradiol < 40 pg/mL (< 147 pmol/L) is confirmatory.

Females of child-bearing potential who are not totally sexually abstinent (ie, refraining from heterosexual intercourse during the entire period of risk associated with study interventions) and intend to be sexually active with a non-sterilised male partner must use at least one highly effective method of contraception from enrolment throughout the study and for CCI [redacted] after the last dose of Dato-DXd (Table F15). A highly effective method of contraception is defined as one that has a failure rate of < 1% per year when used consistently and correctly. Cessation of contraception after this time should be discussed with a responsible physician.

Females on HRT and whose menopausal status is in doubt will be required to use one of the contraception methods outlined for FOCBP if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, they can resume use of HRT during the study without use of a contraceptive method.

Non-sterilised male partners of a woman of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) from the time of screening of their female partner, throughout their participation in the study, and for CCI after their female partner's last dose of Dato-DXd in addition to the female participant using a highly effective contraceptive method. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence (calendar, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP, withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together. Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial. Female participants must not donate, or retrieve for their own use, ova, and should refrain from breastfeeding from the time of screening and throughout the Intervention Period, and for CCI after the last dose of study intervention. Preservation of ova should be considered prior to enrolment in this study.

F 2 Male Participants With a Female Partner of Childbearing Potential

Non-sterilised male participants (including males sterilised by a method other than bilateral orchidectomy, eg, vasectomy) who intend to be sexually active with a female partner of childbearing potential must be using an acceptable method of contraception such as male condom plus spermicide (condom alone in countries where spermicides are not approved) from the time of screening throughout the total duration of the study and the drug washout period (CCI after the last dose of study intervention), in addition to the female partner using a highly effective contraceptive method, to prevent pregnancy in a partner.

Not engaging in sexual activity for the duration of the study and drug washout period is an acceptable practice. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (eg, calendar, ovulation symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together. Male participants should refrain from sperm donation or banking for the duration of the study (from the time of screening) and for 4 months after the last dose of Dato-DXd. Preservation of sperm should be considered prior to enrolment in this study.

Vasectomised males are considered fertile if there was no medical assessment of the surgical success and should still use a male condom plus spermicide as indicated above during the clinical study.

Even if the female partner is pregnant, male participants should still use a condom plus spermicide (where approved), as indicated above during the clinical study, if there is a concern about damaging the developing foetus from drug in ejaculate.

Female partners (of childbearing potential) of male participants must also use a highly effective method of contraception from the time of screening of their male partner, throughout their participation in the study, and for CCI after their male partner's last dose of Dato-DXd (Table F15).

F 3 Highly Effective Methods of Contraception

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly, are described in Table F15. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel, which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table F15 Highly Effective Methods of Contraception (<1% Failure Rate)

Non-Hormonal Methods	Hormonal Methods
• Total sexual abstinence (evaluate in relation to the duration of the clinical study and the preferred and usual lifestyle choice of the participant) • Vasectomised sexual partner (with participant assurance that partner received post-vasectomy confirmation of azoospermia) • Bilateral tubal occlusion • Intrauterine device (provided coils are copper-banded)	• Injection: Medroxyprogesterone injection (eg, Depo-Provera®)[a] • Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a] • Progesterone T intrauterine device • Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®) • Intravaginal devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®) • Combined pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®) • Mini pill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based pill

[a] Hormonal methods not prone to drug-drug interactions.

Appendix G Concomitant Medications

G 1 Guidance Regarding Potential Interactions With Concomitant Medications

The use of any natural/herbal products or other 'folk remedies' should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

Participants should be closely monitored when Dato-DXd is concomitantly used with drugs that inhibit CYP3A, OATP1B1, OATP1B3, MATE2-K, P-gp, BCRP, and MRP1. For a list of inhibitor drugs, refer to the FDA Table of Substrates, Inhibitors and Inducers or locally available sources.

G 2 Restricted, Prohibited, and Permitted Concomitant Medications/Therapies

Restricted, prohibited, and permitted concomitant medications/therapies are described in Table G16, Table G17, and Table G18. Refer also to the dose modification guidelines for management of study intervention-related toxicities in the TMG Annex. Participants must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

For a list of inhibitor drugs, refer to the US Food and Drug Administration Table of Substrates, Inhibitors and Inducers (US FDA 2021) or locally available sources.

