Clinical Study Report Addendum 1 Appendix 16.1.1	
Drug Substance	Datopotamab deruxtecan (Dato-DXd, DS-1062a)
Study Code	D9268C00001

Appendix 16.1.1
Protocol and Protocol Amendments

VERSION OF PROTOCOL OR PROTOCOL AMENDMENT

Global Document Name	Version No	Version Date
Amended CSP	Version 5	11 Dec 2023
Local Amendment 1 European Union	Version 1	22 Apr 2024

Clinical Study Protocol	
Study Intervention	Datopotamab deruxtecan (Dato-DXd, DS-1062a)
Study Code	D9268C00001
Version	V5.0 (Amendment 4)
Date	11 December 2023
EudraCT Number	2020-005620-12
EU CT Number	2023-509631-37

A Phase 3, Open-label, Randomized Study of Dato-DXd Versus Investigator's Choice of Chemotherapy in Participants With Inoperable or Metastatic Hormone Receptor-Positive, HER2-Negative Breast Cancer Who Have Been Treated With One or Two Prior Lines of Systemic Chemotherapy (TROPION-Breast01)

Sponsor Name: AstraZeneca

Legal Registered Address: AstraZeneca AB, 151 85 Södertälje, Sweden.

Regulatory Agency Identifier Number(s):
EudraCT Number: 2020-005620-12; EU CT number: 2023-509631-37; IND Number: 155696

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: D9268C00001

Amendment Number: 4

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

Study Phase: Phase 3

Short Title: A Study of Dato-DXd Versus Investigator's Choice Chemotherapy in Inoperable or Metastatic Hormone Receptor-positive, HER2-negative Breast Cancer

Acronym: TROPION-Breast01

Study Clinical Lead Name and Contact Information will be provided separately.

International Co-ordinating Investigator:

PPD

Massachusetts General Hospital Cancer Center
55 Fruit Street, Boston, MA 02114-2696.

VERSION HISTORY

DOCUMENT HISTORY	
Document	**Date**
Amendment 4 (Version 5.0)	11 December 2023
Amendment 3 (Version 4.0)	10 October 2022
Amendment 2 (Version 3.0)	19 April 2022
Amendment 1 (Version 2.0)	27 August 2021
Original Protocol (Version 1.0)	01 July 2021

Amendment 4 (11 December 2023)

Overall Rationale for the Amendment:

The overall rationale for the amendment is to update the protocol for EU CTR requirements and to align with the latest Dato-DXd program standards.

Other important administrative and operational clarifications have also been made.

The rationale for each of these changes is provided in the table below:

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Title page	EU CT number added	To meet EU CTR requirements.	Non-substantial
Synopsis	Regulatory Agency Identifiers added	For completeness of the Synopsis and to meet EU CTR requirements.	Non-substantial
1.3 Schedule of Activities Table 1 and Table 2, 8.2.5.3 ILD/Pneumonitis Investigation, 8.6.2 Collection of Optional Biomarker Samples	Optional lung biopsy specimen removed	To reflect that lung biopsy is no longer an optional biomarker sample.	Non-substantial
1.3 Schedule of Activities Table 1	Reference to the Dato-DXd Site Ophthalmologic Assessment Manual was added.	To clarify that the Ophthalmologic Assessment form is now included in the Dato-DXd Site Ophthalmologic Assessment Manual.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
1.3 Schedule of Activities Table 1	Oral care plan row, arrow from Cycle 1 through Safety FU assessment was replaced with wording "Daily before dosing, throughout treatment, and up to the first follow-up visit".	To ensure clarity of the oral care protocol and avoid footnote details being missed.	Non-substantial
1.3 Schedule of Activities Table 1, 8.6.2 Collection of Optional Biomarker Samples	Optional bronchoalveolar lavage and lung biopsy sample on suspected ILD/diagnosis of ILD row was deleted.	The lung biopsy will not be collected. The lavage sample will not be collected centrally anymore and is specified in Table 2.	Non-substantial
1.3 Schedule of Activities Table 2	Table for assessments to be performed if ILD/pneumonitis suspected during the intervention period was updated to match the corresponding Section 8.2.5.3 for clarity and consistency eg, physical examination including auscultation of lung field, arterial blood gases if clinically indicated were added to Table 2.	To clarify assessments in case of suspected and/or confirmed ILD/pneumonitis and ensure consistency across protocol sections.	Non-substantial
2.3.1.1 Dato-DXd Table 3 Risk Assessment, 2.2.3 Overall Benefit: Risk Conclusion	IRR was downgraded from important identified risk to the identified risk category. Embryo-fetal toxicity was added as an important potential risk. A sentence was added to clarify that Dato-DXd has not been studied in participants with renal or hepatic impairment. The Summary of Data/Rationale for Risk was updated with the latest safety data from the IB. The Mitigation Strategy was updated to list out the AESIs.	To reflect clinical data for Dato-DXd in alignment with Dato-DXd IB Edition 7.0.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
2.3.3 Overall Benefit: Risk Conclusion, 6.5 Concomitant Therapy, 6.6 Dose Modification, 8.3 Adverse Events and Serious Adverse Events, 8.6.1 Collection of Mandatory Samples for Biomarker Analysis, 8.6.3 Other Study Related Biomarker Assessments, 9.4.1 General Considerations, Appendix I2 (Table 18), Appendix J	COVID-19 specific text was deleted throughout the protocol.	No specific safety concerns have been identified in patients with COVID-19 who have been treated with Dato-DXd.	Non-substantial
4.1 Overall Design, 5 Study Population	A reference for country-specific study requirements provided in Appendix L was added.	Country-specific addendums were added to the appendices to create one global protocol for EU CTR submission.	Non-substantial
4.4 End of Study Definition	The end of study definition was updated to distinguish between end of study (EU definition) and study completion (FDA definition).	To provide a clear definition of end of the study for results disclosure purposes.	Non-substantial
6.1.1 Investigational Products	In Table 5, AxMP was added to the IMP and NIMP row. For the unit dose strength row, ‘vial’ was deleted from ‘100 mg vial’. Reference to GMP Annex 13 was removed from labelling information.	To ensure all interventions are designated as an investigational medicinal product or a non-investigational medicinal product/auxiliary medicinal product. To omit repetition of packaging details in dose unit dose strength information. To ensure country-specific labelling requirements are followed.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
6.2.1 Dato-DXd	Density of Dato-DXd was added. Reference to the Pharmacy Manual was moved to Section 6.2.1.1 and corrected.	To ensure the latest available information is reflected in the protocol and to align with the Pharmacy Manual.	Non-substantial
6.2.1.1 Preparation of Dato-DXd	Guidance for preparation of Dato-DXd has been updated with additional details. A reference to the Pharmacy Manual for administration details provided separately was added.	To ensure the latest available information is reflected in the protocol and to align with the Pharmacy Manual.	Non-substantial
6.2.1.2 Administration of Dato-DXd	Guidance for administration of Dato-DXd has been updated additional details.	To ensure the latest available information is reflected in the protocol and to align with the Pharmacy Manual.	Non-substantial
6.6 Dose Modification	Subheadings were added: 6.6.1 Dose Delays, 6.6.2 Dose Delays for Reasons Other than Treatment-related Toxicity, 6.6.3 Dose Reductions and the text restructured accordingly. Clarification was added around doses delayed for up to 3 consecutive cycles (63 days) from the planned date of administration (ie, 84 days from the last infusion date). Figure 3 Dose Delay Schema for Dato-DXd was added. Section 6.6.2 Dose Delays for Reasons Other Than Treatment-related Toxicity guidance as included.	To clarify dose modification guidance.	Non-substantial
6.7 Intervention after the End of the Study	Section heading was updated to Continued Access to Study Intervention after the End of the Study. Language was added to describe methods of providing participants with access to treatment after data collection in the study has ended.	To clarify intervention available to participants after the end of the study.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
8.2.2 Vital Signs	End of infusion vital signs collection window restriction of ±5 minutes was removed.	To avoid unnecessary protocol deviations since vital signs measurements timing can be more flexible.	Non-substantial
8.2.5.3 ILD/Pneumonitis Investigation	ILD/pneumonitis investigation paragraph was updated for clarity. Signs and symptoms entry was deleted from the list of evaluations. Optional bronchoscopy and bronchoalveolar lavage if clinically indicated text was updated for clarity. Acceptable CT scan was clarified to include non-contrast chest CT with 1 to 2 mm slice thickness recommended. Differential white blood cell count was specified with blood tests for clarification. The additional blood sample for exploratory biomarker analysis was clarified as an optional serum sample when ILD/pneumonitis is suspected and/or diagnosed. An example of other tests that may be needed was added. Text was updated to match the corresponding Section 8.2.5.3 for clarity and consistency.	To clarify ILD/pneumonitis investigations. Signs and symptoms are not assessments and covered under adverse events reporting. To clarify what constitutes an acceptable CT and biomarker sample requirements.	Non-substantial
8.2.5.5 Ophthalmologic Assessments, 8.3.11 Adverse Events of Special Interest	A reference to the Dato-DXd Ophthalmologic Assessment Manual was added. The frequency of use of artificial tears was specified as 4 times daily as preventative measures and up to 8 times daily as clinically needed.	To clarify the frequency of use of artificial tears.	Non-substantial
8.2.5.6 Oral Care Plan	Oral care guidance for participants was updated to state participants receiving ICC are recommended daily use of alcohol-free mouthwash while participants receiving Dato-DXd are recommended to use a steroid-containing mouthwash. A reference to the Dato-DXd TMGs was added.	To specify the recommended mouthwash for oral care with study treatments. To direct reader to TMGs should oral mucosal toxicity arise despite prophylaxis measures.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
8.3 Adverse Events and Serious Adverse Events	The section title was updated to Adverse Events, Serious Adverse Events, and Other Safety Reporting.	To clarify that other safety reporting is also captured in this section.	Non-substantial
8.3.1 Time Period and Frequency for Collecting AE and SAE Information	The reporting period for ILD/pneumonitis events was clarified to extend beyond the 28 + 7 day safety follow-up period. The reporting period for all AESIs was clarified. Reporting instructions for pre-existing medical conditions was included. Clarification was provided for reporting details of hepatic events.	To ensure appropriate data collection on ILD/pneumonitis events and all other AEs and SAEs.	Non-substantial
8.3.11 Adverse Events of Special Interest	Reporting requirements for concomitant medication administered as treatment for drug-related AESIs was specified. IRR was changed from important identified risk to identified risk.	To ensure that concomitant medications for drug-related AESIs are appropriately recorded.	Non-substantial
8.3.15 Medication Error	Section heading was updated to Medication Error, Drug Abuse, and Drug Misuse. Subsections including relevant definitions were added for Medication Error, Drug Abuse, Drug Misuse. A reference to Appendix B4 was added.	To clarify what constitutes a medication error, drug abuse, and drug misuse in the study.	Non-substantial
8.5 Human Biological Samples	For PK and ADA samples retention, the wording “unless consented for future analysis” was deleted. It was clarified that remaining ADA sample aliquots will be retained for a maximum of 5 years after CSR publication. Wording was added to clarify ADA samples collected in China will be disposed of 1 year after CSR publication.	The samples will be used for study analysis only. To clarify sample retention periods.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
8.6.1 Collection of Mandatory Samples for Biomarker Analysis, 1.3 Schedule of Activities Table 1	Additional blood samples for exploratory biomarker analysis to be collected as soon as ILD/pneumonitis is suspected, if feasible was moved to Section 8.6.2 since these are optional samples. In Table 1, It was clarified that the additional exploratory biomarker blood samples are optional. The retention time for residual tumor samples collected for TROP2 IHC testing from Chinese participants was corrected to state samples will be destroyed or repatriated within 1 year after CSR completion.	To clarify that the additional exploratory biomarker samples are optional. To correct residual tumor sample retention for Chinese participants.	Non-substantial
9.3 Populations for Analyses Table 9	ITT and Safety Analysis Set descriptions were updated to specify clinical outcomes assessments included in each set.	To clarify the populations definitions and align with objectives and endpoints.	Non-substantial
Appendix A1 Regulatory and Ethical Considerations	Investigator oversight of the conduct of the study and adherence to regulatory requirements was clarified. A subsection for Regulatory Reporting Requirements of Serious Breaches was added.	To clarify investigator responsibilities and include guidance on reporting serious breaches during study conduct.	Non-substantial
Appendix A6 Dissemination of Clinical Study Data	The timeframe for submitting results summaries to EU CTIS was included. The AstraZeneca website for a description of the study was updated.	To clarify study result submission timelines and include the current AstraZeneca website.	Non-substantial
Appendix A7 Data Quality Assurance	It was clarified that clinical reviews of data from a medical perspective form part of the monitoring strategy. The record and document retention period was clarified.	To clarify the monitoring process and record retention policy.	Non-substantial
Appendix B4 Medication Error	Section heading was updated to Medication Error, Drug Abuse, and Drug Misuse. Subheading for Medication Error as well as a range for dose error was added. Subsections for Drug Abuse and Drug Misuse were added.	To clarify what constitutes a medication error, drug abuse, and drug misuse in the study.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Appendix I2 Restricted, Prohibited, and Permitted Concomitant Medications/Therapies	In Table 17 was updated to include instructions regarding Dato-DXd therapy when palliative radiotherapy is given. It was clarified that curative radiotherapy prohibited.	To clarify Dato-DXd therapy delays in the case of palliative radiotherapy.	Non-substantial
Appendix I2 Supportive Medications/Therapies	Table 19: 'Antihistamines and acetaminophen' was re-labeled as 'pre-medications for prevention of IRR or as supportive treatment of Dato-DXd'. Examples of prophylactic anti-emetic agents was deleted from text in the supportive medication column.	Text was updated to mention examples in the Usage column instead of in the medications/class of drug/therapy column.	Non-substantial
Appendix K Protocol Version History	Previous protocol amendments were moved to Appendix K.	To focus protocol text on current information with additional information provided in appendices.	Non-substantial
Appendix L	Country-specific addendums to the protocol were added in Appendix L.	Country-specific addendums were added to the appendices to create one global protocol for EU CTR submission.	Non-substantial
Throughout	Minor editorial and formatting revisions.	To further clarify.	Non-substantial

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Open-label, Randomized Study of Dato-DXd Versus Investigator's Choice of Chemotherapy in Participants With Inoperable or Metastatic Hormone Receptor-Positive, HER2-Negative Breast Cancer Who Have Been Treated With One or Two Prior Lines of Systemic Chemotherapy (TROPION-Breast01).

Short Title: A Study of Dato-DXd Versus Investigator's Choice Chemotherapy in Inoperable or Metastatic Hormone Receptor-positive, HER2-negative Breast Cancer.

Regulatory Agency Identifier Number(s):

EudraCT Number: 2020-005620-12; IND Number: 155696; EU CT number: 2023-509631-37

Rationale:

Single agent chemotherapy remains the cornerstone of therapy for patients with HR-positive, HER2-negative metastatic breast cancer who have exhausted endocrine therapy options. However, patient prognosis is poor, and durable antineoplastic therapy options are necessary to improve outcomes in this patient population.

Dato-DXd is a TROP2 antibody-drug conjugate (administered via IV infusion, Q3W). Within the Dato-DXd clinical development program, preliminary data supporting the use of Dato-DXd in participants with HR-positive, HER2-negative breast cancer are available from an ongoing phase 1 first-in-human study, TROPION-PanTumor01 (NCT03401385), which is evaluating Dato-DXd in participants with advanced non-small cell lung cancer and triple-negative breast cancer, relapsed or refractory to standard-of-care therapy. These data have demonstrated highly encouraging efficacy across dose groups, with tumor responses observed at doses of 4, 6, and 8 mg/kg and an acceptable and manageable toxicity profile.

Given these encouraging preliminary safety and efficacy data, the current study is designed to provide a robust and detailed understanding of the efficacy and safety of Dato-DXd when compared with Investigator's choice of standard-of-care single-agent chemotherapy (eribulin, capecitabine, vinorelbine, or gemcitabine; henceforth referred to as ICC) in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with one or two prior lines of systemic chemotherapy, for which an unmet medical need remains.

Objectives and Endpoints

Objectives	Endpoints
Dual Primary	
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of PFS in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer, who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting, per BICR.	• PFS is defined as time from randomization until progression per RECIST 1.1, as assessed by BICR, or death due to any cause. The analysis will include all randomized participants as randomized regardless of whether the participant withdraws from therapy, receives another anticancer therapy, or clinically progresses prior to RECIST 1.1. The measure of interest is the hazard ratio of PFS.
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of OS in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer, who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting.	• OS is defined as time from randomization until the date of death due to any cause. The comparison will include all randomized participants as randomized, regardless of whether the participant withdraws from therapy or receives another anticancer therapy. The measure of interest is the hazard ratio of OS.
Secondary	
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of ORR in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer, who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting, per BICR and per investigator assessment.	• ORR is defined as the proportion of participants who have a confirmed CR or PR, as determined by the BICR/Investigator assessment, per RECIST 1.1. The analysis will include all randomized participants as randomized. Data obtained from randomization up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR, regardless of whether the participant withdraws from therapy. Participants who go off treatment without a response or progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR. The measure of interest is the odds ratio of the ORR.
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of DoR in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting.	• DoR is defined as the time from the date of first documented confirmed response until date of documented progression per RECIST 1.1, as assessed by BICR/Investigator assessment or death due to any cause. The analysis will include all randomized participants as randomized who have a confirmed response, regardless of whether the participant withdraws from therapy, receives another anticancer therapy or clinically progresses prior to RECIST 1.1 progression. The measure of interest is the median of DoR.
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of PFS in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting, per investigator assessment.	• PFS is defined as time from randomization until progression per RECIST 1.1, as assessed by investigator assessment, or death due to any cause. The analysis will include all randomized participants as randomized regardless of whether the participant withdraws from therapy, receives another anticancer therapy, or clinically progresses prior to RECIST 1.1. The measure of interest is the hazard ratio of PFS.

Objectives	Endpoints
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of DCR in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer, who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting, per BICR and per investigator assessment.	• DCR at 12 weeks is defined as the percentage of participants who have a confirmed CR or PR or who have SD, per RECIST 1.1, as assessed BICR/per investigator assessment and derived from the raw tumor data for at least 11 weeks after randomization. Data obtained from randomization up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of DCR, regardless of whether the participant withdraws from therapy. Participants who receive a subsequent therapy prior to week 11 will not be considered to have disease control in the analysis. The analysis will include all randomized participants as randomized. The measure of interest is the odds ratio of the DCR.
To assess pain in participants treated with Dato-DXd compared to ICC.	• TTD in pain as measured by the pain scale from EORTC QLQ-C30 TTD is defined as time from the date of randomization to the date of deterioration. Deterioration is defined as change from baseline that reaches a clinically meaningful deterioration threshold. The analysis will include all randomized participants. The measure of interest is the hazard ratio of TTD in pain.
To assess physical functioning in participants treated with Dato-DXd compared to ICC.	• TTD in physical functioning as measured by the physical functioning scale from EORTC QLQ-C30 TTD is defined as time from the date of randomization to the date of deterioration. Deterioration is defined as change from baseline that reaches a clinically meaningful deterioration threshold. The analysis will include all randomized participants. The measure of interest is the hazard ratio of TTD in physical functioning.
To assess global health status/quality of life (GHS/QoL) in participants treated with Dato-DXd compared to ICC.	• TTD in GHS/QoL as measured by the GHS/QoL scale from EORTC QLQ-C30 TTD is defined as time from the date of randomization to the date of deterioration. Deterioration is defined as change from baseline that reaches a clinically meaningful deterioration threshold. The analysis will include all randomized participants. The measure of interest is the hazard ratio of TTD in GHS/QoL.
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of TFST in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting.	• TFST is defined as the time from randomization until the start date of the first subsequent anticancer therapy after discontinuation of randomized treatment, or death due to any cause. The analysis will include all randomized participants as randomized, regardless of progression status. The measure of interest is the hazard ratio of TFST.

Objectives	Endpoints
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of TSST in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting.	• TSST is defined as the time from randomization to until the start date of the second subsequent anticancer therapy after discontinuation of first subsequent treatment, or death due to any cause. The analysis will include all randomized participants as randomized, regardless of progression status on study treatment or first subsequent treatment. The measure of interest is the hazard ratio of TSST.
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of PFS2 in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting.	• PFS2 will be defined as the time from the randomization to the earliest of the progression event (following the initial progression), subsequent to first subsequent therapy, or death. The date of second progression will be recorded by the Investigator in the eCRF and defined according to local standard clinical practice. The comparison will include all randomized participants as randomized regardless of whether the participant withdraws from subsequent therapy and regardless of missed visits. The measure of interest is the hazard ratio of PFS2.
To assess the PK of Dato-DXd 6mg/kg IV Q3W.	• Plasma concentrations of Dato-DXd, total anti-TROP2 antibody, and MAAA-1181a (payload).
To investigate the immunogenicity of Dato-DXd 6mg/kg IV Q3W.	• Presence of ADA.
Safety	
To assess the safety and tolerability profile of Dato-DXd compared to ICC.	Safety and tolerability will be evaluated in terms of adverse events (graded by CTCAE version 5.0), and also in terms of: • ECOG PS • Vital signs, body weight, physical examination • Clinical chemistry, hematology, and urinalysis assessments • ECG, ECHO/MUGA and Ophthalmologic assessments

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

Overall Design

Disclosure Statement: This is a Phase 3, randomized, open-label, 2 arm, multicenter, international study assessing the efficacy and safety of Dato-DXd compared with ICC in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with one or two prior lines of systemic chemotherapy in the inoperable or metastatic setting.

Participant Population: The target population of interest in this study is male or female adult (≥ 18 years participants with inoperable or metastatic HR-positive, HER2 negative breast cancer (per ASCO/CAP guidelines, on local laboratory results) who have progressed on and are not suitable for endocrine therapy per investigator assessment, and have been treated with 1 to 2 lines of prior chemotherapy in the inoperable/metastatic setting. Participants must have documented progression on their most recent line of chemotherapy, and be eligible for one of

the chemotherapy options listed as ICC (eribulin, capecitabine, vinorelbine, gemcitabine), per investigator assessment.

To be eligible for randomization, availability of a FFPE tumor sample (block preferred, or a minimum of 20 freshly cut slides) is required, at the time of screening. This sample can be from either the primary disease setting (surgical resection or diagnostic sample), or from a metastatic lesion (excluding bone). If neither an adequate FFPE block nor the minimum of 20 slides are available, a patient may still be considered eligible. In this situation, approval by the Study Team for patient's entry into the study is required. If there is no written confirmation of the availability of an appropriate tumor sample prior to enrolment, the participant will not be eligible for the study. At the time of enrolment all participants must have an ECOG PS of 0 or 1, and have at least 1 measurable lesion not previously irradiated that qualifies as a RECIST 1.1 target lesion. Participants with clinically inactive brain metastases may be included in the study.

Number of Participants: Approximately 1000 participants will be enrolled to achieve approximately 700 randomly assigned participants to study intervention. If required for regulatory submission purposes, the recruitment of participants in mainland China may continue beyond the close of the global cohort, to include approximately an additional 20 randomized participants in the mainland China cohort. The mainland China cohort is defined as all participants from sites in mainland China randomized into the study. A participant randomized in the mainland China cohort prior to the last participant randomized in the global cohort will be included in both the global and mainland China cohorts. A participant randomized in mainland China after the last participant was randomized in the global cohort will be included only in the mainland China cohort.

Note: "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. Potential participants who are screened for the purpose of determining eligibility for the study, but are not randomly assigned in the study, are considered "screen failures", unless otherwise specified by the protocol.

Intervention Groups and Duration: Participants will be randomized in a 1:1 ratio to one of the following intervention groups:

- **Arm 1:** Dato-DXd (6 mg/kg IV on Day 1, Q3W)
- **Arm 2:** ICC:
  - Capecitabine (1000 or 1250 mg/m^2 oral BID on Days 1 to 14, Q3W); choice between the 2 doses will be determined by standard institutional practice.
  - Gemcitabine (1000 mg/m^2 IV on Day 1 and Day 8, Q3W)

- Eribulin mesylate (1.4 mg/m^2 IV on Days 1 and 8, Q3W)
- Vinorelbine (25 mg/m^2 IV on Days 1 and 8, Q3W)

Randomization will be stratified by the following prognostic and/or predictive factors:

- Number of previous lines of chemotherapy (1 versus 2)
- Geographic region (Region 1 [US, Canada, Europe] versus Region 2 [Rest of World])
- Prior use of CDK4/6 inhibitor (Yes versus No)

A 50% cap will be applied to participants who have had 2 prior lines of chemotherapy in the inoperable/metastatic setting, while a 49% cap will be applied to participants who have not received prior CDK4/6 inhibitor therapy.

All participants will receive study intervention until Investigator-defined disease progression according to RECIST 1.1, or until unacceptable toxicity, withdrawal of consent, or another criterion for discontinuation is met. Continued treatment with the same study drug post-progression may be allowed, based on prior discussion with study physician on case-by-case basis. No crossover between study treatment arms will be allowed.

Follow-up of participants post discontinuation of study intervention

After study intervention discontinuation, all participants will undergo an end-of-treatment visit (to be conducted +7 days of the decision to discontinue treatment) and will be followed up for safety assessments 28 (+7) days after their last dose of study intervention (ie, the safety follow-up visit). If the date of discontinuation is over 35 days from last study intervention administration, then the EoT assessments can also function as the Safety Follow-up visit.

Participants who have discontinued study intervention in the absence of RECIST 1.1-defined radiological progression (by investigator assessment) will be followed up with tumor assessments according to the Schedule of Activities (SoA) until RECIST 1.1-defined PD (as assessed by the Investigator) or death regardless of whether or not the participant started a subsequent anticancer therapy, unless they have withdrawn all consent to study related assessments. Following disease progression, 1 additional follow-up scan should also be performed as per imaging schedule (ie, either 6 weeks or 9 weeks later). In the event the investigator identified progression does not match with the BICR evaluation, this additional scan may identify progression by BICR.

In addition, all participants will be followed up for survival status after intervention discontinuation every 3 months (±14 days) from the date of the date of the Safety Follow-up Visit until death, withdrawal of consent, or the end of the study (ie, progression/survival follow-up), as per the SoA. Participants will be followed up for time to second progression or death (PFS2) and subsequent anticancer therapy use after intervention discontinuation every

3 months (±14 days) from the date of randomization until death, withdrawal of consent, or the end of the study (ie, progression/survival follow-up), as per SoA. The study may continue monitoring participants for OS up to the scheduled final analysis, beyond planned interim analyses, to provide more refined estimates of treatment effects for survival.

See Section 6.7 for a description of assessments following study DCOs.

Independent Data Monitoring Committee (IDMC): An IDMC comprised of independent experts will be convened to review unblinded safety data and make recommendations to continue, amend, or stop the study based on safety findings. In addition, the IDMC may be requested to review efficacy data. For the interim analyses, the IDMC will review unblinded interim data and inform the Sponsor whether the interim boundaries specified in Section 9.5 are crossed. Full details of the IDMC procedures, processes, and interim analyses can be found in the IDMC Charter.

Statistical methods

The study is sized for dual primary endpoints to characterize the PFS and OS benefit of Dato-DXd versus ICC in intent-to-treat (ITT) population. This comprises all participants randomized into the study, excluding participants randomized in mainland China after the global cohort last participant randomized, and will be analyzed according to randomized treatment regardless of the treatment received (ITT principle). The study will be considered positive (a success) if either the PFS analysis results and/or the OS analysis results are statistically significant.

The primary, final analysis of PFS will be performed when approximately 419 PFS BICR events occur, approximately 2 months after the last participant is randomized in the study; 419 PFS BICR events from the ITT population across the Dato-DXd and ICC treatment groups will represent 60% maturity of data. Assuming the true PFS hazard ratio is 0.55 for Dato-DXd versus ICC, the study will have a greater than 99% power to demonstrate statistical significance at the 1.0% level (using a 2-sided test). This assumes median PFS times of 4.7 months and 8.5 months in ICC and Dato-DXd, respectively when the PFS times are exponentially distributed. The smallest treatment difference that could be statistically significant at the final analysis is a hazard ratio of 0.775.

The final analysis of OS will be performed when approximately 444 OS events have occurred across the Dato-DXd and ICC treatment groups (63% maturity). Assuming the true OS hazard ratio is 0.75 for Dato-DXd versus ICC, the study will have 85% power to demonstrate statistical significance at the 5.0% level (using a 2-sided test). This assumes the PFS primary analysis crosses the efficacy threshold, and allowing 2 interim analyses to be conducted at information fractions of approximately 40% and 80% of the target events, respectively (per the O'Brien and Fleming approach). The smallest treatment difference that could be

statistically significant at the final analysis is a hazard ratio of 0.824. If the PFS primary analysis does not cross the efficacy threshold, the OS analysis will have 83% power to demonstrate statistical significance at the 4.0% level (using a 2-sided test). The smallest treatment difference that could be statistically significant at the final analysis is a hazard ratio of 0.817. Calculations assume median OS times of 19.0 months and 25.3 months in ICC and Dato-DXd, respectively when the survival times are exponentially distributed.

The study may continue monitoring participants for OS up to the scheduled final analysis, beyond planned interim analyses, to provide more refined estimates of treatment effects for survival.

A nonuniform accrual of participants (with k = 1.5) is assumed when estimating the analysis times. The total proportion of participants randomized at time t [$t \leq 19$ months] following the start of the study is assumed to be $(t/19)^k$.

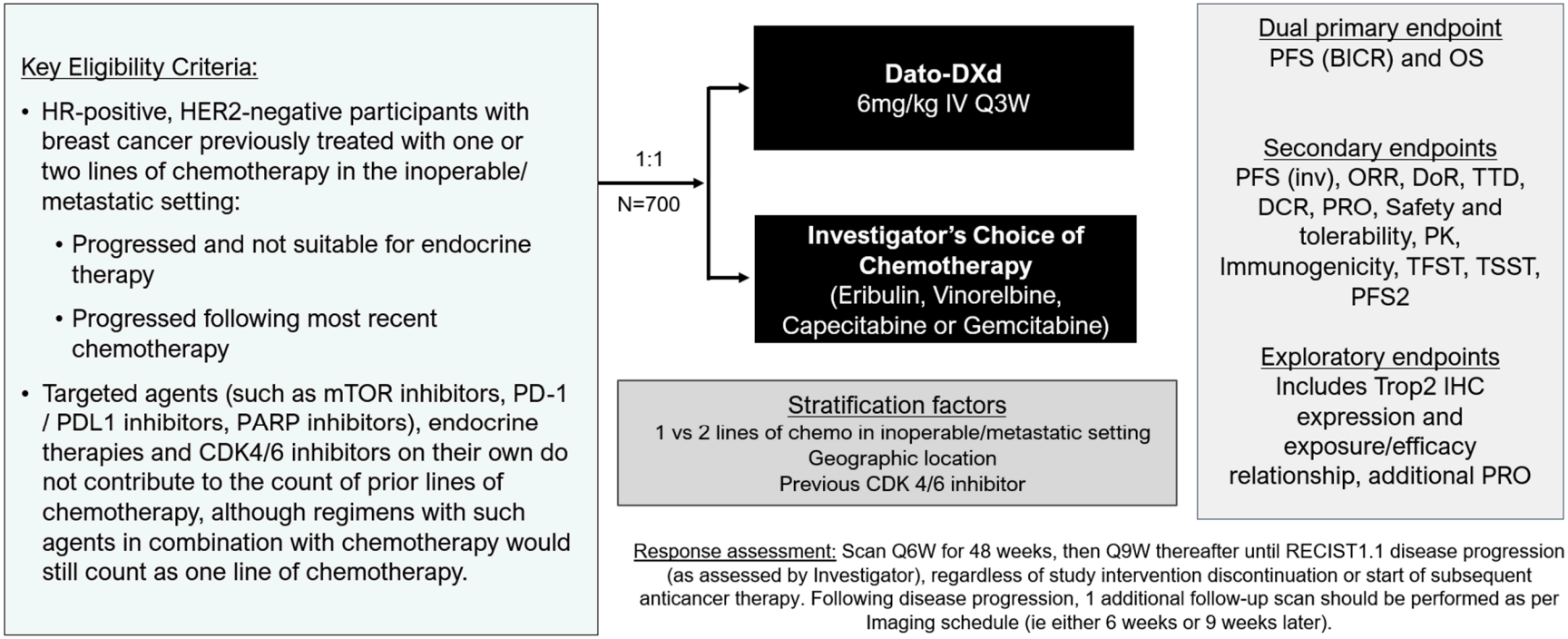
Hypotheses will be tested using a multiple testing procedure (MTP) with an alpha-exhaustive recycling strategy. To strongly control the familywise type I error rate at the 5.0% level (2-sided), an alpha level of 1.0% will be allocated to the PFS dual primary analysis and the remaining 4.0% alpha level will be allocated to the OS analyses. If the PFS dual primary analysis crosses the efficacy threshold, the 1.0% type I error allocated to the PFS endpoint will be reallocated to the OS endpoint for a total 2-sided type I error of 5.0%.

Safety data will be summarized descriptively and will not be formally analyzed unless otherwise specified.

1.2 Schema

The study schema is presented in Figure 1.

Figure 1 Study Design



1.3 Schedule of Activities

The procedures for this study are presented in the SoA (Table 1). Assessments in the event of suspected ILD/pneumonitis are presented separately in Table 2.

Table 1 Schedule of Activities

Procedure	Screening (up to 28 days before C1D1)	Intervention Period				Post-intervention Follow-up Period				Details in CSP Section or Appendix
		Cycle 1		Cycle 2 +		EoT (within 7 days of decision to stop treatment)	Safety FU (28 days after last dose [+7 days]) [a]	At PD	Survival FU (Every 3 months [±14 days]) relative to the date of Safety FU Visit	
		Day 1	Day 8 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)					
Informed consent: main study [b]	X									Section 5.1 and Appendix A 3
Informed consent: genetic sample and analysis (optional)	X									Section 5.1 and Appendix A 3
Study Procedures and Assessments										
Inclusion and exclusion criteria	X									Sections 5.1 & 5.2
Randomization		X [c]								Section 6.3
Demography	X									Section 5.1
Full physical examination (including weight and height)	X									Section 8.2.1
Targeted physical examination (including weight)		X [d]		X [e, f]		X	X			Section 8.2.1
Medical history [g]	X									Sections 5.1 & 5.2
Past and current medical conditions and prior anticancer therapy use	X									Sections 5.1 & 5.2
ECOG performance status	X	X [d]		X [f]		X	X			Section 8.2.5.4
12-lead ECG [h]	X	As clinically indicated				X				Section 8.2.3
Echocardiogram or MUGA (LVEF) [i]	X	As clinically indicated								Section 8.2.5.1
Vital signs including SpO_2 [j]	X	X		X [e]		X	X			Section 8.2.2
Pulmonary function tests [k]	X	If ILD/pneumonitis is suspected								Section 8.2.5.2
ILD/pneumonitis investigation, including HRCT		If ILD/pneumonitis is suspected								Section 8.2.5.3

Table 1 Schedule of Activities

Procedure	Screening (up to 28 days before C1D1)	Intervention Period				Post-intervention Follow-up Period				Details in CSP Section or Appendix
		Cycle 1		Cycle 2 +		EoT (within 7 days of decision to stop treatment)	Safety FU (28 days after last dose [+7 days]) [a]	At PD	Survival FU (Every 3 months [±14 days]) relative to the date of Safety FU Visit	
		Day 1	Day 8 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)					
Ophthalmologic assessments [l]	X	<-------every 3 cycles from C1D1 onwards (eg, C4D1, C7D1, C10D1 etc) within 14 days prior to scheduled cycle Day 1 visit (but not after the scheduled visit) and as clinically indicated---------->				X				Section 8.2.5.5
Oral care plan [m]	X	Daily before dosing, throughout treatment, and up to the first follow-up visit								Section 8.2.5.6
AE [n, o]	X	<---------->				X	X			Section 8.3
Prior and concomitant medication [o]	X	<---------->				X	X			Section 6.5
Subsequent anticancer therapy							X		X	
Clinical Safety Laboratory Assessments										
Serum/urine pregnancy test (WOCBP only) [p]	X	X		X		X	X			Sections 5.1, 5.2 & 8.2.4
Hepatitis B and C serology [q]	X									Sections 5.2 & 8.2.4
HIV antibody test (as required by local regulations or IRB/EC) [q, r]	X									Sections 5.2 & Section 8.2.4
Clinical safety laboratory assessments (clinical chemistry and hematology)	X	X [d]		X [d, e]		X	X			Section 8.2.4
Urinalysis	X	As clinically indicated								Section 8.2.4
Pharmacokinetics Assessments (for participants randomized to Dato-DXd only)										
PK blood sampling (before infusion) [s]		X		X (C2, C4, C6, C8, and C12, then every 4 cycles)		X				Section 8.5.1

Table 1 Schedule of Activities

Procedure	Screening (up to 28 days before C1D1)	Intervention Period				Post-intervention Follow-up Period				Details in CSP Section or Appendix
		Cycle 1		Cycle 2 +		EoT (within 7 days of decision to stop treatment)	Safety FU (28 days after last dose [+7 days]) [a]	At PD	Survival FU (Every 3 months [±14 days]) relative to the date of Safety FU Visit	
		Day 1	Day 8 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)					
PK blood sampling (end of infusion) [t]		X [u]		X (C2, C4, C6, C8)						Section 8.5.1
Immunogenicity Assessments (for participants randomized to Dato-DXd only)										
Blood sample for immunogenicity testing (ADA)		X [s]		X [s] (C2, C4, C6, C8, and C12; then every 4 cycles)		X	X			Section 8.5.2
Biomarker Assessments										
Mandatory tumor sample available (FFPE)	X									Section 8.6.1
Optional tumor biopsy (FFPE/FF) at progression [v]								X		Section 8.6.2
Optional paired tumor biopsy (FFPE/FF) [v]	X			X (C2D1 to C2D7 only)						Section 8.6.2
Plasma samples for biomarker analysis [v]	X	X		X (C2, C4)		X		X		Section 8.6.1
Serum samples for biomarker analysis [v]	X	X		X (C2, C4)		X		X		Section 8.6.1
Optional plasma samples for biomarker analysis on suspected ILD/diagnosis of ILD		As clinically indicated								Section 8.6.1

Table 1 Schedule of Activities

Procedure	Screening (up to 28 days before C1D1)	Intervention Period				Post-intervention Follow-up Period				Details in CSP Section or Appendix
		Cycle 1		Cycle 2 +		EoT (within 7 days of decision to stop treatment)	Safety FU (28 days after last dose [+7 days]) [a]	At PD	Survival FU (Every 3 months [±14 days]) relative to the date of Safety FU Visit	
		Day 1	Day 8 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)					
Optional serum samples for biomarker analysis on suspected ILD/diagnosis of ILD		As clinically indicated								Section 8.6.1
Whole blood sample for gene expression analysis (RNA) [v]	X	X		X (C2, C4)				X		Section 8.6.1
Whole blood sample for gene expression analysis (DNA) [v]	X	X		X (C2, C4)				X		Section 8.6.1
Plasma samples for ctDNA analysis [v]	X	X		X (C2-C6; then Q6W)		X		X		Section 8.6.1
Genomics Initiative (optional)										
Optional exploratory genetic blood sample for Genomics Initiative [v, w]		X								Section 8.7 & Appendix D
Efficacy Assessments										
Tumor imaging (RECIST 1.1) [x]	X	Every 6 weeks (±7 days) from randomization for 48 weeks, then every 9 weeks (±7 days) thereafter until RECIST 1.1 disease progression (as assessed by the Investigator), regardless of study intervention discontinuation or start of subsequent anticancer therapy. Following disease progression, 1 additional follow-up scan should be performed as per imaging schedule (ie, either 6 weeks or 9 weeks later).								Section 8.1.1
Brain MRI/CT imaging [y]	X	Mandated for participants who had brain metastases documented at baseline, per RECIST 1.1 schedule.								Section 8.1.1
Whole body bone scan [z]	X	As clinically indicated								Section 8.1.1
Survival status									X	Section 7.1.3 & 8.1.4
Time to second progression or death (PFS2)							X		X	Section 8.1.3

Table 1 Schedule of Activities

Procedure	Screening (up to 28 days before C1D1)	Intervention Period				Post-intervention Follow-up Period				Details in CSP Section or Appendix
		Cycle 1		Cycle 2 +		EoT (within 7 days of decision to stop treatment)	Safety FU (28 days after last dose [+7 days]) [a]	At PD	Survival FU (Every 3 months [±14 days]) relative to the date of Safety FU Visit	
		Day 1	Day 8 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)					
Clinical Outcome Assessments										
ePRO training and setup		X								Section 8.1.5
EORTC QLQ-C30, EORTC IL116, PGIS, EQ-5D-5L		C1D1, Q3W from C1D1 for the first 48 weeks, and Q6W thereafter until EoT				At EoT visit, then Q6W (relative to C1D1) after EoT until 18 weeks after PD				Section 8.1.5
PRO-CTCAE, EORTC IL117, PGI-TT		C1D1, every week from C1D1 for the first 12 weeks, and Q3W thereafter until EoT				X				Section 8.1.5
PGIC		Q6W from C1D1 for the first 12 weeks (ie, 6 weeks and 12 weeks from C1D1)								Section 8.1.5
Medical Resource Utilization										
HOSPAD [aa]		X	X [bb]	X	X [bb]	X				Section 8.8
Study Intervention Administration										
Dato-DXd administration (IV)		X		X						Section 6
Capecitabine administration (oral)		Days 1 to 14 only, BID		Days 1 to 14 only, BID						Section 6
Eribulin administration (IV)		X	X	X	X					Section 6
Vinorelbine administration (IV)		X	X	X	X					Section 6
Gemcitabine administration (IV)		X	X	X	X					Section 6

[a] The safety follow-up visit will be performed 28 (+7) days after the last study intervention administration. If the date of discontinuation is over 35 days from last study intervention administration, then the EoT assessments can also function as the Safety FU visit.

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

[c] Every effort should be made to minimize the time between randomization and starting treatment (ie, no more than 3 days from the date of randomization).

[d] If safety assessments have been performed within 72 hours prior to starting Day 1 of a cycle, they do not have to be repeated, if the participant's condition has not changed.

[e] For participants randomized to Investigator's Choice of Chemotherapy (ICC), routine clinical care should be performed in accordance with local practice.

[f] Within 3 days prior to administration of study intervention.

[g] Includes ocular history (since prior ocular events may predispose to or cause dry eye/keratitis), as well as history, type and frequency of tobacco use, e-cigarette use, vaping (including dates).

[h] Triplicate ECGs will be taken at screening and EoT. Triplicate ECGs will be taken in close succession, while in a supine/semi-recumbent position. Single ECGs should be taken during treatment as clinically indicated.

[i] The same test must be used for the participant throughout the study. ECHO/MUGA not required at EoT unless clinically indicated.

[j] Vital signs and SpO_2 should be performed both before and after study intervention administration (where applicable), and as clinically indicated during treatment. Participant should remain at the site for at least 1-hour post-infusion (where applicable) for close observation for IRRs.

[k] Pulmonary function tests at a minimum should include spirometry (minimum requirement of: FVC [L], FVC % predicted, FEV1 [L], FEV1 % predicted, FEV1/FVC %). DLCO will be performed (when feasible); however, for participants with prior severe and/or clinically significant pulmonary disorders, DLCO is a requirement.

[l] Ophthalmologic assessments (by a licensed eye care provider) including but not limited to visual acuity testing, fluorescein staining, intraocular pressure, slit-lamp examination and fundoscopy will be performed at screening, and then every 3 cycles from C1D1 onwards (eg, C4D1, C7D1, C10D1 etc) within 14 days prior to scheduled cycle Day 1 visit (but not after the scheduled visit), in addition to as clinically indicated while on trial, and at EoT. (see Section 8.2.5.5 for additional information). Please refer to the Dato-DXd Site Ophthalmologic Assessment Manual for further details.

[m] A daily Oral Care Protocol (OCP) will be started before study drug initiation, and it must be maintained throughout the study until 28 days after last dose. An oral care kit will be provided at study enrolment and monthly thereafter until the safety FU visit, which will include a toothbrush, toothpaste, dental floss, and an alcohol-free mouthwash. An oral care plan participant information guide should be given to each randomized participant before study drug initiation. Strongly consider initiation of dexamethasone oral solution (see Section 8.2.5.6 for details).

[n] Data collection may be conducted by phone if not tied to a visit.

[o] All AEs occurring after the participant signs the ICF and up to 28 (+7) days after the last dose of study drug (ie, the safety follow-up period), whether observed by the Investigator or reported by the participant, will be recorded on the AE eCRF page (see Section 8.3 for additional information).

[p] Negative serum pregnancy test performed within 72 hours before study intervention at screening and repeat urine or serum pregnancy tests (per institutional guideline) performed within 72 hours before infusion of each cycle and at EoT and during safety follow-up. A positive urine pregnancy test result must immediately be confirmed using a serum test.

[q] 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 enrolment. In this case, there is no need for a repeat test during the 28-day screening period.

[r] Participants must be tested for HIV if acceptable by local regulations or an IRB/EC. If an HIV infection meets the criteria outlined in Section 5.2, monitoring of the participants' viral RNA load and CD4+ cell count should be monitored per local SoC (eg, every 3 months).

[s] To be performed within 8 hours prior to the start of Dato-DXd infusion, except for the EoT visit, during which samples can be collected anytime during this visit.

[t] To be performed within 1 hour after the end of Dato-DXd infusion.

[u] An additional PK sample should be taken 5 hours (±1 hour) from the start of Dato-DXd infusion on C1D1.

[v] Not applicable to participants in mainland China.

[w] The sample for genetic research will be obtained at Day 1 pre-dose. If, for any reason, the sample is not drawn at Day 1, it may be taken at any visit until the last study visit. Only 1 sample should be collected per participant for genetics during the study.