Table G16 Restricted Medications/Therapies

Medication/class of drug/therapy	Usage (including limits for duration permitted and special situations in which it is allowed)
Tobacco products, e-cigarettes, and vaping	Use of tobacco products, e-cigarettes, and vaping is strongly discouraged but not prohibited. Any prior or current use of these products must be recorded in the eCRF.
Hormonal therapy	For non-cancer-related conditions (eg, insulin for diabetes and HRT) only.
Corticosteroids	As clinically indicated, eg, for specific adverse drug reactions (refer to TMGs document) and/or acute, symptomatic treatment (see more detailed guidance in Table G18).
CCI [redacted]	Permitted for optimal symptom control or pain management. CCI Dato-DXd therapy for the duration of CCI and restart at least [redacted] weeks after completion of CCI . Curative radiotherapy is CCI .

Medication/class of drug/therapy	Usage (including limits for duration permitted and special situations in which it is allowed)
Anti-resorptive/bone therapy (eg, bisphosphonates, RANKL inhibitors)	For treatment of bone metastases and osteoporosis.

Dato-DXd, datopotamab deruxtecan; eCRF, electronic case report form; HRT, hormone replacement therapy; RANKL, receptor activator of nuclear factor kappa B ligand; TMG, toxicity management guidelines.

Table G17 Prohibited Medications/Therapies

Prohibited medication/class of drug/therapy	Usage
Any concurrent anticancer therapy (including chemotherapy, biologic, targeted agents, immunotherapy, antibody, retinoid, or anti-cancer hormonal treatment) other than those under investigation in this study (including curative radiotherapy and radiotherapy to the thorax)	Must not be given concomitantly while the participant is on study intervention. Concurrent use of hormones for non-cancer-related conditions (eg, insulin for diabetes and HRT) is acceptable.
Chloroquine and hydroxychloroquine	Concomitant treatment with chloroquine or hydroxychloroquine is not allowed while the participant is on Dato-DXd. If treatment with chloroquine or hydroxychloroquine treatment is absolutely required, study intervention must be delayed. If chloroquine or hydroxychloroquine is administered, then a washout period of [redacted] is required before restarting Dato-DXd .

Prohibited medication/class of drug/therapy	Usage
Concomitant use of chronic systemic (IV or oral) corticosteroids or other immunosuppressive medications except for managing AEs	Dato-DXd cannot be administered when the participant is taking immunosuppressive medications, including corticosteroids with the exception of: • short-term courses (<2 weeks) • low to moderate dose • long-term, alternate-day treatment with short-acting preparations; maintenance physiologic doses (replacement therapy) • administered topically (skin or eyes), by aerosol, or by intra-articular, bursal, or tendon injection Treatment with corticosteroids to prevent or treat hypersensitivity reactions to radiographic contrast agents is allowed. A temporary period of steroid treatment will be allowed for different indications after discussion with the sponsor study physician (eg, COPD, radiation, nausea, etc). Use of immunosuppressive medications for the management of study intervention-related AEs or in participants with contrast allergies is acceptable. For the treatment of specific adverse drug reactions (refer to the TMGs in the TMG Annex). Immunosuppressive medications also include drugs like methotrexate, azathioprine, and tumour necrosis factor-alpha blockers.
Other investigational therapeutic agents	Must not be given concomitantly while the participant is on study intervention.
Herbal and natural remedies that may interfere with interpretation of study results	Must not be given concomitantly unless agreed by the sponsor.

AE, adverse event; COVID-19, coronavirus 2019-nCoV; Dato-DXd, datopotamab deruxtecan; HRT, hormone replacement therapy; IV, intravenous; TMGs, toxicity management guidelines.

Table G18 Supportive Medications/Therapies

Supportive medication/class of drug/therapy	Usage
Pre-medications for prevention of IRR or as supportive treatment of Dato-DXd-induced AEs for Dato-DXd	Antihistamines and acetaminophen with or without glucocorticoids must be taken as pre-medication prior to any dose of Dato DXd and may be used as supportive treatment of Dato-DXd-induced AEs..