[x] The baseline tumor assessment must be performed within 28 days before randomization and as close as possible to the start of treatment. The assessment should include CT (preferred) or MRI, with IV contrast, of the chest, abdomen (including the entire liver and both adrenal glands), and pelvis. Any other areas of disease involvement should be additionally imaged at screening based on known metastasis sites or by the signs and symptoms of individual participants. The follow-up assessments should include CT/MRI with IV contrast of the chest, abdomen and pelvis and any other area where disease was identified at baseline. The assessment must continue until **1 visit (per original schedule)** after radiographic disease progression (as assessed by Investigator), whether or not the participant is still on treatment. The same imaging technique (CT or MRI) used to characterize each identified and reported lesion at baseline will be used in the subsequent tumor assessments.

[y] Participants with brain metastases at baseline must have the lesions recorded as part of the RECIST assessment and must have a brain scan performed per the tumor imaging schedule until radiological progression per RECIST. For participants in whom CNS metastases are first discovered at the time of screening, the treating investigator should consider delay of randomization and study intervention to document stability of CNS metastases with repeat imaging at least 4 weeks later (in which case, repeat of all screening activity may be required).

[z] 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.

[aa] The site should complete the “Hospital Admission (HOSPAD)” form at the site at every scheduled clinic visit up to and including the post study treatment discontinuation follow up visit. If the participant discontinues study treatment for reasons other than RECIST progression, the HOSPAD form should continue to be administered until progression has been confirmed. Study mandated visits should not be included as a hospital admission.

[bb] Only applicable to participants who are required to attend study visits on Day 8 of each cycle (ie, those randomized to receive Investigators Choice of Chemotherapy which are administered by IV infusion).

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

Table 2 Assessments if ILD/Pneumonitis is Suspected during the Intervention Period

Procedure	Details in CSP Section
ILD/pneumonitis investigation	Section 8.2.5.3
Detailed past medical history and concomitant medications	Section 8.2.5.3
Physical examination, including auscultation of lung field	Section 8.2.5.3
HRCT of the chest if feasible (otherwise non-contrast chest CT is acceptable)	Section 8.2.5.3
Arterial blood gases if clinically indicated	Section 8.2.5.3
Pulmonary function tests and pulse oximetry (SpO_2)	Sections 8.2.5.2 and 8.2.5.3
Bronchoscopy and bronchoalveolar lavage should be considered if clinically indicated and feasible	Sections 8.2.5.3
Pulmonologist consultation (infectious diseases consultation, as clinically indicated)	Section 8.2.5.3
Blood culture, complete blood count, and differential white blood cell count; other blood tests could be considered as needed	Section 8.2.5.3
Troponin measurements to rule out cardiac etiology	Section 8.2.5.3
Additional optional blood sample for plasma exploratory ILD/pneumonitis analysis as soon as ILD/pneumonitis is suspected and/or diagnosed [a]	Sections 8.2.5.3 and 8.6.1
Additional optional blood sample for serum exploratory ILD/pneumonitis analysis as soon as ILD/pneumonitis is suspected and/or diagnosed [a]	Sections 8.2.5.3 and 8.6.1

Note: Other tests could be considered, as needed (eg, COVID-19 test).

[a] Whenever ECGs, vital signs and blood draws are scheduled for the same day, the assessments should occur in the following order: ECG, vital signs and then blood draws. The timing of the ECG and vital signs assessments must allow for the blood draw (eg, PK blood sample) to occur at the scheduled time points specified in Table 1. Pulse oximetry (SpO_2) will be performed at the same time as vital signs.

2 INTRODUCTION

Datopotamab deruxtecan (Dato-DXd, DS-1062a) is an antibody-drug conjugate (ADC) that comprises a recombinant humanized anti-TROP2 IgG1 monoclonal antibody, which is covalently conjugated to a drug linker via thioether bonds.

Antibody-drug conjugates are targeted anticancer medicines that deliver cytotoxic chemotherapy (‘payload’) to cancer cells via a linker attached to a monoclonal antibody that binds to a specific target expressed on cancer cells. Antibody-drug conjugates provide a unique opportunity to deliver drugs to tumor cells while minimizing toxicity to normal tissue.

Dato-DXd binds to trophoblast cell surface protein 2 (TROP2), also known as tumor-associated calcium signal transducer 2. Dato-DXd is in development as a candidate therapy for cancer.

2.1 Study Rationale

Single agent chemotherapy remains the cornerstone of therapy for patients with HR-positive, HER2-negative metastatic breast cancer who have exhausted endocrine therapy options. However, patient prognosis is poor, and durable antineoplastic therapy options are necessary to improve outcomes in this patient population (see Section 2.2.1 for further details).

TROP2 is a type I transmembrane glycoprotein originally identified in human trophoblast cells (Fornaro et al 1995, Alberti et al 1992, Lipinski et al 1981). TROP2 is highly expressed in a number of normal tissues and several cancers and has been recognized as a novel promising antigen for ADCs due to its high expression in breast tumors (Pau Ni et al 2010). Furthermore, increased TROP2 mRNA in breast cancer has been shown to be a predictor of lymph node involvement, distant metastasis, and poor OS (Zhao et al 2018).

The potential for TROP2 ADCs in the treatment of breast cancer has been demonstrated with the FDA approval of sacituzumab govitecan (TRODELVY; IMMU-132; Gilead Sciences, Inc.) for patients with locally advanced and metastatic TNBC who have received at least 2 prior systemic therapies, at least one of them for metastatic disease. Most recent data in HR-positive, HER2-negative metastatic breast cancer population treated with sacituzumab govitecan, who have received at least 2 prior lines of therapy, with a median follow-up of 11.5 months, has shown that the ORR was 31.5% (95% CI: 19.5, 45.6; 17 partial responses); median DoR was 8.7 months (95% CI: 3.7, 12.7), median PFS was 5.5 months (95% CI: 3.6, 7.6), and median OS was 12 months (95% CI: 9.0, 18.2) (Kalinsky et al 2020). Of note, significant toxicities in sacituzumab govitecan treated participants have been reported, which include myelosuppression and diarrhea (Bardia et al 2020). Furthermore, the efficacy of ADCs in breast cancer has been demonstrated from the approval of ENHERTU (T-DXd) and KADCYLA (T-DM1), two HER2-targeted ADCs indicated for HER2-positive breast cancer (Modi et al 2020, Von Minckwitz et al 2019).

Dato-DXd is a TROP2 ADC (administered via IV infusion, Q3W) that binds to TROP2, is internalized, and after enzymatic processing, the topoisomerase I inhibitor, MAAA-1181a, is released, leading to inhibition of tumor growth, DNA damage, and apoptosis of target cells. The cytotoxic payload of Dato-DXd is the same as T-DXd. Preclinical data has demonstrated that Dato-DXd exerts specific cell growth inhibitory activity against TROP2-expressing cells, but it does not have cell growth inhibitory against TROP2-negative cells.

Within the Dato-DXd clinical development program, preliminary data supporting the use of Dato-DXd in participants with HR-positive, HER2-negative breast cancer are available from an ongoing phase 1 FIH study, TROPION-PanTumor01 (NCT03401385), which is evaluating escalating doses of Dato-DXd (0.27 mg/kg to 10 mg/kg) in participants with advanced NSCLC and TNBC, relapsed or refractory to SoC therapy. These data have demonstrated highly encouraging efficacy across dose groups, with tumor responses observed at doses of 4,

6, and 8 mg/kg and an acceptable and manageable toxicity profile (see Section 2.2.2.1). An additional cohort of participants with HR-positive, HER2-negative breast cancer is currently recruiting as of March 2021.

Given the biological rationale and encouraging preliminary safety and efficacy data obtained from the TROPION-PanTumor01 study, the current study is designed to provide a robust and detailed understanding of the efficacy and safety of Dato-DXd when compared with Investigator's choice of standard-of-care single-agent chemotherapy (eribulin, capecitabine, vinorelbine, or gemcitabine; henceforth referred to as ICC) in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with one or two prior lines of systemic chemotherapy, for which an unmet medical need remains.

2.2 Background

2.2.1 HR-positive, HER2-negative, inoperable/metastatic breast cancer

Breast cancer is the most common cancer in the world, with an estimated 2.2 million new cases in 2020 globally (11.7% of all new cancers). Breast cancer is also the fifth most common cause of death from cancer, with an estimated 684000 deaths in 2020 (Sung et al 2021). In Europe, an estimated 531000 patients were diagnosed with breast cancer in 2020, and 141000 died from the disease. Despite advances in the diagnosis and treatment of breast cancer, around 6% of women diagnosed with breast cancer in the US have metastatic disease at time of diagnosis, and up to 30% of women with early-stage non-metastatic breast cancer will develop metastatic disease (O'Shaughnessy 2005). Although treatable, metastatic breast cancer remains virtually incurable, with a median survival of approximately 3 years and a 5-year survival rate of approximately 25% (Cardoso et al 2018).

Currently, clinical practice typically uses a surrogate classification of three breast cancer subtypes, based on molecular characteristics: HER2-positive, HR-positive but HER2-negative, and triple-negative. Tumors expressing ER and/or PR are considered HR-positive breast cancers, whereas tumors that do not express ER, PR or HER2 are defined as TNBC (Harbeck et al 2019). Approximately 70% of all breast cancers are HR-positive, HER2-negative (Howlader et al 2014).

In patients with metastatic HR-positive, HER2-negative breast cancer, the preferred initial treatment of choice is endocrine therapy, given either alone or in combination with targeted therapies such as CDK4/6 inhibitors, PI3-K, and mTOR inhibitors (Matutino et al 2018, André et al 2019). Within these, CDK4/6 as a class has shown to improve both PFS and OS in a meta-analysis (Cardoso et al 2018); however, the optimal sequence and integration of the agents is not fully established and is largely determined by geographic availability, which treatments were previously administered, the response obtained, and individual patient and disease characteristics.

In patients with metastatic HR-positive, HER2-negative breast cancer, who have exhausted or are not suitable for endocrine therapy, first-line chemotherapy is the SoC, with sequential single-agent chemotherapy (such as eribulin, capecitabine, gemcitabine, vinorelbine) generally preferred over combination therapy due to lack of consistent OS benefit and poor tolerability with combination therapy (Cardoso et al 2020, NCCN Guidelines 2020).

The following baseline clinico-pathological characteristics/factors could be clinically relevant to the targeted study population of interest for this study:

- Proportion of patients with 1 versus 2 prior lines of chemotherapy in the metastatic or inoperable setting
- Prior CDK4/6 inhibitor use (yes versus no)
- History of brain metastasis (yes versus no).

These and other factors may be recorded in IRT and could be included as part of routine monitoring throughout enrolment of the study. Unexpected variations could be evaluated by the Sponsor (see Appendix A).

2.2.1.1 Unmet medical need

The SoC of single agent chemotherapy in the HR-positive, HER2-negative metastatic breast cancer population has led to reported response rates of approximately 23%, a median PFS of 7 to 10 months, and a median OS of 26 to 36 months (Jerusalem et al 2018, Kaufman et al 2015, Twelves et al 2016). After two prior lines of chemotherapy, a median PFS of between 4 and 5 months and a median OS of between 14 and 24 months has been reported (Twelves et al 2016, Brufsky 2011, Miller et al 2005, Sparano et al 2010, Barrios 2010, Thomas et al 2007). Data after three lines of chemotherapy report a median PFS of approximately 3 to 4 months and median OS of between 11 to 16 months (Cortes et al 2011, Yardley et al 2013, Martín et al 2007, Yuan et al 2019). These data indicate that patients who are not suitable for, or who have exhausted, endocrine treatment options have an increasingly poor prognosis, with the greatest unmet medical need arising in patients who have received two or three prior lines of chemotherapy, for whom median survival is currently less than 2 years.

Chemotherapy is also associated with significant toxicities, including hematologic adverse effects, gastrointestinal toxicities including diarrhea, nausea, vomiting, alopecia, and skin reactions (Gradishar et al 2005, Miller et al 2007, Piccart-Gebhart et al 2008), which can have a significant impact on patient quality of life. Consequently, new and novel treatments for participants with HR-positive, HER2-negative advanced breast cancer are still needed to improve prognosis, control disease and prevent symptoms while minimizing toxicity, and therefore represents an area of considerable unmet medical need. A new class of therapy with better efficacy and relatively fewer side effects would therefore be a preferred option in this

treatment setting, to offer an alternative after traditional standard chemotherapies.

2.2.2 Dato-DXd

Dato-DXd is being co-developed by Daiichi Sankyo and AstraZeneca as an anticancer agent.

To date, clinical (preliminary safety and efficacy) data is currently available from one ongoing study (TROPION-PanTumor01; sponsored by Daiichi Sankyo). A summary of recent data from this study is presented in Section 2.2.2.1. Please refer to the Dato-DXd IB for a list of all studies in the Dato-DXd clinical development program, including participant exposure.

A detailed description of the chemistry, pharmacology, mechanism of action, efficacy, and safety of Dato-DXd is provided in the IB.

2.2.2.1 TROPION-PanTumor01 study

This ongoing Phase I FIH study evaluated escalating doses (0.27 to 10 mg/kg) of Dato-DXd in advanced solid tumors in participants with unresectable advanced NSCLC, and is currently in the dose expansion phase evaluating selected doses of Dato-DXd in participants with NSCLC, TNBC, and ER-positive, HER2-negative breast cancer who have been refractory to or relapsed on standard treatment or for which no standard treatment is available.

At the efficacy DCO date, 30 July 2021, preliminary efficacy data from the ongoing DS1062-A-J101 study were available. A total of 254 participants were evaluable for response assessments (210 with NSCLC and 44 with TNBC), defined as participants who received at least 1 dose of Dato-DXd and had pre-treatment and at least 1 post-treatment tumor assessment or discontinued from study drug. For participants with TNBC, the DCR was 76.2% (13 PRs and 16 SDs in 42 participants) in the 6 mg/kg dose group and 100% (1 PR and 1 SD in 2 participants) in the 8 mg/kg dose group.

Preliminary safety summary, as of 30 July 2021, in participants with breast cancer (TNBC and HR+/HER2-breast cancer) are summarized below. A total of 75 (93.8%) participants experienced at least 1 TEAE. The most frequently (≥ 15% of participants) reported TEAEs were nausea (45 [56.3%] participants), stomatitis (37 [46.3%] participants), alopecia (24 [30.0%] participants), fatigue (24 [30.0%] participants), vomiting (22 [27.5%] participants), constipation (16 [20.0%] participants), mucosal inflammation (18 [22.5%] participants), and headache (17 [21.3%] participants).

A total of 28 (35.0%) participants experienced ≥ Grade 3 TEAEs. The most commonly (> 2.5% of participants) reported ≥Grade 3 events by investigator-reported PT were lymphocyte count decreased (4 [5.0%] participants), stomatitis (4 [5.0%] participants), fatigue (3 [3.8%] participants), and lymphopenia (3 [3.8%] participants). A total of 1 (1.3%) participant had TEAEs associated with study treatment discontinuation due to investigator-reported PT of pneumonitis. A total of 1 (1.3%) participant experienced TEAEs

associated with an outcome of death due to investigator-reported PT of dyspnea. A total of 12 participants experienced serious TEAEs.

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 expected benefits and risks and the overall efficacy and safety profiles of Dato-DXd are found below and in the IB.

2.3.1 Risk Assessment

2.3.1.1 Dato-DXd

Based on safety data from nonclinical toxicology studies and clinical data available to date, the risks associated with Dato-DXd are presented in Table 3.

Table 3 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Dato-DXd		
• *Important identified risks:* ILD/pneumonitis. • *Identified risks*: IRR, anemia, fatigue, nausea, vomiting, diarrhea, decreased appetite, dry eye, alopecia, stomatitis/oral mucositis, mucosal inflammation other than oral mucositis/stomatitis, and rash/maculopapular rash. • *Important potential risk:* Embryo-fetal toxicity • *Potential risks*: Keratitis, skin pigmentation, increased ALT, increased AST, and constipation. • *AESIs*: ILD/pneumonitis, IRRs, oral mucositis/stomatitis, mucosal inflammation other than oral mucositis/stomatitis, and ocular surface toxicity.	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 ILD/pneumonitis. Embryo-fetal toxicity is considered an important potential risk.	Clinical experience in the Dato-DXd clinical development program to date has demonstrated that these identified and potential risks have been manageable through dose modification and routine clinical practice. However, specific inclusion/exclusion criteria (see Section 5) and monitoring/management guidelines (see Section 6.6) are currently in place to mitigate the important identified risks and AESIs (ILD/pneumonitis, IRR, oral mucositis/stomatitis, mucosal inflammation other than oral mucositis/stomatitis, and ocular surface toxicity). To specifically mitigate the incidence of pulmonary toxicities, inclusion/exclusion criteria are included prohibiting participants with relevant pre-existing pulmonary co-morbidities from entering the study. In addition, baseline pulmonary function tests will be performed for all participants. Potential ILD cases will be monitored closely for confirmatory signs and symptoms of ILD

Table 3 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Dato-DXd has not been studied in participants with renal or hepatic impairment. Information on AEs is presented in Section 8.3.	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 program.	and reviewed by an independent, blinded, ILD Adjudication Committee, which has been established for the Dato-DXd program to ensure adequate evaluation of events of interest (see Section 9.6.2). To mitigate the risk of IRRs, participants with a history of hypersensitivity reactions to any of the Dato-DXd excipients are excluded from participation in the study. Guidance on required pre-medication for the prevention of IRRs is also provided (see Section 6.6). To mitigate the risk of ocular surface toxicity, participants with clinically significant corneal disease are excluded from participation in the study. In addition, baseline, periodic and EoT ophthalmologic assessments will be performed by a licensed eye care provider. Ophthalmologic assessment data will be reviewed by an independent Ophthalmologic Data Review Committee (see Section 9.6.3). Guidance on prevention and management of ocular surface toxicity is provided (see Sections 8.2.5.5 and 6.6).

2.3.2 Benefit Assessment

Dato-DXd is under development for the treatment of lung, breast, and other advanced solid tumors. Data from the ongoing TROPION-PanTumor01 study demonstrate efficacy across dose groups, with tumor responses observed at starting doses of 4, 6, and 8 mg/kg and an acceptable and manageable toxicity profile across doses of Dato-DXd (see Section 2.2.2.1). Consequently, it is hypothesized that participants randomized to receive Dato-DXd may derive benefit from a potentially efficacious agent, whilst participants randomized to receive ICC will be treated in accordance with the current SoC for HR-positive, HER2-negative inoperable or metastatic breast cancer. Furthermore, compared to the toxicities of the comparator ICC agents, Dato-DXd appears to have a more favorable safety profile.

Other participant benefits include the less frequent infusions of Dato-DXd (Q3W) compared to comparator ICC schedules, making Dato-DXd treatment potentially more convenient. Additionally, at the time of disease progression, participants will be offered an optional tumor

biopsy, which will provide real-time next-generation sequencing results from the FoundationOne®CDx, that may help guide next treatment options.

Overall, participants enrolling onto this study will have a 1:1 chance of the receiving either the experimental drug Dato-DXd, or a standard chemotherapy agent. All participants will be contributing to the process of developing new therapies in an area of great unmet medical need.

2.3.3 Overall Benefit: Risk Conclusion

There is an unmet medical need for efficacious and safe therapies in treatment of HR-positive, HER2-negative inoperable or metastatic breast cancer in order to improve clinical outcomes. The extensive expression of TROP2 in breast cancers and the proof-of-concept shown by sacituzumab govitecan in HR-positive, HER2-negative (and TNBC) metastatic breast cancer has demonstrated the strong rationale of using an anti-TROP2-ADC in the HR-positive, HER2-negative population (Bardia et al 2021, Kalinsky et al 2020).

Preliminary results from the TNBC cohort of the TROPION-PanTumor01 study have shown promising efficacy of Dato-DXd at a dose of 6 mg/kg Q3W and support the further evaluation of Dato-DXd in the HR-positive, HER2-negative breast cancer population. In this cohort, the most common TEAEs were nausea, stomatitis, alopecia, fatigue, vomiting, constipation, mucosal inflammation, and headache. The most common Grade ≥ 3 TEAEs were lymphocyte count decreased, stomatitis, fatigue, and lymphopenia. One participant had TEAEs associated with study treatment discontinuation and one participant experienced TEAEs associated with an outcome of death.

The 2 most relevant risks considered for the benefit/risk assessment are the important identified risk of ILD/pneumonitis and the identified risk of IRR. Both of these risks can be fatal. Several measures have been put into place within the CSP to mitigate the incidence of pulmonary toxicities, including eligibility criteria that prohibit participants with pre-existing pulmonary co-morbidities from entering the study. In addition, baseline pulmonary function tests will be performed for all participants. Participants will be monitored closely throughout the study and clinical and laboratory assessments will be performed before every cycle. Toxicity Management Guidelines are also provided to assist with the management of the most commonly reported AEs and AESIs (see the Annex document to this CSP).

Consequently, compared to the safety profile of SoC chemotherapies, Dato-DXd is a potent anticancer therapy with the potential to provide an improved meaningful clinical benefit and a more favorable safety profile. Furthermore, the long half-life of Dato-DXd also enables a single IV, Q3W regimen, providing convenience to patients. It is therefore of key importance to evaluate the role of Dato-DXd in the HR-positive, HER2-negative inoperable or metastatic breast cancer population who have had progression of disease on 1 or 2 lines of chemotherapy,

and considering the measures to minimize risks to participants, the benefit/risk assessment supports the proposed study.

3 OBJECTIVES AND ENDPOINTS

Table 4 Objectives and Endpoints

Objectives	Endpoints
Dual Primary	
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of PFS in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer, who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting, per BICR.	• PFS is defined as time from randomization until progression per RECIST 1.1, as assessed by BICR, or death due to any cause. The analysis will include all randomized participants as randomized regardless of whether the participant withdraws from therapy, receives another anticancer therapy, or clinically progresses prior to RECIST 1.1. The measure of interest is the hazard ratio of PFS.
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of OS in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer, who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting.	• OS is defined as time from randomization until the date of death due to any cause. The comparison will include all randomized participants as randomized, regardless of whether the participant withdraws from therapy or receives another anticancer therapy. The measure of interest is the hazard ratio of OS.
Secondary	
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of ORR in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer, who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting, per BICR and per investigator assessment.	• ORR is defined as the proportion of participants who have a confirmed CR or PR, as determined by the BICR/Investigator assessment, per RECIST 1.1. The analysis will include all randomized participants as randomized. Data obtained from randomization up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR, regardless of whether the participant withdraws from therapy. Participants who go off treatment without a response or progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR. The measure of interest is the odds ratio of the ORR.
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of DoR in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting.	• DoR is defined as the time from the date of first documented confirmed response until date of documented progression per RECIST 1.1, as assessed by BICR/Investigator assessment or death due to any cause. The analysis will include all randomized participants as randomized who have a confirmed response, regardless of whether the participant withdraws from therapy, receives another anticancer therapy or clinically progresses prior to RECIST 1.1 progression. The measure of interest is the median of DoR.

Objectives	Endpoints
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of PFS in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting, per investigator assessment.	• PFS is defined as time from randomization until progression per RECIST 1.1, as assessed by investigator assessment, or death due to any cause. The analysis will include all randomized participants as randomized regardless of whether the participant withdraws from therapy, receives another anticancer therapy, or clinically progresses prior to RECIST 1.1. The measure of interest is the hazard ratio of PFS.
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of DCR in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer, who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting, per BICR and per investigator assessment.	• DCR at 12 weeks is defined as the percentage of participants who have a confirmed CR or PR or who have SD, per RECIST 1.1, as assessed BICR/per investigator assessment and derived from the raw tumor data for at least 11 weeks after randomization. Data obtained from randomization up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of DCR, regardless of whether the participant withdraws from therapy. Participants who receive a subsequent therapy prior to week 11 will not be considered to have disease control in the analysis. The analysis will include all randomized participants as randomized. The measure of interest is the odds ratio of the DCR.
To assess pain in participants treated with Dato-DXd compared to ICC.	• TTD in pain as measured by the pain scale from EORTC QLQ-C30 TTD is defined as time from the date of randomization to the date of deterioration. Deterioration is defined as change from baseline that reaches a clinically meaningful deterioration threshold. The analysis will include all randomized participants. The measure of interest is the hazard ratio of TTD in pain.
To assess physical functioning in participants treated with Dato-DXd compared to ICC.	• TTD in physical functioning as measured by the physical functioning scale from EORTC QLQ-C30 TTD is defined as time from the date of randomization to the date of deterioration. Deterioration is defined as change from baseline that reaches a clinically meaningful deterioration threshold. The analysis will include all randomized participants. The measure of interest is the hazard ratio of TTD in physical functioning.
To assess global health status/quality of life (GHS/QoL) in participants treated with Dato-DXd compared to ICC.	• TTD in GHS/QoL as measured by the GHS/QoL scale from EORTC QLQ-C30 TTD is defined as time from the date of randomization to the date of deterioration. Deterioration is defined as change from baseline that reaches a clinically meaningful deterioration threshold. The analysis will include all randomized participants. The measure of interest is the hazard ratio of TTD in GHS/QoL.

Objectives	Endpoints
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of TFST in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting.	• TFST is defined as the time from randomization until the start date of the first subsequent anticancer therapy after discontinuation of randomized treatment, or death due to any cause. The analysis will include all randomized participants as randomized, regardless of progression status. The measure of interest is the hazard ratio of TFST.
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of TSST in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting.	• TSST is defined as the time from randomization to until the start date of the second subsequent anticancer therapy after discontinuation of first subsequent treatment, or death due to any cause. The analysis will include all randomized participants as randomized, regardless of progression status on study treatment or first subsequent treatment. The measure of interest is the hazard ratio of TSST.
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of PFS2 in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting.	• PFS2 will be defined as the time from the randomization to the earliest of the progression event (following the initial progression), subsequent to first subsequent therapy, or death. The date of second progression will be recorded by the Investigator in the eCRF and defined according to local standard clinical practice. The comparison will include all randomized participants as randomized regardless of whether the participant withdraws from subsequent therapy and regardless of missed visits. The measure of interest is the hazard ratio of PFS2.
To assess the PK of Dato-DXd 6mg/kg IV Q3W.	• Plasma concentrations of Dato-DXd, total anti-TROP2 antibody, and MAAA-1181a (payload).
To investigate the immunogenicity of Dato-DXd 6mg/kg IV Q3W.	• Presence of ADA.
Safety	
To assess the safety and tolerability profile of Dato-DXd compared to ICC.	Safety and tolerability will be evaluated in terms of adverse events (graded by CTCAE version 5.0), and also in terms of: • ECOG PS • Vital signs, body weight, physical examination • Clinical chemistry, hematology, and urinalysis assessments • ECG, ECHO/MUGA and Ophthalmologic assessments
Exploratory	
To assess participant-reported symptomatic AEs and treatment tolerability.	Proportion of participants experiencing different levels of symptomatic AEs as measured by selected items from the PRO-CTCAE and EORTC Item Library (IL; ie, EORTC IL117) and reporting different levels of overall tolerability as measured by the PGI-TT. The analysis will include all dosed participants. The measure of interest will be proportion of participants reporting different levels of symptomatic AEs and overall tolerability.

Objectives	Endpoints
To assess participant-reported global impression of the severity of overall cancer symptoms.	Proportion of participants reporting different levels of global impression of the severity of overall cancer symptoms as measured by PGIS. The analysis will include all randomized participants. The measure of interest will be proportion of participants reporting different levels of global impression of the severity of overall cancer symptoms.
To assess participant-reported global impression of change in health status.	Proportion of participants reporting different levels of global impression of change in health status as measured by PGIC. The analysis will include all randomized participants. The measure of interest will be proportion of participants reporting different levels of global impression of change in health status.
To assess participant-reported symptoms, functioning and health-related QoL.	• TTD in fatigue and other symptoms as measured by EORTC QLQ-C30 • TTD in other functioning as measured by EORTC QLQ-C30 • Change from baseline of symptom, functioning and GHS/QoL scores as measured by EORTC QLQ-C30 The analysis will include all randomized participants. The measure of interest will be hazard ratio of TTD in fatigue and other symptoms, TTD in other functioning, and mean change from baseline of symptom, functioning and GHS/QoL scores.
To assess breast and arm symptoms in participants treated with Dato-DXd compared to ICC.	• TTD in breast symptoms as measured by the breast symptoms scale from EORTC QLQ-BR45/IL116 • TTD in arm symptoms as measured by the arm symptoms scale from EORTC QLQ-BR45/IL116 TTD is defined as time from the date of randomization to the date of deterioration. Deterioration is defined as change from baseline that reaches a clinically meaningful deterioration threshold. The analysis will include all randomized participants. • The measure of interest is the hazard ratio of TTD in breast symptoms/arm symptoms.
To assess participant-reported health status.	• VAS score, its change from baseline and 5-dimension scores as measured by EQ-5D-5L The analysis will include all randomized participants. The measure of interest will be mean and mean change from baseline of VAS score, and proportion of participants reporting different levels of each of 5-dimension scores.
Association of TROP2 or other tumor derived biomarkers with response and tolerability to Dato-DXd and ICC. [a]	• Correlation of biomarkers with clinical response (BoR, DoR, PFS, OS and other relevant efficacy endpoints) and/or development of cancer • Correlation of biomarkers with safety and tolerability endpoints Analysis may include, but is not limited to, the analysis of tumor biomarkers which include DNA, RNA, proteins or metabolite analysis

Objectives	Endpoints
Association of exploratory biomarkers in tumor, plasma, whole blood, or serum collected before, during treatment or at disease progression with disease status and/or response and tolerability to Dato-DXd. [a]	• Correlation of biomarkers with clinical response (BoR, DoR, PFS, OS and other relevant efficacy endpoints) and/or development of cancer • Correlation of biomarkers with safety and tolerability endpoints Analysis may include, but is not limited to, the analysis of tumor biomarkers which include DNA, RNA, proteins or metabolite analysis
Assessment of ctDNA mutational profile and dynamic changes as an indicator for early response and/or relapse on Dato-DXd, and assessment of molecular and genomic determinants of response to Dato-DXd in tumor and blood. [a]	• Assessment of ctDNA levels and mutational status of cancer-associated genes in ctDNA, including dynamic changes on treatment and correlation with clinical response on Dato-DXd and ICC, and correlation of gene expression and cancer gene mutational profile with clinical response.
To explore the impact of treatment and disease on health care resource use.	• The HOSPAD module will be used to collect information on key health care resource use beyond study mandated visits.

[a] Optional biomarker samples will not be collected in mainland China.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, open-label, randomized study of Dato-DXd versus ICC in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with one or two prior lines of systemic chemotherapy in the inoperable or metastatic setting. For an overview of the study design, see Figure 1.

Approximately 700 participants will be randomized in a 1:1 ratio to one of 2 intervention arms. If required for regulatory submission purposes, the recruitment of participants in mainland China may continue beyond the close of the global cohort, to include approximately an additional 20 randomized participants in the mainland China cohort. The mainland China cohort is defined as all participants from sites in mainland China randomized into the study. A participant randomized in the mainland China cohort prior to the last participant randomized in the global cohort will be included in both the global and mainland China cohorts. A participant randomized in mainland China after the last participant was randomized in the global cohort will be included only in the mainland China cohort.

Randomization will be stratified by the following prognostic and/or predictive factors:

- Number of previous lines of chemotherapy (1 versus 2)
- Geographic region (Region 1 [US, Canada, Europe] versus Region 2 [Rest of World])
- Prior use of CDK4/6 inhibitor (Yes versus No)

A 50% cap will be applied to participants who have had 2 prior lines of chemotherapy in the inoperable/metastatic setting.

CDK4/6 inhibitors are being increasingly utilized as part of standard of care for patients with HR+ breast cancer. To ensure that majority of participants have received prior CDK4/6 inhibitor therapy in the HER2 negative, HR-positive population, a cap of 49% will be applied to participants who have NOT received prior CDK4/6 inhibitor therapy.

The study intervention arms are:

- **Arm 1:** Dato-DXd (6 mg/kg IV on Day 1, Q3W)
- **Arm 2:** ICC:
  - Capecitabine (1000 or 1250 mg/m^2 oral BID on Days 1 to 14, Q3W); choice between the 2 doses will be determined by standard institutional practice.
  - Gemcitabine (1000 mg/m^2 IV on Day 1 and Day 8, Q3W)
  - Eribulin mesylate (1.4 mg/m^2 IV on Days 1 and 8, Q3W)
  - Vinorelbine (25 mg/m^2 IV on Days 1 and 8, Q3W)

Further details of all study interventions are provided in Section 6. All participants will receive study intervention until Investigator-defined disease progression according to RECIST 1.1, or until unacceptable toxicity, withdrawal of consent, or another criterion for discontinuation is met (see Section 7 for further details). Continued treatment with the same study drug post-progression may be allowed, based on prior discussion with study physician on case-by-case basis. No crossover between study treatment arms will be allowed.

The study is powered to assess the efficacy of Dato-DXd compared to ICC for the dual primary objectives of PFS (per RECIST 1.1, as assessed by BICR) and OS. Other measures of efficacy (ORR, DoR, DCR, TFST, TSST, PFS2) and HRQoL will also be evaluated during the study, in addition to the safety and tolerability profile of Dato-DXd, PK parameters, and immunogenicity. Details of all study objectives and corresponding endpoints are provided in Section 3.

All participants must have available a FFPE tumor sample (block preferred, or minimum of 20 freshly cut slides), at the time of screening. This can be from either the primary disease setting (surgical resection or diagnostic sample), or from a metastatic lesion (excluding bone) for tissue-based analysis (including but not restricted/limited to IHC staining of potential predictive biomarkers as well as tumor mutational analysis). The mandatory FFPE tumor sample submitted for analysis should be obtained as close to the time of diagnosis of metastatic or inoperable disease as possible.

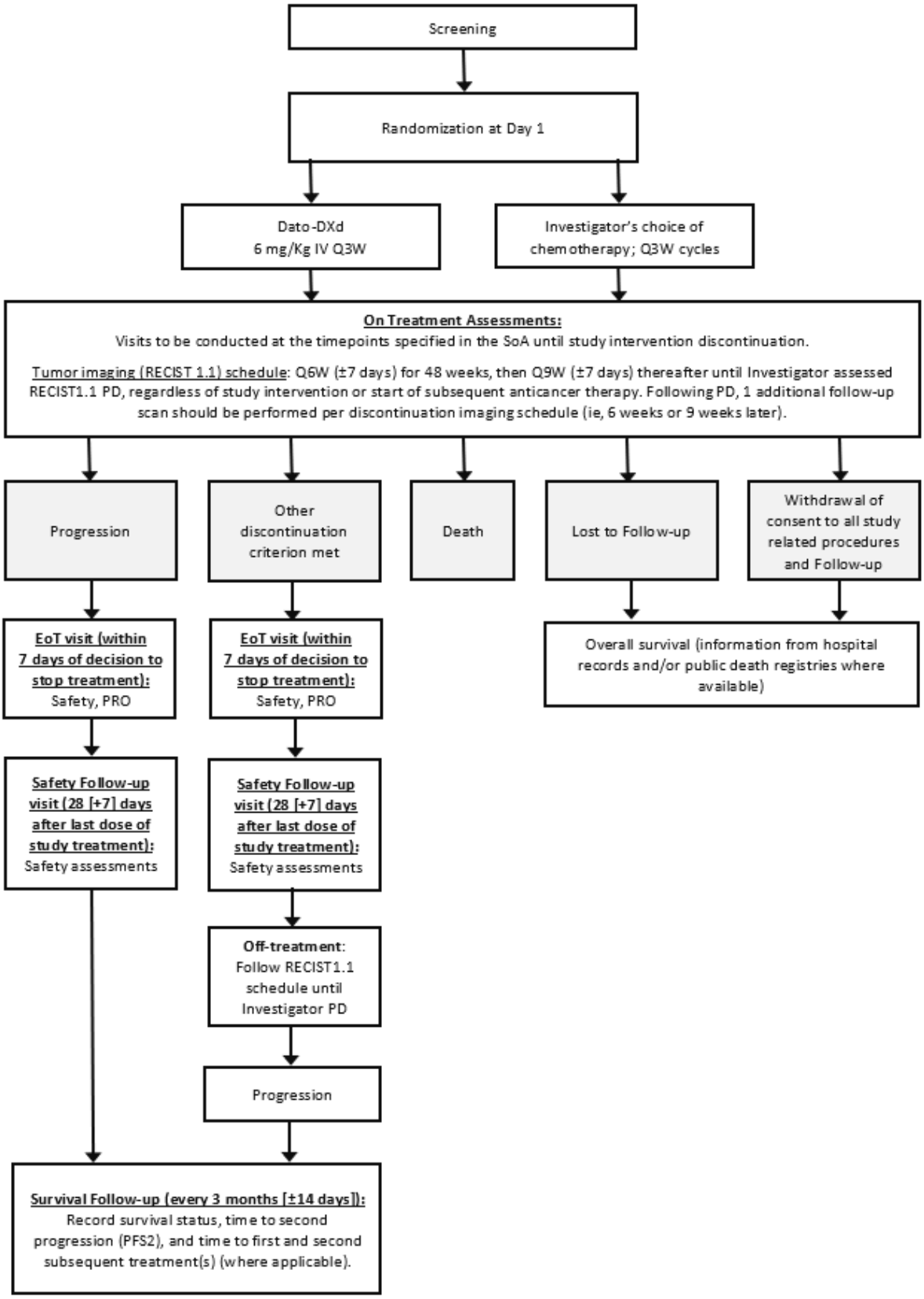
If neither an adequate FFPE block nor the minimum of 20 slides are available, a patient may still be considered eligible. In this situation, approval by the Study Team for patient's entry into the study is required. If there is no written confirmation of the availability of an appropriate tumor sample prior to enrolment, the participant will not be eligible for the study. At the time of enrolment all participants must have an ECOG PS of 0 or 1.

Note: Sample collection in mainland China will follow local regulatory approval.

A summary of the study periods and timings of study visits and main efficacy assessments is provided in Figure 2.

Country-specific study requirements are provided in Appendix L.

Figure 2 Study Flow Chart



4.1.1 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 SARS-CoV-2 or 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 minimize risks to study integrity. Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the ICF should be signed at the participant's next contact with the study site).
- Rescreening: Extended rescreening period 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 Health Care Professional (HCP) or HCP provided by a third-party vendor (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 J.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Design

This randomized, open-label, 2-arm study will investigate Dato-DXd monotherapy versus ICC (eribulin, vinorelbine, capecitabine, or gemcitabine). The open-label design was chosen due to the differing dosing schedules of the ICC treatments; however, the trial will be conducted as "sponsor-blind" and the specific study intervention (Dato-DXd or ICC) to be taken by a participant will be assigned in a randomized manner. To maintain the integrity of the study, Sponsor personnel directly involved in the study conduct will not undertake or have access to efficacy data aggregated by treatment arm prior to final data readout for the dual primary

endpoint of PFS. At Sponsor discretion, the sponsor blind may be dropped if the dual primary endpoint of PFS achieves statistical significance at its primary analysis.

4.2.2 Rationale for Choice of Comparator Treatments

Chemotherapy (single agent or doublet) is considered the main treatment option for patients who have exhausted or are not suitable for endocrine therapy in the metastatic setting. Combination chemotherapy has shown higher ORR, however, could not clearly show an OS benefit (Schott 2021). In addition, to balance the OS benefits with the toxicities between single agent and combination therapy, single agent sequential chemotherapies are recommended. Preferred agents in this setting include capecitabine, gemcitabine, vinorelbine, and eribulin (NCCN Guidelines 2020, Cardoso et al 2020).

Capecitabine is frequently the first choice because of oral administration and low risk of alopecia and myelotoxicity. In the large phase 2 study in participants with metastatic breast cancer, capecitabine monotherapy achieved an ORR of 20% and median OS of 12.6 months (Blum et al 1999). Gastrointestinal side effects and hand-foot syndrome were the most commonly occurring adverse events.

Eribulin has demonstrated anti-tumor activity as single-agent in metastatic breast cancer participants. In the EMBRACE trial, eribulin significantly improved OS in heavily pre-treated metastatic breast cancer participants as compared to SoC (median OS of 13.1 months versus 10.6 months). The primary toxicity with eribulin was neutropenia whereas peripheral neuropathy was the most common adverse event leading to discontinuation of eribulin (Cortes et al 2011).

Vinorelbine has demonstrated activity even in heavily pre-treated participants with metastatic breast cancer. In a Phase 3 study of vinorelbine monotherapy versus gemcitabine plus vinorelbine, median PFS in the single-agent vinorelbine arm was 4.0 months and OS was 16.4 months (Martín et al 2007). Vinorelbine rarely induces total alopecia or severe gastrointestinal events or symptomatic cardiac events. The major dose-limiting hematological toxicity associated with vinorelbine is neutropenia (Domenech and Vogel 2001).

Gemcitabine is active in metastatic breast cancer, with a response rate of approximately 25% and a median DoR of 13.5 months. A median OS of 15.2 months has also been reported (Possinger et al 1999). The drug is relatively well tolerated; alopecia and gastrointestinal toxicity are mild, and its use is not associated with significant neuropathy. Thrombocytopenia can be a dose-limiting toxicity. Gemcitabine appears to cross the blood brain barrier and may be a good option in participants with a history of CNS metastases (Gridelli et al 1999).

4.2.3 Rationale for Stratification Factors

4.2.3.1 Stratification based on previous lines of chemotherapy

The proposed dual primary endpoints of this study are PFS and OS, which are expected to differ in their magnitude dependent on whether a participant has received 1 or 2 lines of prior chemotherapy (see Section 2.2.1.1 for further details). Therefore, stratification by lines of chemotherapy (1 versus 2) has been chosen. Additionally, the study will also cap enrolment at 50% for participants who have received 2 prior lines of chemotherapy.

4.2.3.2 Stratification based on prior CDK4/6 inhibitor use

Differences in the magnitude of benefit in PFS and OS are also expected in participants receiving TROP2 inhibitors, dependent on whether treatment with a prior CDK4/6 inhibitor has been received. In HR-positive, HER2-negative participants treated with sacituzumab govitecan (a TROP2 ADC approved for use in metastatic TNBC by in the US), a subgroup analysis performed on prior CDK4/6 inhibitor use (no prior use versus prior use) demonstrated notable differences in median PFS, OS, and ORR (Kalinsky et al 2020). It is expected that the majority of study participants will have received CDK4/6 inhibitors. There are however global regions where CDK4/6 inhibitors are not yet adopted, and as such patients may be enrolled, stratification based on prior CDK4/6 inhibitor use are proposed.

4.2.3.3 Stratification based on geographical region

Mortality rates from breast cancer vary by geographic region, due to regional differences in drug availability and medical practice. In many western countries, mortality rates due to breast cancer are decreasing, which has been attributed to a combination of early detection using mammographic screening and improved treatment options. In contrast, mortality rates in many South American, African, and Asian countries increased (Youlden et al 2012). Given these examples of differences in outcomes in various regions, stratification based on geographical region is proposed.

4.2.4 Rationale for Primary Efficacy Endpoints

The primary dual endpoints of the study are OS and PFS by BICR, according to RECIST 1.1 in the ITT. These endpoints are in line with the guidelines outlined by the NCI Breast Cancer Steering Committee Working Group Report (Seidman et al 2018), which recommends OS to be a primary endpoint in poor prognosis disease settings, and PFS to be a most robust and appropriate endpoint in HR-positive, HER2-negative disease, which has longer post-progression survival.

Overall survival is a clinically meaningful and direct measure of overall efficacy in metastatic breast cancer disease, and both the EMA (EMA 2017) and FDA (FDA 2018) advice consider OS as the most persuasive and reliable endpoint. However, both Agencies also consider PFS as an acceptable endpoint, dependent on the disease under study and other factors. For a randomized Phase 3 study, PFS is a relevant measure of clinical benefit that demonstrates

superiority of a new antineoplastic therapy, particularly in a setting where patients may frequently change chemotherapy agents due to side effects or progressive disease. Progression-free survival is an objective endpoint and is potentially less affected by post discontinuation therapies (as opposed to OS). A sufficiently prolonged PFS may therefore be considered in itself a clinically relevant effect, provided detriments on other important endpoints can be excluded, particularly if the magnitude of effect is large and the therapy has an acceptable risk/benefit profile. When rigorously tested, a robust treatment effect based on PFS complemented by no detriment in OS, can offer treatments to be made available early for patients with limited options especially in studies with long OS.

Given these factors, and in recognizing the value of both PFS and OS as measures of overall efficacy, both are planned as dual primary endpoints.

4.2.5 Rationale for Other Study Endpoints

The secondary endpoints of this study are in line with the recommendations outlined in the NCI Breast Cancer Steering Committee Working Group Report (Seidman et al 2018).

The secondary participant-reported pain, physical functioning and global health status/quality of life endpoints, assessed using EORTC QLQ-C30, as well as participant-reported symptomatic AEs measured by selected items from the PRO-CTCAE/EORTC IL117 will show the overall influence of the benefits and toxicity of the treatment from the participant's perspective and will aid in understanding the benefit/risk evaluation. These PRO questionnaires are well-established instruments that have been previously included in cancer clinical studies.

Biological samples will be used to explore potential biomarkers in tumor, plasma, and/or serum, which may predict the progression of cancer (and associated clinical characteristics) and/or tumor response. By mandating tumor sample collection as part of the study design, TROP2 expression will be tested retrospectively by IHC, to explore correlation with treatment response. Increased TROP2 mRNA in breast cancer has been shown to be a predictor of lymph node involvement, distant metastasis, and poor OS (Zhao et al 2018). In one heterogenous breast cancer series, TROP2 analysis by IHC showed 92.6% (38/42) of tumors expressed TROP2 (Yang et al 2021). Internal AstraZeneca analysis of TROP2 expression also shows broad levels of expression in > 90% of HR-positive breast cancer clinical samples (unpublished data).

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.

4.3 Justification for Dose

4.3.1 Dato-DXd

The 6.0 mg/kg IV dose of Dato-DXd was selected based on preliminary results of the ongoing Phase 1, 2-part (dose escalation and dose expansion), multicenter, nonrandomized, open-label, multiple dose, first-in-human study (Study DS1062-A-J101) in participants with solid tumors. 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 8.0 mg/kg. During the dose escalation phase, the non-tolerated dose for Dato-DXd was 10.0 mg/kg, where 2 participants had Grade 3 dose-limiting toxicities of mucosal inflammation and stomatitis. One participant at 6.0 mg/kg had a dose-limiting toxicity of Grade 3 maculopapular rash. The maximum tolerated dose (8.0 mg/kg) was determined during the dose escalation phase.