Supportive medication/class of drug/therapy	Usage
CCI agents for Dato-DXd	Based on the currently available clinical safety data, it is highly recommended that participants receive CCI agents prior to infusion of Dato-DXd and on subsequent days as needed. CCI such as CCI and CCI should be considered and administered in accordance with the prescribing information or institutional guidelines. CCI can be used, if needed..
CCI agents	CCI formulations are permitted to prevent and manage certain AEs (see Section 8.3.5.6).
Concomitant medications or prophylactic or supportive treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate AE management, except for those medications identified as "prohibited," as listed above	As per TMGs, investigator's discretion and institutional guidelines. To be administered as prescribed by the investigator except for those medications identified as "prohibited," as listed in Table G17.
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management CCI except for those medications identified as "prohibited," as listed above	Should be used, when necessary, for all participants except for those medications identified as "prohibited," as listed in Table G17.
Dietary supplements, medications not prescribed by the investigator, and alternative/complementary treatments	Concomitant use is discouraged but not prohibited.
Participants with bronchopulmonary disorders who require intermittent use of bronchodilators (eg, albuterol)	Permitted.
Inhaled steroids, intra-articular steroid injections, and other topical steroid formulations	Permitted.
Foods or medications that are moderate inducers or inhibitors of CYP3A4/5	Permitted.
Required for management of other medical conditions	As required except for those identified as 'prohibited,' as listed in Table G17.

5-HT3, 5-hydroxytryptamine 3; AE, adverse event; CYP, cytochrome P450; Dato-DXd, datopotamab deruxtecan; NK1, neurokinin-1; IRR, infusion-related reaction; RANKL, receptor activator of nuclear factor kappa B ligand; SAE, serious adverse event; TMGs, toxicity management guidelines.

Appendix H Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with COVID-19 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

Please note that during civil crisis, natural disaster, or public health crisis, some study assessments and procedures may not be conducted due to international or local policies or guidelines, hospital or clinic restrictions and other measures implemented to ensure the participant's safety. If in doubt, please contact the AstraZeneca Study Physician.

H 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections H 2 to H 5. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note: in the case of verbal reconsent, the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

H 2 Rescreening of Participants to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The investigator should confirm this with the designated study physician.

In addition, during study disruption there may be a delay between confirming eligibility of a participant and either enrolment into the study or commencing of dosing with study intervention. If this delay is outside the screening window specified in Section 1.3, the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a participant in addition to that detailed in Section 5.4. The procedures detailed in Section 1.3 must be undertaken to confirm eligibility using the same enrolment number as for the participant.

H 3 Home or Remote Visit to Replace On-site Visit (Where Applicable)

A qualified HCP from the study site or TPV service will visit the participants home or other remote location as per local standard operating procedures as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

H 4 Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix, the term telemedicine visit refers to remote contact with the participants using telecommunications technology, including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow adverse events, concomitant medication, and other information to be reported and documented.

H 5 Data Capture During Telemedicine or Home or Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or TPV service.

Appendix I Abbreviations

Abbreviation or Special Term	Explanation
ADA	anti-drug antibody
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse event of special interest
AGA	actionable genomic alteration
AIDS	acquired immunodeficiency syndrome
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-}17d}$	area under the curve from 0 to 17 days
AUC_{tau}	area under the plasma concentration-time curve during the dosing interval
BCRP	breast cancer resistance protein
BOR	best overall response
BRAF/RAF	B-Raf proto-oncogene/Raf proto-oncogene
BRCA	breast cancer gene
CD	cluster of differentiation
CI	confidence interval
CL	total body clearance
C_{max}	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus 2019-nCoV
CR	complete response
CRF	case report form
CrCL	creatinine clearance
CRO	Contract Research Organisation
CSCO	Chinese Society of Clinical Oncology
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	computed tomography
CTCAE 5.0	National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0
CYP	cytochrome P450

Abbreviation or Special Term	Explanation
Dato-DXd	datopotamab deruxtecan
DCO	data cut-off
DCR	disease control rate
DDI	drug-drug interaction
DES	AstraZeneca Patient Safety data entry site
DFI	disease-free interval
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DoR	duration of response
DXd	MAAA-1181a; released drug in datopotamab deruxtecan
E-R	exposure-response
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EoT	end of treatment
FAS	full analysis set
FDA	Food and Drug Administration
FFPE	formalin fixed and paraffin embedded
FOCBP	female of childbearing potential
GCP	Good Clinical Practice
GEJ	gastroesophageal junction
HBc	hepatitis B core antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCP	health care professional
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HGR	human genomic resources
HIV	human immunodeficiency virus
HL	Hy’s Law