However, an ongoing review of emerging Phase 1 study data has allowed a closer evaluation of the benefit/risk balance by dose. Based on these data, the Dato-DXd 6 mg/kg dose has a more favorable benefit/risk balance than the 8 mg/kg dose; thus, the 6 mg/kg is the optimal monotherapy dose for further development of Dato-DXd in clinical studies.

Based on review of the safety data as of 16 November 2021, Dato-DXd exhibited an acceptable safety profile with established risk monitoring and risk mitigation measures for the important identified risks of ILD/pneumonitis and IRR as well as the AESIs of ILD/pneumonitis, IRR, oral mucositis/stomatitis, mucosal inflammation other than oral mucositis/stomatitis, and ocular surface toxicity.

Overall, the safety and tolerability profile of Dato-DXd 6 mg/kg remains acceptable and manageable. The 6 mg/kg dose has a better benefit/risk profile than the 8 mg/kg dose and thus supports continued clinical development of Dato-DXd at this dose.

The mean terminal half-life of Dato-DXd was 4.82 days at the 6.0 mg/kg dose, thus supporting a Q3W dosing schedule.

For information on dose modifications for Dato-DXd, see Section 6.6.

4.3.2 Investigator Choice of Chemotherapy (ICC)

The dosages of the ICC agents (capecitabine, gemcitabine, vinorelbine, eribulin) to be used in the current study are based on recommendations in the Prescribing Information for each agent, and are in accordance with current international breast cancer treatment guidelines (NCCN Guidelines 2020, Cardoso et al 2020).

In specific relation to capecitabine, 2 dose options have been selected for use (to be determined by standard institutional practice), as dose tolerance is different between some patients due to pharmacogenetic differences (Midgley and Kerr 2008). For example, in the FDA label for capecitabine, Japanese patients had a lower concentration (C_{max}) of drug at the

same dose given to Caucasian patients (Capecitabine USPI 2015).

4.4 End of Study Definition

For the purpose of Clinical Trial Transparency, the definition of the end of the study differs under FDA and EU regulatory requirements:

- European Union requirements define study completion as the last visit of the last subject for any protocol related activity.
- United States FDA requirements defines 2 completion dates:
  - Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all the primary outcomes.
  - Study Completion Date – is defined as the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measure and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if they have 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.

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

5 STUDY POPULATION

The target population of interest in this study is participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with one or two prior lines of systemic chemotherapy in the inoperable/metastatic setting.

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

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

Country-specific study requirements are provided in Appendix L.

5.1 Inclusion Criteria

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

Age

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

Type of Participant and Disease Characteristics

2 Inoperable or metastatic HR-positive, HER2-negative breast cancer (per ASCO/CAP guidelines, on local laboratory results); ie, is documented as HR-positive (either ER and/or PgR positive [ER or PgR ≥ 1%]) and HER2-negative. If a participant had multiple results after metastatic disease, the most recent local test result will be used to confirm eligibility (Allison et al 2020, Wolff et al 2018).

3 Progressed on and not suitable for endocrine therapy per investigator assessment, and treated with 1 to 2 lines of prior standard of care chemotherapy in the inoperable/metastatic setting. Participant must have documented progression on their most recent line of chemotherapy.

Note: If a chemotherapy drug is changed within 28 days of use to another drug in the same class (ie, antimetabolite to antimetabolite) for any reason, the first drug is not counted as a line.

Targeted agents (such as mTOR inhibitors, PD-1/PD-L1 inhibitors, PARP inhibitors), endocrine therapies, and CDK4/6 inhibitors on their own do not contribute to the count of prior lines of chemotherapy; however, regimens with such agents in combination with metastatic chemotherapy should be classified as one line of chemotherapy.

4 Eligible for one of the chemotherapy options listed as ICC (eribulin, capecitabine, vinorelbine, gemcitabine), per investigator assessment.

Note: Participants who previously received any of these agents are eligible for enrolment to another ICC agent in this study.

5 ECOG PS of 0 or 1, with no deterioration over the previous 2 weeks prior to day of first dosing.

6 At least 1 measurable 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, which is suitable for accurate repeated measurements.

Note: Participants with bone-only metastases are not permitted.

7 Participants with a history of previously treated neoplastic spinal cord compression, or clinically inactive brain metastases, who require no treatment with corticosteroids or anticonvulsants, may be included in the study, if they have recovered from the acute toxic

effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of radiotherapy and study enrolment.

8 Adequate organ and bone marrow function within 7 days before day of first dosing as follows:

- *Hemoglobin*: ≥ 9.0 g/dL. Red blood cell/plasma transfusion is not permitted within 1 week prior to screening assessment.
- *Absolute neutrophil count*: ≥ 1500/mm^3. Granulocyte colony-stimulating factor administration is not permitted within 1 week prior to screening assessment.
- *Platelet count*: ≥ 100000/mm^3. Platelet transfusion is not permitted within 1 week prior to screening assessment.
- *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.
- *ALT and AST*: ≤ 3 × ULN for AST/ALT; however, if elevation is due to liver metastases, ≤ 5.0 × ULN is allowed.
- *Calculated creatinine clearance*: ≥ 30 mL/min as calculated using the Cockcroft-Gault equation (using actual body weight):

$$\textit{Female}: \quad \text{CrCl (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

$$\textit{Male}: \quad \text{CrCl (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

9 LVEF ≥ 50% by either an echocardiogram or MUGA within 28 days of first dosing.

10 Has had an adequate treatment washout period before Cycle 1 Day 1, defined as:

- Major surgery: ≥ 3 weeks.
- Radiation therapy including palliative radiation to chest: ≥ 4 weeks (palliative radiation therapy to other areas ≥ 2 weeks).
- Anticancer therapy including hormonal therapy: ≥ 3 weeks (for small molecule targeted agents: ≥ 2 weeks or 5 half-lives, whichever is longer).
- Antibody-based anticancer therapy: ≥ 4 weeks with the exception of receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors (eg, denosumab for the treatment of bone metastases).
- Immunotherapy (non-antibody-based therapy): ≥ 2 weeks or 5 times the terminal elimination T½ of the agent, whichever is longer.

- Chloroquine/hydroxychloroquine: ≥ 14 days.

11 All participants must have available a FFPE tumor sample (block preferred, or a minimum of 20 freshly cut slides), at the time of screening. This can be from either the primary disease setting (surgical resection or diagnostic sample), or from a metastatic lesion (excluding bone) for tissue-based analysis (including but not restricted/limited to IHC staining of potential predictive biomarkers as well as tumor mutational analysis). The mandatory FFPE tumor sample submitted for analysis should be obtained as close to the time of diagnosis of metastatic or inoperable disease as possible. If neither an adequate FFPE block nor the minimum of 20 slides are available, a patient may still be considered eligible. In this situation, approval by the Study Team for patient's entry into the study is required.

Note: Sample collection in mainland China will comply with local regulatory approval.

12 Minimum life expectancy of 12 weeks at screening.

Sex

13 Male 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; however, oral estrogens are not permitted.

Reproduction

14 Negative pregnancy test (serum) for women of childbearing potential.

15 Female participants must be post-menopausal for at least 1 year, surgically sterile, or using one highly effective form of birth control (a highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly). For female contraception, please refer to Appendix G. Women of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control. They should have been stable on their chosen method of birth control starting at a minimum of 3 months before C1D1 to at least 7 months after the last dose (see Appendix G for complete list of highly effective birth control methods). Female participants must refrain from egg cell donation and breastfeeding while on study and for at least 7 months after the last dose of study intervention. Non-sterilized male partners of a woman of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) throughout this period.

16 Male participants who intend to be sexually active with a female partner of childbearing potential must be surgically sterile or using a highly effective method of contraception

(see Appendix G) from the time of screening throughout the total duration of the study and the drug washout period (at least 4 months after the last dose of study intervention) to prevent pregnancy in a partner. Male participants must not donate or bank sperm during this same time period. Not engaging in heterosexual activity (sexual abstinence) for the duration of the study and drug washout period is an acceptable practice if this is the preferred usual lifestyle of the participant; however, periodic or occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female partners of male participants are allowed to use HRT for contraception.

Informed Consent

17 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 protocol.

18 Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of sample for optional genetic research that supports Genomic Initiative.

5.2 Exclusion Criteria

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

Medical Conditions

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

2 History of another primary malignancy except for malignancy treated with curative intent with no known active disease within 3 years before the first dose of study intervention and of low potential risk for recurrence. Exceptions include basal cell carcinoma of the skin and squamous cell carcinoma of the skin that has undergone potentially curative therapy, adequately resected non-melanoma skin cancer, curatively treated in situ disease, or other solid tumors curatively treated.

3 Persistent toxicities caused by previous anticancer therapy (excluding alopecia), not yet improved to CTCAE Version 5.0 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 first dosing 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 I diabetes.
    - Hyperglycaemia.
    - Adrenal insufficiency
  - Adrenalitis.
- Skin hypopigmentation (vitiligo).

4 Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals; suspected infections (eg, prodromal symptoms); or inability to rule out infections.

Note: Participants with localized fungal infections of skin or nails are eligible.

5 Known active or uncontrolled hepatitis B or C infection. 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+ (i.e., those who have cleared HBV after infection) and meet conditions i-iii below:

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

i. HBV DNA viral load < 2000 IU/mL

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

6 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, CD4+ count > 350 cells/mm^3, no history of AIDs-defining opportunistic infection within the past 12 months, and stable for at least 4 weeks on same anti-HIV retroviral medications (meaning there are no expected further changes in that time to the number or type of antiretroviral drugs in the regimen). If an HIV infection meets the above criteria, 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.

7 Uncontrolled or significant cardiac disease, including myocardial infarction or uncontrolled/unstable angina within 6 months prior to C1D1, CHF (New York Heart Association Class II to IV), uncontrolled or significant cardiac arrhythmia, or uncontrolled hypertension (resting systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg).

8 Investigator judgment of 1 or more of the following:

- Mean resting corrected QTcF interval > 470 ms, obtained from triplicate ECGs performed at screening.
- 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.

9 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.
Note: Participants found to have ILD/pneumonitis on baseline screening chest CT are not eligible.

10 Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (ie, pulmonary emboli within three months of first dosing, severe asthma, severe COPD, restrictive lung disease, pleural effusion etc), or any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (ie, Rheumatoid arthritis, Sjogren's, sarcoidosis etc), or prior pneumonectomy.

11 Leptomeningeal carcinomatosis.

12 Clinically significant corneal disease.

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

Prior/Concomitant Therapy

14 Any of the following prior anticancer therapies:

- Any treatment (including ADC) containing a chemotherapeutic agent targeting topoisomerase I
- TROP2-targeted therapy
- Prior treatment with same ICC agent

(**Note**: Participants are eligible for enrolment into this study if they able to receive treatment with another ICC agent not previously received; see Inclusion Criterion 4)

15 Any concurrent anticancer treatment, with the exception of bisphosphonates, denosumab, for the treatment of bone metastases.

16 Concurrent use of systemic hormonal replacement therapy (eg, estrogen). However, concurrent use of hormones for non-cancer related conditions (eg, insulin for diabetes) is acceptable.

17 Major surgical procedure (excluding placement of vascular access) or significant traumatic injury within 3 weeks of the first dose of study intervention or an anticipated need for major surgery during the study.

18 Receipt of live, attenuated vaccine within 30 days prior to the first dose of study treatment.

19 Criterion removed in Protocol version 3.0.

Prior/Concurrent Clinical Study Experience

20 Previous treatment in the present study.

21 Participation in another clinical study with a study intervention or investigational medicinal device administered in the last 4 weeks prior to first dosing, randomization into a prior Dato-DXd or T-DXd (trastuzumab deruxtecan) study regardless of treatment assignment, or concurrent enrolment in another clinical study, unless it is an observational (noninterventional) clinical study or during the follow-up period of an interventional study.

22 Participants with a known hypersensitivity to Dato-DXd, or any of the excipients of the product (including, but not limited to, polysorbate 80).

23 Known history of severe hypersensitivity reactions to other monoclonal antibodies.

Other Exclusions

24 Involvement 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 women only, currently pregnant (confirmed with positive pregnancy test) or breastfeeding, or who are planning to become pregnant.

5.3 Lifestyle Considerations

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

- Participants must follow the contraception requirements outlined in Appendix G.
- Participants should not donate blood or blood components while participating in this study and through 28 (+7) days after the last dose of study intervention. Preservation of ova and sperm should be considered prior to enrolment in this study.
- 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.

Restrictions relating to concomitant therapies are described in Appendix I 2.

5.4 Screen Failures

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

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 any effect on study results can be assessed.

All assessments must be repeated for rescreening unless they are within 28 days of randomization.

Screen failure 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 randomized).

Participant enrolment and randomization is described in Section 6.3.

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

6.1.1 Investigational Products

AstraZeneca will supply datopotamab deruxtecan (Dato-DXd). Investigator's Choice of Chemotherapy agents (capecitabine, gemcitabine, eribulin, or vinorelbine) will be supplied locally. Under certain circumstances, when local sourcing is not feasible, these agents may be supplied centrally through AstraZeneca.

Dose modifications are described in Section 6.6.

A summary of study treatments is provided in Table 5.

Table 5 Investigational Products

Arm name / Intervention Name	Arm 1: Dato-DXd	Arm 2: Investigator's Choice of Chemotherapy			
		Capecitabine	Gemcitabine	Eribulin mesylate	Vinorelbine
Type	Drug	Drug	Drug	Drug	Drug
Dose Formulation	Lyophilized powder for concentrate for solution for infusion	Tablet	Injection	Solution for injection	Injection
Unit Dose Strength(s)	100 mg	As sourced locally [a]	As sourced locally [a]	As sourced locally [a]	As sourced locally [a]
Dosage Level(s)	6 mg/kg on Day 1 of each 21-day cycle	1000 or 1250 mg/m^2 BID on Days 1 to 14 of a 21-day cycle [b]	1000 mg/m^2 on Days 1 and 8 of a 21-day cycle	1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle [c]	25 mg/m^2 on Day 1 and 8 of a 21-day cycle [d]
Route of Administration	IV infusion	Oral	IV infusion	IV infusion	IV infusion
Use	Experimental	Active comparator	Active comparator	Active comparator	Active comparator
IMP/ NIMP/ AxMP	IMP	IMP	IMP	IMP	IMP

Table 5 Investigational Products

Arm name / Intervention Name	Arm 1: Dato-DXd	Arm 2: Investigator's Choice of Chemotherapy			
		Capecitabine	Gemcitabine	Eribulin mesylate	Vinorelbine
Sourcing	Central	As sourced locally [a]	As sourced locally [a]	As sourced locally [a]	As sourced locally [a]
Packaging and Labelling	Dato-DXd will be provided in 100 mg vials in a carton. Each vial and carton will be labelled as required per country regulatory requirements [e]	As sourced locally [a]	As sourced locally [a]	As sourced locally [a]	As sourced locally [a]
Current/ Former Name or Alias	DS-1062a	Not applicable	Not applicable	Not applicable	Not applicable

[a] Under certain circumstances when local sourcing is not feasible, an ICC treatment may be supplied centrally through AstraZeneca.
[b] The choice of dose will be determined by standard institutional practice. Reduce the dose by 25% in participants with moderate (CrCl 30-49 mL/min) renal impairment.
[c] A lower starting dose of 1.1 mg/m^2 is recommended for participants with moderate (CrCl 30-49 mL/min) renal impairment, or mild hepatic impairment (Child-Pugh A).
[d] Exercise caution in participants currently taking drugs known to inhibit CYP3A. Concurrent administration of vinorelbine with a CYP3A inhibitor may cause an earlier onset and/or an increased severity of adverse reactions.
[e] Label text for Dato-DXd (DS-1062a) may show "DS-1062a" depending on the agreed product name used in the respective approved study master label document. All naming conventions for these compounds are correct during the transitional period.

6.1.1.1 Duration of Treatment

All study treatments are to be administered until RECIST 1.1-defined radiological progression (as determined by the Investigator) or until meeting any other reason to discontinue study intervention (see Section 7.1). Continued treatment with the same study drug post-progression may be allowed, based on prior discussion with study physician on case-by-case basis. No crossover between study treatment arms will be allowed.

6.1.2 Medical Devices

Not applicable.

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 authorization is provided for on-site destruction or removal of the study intervention, reflecting completion of the study. In the event that a

temperature excursion is 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 authorized 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 authorized 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. The investigator (or designee) is responsible for ensuring that the participant has returned all unused study intervention.

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

6.2.1 Dato-DXd

Dato-DXd will be supplied as a 100 mg lyophilized powder for concentrate for solution for infusion. The reconstituted solution contains 20 mg/mL Dato-DXd in CCI mM histidine/histidine HCl, CCI % (w/v) sucrose, CCI % (w/v) polysorbate 80; it has a pH of 6.0 and density of 1.04 g/mL. The post-reconstitution volume is 5 mL. The reconstituted drug product is a clear to slightly opalescent, colorless to slightly yellow liquid and practically free from visible particles.

6.2.1.1 Preparation of Dato-DXd

The dose of Dato-DXd for administration must be prepared by the pharmacy staff members (or an appropriate designee trained in study drug preparation), using aseptic technique in compliance with local regulations and site requirements.

Dato-DXd should be handled in accordance with practices required for hazardous drugs (i.e., chemotherapy).

Incompatibilities have been identified with 0.9% sodium chloride for injection and **must not** be used for dose preparation.

The total time from needle puncture of the Dato-DXd vial to the start of administration must not exceed 24 hours at 2 °C to 8 °C (36 °F to 46 °F), otherwise a new dose must be prepared from new vials.

Following preparation and during administration, the prepared IV bag must be covered by a light protection cover; the cover must be applied immediately after dose preparation and

remain on throughout the administration time.

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

6.2.1.2 Administration of Dato-DXd

Pre-medication is required prior to any dose of Dato-DXd and must include antihistamines and acetaminophen, with or without glucocorticoids. Participants should remain at the site for at least 1-hour post-infusion of every dose of Dato-DXd for close observation for possible IRRs.

It is also highly recommended that participants receive prophylactic anti-emetic agents prior to infusion of Dato-DXd and on subsequent days as needed. Antiemetics such as 5-HT3 receptor antagonists, NK1 receptor antagonists and steroids (eg, dexamethasone) should be considered and administered in accordance with the prescribing information or institutional guidelines.

Dato-DXd must reach room temperature prior to administration.

Incompatibilities have been observed with 0.9% sodium chloride for injection and must not be used for drug administration; additionally these solutions must not be co-infused in the same IV line as Dato-DXd.

Dato-DXd will be administered using an IV bag containing 5% dextrose injection through an IV administration set, using local practices. Do not shake the prepared IV bag.

The infusion must be administered with a 0.2- or 0.22-µm filter; acceptable configurations include an IV set containing an in-line filter or the attachment of a separate filter to the distal end of the IV tubing.

Dato-DXd infusion time is approximately 90 minutes (±10 minutes) for the first infusion. If the first infusion is well tolerated and the participant does not experience an infusion-related reaction, then the minimum infusion time for subsequent cycles is 30 minutes.

In case of interruptions, the total cumulative time from needle puncture of the Dato-DXd vial to the end of infusion must not exceed 4.5 hours with the IV bag kept at room temperature, otherwise a new dose must be prepared from new vials to complete the dose.

Do not co-administer other drugs through the same IV line.

After the content of the IV bag is administered, the IV line will be flushed with a volume of 5% dextrose for injection equal to the IV-line volume, at the same rate as infusion according to local practices, to ensure the full dose is administered.

The total infusion time recorded in the EDC system reflects when the infusion IV bag is empty; this time does not include the post-infusion flush.

If an IRR (such as fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnea, hypotension) is observed during administration, the infusion speed should be reduced by 50% and participants should be closely monitored.

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 ≥ ±10%, the participant's dose will be recalculated based on the participant's updated weight. After the re-calculation, the participant's updated weight will be used as the new baseline weight. The site may follow local institutional policy for recalculating dose based on weight changes less than 10%.

6.2.1.3 Monitoring of Dato-DXd Administration

Participants will be monitored during and after infusion of Dato-DXd. Vital signs will be measured according to the SoA and Section 8.2.2.

Management of study intervention-related toxicities are described in the TMGs for Dato-DXd, (see the Annex document to this CSP). As with any biologic product, IRRs 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 recognize and treat anaphylaxis.

6.2.1.4 Storage of Dato-DXd

The investigator, or an appropriate delegate, will ensure that all study intervention is stored in a secured 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.

Investigational product vials are stored at 2 °C to 8 °C (36 °F to 46 °F) and must not be frozen. Investigational product must be kept in original packaging until use to prevent prolonged light exposure.

6.2.2 Investigator's Choice of Chemotherapy

Participants will receive ICC (eribulin, capecitabine, vinorelbine and gemcitabine) at the doses specified in Table 5. The choice of chemotherapy must be pre-defined prior to randomization. The number of treatment cycles for ICC is not fixed. Refer to the local label for details on handling.

The ICC agents will either be locally sourced by the study site or centrally supplied by AstraZeneca and will be administered according to Prescribing Information or treatment guidance in general use by the investigating site. Under certain circumstances when local sourcing by the study site is not feasible, AstraZeneca will centrally supply the drug, which will be labelled with local language translated text in accordance with regulatory guidelines.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Participant Enrolment and Randomization

All participants will be centrally assigned to randomized study intervention using an IRT. Before the study is initiated, the call/log-in directions and user guides for the IRT will be provided to each site.

If a participant withdraws from the study, then their enrolment 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 (up to 28 days before C1D1), the investigators (or suitably trained delegate) will:

- 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 randomization except for virus antibody test results and hepatitis B virus surface antigen, which can be used if performed within 120 days before screening.
- Participants will be identified to the IRT per country regulations. Obtain a unique 7-digit enrolment number (E-code) through the IRT in the following format: PPD PPD . 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).
- Obtain signed informed consent for the optional Genomics Initiative. Participants who decide not to sign the specific genetic ICF, but the general study ICF, are eligible for study enrolment and all other study procedures.

At randomization, once the participant is confirmed to be eligible, the investigator (or suitably trained delegate) will:

- Select the ICC treatment (based on the most appropriate option for the participant) that the participant would receive if randomized to the ICC group prior to randomization of the participant. This must be completed for all participants. The selection will be recorded in the IRT system.
- Assign a randomized treatment group via the IRT. Randomization codes will be assigned strictly sequentially within each stratum and site/country/region as participants become eligible for randomization. The system will randomize the eligible participant to one of the 2 treatment groups.

If the participant is ineligible and not randomized, the IRT should be accessed to terminate the participant in the system.

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

6.3.2 Procedures for Handling Incorrectly Enrolled or Randomized Participants

Participants who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. 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 randomized or started on study intervention and must be withdrawn from the study.

Where a participant does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the participant from treatment. The AstraZeneca study physician 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

The actual treatment given to participants will be determined by the randomization scheme in the IRT. The randomization scheme will be produced by a computer software program that incorporates a standard procedure for generating randomization numbers. One randomization list will be produced for each of the randomization strata. A blocked randomization will be generated, and all centers will use the same list in order to minimize any imbalance in the number of participants randomized to each treatment group.

Randomization codes will be assigned strictly sequentially (refer to the 3 stratification factors in Section 4.1), as participants become eligible for randomization. When study intervention is provided centrally by AstraZeneca, the IRT will provide the kit identification number to be allocated to the participant at the randomization visit and subsequent treatment visits. If

medication is provided locally, IRT will not provide kit numbers.

6.3.4 Methods for Ensuring Blinding

This is an open-label study for the personnel at study sites; however, the trial will be conducted as "sponsor-blind" and the specific study intervention (Dato-DXd or ICC) to be taken by a participant will be assigned using an IRT. To maintain the integrity of the study, AstraZeneca personnel directly involved in the study conduct will not undertake or have access to efficacy data aggregated by treatment arm prior to final data readout for the primary endpoint. Before the first participant is randomized, a Study Integrity Plan document will be generated, in which data access levels for relevant AstraZeneca personnel will be pre-specified.

6.4 Study Intervention Compliance

When participants are dosed at the study site (applicable to Dato-DXd and ICC agents gemcitabine, eribulin and vinorelbine), 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.

When participants self-administer study intervention(s) at home (as applicable to the ICC agent capecitabine), compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned tablets, as well as by the review of participant completed dosing diaries during the site visits and documented in the source documents and eCRF. A record of the number of capecitabine tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

The Investigational Product Storage Manager is responsible for managing the study intervention from receipt by the study site until the destruction or return of all unused study intervention.

6.5 Concomitant Therapy

Any concomitant treatment, procedure, vaccine, or other medication considered necessary by the investigator for the participant's safety and wellbeing (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 28 (+7) day safety follow-up period following the last dose of study

intervention must be recorded in the eCRF along with:

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

The Study Clinical Lead 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 I 2.

For participants randomized to receive ICC, refer to the local Prescribing Information with regard to warnings, precautions, and contraindications.

Guidance regarding potential interactions with concomitant medications is provided in Appendix I 1.

All concomitant medications administered during the study should be recorded until the end of the safety follow-up period. Concomitant medications administered as treatment for drug-related AESIs should be recorded in eCRF until either event resolution, end of study, trial termination, withdrawal of consent, or subject death.

Drug-drug Interactions

Nonclinical PK studies have indicated that MAAA 1181a (payload: deruxtecan) is primarily metabolized by CYP3A4 and is a substrate for OATP1B1, OATP1B3, MATE2-K, P-gp, BCRP, and MRP1.

No formal drug-drug interaction studies with Dato-DXd have been conducted in humans. Since drug-drug interactions are primarily driven by MAAA-1181a, the drug component of Dato-DXd, a drug-drug interaction study of trastuzumab deruxtecan, which has the same payload, is considered of relevance. Recent results from a clinical drug-drug interaction study of trastuzumab deruxtecan (Study NCT03383692) showed that co-administration of a dual inhibitor of OATP1B/CYP3A, ritonavir, and a strong CYP3A inhibitor, itraconazole, increased MAAA-1181a AUC17d by 22% and 18%, respectively. Therefore, the effect of the CYP3A/OATP1B inhibitors on MAAA-1181a is not considered clinically meaningful and as a

result, concomitant use of CYP3A/OATP1B inhibitors with Dato-DXd is allowed. However, caution must be followed by the investigator in case of concomitant use of Dato-DXd and CYP3A inhibitors, or drugs that inhibit OATP1B1, OATP1B3, MATE2-K, P-gp, BCRP, and MRP1. Patients must be closely monitored in these cases.

Concomitant use of drugs that inhibit MATE2-K, P-gp, BCRP, and MRP1 is allowed, although participants should be closely monitored for adverse reactions. Because the urinary excretion of MAAA-1181a 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 MAAA-1181a. In addition, multiple efflux transporters such as P-gp and BCRP are involved in the excretion of MAAA-1181a; 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.

Concomitant use of drugs that are substrates of OAT1 and OATP1B1 is allowed. Because the exposure of MAAA-1181a is expected to be low with Dato-DXd at doses administered in clinical studies, the inhibition of OAT1 and OATP1B1 by MAAA-1181a 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 ≥14 days is required before restarting study intervention.

Guidance regarding potential interactions with concomitant medications is provided in Appendix I 1.

6.6 Dose Modification

Dosing modification guidelines and TMGs are included in the Annex document to this CSP. Dose delays are permitted for Dato-DXd. Dose reductions are permitted for Dato-DXd. All dose reductions and delays (including any missed doses), and the reasons for the reductions/delays are to be recorded in the eCRF.

Refer to Section 4.3.1for the justification for dose for Dato-DXd.

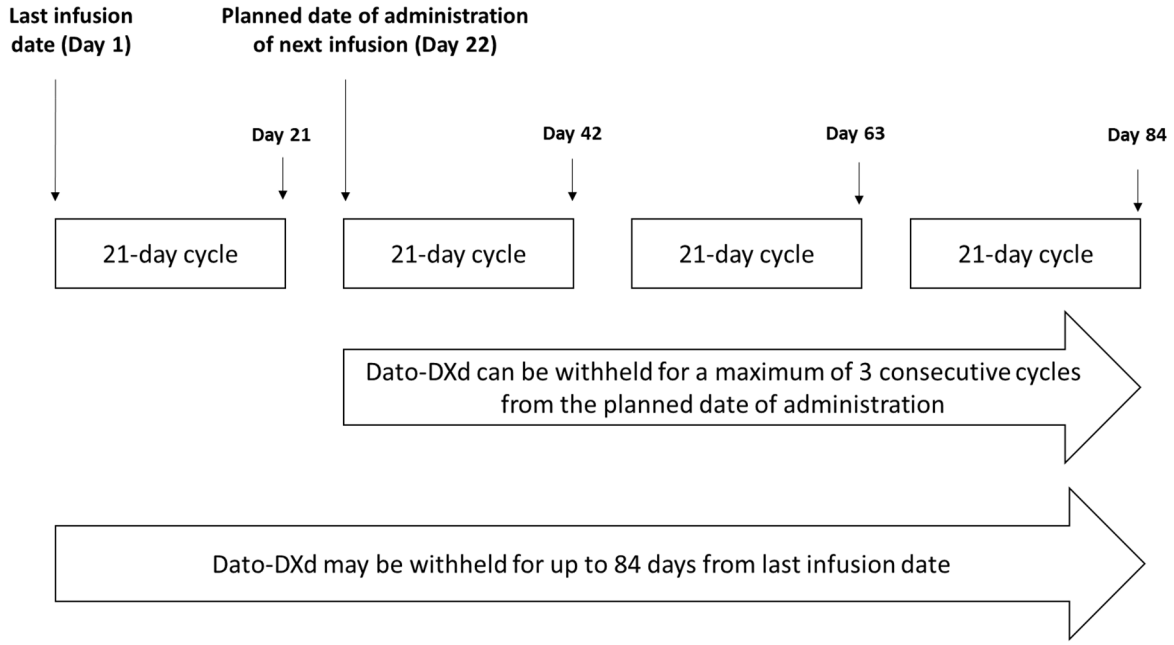
6.6.1 Dose Delays

Dose delays are permitted for Dato-DXd treatment and the dosing interval for the next Dato-DXd cycle may be shortened, as clinically feasible to gradually align with the schedule

of tumor efficacy assessment. Two consecutive doses must be administered at least 19 days apart.

Study treatment dose delay for conditions other than toxicity resolution should be kept as short as possible. A dose can be delayed for up to 3 consecutive cycles (63 days) from the planned date of administration (ie, 84 days from the last infusion date). If a participant is assessed as requiring a dose delay longer than 3 consecutive cycles (ie, > 84 days from last infusion date to the planned date of administration on a Q3W schedule), the subject/participant must discontinue study treatment (see Figure 3).

Figure 3 Dose Delay Schema for Dato-DXd



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.

In the event of a dose interruption occurring prior to completion of PK/pharmacodynamic 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. If a participant cannot restart study treatment within 84 days from the last infusion date for resolution of intercurrent conditions not related to PD or toxicity, the case should be discussed with the Study Clinical Lead.

6.6.3 Dose Reductions

In case a dose reduction is necessary, Dato-DXd will be modified as follows.

Up to 2 dose reductions will be permitted for participants receiving Dato-DXd (see Table 6 for dosing levels). Once the dose of Dato-DXd has been reduced, no dose re-escalation is permitted. After the permitted dose reductions, if further toxicity meeting the requirement for dose reduction occurs, the participant will be withdrawn from the study intervention.

In a rare circumstance, one additional dose reduction may be possible on a case-by-case basis only after discussion and agreement between the Investigator and Sponsor.

Table 6 Dose Reduction Levels of Dato-DXd

Starting Dose (Dose Level 1)	Dose Level -1	Dose Level -2
6.0 mg/kg IV, Q3W	4.0 mg/kg IV, Q3W	3.0 mg/kg IV, Q3W

Investigators should consider dose reductions or discontinuations of Dato-DXd according to the participant's condition and after discussion with the study clinical lead or designee (see the Annex document to this CSP for details of when dose reductions may be required).

Refer to Section 4.3 for the justification of dose for Dato-DXd.

6.6.4 Management of Toxicities

Full TMGs for Dato-DXd are included in the Annex document to this CSP. 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. Please refer to the Annex document to this CSP for the management of drug-induced ILD/pneumonitis.

Specific criteria for 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.

On improvement of an AE for which Dato-DXd was temporarily interrupted, 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 interruption, or if a different AE subsequently requires dose interruption, Dato-DXd may be restarted at a 1 dose level reduction on improvement of the AE or discontinued if the participant is receiving the lowest protocol-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 interrupted or permanently discontinued in accordance with the TMGs and supportive therapy administered as required.

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

For management of toxicities due to ICC, refer to the locally approved Prescribing Information or manage in accordance with institutional guidelines.

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 all participants have discontinued study intervention and completed their last expected visit/contact. No intervention is planned after the end of the study.

After the final DCO for this study, AstraZeneca will continue to supply open-label treatment in the continued access phase of this study and after completion of this study to participants who received Dato-DXd or centrally supplied ICC while, in the opinion of the investigator, the participant is benefiting until PD occurs (as judged by the investigator), or until meeting any other discontinuation criteria as defined in Section 7.1.

Participants should be followed according to the institution's SoC assessments. No further data collection is required, except for reporting of SAEs.

Participants who were randomized to receive other study interventions (ie, locally supplied ICC), or who discontinue from the study, should continue appropriate treatment at the discretion of the investigator.

Where possible, if commercial supply of Dato-DXd is available in the local market then this route should be used. 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 a roll-over or safety extension study is available at the time of the final DCO and database closure, participants currently receiving treatment with Dato-DXd may be transitioned to such a study. The roll-over or extension study would ensure treatment continuation with visit assessments per its protocol, as applicable. Any participant who would

be proposed to move to such a study would be given a new informed consent, as applicable.

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 PFS (if the participant has not progressed according to RECIST 1.1), PFS2, OS, TFST and TSST. 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. All study intervention should be returned by the participant at their next on-site study visit or unscheduled visit.

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

- RECIST 1.1-defined radiological progression (refer to Section 8.1.1 and Appendix F).
- An AE that, in the opinion of the investigator or AstraZeneca, contraindicates further dosing.
- Any AE that meets criteria for discontinuation defined in the TMGs (see the Annex document to this CSP), or as defined in the local Prescribing Information for the ICC agents.
- 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 (refer to Appendix G and Section 8.3.14).
- Initiation of subsequent anticancer therapy, including another investigational agent.

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

Crossover within the study is not permitted.

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 28 (+7) days after their last dose of study intervention. Additional assessments to be performed at the time of the safety follow-up visit are detailed in the SoA (Table 1). For ILD/pneumonitis, safety follow-up will continue until the resolution of ILD/pneumonitis.

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 tumor and survival assessments as indicated in the SoA (Table 1) until one visit after investigator-defined PD according to RECIST 1.1, or death regardless of whether or not the participant started a subsequent anticancer therapy, unless they have withdrawn all consent to study-related assessments.

See the SoA (Table 1) for data to be collected at the time of intervention discontinuation (ie, the end-of-treatment visit) and follow-up and for any further evaluations that need to be completed.

7.1.2 Follow-up of Participants to PFS2

Following objective progression, participants will have their subsequent progression status recorded every 3 months (±14 days) per local standard clinical practice to assess PFS2. Assessments will be performed according to the local practice, and formal RECIST 1.1 measurements will not be collected for assessment of PFS2. See Section 8.1.3 for additional information.

7.1.3 Follow-up for Survival

Participants will be followed up for survival status as indicated in the SoA (Table 1) 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, by contact with the participant's current physician, or local death registries (if allowed by local regulations). Additional assessments to be performed at the time of survival follow-up are detailed in the SoA (Table 1). The study may continue monitoring participants for OS up to the scheduled final analysis, beyond planned interim analyses, to provide more refined estimates of treatment effects for survival.

Telephone calls to assess survival 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 the 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.

7.2 Participant 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, behavioral, 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 of any ongoing AEs and concomitant medications (eg, telephone contact 28 [+7] days 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 EoT visit and a safety follow-up visit should be conducted, as shown in the SoA (Table 1). 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 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 Global Study Team.

7.3 Lost 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 protocol.

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 randomized, including those who did not get study intervention. Public sources may be searched for vital status information. 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 key efficacy endpoints of PFS and OS, the survival status of all participants in the ITT population and the Safety 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 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 summarized in the SoA (Table 1). Data collection following study analysis until the end of the study is described below.

- 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 (Table 1), 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 utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 1).

Data Collection Following Study Analysis until the End of the Study

Following the DCO for the primary PFS efficacy endpoint, assessments for PK will be discontinued. Participants will continue with all other assessments as indicated in the SoA (Table 1).

For SAE reporting and laboratory assessment collection after final analysis, see Section 8.3.12. After the final DCO and database closure, only SAEs will be reported for the purposes of this study (see Section 8.3.12).

8.1 Efficacy Assessments

Efficacy assessments of PFS, ORR, DoR, and DCR will be evaluated based on RECIST 1.1 tumor assessments.

8.1.1 Imaging Tumor Assessments

Tumor assessments use images from CT (preferred) or MRI, with IV contrast, of the chest, abdomen (including the entire liver and both adrenal glands), and pelvis, collected during screening/baseline and at regular (follow-up) intervals during study intervention as defined in the SoA (Table 1).

An MRI (preferred) or CT of the brain will also be collected for all participants at baseline. Follow-up brain scans are subsequently mandatory for all participants randomized with stable brain metastases at baseline, whilst participants without brain metastases do not need additional brain scans for subsequent tumor assessments, unless clinically indicated.

All participants should have a baseline whole body bone scan or skeletal survey. For participants with no bone lesion, a historical bone scan documenting absence of bone lesions

performed no more than 12 weeks before randomization could be provided. For participants with documented bone lesion at baseline, the bone scan must be performed no more than 28 days before randomization. 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 less than 28 days before randomization, it may be utilized as screening scan to document bone disease. Bone lesions identified on bone scan at baseline must be confirmed by CT, MRI, or X-ray to be recorded as NTLs and followed by the same method (CT, MRI, or X-ray), as indicated in the SoA (Table 1).

Any other areas of disease involvement should be additionally imaged at screening based on known metastasis sites or by the signs and symptoms of individual participants.

The imaging modality used for baseline tumor assessment, CT/MRI for chest and abdomen and MRI for brain, should be kept the same consistently at each subsequent follow-up assessment throughout the study if possible. It is important to follow the tumor assessment schedule as closely as possible (refer to the SoA [Table 1]) relative to randomization.

New lesions may also be identified by fluorodeoxyglucose-PET scans, X-ray, bone (scintigraphy) scans. If an unscheduled assessment was performed (eg, to investigate clinical signs/symptoms of progression) and the disease has not progressed, every attempt should be made to perform the subsequent imaging at the next regularly scheduled visit. Digital copies of all scans should be maintained at the site as source documents.

Screening/baseline imaging should be performed no more than 28 days before randomization and ideally should be performed as close as possible to and prior randomization.

Treatment continues until RECIST 1.1-defined radiological progression by Investigator assessment (refer to Appendix F). Following disease progression, 1 additional follow-up scan should be performed as per imaging schedule (ie, either 6 weeks or 9 weeks later). In the event the investigator identified progression does not match with the BICR evaluation, this additional scan may identify progression by BICR.

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 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).

8.1.2 Central Reading of Scans

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed iCRO for quality control, storage, and for BICR. 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. A BICR 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 tumor assessments will not be shared with the central reviewers.

The management of participants will be based upon the results of RECIST 1.1 assessments conducted by the Investigator. After the primary PFS analysis, central review of scans will no longer be required, and investigators will be advised when to stop sending copies of the scans to the iCRO conducting the central review; however, digital copies of all original scans should continue to be stored at the investigator site as source documents.

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

8.1.3 Time to Second Progression or Death

Following objective progression, participants will have their subsequent progression status recorded every 3 months (±14 days) per local standard clinical practice to assess PFS2.

A participant's PFS2 status is defined according to the local practice and may involve any of:

- objective radiological progression (preferred),
- symptomatic progression, or
- death.

Scans will be performed according to the local practice and formal RECIST 1.1 measurements will not be collected for assessment of PFS2. The second progression event must have occurred during or after anticancer treatment with a subsequent treatment after the progression event used for the primary variable PFS or death. The date of PFS2 assessment and investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the source documents and the eCRF.

8.1.4 Overall Survival

Assessments for survival will be conducted every 3 months (±14 days) following objective PD or treatment discontinuation until 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 as described in Section 7.2. The study may continue monitoring participants for OS up to the scheduled final analysis, beyond

planned interim analyses, to provide more refined estimates of treatment effects for survival.

8.1.5 Clinical Outcome Assessments (COA)

A COA is any assessment that may be influenced by human choices, judgment, or motivation and may support either direct or indirect evidence of treatment benefit. COAs can be reported by a participant (PRO), a clinician (ClinRO), an observer (ObsRO), or through a performance-based assessment (FDA-NIH BEST Resource). A COA may be used in clinical studies to provide either direct or indirect evidence of treatment benefit. It is important to examine the impact of therapy on symptoms, function, and other health-related QoL of the participant to aid understanding of the risk-benefit profile.

Patient Reported Outcome (PRO) assessment is one type of COA and is a general term referring to all outcomes and symptoms that are directly reported by the participant. Patient Reported Outcomes have become important in evaluating the efficacy and tolerability of study interventions in clinical studies and will aid in understanding of the benefit/risk evaluation (Kluetz et al 2018).

The following PRO instruments will be administered in this study (see Appendix H):

- EORTC QLQ-C30 (see Section 8.1.5.1)
- EORTC IL116: selected breast and arm symptom scales from EORTC QLQ-BR45/IL (see Section 8.1.5.2)
- Selected items from PRO-CTCAE (see Section 8.1.5.3)
- EORTC IL117: selected symptomatic AE items from EORTC IL (see Section 8.1.5.4)
- PGI-TT (see Section 8.1.5.5)
- PGIS (see Section 8.1.5.6)
- PGIC (see Section 8.1.5.7)
- EQ-5D-5L (see Section 8.1.5.8)

Patient Reported Outcome questionnaires will be administered according to the SoA (Table 1). The PRO questionnaires will be completed by participants if a linguistically validated version is available in their language for the country in which they live.

8.1.5.1 EORTC QLQ-C30

The EORTC QLQ-C30 was developed by the EORTC QoL Group 1993. It consists of 30 item and measures symptoms, functioning, and global health status/QoL (Aaronson et al 1993) for all cancer types. Questions are grouped into 5 multi-item functional scales (physical, role, emotional, cognitive, and social), 3 multi-item symptom scales (fatigue, pain, and nausea/vomiting), a 2-item global QoL scale, 5 single items assessing additional symptoms

commonly reported by cancer participants (dyspnea, loss of appetite, insomnia, constipation, and diarrhea), and 1 item on the financial impact of the disease. The EORTC QLQ-C30 is a valid and reliable PRO instrument in this participant population.

8.1.5.2 EORTC IL116: selected breast and arm symptom scales from EORTC QLQ-BR45/IL

The EORTC QLQ-BR45 is an updated version of the BR23, a validated breast cancer-specific module used in conjunction with the core QLQ-C30 to assess breast cancer-specific HRQoL (Bjelic-Radisic et al 2020; Sprangers et al 1996). New breast cancer treatments and diagnostics prompted the update of the QLQ-BR23 to include an additional 22 items. Items are scored on a 4-point verbal rating scale: “Not at All,” “A Little,” “Quite a Bit,” and “Very Much”. Scores are transformed to a 0 to 100 scale, where higher scores for functioning scales or items indicate better functioning, whereas higher scores for symptom scales or items represent a worse level of symptoms.

The current study will only include the breast symptoms and arm symptoms scales (7 items) from the BR45, ie, EORTC IL116.

8.1.5.3 PRO-CTCAE

The PRO-CTCAE was developed to evaluate symptomatic toxicity in participants in cancer trials. The PRO-CTCAE will only be administered in those countries where a linguistically validated version is available. PRO-CTCAE is an item library of symptoms experienced by participants while undergoing treatment of their cancer. It has been carefully and systematically developed based on the NCI-CTCAE to provide participant-reported assessment of common adverse effects of cancer treatments, including a library of 124 items, representing 78 symptomatic toxicities. The items have previously undergone extensive qualitative and quantitative evaluation to support their validity and reliability (Basch et al 2014, Dueck et al 2015, Hay et al 2014). For each symptomatic AE (eg, headache), there are up to three questions related to key symptom attributes, including the symptom frequency, severity, and interference with daily activities. Each question uses a 7-day recall with a 5-point ordinal response scale.

The items pre-selected for this study include mouth/throat sores, decreased appetite, nausea, vomiting, constipation, diarrhea, abdominal pain, shortness of breath, cough, rash, hair loss, hand-foot syndrome, numbness/tingling, and fatigue. These items are based on a review of the core symptom set from NCI, expected treatment-related symptoms, and in consideration of symptoms that are already captured in the other PRO instruments with a view to minimize participant burden. The free text item in the PRO-CTCAE instrument is not included in the study, as the utility of this information and the analysis method have not been established.

8.1.5.4 EORTC IL117: selected symptomatic AE items from EORTC IL

The EORTC IL is an online platform comprised of more than 900 individual items from over

60 EORTC questionnaires. As the static questionnaires might not always be sufficient to meet the demands of quickly evolving treatment modalities, selecting items from EORTC IL offers new opportunities to leverage existing EORTC items for capturing the additional symptoms that are relevant to a given study.

The pre-selected items for this study will include dry eyes, mouth pain, and sore mouth (ie, EORTC IL117). These items were selected using the same methodologies as described in Section 8.1.5.3 (PRO-CTCAE) to measure additional participant-reported symptomatic AEs which are not captured in the PRO-CTCAE. The recall period is during the past week. Items are scored on a 4-point verbal rating scale: "Not at all", "A little", "Quite a bit", and "Very much".

8.1.5.5 PGI-TT

The PGI-TT item is included to assess how a participant perceives the overall burden of treatment-related side effects of cancer treatment over the past 1 week. Participants will be asked to choose the response that best describes the level of burden by the side effect of their cancer treatment over the past week. The response options are: “not at all”, “a little bit”, “somewhat”, “quite a bit”, and “very much”. This item is included to aid in the interpretation of other PRO measures and to evaluate the overall impact of treatment-related side effects.