Abbreviation or Special Term	Explanation
HRCT	high-resolution CT
HRT	hormone replacement therapy
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICR	independent central review
iCRO	imaging CRO
IEC	Independent Ethics Committee
ILD	interstitial lung disease
IMP	investigational medicinal product
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	Interactive Response Technology
ITT	intent to treat
IV	intravenous
LVEF	left ventricular ejection fraction
MATE2-K	multidrug and toxin extrusion 2-K
MedDRA	Medical Dictionary for Regulatory Activities
METex14	MET proto-oncogene exon 14
MRI	magnetic resonance imaging
MRP1	multidrug resistance protein 1
MUGA	multigated acquisition
NAbs	neutralising antibodies
NCCN	National Comprehensive Cancer Network
NE	not evaluable
NF	nuclear factor
NIMP	non-investigational medicinal product
NL	new lesion
NSCLC	non-small-cell lung cancer
NTL	non-target lesion
NTRK	Neurotrophic tyrosine receptor kinase
OAT/OATP	organic anion transporter/organic anion transporter polypeptide
OCP	oral care plan
ORR	objective response rate

Abbreviation or Special Term	Explanation
OS	overall survival
P-gp	P-glycoprotein
PARP	Poly (ADP-ribose) polymerase
PCR	polymerase chain reaction
PD	progression of disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PHL	Potential Hy's Law
PK	Pharmacokinetic(s)
PopPK	population pharmacokinetic
PR	partial response
PT	Preferred Term
Q3W	every 3 weeks
QTcF	QT interval corrected by Fridericia's formula
RANKL	receptor activator of nuclear factor kappa B ligand
RECIST 1.1	Response Evaluation Criteria in Solid Tumours, Version 1.1
RES	Response Evaluable Set
RET	rearranged during transfection
RNA	ribonucleic acid
ROS1	ROS proto-oncogene 1
RTSM	Randomisation and Trial Supply Management
SCLC	small-cell lung cancer
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SMQ	standardised MedDRA query
SoA	Schedule of Activities
SoC	standard of care
CCI	CCI [redacted]
$t_{1/2}$	half-life
TA	therapeutic area
TBL	total bilirubin

Abbreviation or Special Term	Explanation
TEAE	treatment-emergent adverse event
TL	target lesion
T_{max}	time to C_{max}
TMG	toxicity management guideline
TNBC	triple-negative breast cancer
TPV	third party vendor
TROP2	trophoblast cell surface protein 2
CCI	CCI
TTR	time to response
ULN	upper limit of normal
US	United States
WHO	World Health Organisation
w/v	weight/volume

Appendix J Protocol Amendment History

The Protocol Amendment Summary of Changes table for the current amendment is located directly before the Table of Contents.

Amendment 2 (Version 3.0; 31 March 2022)

The overall rationale for this amendment is to accomplish the following:

- Expand the inclusion criteria for the NSCLC cohort to include participants with AGAs
- Clarify that the tumour sample collection for TROP2 testing will align with local HGR regulations
- Clarify the process for Hy's law testing in China
- Align the protocol with the new Product Safety Requirements (PSR V7.0) and the Oncology Late Phase Master Clinical Study Protocol (Template V2.0).
- Adjust the analysis plan so the primary analysis is based on the RES population, which has received at least one dose of study intervention and has measurable disease at baseline by ICR

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
1.1. Synopsis; 1.2. Schema; 2.1. Study Rationale; 4.1. Study Overview; 5. Study Population	Changed the description of the NSCLC population to include those with and without AGAs and clarified that approximately 6 participants with AGAs will be enrolled.	Expand the eligible study population	Substantial
2.2.2. Non-small-cell Lung Cancer	Added a description of the typical treatment for NSCLC with AGAs		
2.3.2. Benefit and Risk Assessment	Clarified the AGA status of participants in prior studies and added efficacy and safety data for Dato-DXd in NSCLC with AGAs.		
5.1. Inclusion Criteria	Added inclusion criteria specific for NSCLC participants with AGAs and clarified the criteria for participants without AGAs		
1.1. Synopsis; 7.3. Loss to Follow-up; 9.3. Populations for Analysis; 9.4.1.	1) Changed the primary efficacy analysis to be based on the RES	1,2) Improve the accuracy of the primary analysis by	Substantial