8.1.5.6 PGIS

The PGIS item is included to assess how a participant perceives the overall severity of cancer symptoms over the past 1 week. Participants will be asked to choose the response that best describes the severity of their overall cancer symptoms over the past week. The response options are: “none”, “mild”, “moderate”, and “severe”. This item is included to aid in the interpretation of other PRO measures and to evaluate the overall impact of treatment on the global severity of cancer symptoms.

8.1.5.7 PGIC

The PGIC item is included to assess how a participant perceives their overall change in health status since the start of study treatment. This is single-item questionnaire and participants will choose from response options ranging from “Much better” to “Much worse”.

8.1.5.8 EQ-5D-5L

The EQ-5D-5L will be used to explore the impact of treatment and disease state on health state utility.

The EQ-5D-5L, developed by the EuroQoL Group, is a generic questionnaire that provides a simple descriptive profile of health and a single index value for health status for economic appraisal (EuroQol 2019). The EQ-5D-5L questionnaire comprises 6 questions that cover 5 dimensions of health (eg, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Respondents also assess their health today using the EQ-VAS, which

ranges from 0 (worst imaginable health) to 100 (best imaginable health) (see Appendix H).

8.1.5.9 Administration of Electronic PRO (ePRO) Questionnaires

Patient Reported Outcome questionnaires will be self-administered electronically at home by the participants using an application installed on their personal mobile device, or a handheld device (if their personal device is not compatible or preferred) at the time points indicated in the SoA (Table 1). Participants should complete the ePROs prior to or at the sites if the assessment time point coincides with a scheduled site visit. Participants must be instructed to bring their device to all visits.

Each site must allocate the responsibility for the administration of the ePRO instruments to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a back-up person to cover if that individual is absent.

A web back-up may be available to answer the questionnaires if there are technical problems with the device.

Approximately 10 to 20 minutes is required for participants to complete the questionnaires.

The below instructions should be followed when collecting PRO data:

- The research nurse or appointed site staff should explain to participants the value and relevance of these data, so they are motivated to comply with questionnaire completion. Inform the participant that these questions are being asked to find out, directly from them, how they feel.
- Participants must not be onboarded onto the ePRO application (ie, must not have their account set up or invitation email sent) until the actual day of their C1D1 visit. This is required to ensure that the correct C1D1 date is registered in the ePRO system.
- It is vital that the ePRO reporting is initiated prior to dosing or any other study procedure on C1D1, as specified in the SoA (Table 1) to capture the effect of the study intervention. The ePRO device must be charged and fully functional at the beginning of the baseline (ie, C1D1) visit to ensure that the PROs can be completed at the start of the visit.
- The participant should bring their device to each site visit so the research nurse or appointed site staff can check if there are available PRO questionnaire to be completed and that the device is functioning properly.
- Patient Reported Outcome questionnaires completed at the sites must be completed prior to treatment administration or any other study procedures performed at the site and ideally before any discussions of health status (following informed consent), including medication treatments, and before discussion of PD to avoid biasing the participant's responses to the questions. As feasible, site staff should also ensure PRO questionnaires

are completed prior to other study procedures, such as collection of laboratory samples, to further minimize bias.

- On completion of the questionnaire at the site, the device should be handed back to the research nurse or appointed staff, who should check that all questionnaires were completed.
- When each instrument is due to be completed, the following order must be observed (however although the order will be pre-programmed into the ePRO):
  - EORTC QLQ-C30
  - EORTC IL116
  - PRO-CTCAE
  - EORTC IL117
  - PGI-TT
  - PGIS
  - PGIC
  - EQ-5D-5L
- Patient Reported Outcome questionnaires should be completed by the participant in a quiet and private location.
- The participant should be given sufficient time to complete the PRO questionnaires at their own speed.
- The research nurse or appointed site staff should stress that the information is not routinely shared with study staff. Therefore, if the participant has any medical problems, he/she should discuss them with the doctor or research nurse separately from the ePRO assessment.
- The research nurse or appointed site staff must train the participant on how to use the ePRO device/application using the materials and training provided by the ePRO vendor.
- The research nurse or appointed site staff must provide guidance on whom to call if there are problems with the device when the participant is completing the ePRO at home.
- All PRO questionnaires are to be completed using the ePRO application and/or assigned device. If technical or other device-related issues prohibit completion on the device, an appropriate back-up option may be considered with prior approval from AstraZeneca.
- The research nurse or appointed site staff must remind the participant that there are no right or wrong answers and avoid introducing bias by not clarifying items.
- The participant must not receive help from relatives, friends, or clinic staff deciding on answers to the ePRO questionnaires. The responses are the participant's alone.

- If a participant uses visual aids (eg, glasses or contact lenses) for reading and does not have them when he or she attends the site visit, the participant may be exempted from completing the PRO questionnaires at that site visit.
- Site staff must not read or complete the ePRO questionnaires on behalf of the participant. If the participant is unable to read the questionnaire (eg, is blind or illiterate or not fluent in the available language), that participant is exempted from completing PRO questionnaires but may still participate in the study. If the participant cannot complete the PRO questionnaires due to reasons other than being blind, illiterate, or not fluent in an available language, the AstraZeneca study team must be contacted to determine if they can be exempted. Participants exempted in any regard should be flagged appropriately by the site staff in the source documents and in the designated eCRF.
- Questions must not be translated from an available language in the device into the language for the participant speaks.
- Reminders should be provided to participants as needed to ensure compliance with the assessment schedules.
- The research nurse or appointed site staff must monitor compliance since minimizing missing data is a key aspect of the study success.
- Finally, the research nurse or appointed site staff will review the completion status of questionnaires during site visits and document the reason(s) why a participant could not complete assessments, in the source documents and in the designated eCRF. If the site receives an email notification regarding the participant's compliance, appropriate action will be taken (eg, discussion with participant to improve compliance, a check in call from the site to ask the participant if they have any difficulties in completing questionnaires on schedule, etc). A solution to enhance/resolve compliance should be discussed with the participant. Discussion and compliance review should be reflected in source documents.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1).

8.2.1 Physical Examinations

Physical examination, as well as assessment of height and weight, will be performed at the timings specified in the SoA (Table 1); investigators should pay special attention to clinical signs related to previous serious illnesses, as new or worsening abnormalities may qualify as AEs; see Section 8.3.5 for details.

A full physical examination includes assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), oral (mouth), lymph nodes, thyroid, musculoskeletal (including spine and extremities), urogenital, dermatological, gastrointestinal, endocrine, hematologic/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 includes at a minimum, assessments of the skin, lungs, oral, cardiovascular system, and abdomen (liver and spleen).

8.2.2 Vital Signs

Vital signs will be performed at timelines as specified in the SoA (Table 1). Temperature, pulse rate, respiratory rate, pulse oximetry (SpO_2), and blood pressure will be assessed. The participant should remain at the site for at least 1-hour post-infusion for close observation for possible IRRs (for participants receiving Dato-DXd only).

Blood pressure and pulse measurements will be assessed in a supine, semi-recumbent, or seated position with a completely automated device, whenever possible. 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, cell phones).

Vital signs will be evaluated and recorded in eCRF.

Where applicable, blood pressure and pulse rate should be collected prior to the beginning of study intervention infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion]) and at the end of the infusion. These measurements may also be taken more frequently if clinically indicated.

Situations in which vital signs results should be reported as AEs are described in Section 8.3.5.

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

8.2.3 Electrocardiograms

Triplicate 12-lead ECGs will be performed at screening and at the EoT visit. The 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.

Electrocardiograms will be performed at timelines as specified in the SoA (Table 1) after the participant has been resting supine/semi-recumbent for at least 5 minutes and recorded while the participant remains in that position using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals, as possible.

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.

Situations in which ECG results should be reported as AEs are described in Section 8.3.5.

Whenever ECGs, vital signs, and blood draws are scheduled for the same nominal time, ECG assessments should occur first, then vital signs assessments, and then blood draws; the timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in the SoA (Table 1).

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, hematology, coagulation, and urinalysis will be taken at the visits indicated in the SoA (Table 1).

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. Laboratory assessments for off-schedule study drug dosing may be entered in the eCRF as unscheduled visits.

The clinical chemistry, hematology and urinalysis will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample volumes may vary depending on laboratory method used and routine practice at the site.

Other safety laboratory tests include assessment for pregnancy (serum at screening and urine at all other time points), and hepatitis B and C serology, and HIV antibody test.

Pregnancy tests may be performed at the site using a licensed test. A negative result from a serum pregnancy test (which must have a sensitivity of at least 25 mIU/mL) must be available at the screening visit. Pregnancy tests should be conducted within 72 hours prior to randomization for all female participants of childbearing potential. Repeat pregnancy tests (urine beta-human chorionic gonadotropin or serum test per institutional guideline) should be performed 72 hours before infusion of each cycle and at the EoT visit. If a positive urine pregnancy test result is confirmed using a serum test in a female participant of childbearing potential, then the participant should not be treated.

Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

The laboratory variables to be measured are presented in Table 7.

Table 7 Laboratory Safety Variables

Hematology/Haemostasis (Whole Blood)	Clinical Chemistry (Serum or Plasma)
Hemoglobin	Creatinine
White blood cell count	Bilirubin, total
Leukocyte differential count (absolute count and/or %; neutrophils, lymphocytes, monocytes, eosinophils, basophils)	Alkaline phosphatase
	AST
Platelet count	ALT
Hematocrit	Albumin
Red blood cell count	Potassium
Urinalysis	Calcium (total) or Calcium (ionized)
Hemoglobin/Erythrocytes/Blood	Sodium
Protein/Albumin	Lactate dehydrogenase
Glucose	Protein, total
	Urea nitrogen or blood urea nitrogen or urea
	Magnesium
	Chloride

The investigator should assess the available results with regard to clinically relevant abnormalities in documentation. Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 8.3.5.

All participants with Grade 3 or 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 2, unless these values are not likely to improve because of the underlying disease.

NB. If a participant has an AST **or** ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN, refer to Appendix E for further instructions.

8.2.5 Other Safety Assessments

8.2.5.1 Echocardiogram/Multigated Acquisition Scan

An echocardiogram or MUGA scan to assess LVEF will be performed at the visits indicated in SoA (Table 1). The modality of the cardiac function assessments must be consistent for a given participant (ie, if echocardiogram is used for the screening assessment for a given participant, then echocardiogram 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%).

The EoT echocardiogram/MUGA scan is not required unless clinically indicated. If a participant has any clinically significant decrease in LVEF (greater than 10 percentage points to below 50%), there should be follow-up within 4 weeks until resolution.

Situations in which echocardiogram or MUGA results should be reported as AEs are described in Section 8.3.5.

8.2.5.2 Pulmonary Function Tests

Pulse oximetry (SpO_2) should be evaluated by the investigator or the delegate physician at the time points outlined in the SoA and as clinically indicated. The SpO_2 should be measured at the same time as vital signs.

Pulmonary function tests should include basic spirometry at a minimum with optional additional components as mentioned in Table 8.

Table 8 Spirometry Component

Required spirometry components	Optional spirometry components
FVC (L)	PEF
FVC % predicted	DLCO
FEV1 (L)	FEV6
FEV1 % predicted	TLC
FEV1/FVC %	RV

Diffusion capacity of the lungs for carbon monoxide will be performed/encouraged if feasible, but for participants with prior severe and/or prior clinically significant pulmonary disorders, DLCO is a requirement. In event of suspected ILD/pneumonitis, refer to Section 8.2.5.3 additional pulmonary assessments.

8.2.5.3 ILD/Pneumonitis Investigation

For suspected ILD/pneumonitis (ie, if new or worsening pulmonary symptoms [eg, dyspnea, 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 Annex document to this CSP).

Evaluations should include:

- Detailed past medical history (including concomitant medications, ocular history, and previous use of tobacco, e-cigarettes, and/or vaping, etc.)
- Physical examination, including auscultation of lung field

- Arterial blood gases (if clinically indicated)
- Pulmonary function tests (see Section 8.2.5.2) and pulse oximetry (SpO_2)
- Bronchoscopy and bronchoalveolar lavage should be considered if clinically indicated and feasible.
- HRCT of the chest (if feasible, otherwise non-contrast chest CT is acceptable [1 to 2 mm slice thickness recommended]). If both a non-contrast chest HRCT scan for assessment of ILD/pneumonitis and a diagnostic IV contrast enhanced chest CT scan for tumor response assessment (as part of chest-abdomen-pelvis imaging) are to be acquired in the same imaging session, HRCT should be performed first.
- Pulmonologist consultation (infectious disease consultation as clinically indicated)
- Blood culture, complete blood count, and differential white blood cell count; other blood tests could be considered as needed.
- Troponin measurements will be done to rule out cardiac etiology.
- Additional optional blood samples for serum exploratory ILD/pneumonitis biomarker analysis as soon as ILD/pneumonitis is suspected and/or diagnosed (see Section 8.6.1)
- Additional optional blood sample for plasma exploratory ILD/pneumonitis biomarker analysis as soon as ILD/pneumonitis is suspected and/or diagnosed (see Section 8.6.1).

Other tests may be considered, as needed (eg, COVID-19 test).

The results of the full diagnostic workup (including HRCT, blood and sputum culture, hematological parameters, etc) is to be captured in the eCRF. A full diagnostic workup is strongly recommended to exclude alternative causes, such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of ILD/pneumonitis should be considered and the TMGs should be followed (see the Annex document to this CSP).

When ILD/pneumonitis is suspected during study treatment, the following markers should be collected where possible:

- Interstitial lung disease/pneumonitis markers: KL-6, SP-D, and β-D-glucan
- Tumor markers: particular tumor markers that are related to disease progression (carcinoembryonic antigen)
- Additional clinical chemistry: C-reactive protein, lactate dehydrogenase

8.2.5.4 ECOG Performance Status

Eastern Cooperative Oncology Group performance status will be assessed at the times specified in the SoA (Table 1) 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.

8.2.5.5 Ophthalmologic Assessments

Ophthalmologic assessments by a licensed eye care provider, including but not limited to visual acuity testing, fluorescein staining, intraocular pressure, slit-lamp examination, and fundoscopy, will be performed as specified in the SoA (Table 1) by an ophthalmologist, or if unavailable, another licensed eye care provider. This will be done at screening, and then every 3 cycles from C1D1 onwards (eg, C4D1, C7D1, C10D1 etc) within 14 days prior to scheduled cycle Day 1 visit (but not after scheduled visit), in addition to being done as clinically indicated while on trial, and at EoT. 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 ophthalmologic assessments should be entered into the eCRF and copies of all consultation reports should be filed in source notes. Please refer to the Dato-DXd Site Ophthalmologic Assessment Manual for further details.

It should be strongly considered for all participants to avoid the use of contact lenses and to use artificial tears 4 times daily as preventative measure and up to 8 times daily as clinically needed while participating in the trial, starting at C1D1. 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. Data from the ophthalmologic assessments on the first 100 randomized participants (approximately 50 in each arm, Dato-DXd and ICC) will be reviewed by a dedicated Ophthalmologic Data Review Committee (Section 9.6.3). The proposed data cutoff will be after completion of the last ophthalmologic assessment and a minimum of 2 assessments per participant for the first approximately 100 randomized participants. Until data collection has been completed and reviewed on the first approximately 100 participants, ophthalmologic assessments will continue for enrolled participants, and participants should continue to be advised to strongly consider using artificial tears and avoiding use of contact lenses. Data from these ophthalmologic assessments on the first

approximately 100 randomized participants will be reviewed by an Ophthalmologic Data Review Committee (Section 9.6.3). Review of the Ophthalmologic Data Review Committee findings will further inform the ophthalmologic assessment and monitoring plan.

The Dato-DXd Site Ophthalmologic Assessment Manual will be supplied by AZ, which provides assistance to the licensed eye care provider to assess any ocular surface toxicity.

Any significant change from baseline must be reported as an AE (see Section 8.3.5).

8.2.5.6 Oral Care Plan

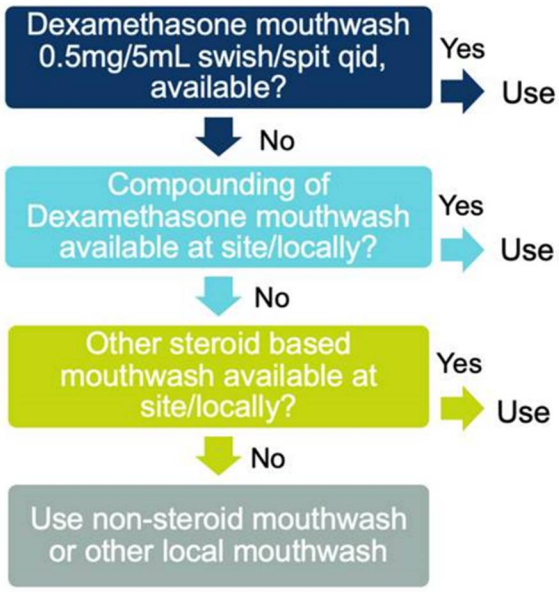
A daily Oral Care Protocol (OCP) will be started before study drug initiation for all randomized participants (both Dato-DXd and ICC arms), and it must be maintained throughout the study as specified in the SoA (Table 1). An oral care kit will be provided at study enrolment and monthly thereafter until the safety FU visit, which will include a toothbrush, toothpaste, dental floss, and an alcohol-free mouthwash, as well as an oral care plan participant information guide will be provided to each randomized participant before study drug initiation.

Participants should adhere to the following guidance:

- Gently brush their teeth after meals and at bedtime using a soft or ultra-soft toothbrush (or swab) and a bland-flavored fluoride-containing toothpaste.
- Floss their teeth every day, if able to do so without pain or causing gingival bleeding.
- For participants receiving ICC, daily use of alcohol-free mouthwash is recommended.
- For participants receiving Dato-DXd:
  Daily use of prophylaxis with a steroid-containing mouthwash (eg, dexamethasone oral solution 0.1 mg/mL 10 mL 4 times daily swish for 1 to 2 minutes then spit out; or a similar mouthwash regimen using an alternative steroid advocated by institutional/local guidelines) is highly recommended.
  - Note: Participants are allowed to take oral nystatin suspension or other topical antifungal agents after the steroid-containing mouthwash according to clinician preference based on institutional/local guidelines.
- In the absence of a prophylactic steroid-containing mouthwash, daily use of inert, bland mouth rinses (eg, with a non-alcoholic and/or bicarbonate-containing mouthwash, 4 to 6 times a day).
  - Prophylactic cryotherapy (ice chips or ice water held in the mouth throughout the infusion) should also be considered.

The algorithm in Figure 4 may be used as a guidance to select an appropriate prophylaxis mouthwash:

Figure 4 Prophylactic Mouthwash Algorithm



As per Investigator judgment, a professional dental evaluation before study drug initiation and dental treatment if indicated, may reduce the risk of local and systemic infections from odontogenic sources.

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

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

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 authorized representative).

Grade ≥ 3 ocular surface toxicity events should be reported in the EDC system within 24 hours of awareness.

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

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events and SAEs (other than ILD/pneumonitis) will be collected from the time of signature of the ICF, throughout the treatment period and including the safety follow-up

period (28 [+7] days) after the discontinuation of study intervention). All ILD/pneumonitis events regardless of severity should be reported beyond the 28 + 7-day 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 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 AE or SAE as applicable.

Collection and reporting of AEs and SAEs after the final DCO is described in Section 8.3.12.

Pre-existing medical conditions that may have been identified by mandatory screening procedures (eg, cataract on baseline ophthalmologic assessment, 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 should be reported by the investigator in eCRF EDC AE page(s) in the clinical study database/paper SAE report form within 24 hours of becoming aware:

- SAEs (see Section 8.3.2).
- All potential ILD/pneumonitis cases, including both serious and non-serious potential ILD/pneumonitis cases (potential ILD/pneumonitis is described by the Event Adjudication Site Manual).
- 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 either at different time points or simultaneously at any time during this study 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. If the participant discontinues study intervention due to liver enzyme abnormalities, the participant will have additional clinical and laboratory evaluations as described in Appendix E in order to determine the nature and severity of the potential liver injury.
- Grade ≥ 3 IRR.
- Grade ≥ 3 ocular surface toxicity events.
- Grade ≥ 2 keratitis events (includes keratitis, punctate keratitis, and ulcerative keratitis).
- Overdose (see Section 8.4).

Additional relevant information regarding the AESIs, regardless of seriousness, is to be collected through targeted questionnaires within the clinical study database (see

Section 8.3.11).

8.3.2 Follow-up of AEs and SAEs

Any AE that is unresolved at the participant's last AE assessment in the study should be 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).
- The date when the AE started and stopped.
- CTCAE grade/changes in CTCAE grade (report only the maximum CTCAE grade for a calendar day).
- 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 hospitalization.
- 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 NCI-CTCAE Version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into

CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.3.3 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 investigational product?"

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 to the CSP.

8.3.4 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.

8.3.5 Adverse Events Based on Examinations and Tests

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

Deterioration as compared with baseline in protocol-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 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 interruption).

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, anemia versus low hemoglobin 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, which 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.

8.3.6 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. A targeted questionnaire in the eCRF needs to be filled out for every case that meets these pre-specified laboratory criteria.

8.3.7 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 metastases or progression of existing metastasis to the primary cancer under study should be considered as PD and not an AE. Events, which are unequivocally due to PD, should not be reported as an AE during the study. Death due to disease progression should be recorded on the Death eCRF.

8.3.8 Disease Under Study

Symptoms of disease under study are those which might be expected to occur as a direct result of breast cancer. Events which are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the study intervention.

8.3.9 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.

8.3.10 Deaths

All deaths that occur during the study intervention period, or within the protocol-defined 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 protocol-defined 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 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.

8.3.11 Adverse Events of Special Interest

Adverse events of special interest are events of scientific and medical interest specific to the further understanding of the Dato-DXd safety profile and require close monitoring and rapid communication by investigators to AstraZeneca. An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF using a recognized medical term or diagnosis that accurately reflects the event. Serious AESIs will be recorded and reported as per Section 8.3.13.

For the Dato-DXd clinical program, based on the available preclinical data, review of the cumulative literature, reported toxicities for drugs with a similar monoclonal antibody and payload of Dato-DXd, and biological plausibility, the following are considered AESIs:

- ILD/pneumonitis
- IRR
- Oral mucositis/stomatitis
- Mucosal inflammation other than oral mucositis/stomatitis
- Ocular surface toxicity

All AESIs, regardless of severity or seriousness, must be followed until either event resolution, end of study, 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.

ILD/pneumonitis

Interstitial lung disease/pneumonitis is considered an important identified risk for Dato-DXd 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 payload as Dato-DXd. Refer to the current IB for a summary of preliminary clinical study data.

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 targeted questionnaire is built within the eCRF to collect relevant additional information for these potential cases regardless of seriousness.

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 dyspnea, cough or fever. For further guidance on the management of suspected ILD/pneumonitis events, refer to Section 8.2.5.3 and the Annex document to this CSP.