General Considerations; 9.4.2.1.1.3. Primary Endpoint: Confirmed ORR by ICR; 9.4.2.2.1. Confirmed Objective Response Rate by Investigator Assessment; 9.4.2.2.2. Duration of Response; 9.4.2.2.3. Disease Control Rate; 9.4.2.2.5. Time to Response; 9.4.2.2.6. Progression-free Survival; 9.4.2.2.7. Overall Survival; 9.4.3. Safety	population and the supplementary analysis to be based on the FAS population. 2) Changed the secondary efficacy analysis of ORR, DCR, BOR, DoR, and TTR to be based on the RES population and PFS and OS to be based on the FAS population. 3) Clarified that the FAS population, along with the RES population, will include only participants who received at least one dose of study intervention. 4) Removed all mention of the Safety Analysis Set and clarified that safety analysis will be based on the FAS.	including only those with measurable disease at baseline as determined by ICR 3) Adjust the analysis to include only participants receiving at least one dose of study treatment (to align with the ITT principles for single-arm studies in the Center for Drug Evaluation of China statistical guidance for oncology clinical trials).	
1.1. Synopsis; 9.4.1. General Considerations	Added additional analysis at the 6-month time point (BOR, TTR, OS)	Expand the data analysis conducted at 6 months	Substantial
1.2. Schema; 1.3. Schedule of Activities; 5.1. Inclusion Criteria; 5.4. Screen Failures; 6.3.1. Participant Enrolment; 8.6.1. Collection of Mandatory Samples for Biomarker Analysis	Modified the instructions for the tumour sample to clarify that it will be collected for enrolled participants only and will be based on local approval.	Increase the flexibility to enrol participants without tumour samples in case of a delay or rejection in the HGR submission.	Substantial
1.3. Schedule of Activities	Updated the instructions for oral care and the footnotes. Added notes to clarify procedures.	Align with PSR V7.0 and Template V2.0	Substantial
2.2.1. Dato-DXd; 2.3.1. Risk Assessment; 4.3 Justification for Dose; 5.1. Inclusion Criteria; 5.2. Exclusion Criteria; 5.3.1. Meals and Dietary Restrictions; 6.3.1.	Made various updates to the text to align with Template V2.0.		

Participant Enrolment; 7.1.1. Follow-up of Participants Post Discontinuation of Study Intervention; 7.1.2. Follow-up for Survival; 8.1.1. Imaging Tumour Assessments; 8.1.3. Bone Scan or Skeletal Survey; 8.1.4. Overall Survival; 8.2.3. Electrocardiograms; 8.2.4. Clinical Safety Laboratory Assessments; 8.2.5.1. Echocardiogram/Multigated Acquisition Scan; 8.2.5.3. ILD/Pneumonitis Investigation; 8.3.1. Time Period and Frequency for Collecting AE and SAE Information; 8.3.2. Follow-up of AEs and SAEs; 8.3.5. Adverse Events Based on Examinations and Tests; 8.3.11. Adverse Events of Special Interest; 8.3.15. Special Situations of Medication Error, Drug Abuse, or Drug Misuse; Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting; Appendix G Concomitant Medications; Appendix I Instructions Related to COVID-19			
6.2.2. Preparation of Dato-DXd; 6.2.2.1. Administration of Dato-DXd	Updated the time allowed for a prepared dose of Dato-DXd to match the handling instructions		
6.2.2.1. Administration of Dato-DXd; 8.2.5.7. Oral Care Plan	Moved the description of the oral care plan to Section 8.2.5.7 Oral Care Plan		

6.6. Dose Modification; 6.6.1. Management of Toxicities	Added a summary of management strategies and removed the specific instructions previously in subheadings.		
8.2.5.5. IRR Including Anaphylaxis; 8.2.5.6. Ophthalmologic Assessments; 8.2.5.7. Oral Care Plan; 8.2.5.8. Nausea and Vomiting	Added sections about assessment of IRR, oral care, and nausea and vomiting and updated the description for ophthalmologic assessments		
Appendix K	Added an appendix with the Ophthalmologic Assessment Form		
5.1 Inclusion Criteria	Changed the criteria for the TNBC cohort to clarify that if a chemotherapy drug is changed within 28 days of use to another drug, the first drug is not counted as a prior chemotherapy regimen.	Ensure that participants have received at least 2 prior chemotherapy regimens.	Substantial
8.1.3. Bone Scan or Skeletal Survey	Removed the sentence about measurable or evaluable lesions for consistency with the inclusion criteria	Correct an inconsistency	Non-substantial
8.2.4. Clinical Safety Laboratory Assessments	Adjusted the wording to align with Section 1.3 Schedule of Assessments	Increase clarity	Non-substantial
8.3.14.2 Paternal Exposure	Changed the duration of follow-up for partner's pregnancies from 7 to 4 months.	Increase consistency with other sections of the CSP	Non-Substantial
9.2. Sample Size Determination	Expanded the sample size justifications	Increase clarity	Non-substantial
Appendix D. Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law	Modified the text to clarify that Hy's Law laboratory tests will be performed by local laboratories and adjusted the list of tests	Align with the process for Hy's Law testing in China	Non-substantial

Appendix E. Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)	Removed guidance about previously irradiated lesions	Improve consistency with the inclusion criteria	Non-substantial
Throughout	Minor editorial and document formatting revisions	Minor and therefore have not been summarised	Non-substantial

AE, adverse event; AESI, adverse event of special interest; AGA, actionable genomic alteration; BOR, best overall response; Dato-DXd, Datopotamab deruxtecan; FAS, full analysis set; HGR, human genetic resources; HIV, human immunodeficiency virus; ICR, independent central review; ILD, interstitial lung disease; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PSR, product safety requirements; RES, response evaluable set; SAE, serious adverse event; SOA, Schedule of Activities; TNBC, triple negative breast cancer; TTR, time-to-response

Version 2.0, 17 November 2021

Section 1.3 – Schedule of Activities

Added oral care ptotocol in SoA and clarified daily oral care protocol throughout the study.

For footnote s to Table 1, clarified that artificial tears should be used daily.

For footnote k to Table 1, clarified that flash frozen tissue is not acceptable and remove the requirement.

Section 2.3.1 – Risk Assessment

Combined elevations of aminotransferases and bilirubin is removed from AESI list, and mucosal inflammation other than oral mucositis/stomatitis is added as AESI.

Section 5.1 – Inclusion Criteria

Clarified that for Cohort 2 if a chemotherapy drug is changed within 28 days of use to another drug in the same class (eg, antimetabolite to antimetabolite) for any reason other than PD, the first drug is not counted as a prior chemotherapy regimen.

Section 5.2 – Exclusion Criteria

Updated the requirement on washout period of prior anti-cancer therapies to include chemotherapy.

Section 6.6.1.3 – Ocular Assessment

Added clarification that section 6.6.1.3 links to section 8.2.5.5 for ocular assessment.

Section 8.1.1 – Imaging Tumour Assessments

Specified that any other areas of disease involvement should be imaged at regular intervals in addition to screening/baseline.

Removed mandatory pelvis scan at regular intervals and following PD assessment for participants without pelvis involvement at baseline in Cohort 1 and Cohort 2 to reduce unnecessary scan.

Section 8.2.2 – Vital Signs

Updated that blood pressure and pulse measurements will be assessed in the seated or supine/semi-recumbent position.

Section 8.2.4 – Clinical Safety Laboratory Assessments

Updated the list of acceptable values for calcium and urea nitrogen to accommodate sites only able to provide ionized calcium and urea.

Section 8.2.5.5 – Ophthalmologic Assessments

Added the updated safety information for use of artificial tears and other eye medications.

Section 8.3.1 – Time Period and Frequency for Collection AE and SAE Information

Updated that Grade ≥ 1 oral mucositis/stomatitis, all mucosal inflammation other than oral mucositis/stomatitis events regardless of CTCAE grade and Grade ≥ 1 ocular surface toxicities should be reported within 24hours of investigator becoming aware.

Section 8.3.11 – Adverse Events of Special Interest

Combined elevations of aminotransferases and bilirubin is removed from AESI list, and mucosal inflammation other than oral mucositis/stomatitis is added as AESI.

Section 8.6.1 – Collection of Mandatory Samples for Biomarker Analysis

Removed the requirement of flash frozen tissues for biomarker analysis.

Appendix E – Guidelines for Evaluation of Objective Tumour

Updated the table for algorithm of overall visit response to align with RECIST 1.1.

Appendix G – Concomitant Medications Add clarification that mouthwash for stomatitis prophylaxis/treatment is allowed for ChronicTable G17. **Throughout** Minor revisions in protocol wording and document format to further clarify.
Version 1.0, 20 October 2021
Initial creation

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