If the AE is suspected to be ILD/pneumonitis, treatment with study intervention should be interrupted pending further evaluations. Evaluations should include those outlined in Section 8.2.5.3. If the AE is confirmed to be ILD/pneumonitis, follow the management guidance outlined in the TMGs (see the Annex document to this CSP). All events of ILD/pneumonitis, regardless of severity or seriousness, will be followed until resolution including after Dato-DXd discontinuation. An autopsy in cases of Grade 5 ILD/pneumonitis is encouraged. An independent ILD Adjudication Committee for the Dato-DXd program is responsible for reviewing all cases of potential ILD/pneumonitis. See Section 9.6.2 for further details.

IRR

Infusion-related reaction is an identified risk for Dato-DXd. A Grade 3 IRR was reported and was assessed by an external consultant as anaphylaxis. A targeted questionnaire for ≥ Grade 3 IRR will be available as an eCRF to collect relevant additional information for these potential cases. All grade ≥ 3 events of IRR, regardless of seriousness, must be reported in EDC within 24 hours. Refer to the current IB for a summary of preliminary clinical study data.

Pre-medication is required prior to any dose of Dato-DXd and must include antihistamines and acetaminophen with or without glucocorticoids. If there are any signs or symptoms of a grade 1 or 2 IRR, the infusion of Dato-DXd must be either slowed down or interrupted based on severity of the infusion-related reaction (see Section 6.2.1.2). If the IRR is grade 3 or 4, or if there are any signs of anaphylaxis, the infusion of Dato-DXd must be discontinued. Please refer to the IRR management guidance outlined in the TMGs (see the Annex document to this CSP).

Oral Mucositis/Stomatitis

Oral mucositis/stomatitis AEs are considered as identified risks and AESIs associated with Dato-DXd treatment. Oral mucositis/stomatitis is considered as a separate AESI from mucosal inflammation other than oral mucositis/stomatitis. Recommendations for preventing and treating oral mucositis/stomatitis are outlined in the SoA (Table 1), Section 8.2.5.6, and the TMGs (see the Annex document to this CSP).

Mucosal Inflammation other than Oral Mucositis/Stomatitis

Mucosal inflammation AEs are considered as identified risks associated with Dato-DXd treatment and as a separate AESI from oral mucositis/stomatitis.

Ocular Surface Toxicity

Ocular surface toxicity (eg, dry eye, keratitis) is considered an AESI associated with Dato-DXd. Dry eye is considered as an identified risk and keratitis as a potential risk within this AESI. Participants are advised to use artificial tears daily and to avoid contact lenses. Recommendations for preventing and treating ocular surface toxicity are available in the SoA (Table 1), Section 8.2.5.5 and the TMGs (see the Annex document to this CSP).

The Dato-DXd Site Ophthalmologic Assessment Manual will be supplied by AstraZeneca to provide assistance to the licensed eye care provider to assess any ocular surface toxicity.

8.3.12 Safety Data to be Collected Following the Final Data Cutoff of the Study

For participants continuing to receive study intervention after the final DCO, AEs and SAEs will be collected, but only SAEs will be reported. In addition, it is recommended that investigators monitor all participant's safety laboratory results periodically during treatment with study intervention in order to manage AEs, consistent with the TMGs (see the Annex document to this CSP). 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 study intervention (or within the 28 [+7] days following the last dose of study intervention) after the final DCO must be

reported as detailed in Section 8.3.13.

8.3.13 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. For further guidance on the definition of an SAE, see Appendix B.

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 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 1 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 1 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.

The reference document for definition of expectedness is the IB for Dato-DXd, and respective EU SmPCs for the active comparator products.

8.3.14 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.

Female participants must not donate, or retrieve for their own use, ova from the time of Screening and throughout the study treatment period, and for at least 7 months after the final study drug administration.

8.3.14.1 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 female 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 abnormalities/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 during the course of the study, the investigator or other site personnel must inform the appropriate AstraZeneca representatives within 1 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 1 or 5 calendar days for SAEs (see Section 8.3.13) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

8.3.14.2 Paternal Exposure

Non-sterilized male participants who intend to be sexually active with a female partner of childbearing potential 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 study intervention.

Participants in the ICC (capecitabine, eribulin, vinorelbine or gemcitabine) arm should follow the local Prescribing Information relating to contraception, the time limits for such precautions, and any additional restrictions for ICC agents.

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 7 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 local 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.

8.3.15 Medication Error, Drug Abuse, and Drug Misuse

8.3.15.1.1 Timelines

If an event of medication error, drug abuse **or** drug misuse occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar 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 **1** (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 medication error (see Section 8.3.13) and **within 30 days** for all other medication errors.

8.3.15.2 Medication Error

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

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

8.3.15.3 Drug Abuse

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

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

8.3.15.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP/study intervention or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs/study intervention(s) or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

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

8.3.16 Medical Device Deficiencies

This section is not applicable.

8.4 Overdose

The use of Dato-DXd in doses exceeding that specified in the protocol 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. An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules 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 1 or 5 calendar days for overdoses associated with an SAE (see Section 8.3.13) and within 30 days for all other overdoses.

For participants receiving ICC (capecitabine, eribulin, vinorelbine or gemcitabine), refer to the local Prescribing Information for treatment of cases of overdose. If any overdose is associated with an AE or SAE, record the AE/SAE diagnosis or symptoms in the relevant AE modules only of the eCRF.

8.5 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 may be stored for a maximum of 15 years from the end of the study (as defined in the Section 4.4) in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier).

  - Samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
  - Samples collected in mainland China will be stored and disposed of according to local laws and regulations. PK samples collected in mainland China will be destroyed after finalization of Bioanalytical Report or completion of CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 5 years from the CSR publication. ADA samples collected in China will be disposed of within 1 year of CSR publication. Additional use includes, but is not limited to, further characterization of any ADAs, evaluation of novel and emerging biomarkers, confirmation and/or requalification of the assay, and/or diagnostic assay development. The results from future analysis will not be reported in the CSR.

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

8.5.1 Pharmacokinetics

Whole blood samples will be collected for participants receiving Dato-DXd treatment for measurement of plasma concentrations of Dato-DXd, total anti-TROP2 antibody, and MAAA-1181a, per the schedule specified in the SoA (Table 1). The actual date and time (24-hour clock time) of each sample should be recorded.

Samples may also be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor (eg, for safety reasons). The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

8.5.1.1 Determination of Drug Concentration

Samples for determination of Dato-DXd, total anti-TROP2 antibody, and MAAA-1181a 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.

8.5.2 Immunogenicity Assessments

Whole blood samples for determination of ADA for Dato-DXd in plasma will be collected from participants receiving Dato-DXd per the schedule specified in the SoA (Table 1). The

ADA samples may also be further tested for characterization of the ADA response. The ADA titer, and the presence of neutralizing ADA will be tested for positive ADA samples.

Samples will be 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.

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

Participant consent to the study includes participation in the mandatory biomarker assessment components of the study.

Samples for biomarker assessment are required and will be collected from all participants in this study as specified in the SoA (Table 1). In mainland China, tumor sample collection and tests will follow local regulatory requirements.

The following mandatory samples will be collected from all randomized participants:

Tumor tissue

Tumor samples are mandatory for all participants in this study and must be available at the time of screening. This can be from either the primary disease setting (surgical resection or diagnostic sample), or from a metastatic lesion (excluding bone). The mandatory FFPE tumor sample submitted for analysis should be obtained as close to the time of diagnosis of metastatic or inoperable disease as possible.

If neither an adequate FFPE block nor the minimum of 20 slides are available, a patient may still be considered eligible. In this situation, approval by the Global Study Team for patient's entry into the study is required.

If a block is not available, a minimum of 20 slides of freshly prepared, unstained, 4 to 5-micron sections from the archival tumor block. As uncontrolled oxidation processes affect tumor sections, tumor tissue blocks are preferred.

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

In mainland China, tumor sample collection and testing will follow local regulatory approval.

Samples may be tested for biomarkers including (but not limited to) TROP2 protein and gene

expression, TROP2-interacting proteins and TOPO-1 expression, and tumor mutational profile to evaluate their association with the observed clinical responses to Dato-DXd (including but not limited to PFS and OS, as well as key safety endpoints).

Based on availability of tissue, further additional exploratory biomarkers may be evaluated, which may include (but are not limited to), cell death and immunological biomarkers such as PD-L1 expression and tumor infiltrating lymphocyte, and gene-expression based tumor subtyping.

Blood-borne Biomarkers

- Blood samples to perform exploratory circulating biomarker, safety or clinical analyses on plasma and serum to identify candidate factors that may correlate with drug response, likelihood of clinical benefit and tolerability.

  These analyses may include, but are not limited to, cytokines and chemokines, to assess a range of oncology, immunological and safety biomarkers, the detection of the presence of viruses. Plasma may also be used for the detection/quantification of autoantibodies (against tumor-associated antigens).
- Blood sample for the isolation of plasma and buffy coat to enable analysis and interpretation of ctDNA, to characterize changes in mutational profile (single nucleotide variant and copy number alteration) and allele frequency, between baseline and on-treatment as a predictive marker for clinical outcomes as exploratory endpoints.

  The buffy coat layer obtained during the plasma isolation process of the baseline sample will be taken, to enable assessment, analysis and interpretation of ctDNA:
  - ctDNA samples will be analyzed for predictive biomarkers of response to treatment. The sample is requested prior to treatment in order to maximize the probability of detecting ctDNA where the tumor burden is relatively high.
  - ctDNA samples taken during treatment and a final sample taken at disease progression will be used for additional exploratory research which may include but is not limited to interrogation of changes in genetic alterations, ctDNA levels as well as the dynamics changes of the biomarkers on treatment and potential mechanisms of resistance to treatment.
- Whole blood sample for RNA and DNA to conduct gene expression and mutational analyses to understand immunological changes following treatment with Dato-DXd and to assess gene signatures that may predict treatment response.

These samples will be taken at multiple timepoints and analyzed for a range of oncology and immunological biomarkers that may correlate with drug response. These biomarkers may include but are not limited to T-cell receptor repertoire analysis and analysis of gene expression biomarkers associated with immunomodulatory effects.

Samples may be retained in all regions to allow for potential diagnostic development, while mainland China sample usage will still follow local regulatory approval.

Test residual tumor samples collected for TROP2 IHC testing from Chinese participants will be destroyed or repatriated within 1 year after CSR completion.

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

8.6.2 Collection of Optional Biomarker Samples

Collection of optional samples for biomarker assessment is also part of this study (as specified in the SoA; Table 1) and is subject to agreement to optional consent. Collection of some optional samples will be mandated at select sites.

Note: Optional biomarker samples will not be collected in mainland China.

Optional tumor tissue samples for exploratory biomarker research

- *Paired tumor biopsy*: A baseline biopsy will be taken (where the participant has provided informed consent) before initial dosing of study intervention (at screening or pre-dose on C1D1), and a paired (second) biopsy will be taken on-treatment. The paired on-treatment biopsy can be collected C2D1 and C2D7. On-treatment sample may also be collected outside of this specified timepoint with prior agreement from the Sponsor. Paired pre-treatment and on-treatment tumor samples must be obtained from the same lesion where clinically feasible to maximize the utility for assessment of pharmacodynamic changes. These optional paired tumor samples will be mandatory at select sites.
- *Tumor biopsy on disease progression:* An additional tumor biopsy sample should be obtained at termination of treatment/documented RECIST 1.1 disease progression in participants that have signed the additional optional consent. These samples will be used to explore mechanisms of resistance. The on-study provision of tumor tissue is encouraged only if clinically appropriate and not considered detrimental to participant care.

Biopsies at study entry, on treatment, and progression are optional for the majority of participants in this study, and participants will not be excluded from the study if these samples are not collected. These optional biopsy samples will be mandatory at select sites.

ILD related samples

Participants will sign an informed consent for optional tissue samples to be taken in the event of suspected or diagnosed ILD.

Additional optional blood samples (serum and plasma) will be collected for exploratory biomarker analysis as soon as ILD/pneumonitis is suspected and/or diagnosed, if feasible (see Section 8.2.5.3).

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

8.6.3 Other Study Related Biomarker Assessments

Already collected samples may be analyzed on different biomarkers thought to play a role in efficacy and safety outcomes including, but not limited to, serum analytes, or tissue biomarkers and/or specific candidate genes/genome-wide analysis for RNA, to evaluate their association with observed clinical responses to Dato-DXd. The presence of viruses may also be investigated.

Additional exploratory analyses may be undertaken on participants' samples to identify other biomarkers of sensitivity and resistance to study interventions and our understanding of cancer. These studies would extend the search for other potential biomarkers relevant to the effects of Dato-DXd, cancer and/or the response/resistance to the study intervention. This may include the development of ways to detect, monitor or treat cancer. These additional investigations would be dependent upon clinical outcome, reagent, and sample availability.

Samples collected in China will not be used for additional exploratory biomarker analyses beyond initial TROP2 IHC testing.

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

8.7 Optional Genomics Initiative Sample

Collection of optional samples for genomics initiative research is also part of this study as specified in the SoA (Table 1) and is subject to agreement in the ICF addendum. Samples will be collected according to local regulatory approval.

Blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

See Appendix D for information regarding the storage and destruction of Genomics Initiative genetic sample. Details on processes for collection, shipment and destruction of these samples can be found in the Laboratory Manual.

Note: These samples will not be collected in mainland China.

8.8 Medical Resource Utilization and Health Economics

Health care resource use data associated with medical encounters, will be collected in the eCRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The assessment of health care resource use will increase the understanding regarding the relationship between treatment and tumor-related cancer symptoms on resource use. This will be captured and analyzed to inform submissions to payers.

The HOSPAD eCRF module will be used to collect information on key health care resource use beyond study mandated visits. To investigate the impact of treatment and disease on health care resource use and to conduct exploratory economic analyses, the following variables will be captured:

- Planned and unplanned hospital attendances beyond trial protocol-mandated visits (including inpatient or outpatient physician visits, emergency room visits, surgeries, day cases and admissions)
- Primary sign or symptom the participant presents with
- Length of hospital stay
- Length of any time spent in an intensive care unit
- Number and type of diagnostic and therapeutic tests and procedures
- Any other medical encounters and interventions (including physician or emergency room visits, tests and procedures, and medications).

9 STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by AstraZeneca or its representatives.

A comprehensive SAP will be prepared prior to 3 months post-FSI, with final amendments completed prior to database lock.

9.1 Statistical Hypotheses

The hypotheses of interest with regards to the efficacy for the dual primary endpoints are:

- H0: No differences between Dato-DXd and ICC for PFS and OS.
- H1: Differences between Dato-DXd and ICC for PFS and/or OS.

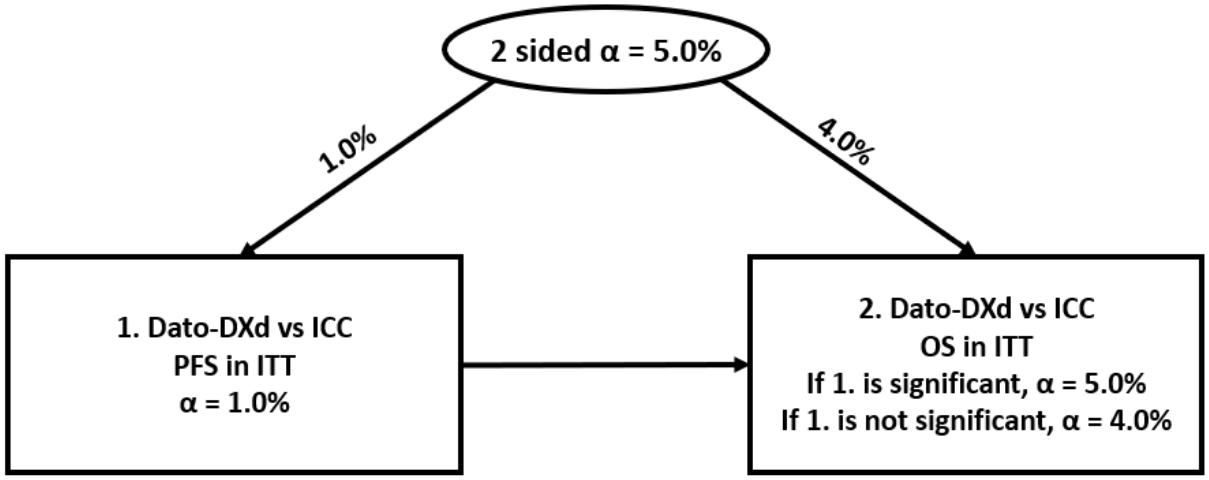
The MTP will define which significance levels should be applied to the interpretation of the raw p-values for the dual primary endpoints of PFS and OS. Hypotheses will be tested using a MTP with an alpha-exhaustive recycling strategy (Burman et al 2009).

To strongly control the familywise type I error rate at the 5.0% level (2-sided), an alpha level of 1.0% will be allocated to the PFS dual primary analysis and the remaining 4.0% alpha level will be allocated to the OS analyses. If the PFS dual primary analysis crosses the efficacy threshold, the 1.0% type I error allocated to the PFS endpoint will be reallocated (Burman et al 2009) to the OS endpoint for a total 2-sided type I error of 5.0%.

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

To preserve the overall type I error (familywise error rate) in the strong sense, an MTP including the dual primary endpoints will be implemented. The MTP will be fully specified in the SAP. The MTP for the dual primary endpoints is described in Figure 5.

Figure 5 Multiple Testing Procedure



9.2 Sample Size Determination

Approximately 1000 participants will be enrolled to achieve approximately 700 participants randomly assigned to study intervention.

Note: "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. Potential participants who are screened for the purpose of determining eligibility for the study but are not randomly assigned/assigned in the study, are considered "screen failures", unless otherwise specified by the protocol.

The study is sized for dual primary endpoints to characterize the PFS and OS benefit of Dato-DXd versus ICC in the participants with HR-positive, HER2-negative breast cancer who

have been treated with one or two prior lines of systemic chemotherapy in the inoperable/metastatic setting. The study will be considered positive (a success) if either the PFS analysis results and/or the OS analysis results are statistically significant.

The primary, final analysis of PFS will be performed when approximately 419 PFS BICR events occur, approximately 2 months after the last participant is randomized in the study; 419 PFS BICR events from the ITT population across the Dato-DXd and ICC treatment groups will represent 60% maturity of data. Assuming the true PFS hazard ratio is 0.55 for Dato-DXd versus ICC, the study will have a greater than 99% power to demonstrate statistical significance at the 1.0% level (using a 2-sided test). This assumes median PFS times of 4.7 months and 8.5 months in ICC and Dato-DXd, respectively when the PFS times are exponentially distributed. The smallest treatment difference that could be statistically significant at the final analysis is a hazard ratio of 0.775.

The final analysis of OS will be performed when approximately 444 OS events have occurred across the Dato-DXd and ICC treatment groups (63% maturity). Assuming the true OS hazard ratio is 0.75 for Dato-DXd versus ICC, the study will have 85% power to demonstrate statistical significance at the 5.0% level (using a 2-sided test). This assumes the PFS primary analysis crosses the efficacy threshold, and allowing 2 interim analyses to be conducted at information fractions of approximately 40% and 80% of the target events, respectively (per the O'Brien and Fleming approach [Lan and DeMets 1983]). The smallest treatment difference that could be statistically significant at the final analysis is a hazard ratio of 0.824. If the PFS primary analysis does not cross the efficacy threshold, the OS analysis will have 83% power to demonstrate statistical significance at the 4.0% level (using a 2-sided test). The smallest treatment difference that could be statistically significant at the final analysis is a hazard ratio of 0.817. Calculations assume median OS times of 19.0 months and 25.3 months in ICC and Dato-DXd, respectively when the survival times are exponentially distributed. The study may continue monitoring participants for OS up to the scheduled final analysis, beyond planned interim analyses, to provide more refined estimates of treatment effects for survival. Further details of the interim analyses are presented in Section 9.5.

A nonuniform accrual of participants (with k = 1.5) is assumed when estimating the analysis times. The total proportion of participants randomized at time t [t ≤ 19 months] following the start of the study is assumed to be $(t/19)^k$.

Dual Primary Endpoints

- ***Dato-DXd versus ICC (PFS in the ITT):***

  Assuming the true PFS treatment effect under the alternative hypothesis is a hazard ratio of 0.55 for Dato-DXd versus ICC, and the median PFS in ICC is 4.7 months, 419 PFS events from the ITT population (60% maturity) will provide greater than 99% power to demonstrate statistical significance at the 2-sided alpha level of 1.0%. The smallest

treatment difference that is statistically significant will be a hazard ratio of 0.775. Assuming a recruitment period of 19 months, this analysis is anticipated to be 21 months after the first participant has been randomized.

- ***Dato-DXd versus ICC (OS in the ITT):***

  Assuming the true OS treatment effect under the alternative hypothesis is a hazard ratio of 0.75 for Dato-DXd versus ICC, and the median OS in ICC is 19.0 months, 444 OS events from the ITT population (63% maturity) will provide approximately 83% power to demonstrate statistical significance at the 2-sided alpha level of 4.0%. The smallest treatment difference that is statistically significant will be a hazard ratio of 0.817. If the PFS dual primary analysis crosses the efficacy threshold, OS will be tested at the 2-sided alpha level of 5.0% and the analysis will have 85% power to demonstrate statistical significance. The smallest treatment difference that is statistically significant will be a hazard ratio of 0.824. With a recruitment period of approximately 19 months it is anticipated that the primary/final OS analysis will occur approximately 44 months after the first participant has been randomized.

9.3 Populations for Analyses

The populations for analysis are defined in Table 9.

Table 9 Populations for Analysis

Population/Analysis Set	Description
Enrolled	All participants who sign the ICF.
Intent-to-treat (ITT) population	All participants who are randomized in the study, excluding participants randomized in mainland China after the global cohort last participant randomized, if applicable. The ITT will be used for all the efficacy analyses (including PROs: EORTC QLQ-C30, EORTC IL116, EQ-5D-5L, PGIS, PGIC). Treatment groups will be compared on the basis of randomized study intervention, regardless of the intervention actually received. Participants who were randomized but did not subsequently receive study intervention are included in the analysis in the intervention group to which they were randomized.

Table 9 Populations for Analysis

Population/Analysis Set	Description
Safety Analysis Set (SAS)	Participants in the ITT who have received at least 1 dose of study intervention. Safety data will not be formally analyzed but summarized using the SAS according to actual study intervention received (including PROs: PGI-TT, PRO-CTCAE, EORTC IL117).
Ophthalmologic Analysis Set (OAS)	Approximately the first 100 randomized participants (approximately 50 per arm, Dato-DXd and ICC) in the ITT. See section 8.2.5.5 for details.
Pharmacokinetic Analysis Set (PAS)	All participants in the ITT randomly assigned to study intervention who received at least 1 dose of study intervention for whom any post-dose PK data are available and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses. The population will be defined by the sponsor Study Physician, Pharmacokineticist, and Statistician prior to any analyses being performed.

9.4 Statistical Analyses

The SAP will be finalized prior to 3 months post-FSI of the first randomized participant, and 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 key secondary endpoints.

9.4.1 General Considerations

More detail will be provided in the SAP.

9.4.2 Efficacy

9.4.2.1 Primary Endpoints

Table 10 Pre-planned Statistical and Sensitivity Analyses to be Conducted for Primary Endpoints

Endpoints analyzed	Notes
Progression-free survival	Stratified log-rank test for: Dual primary analysis using BICR RECIST 1.1 assessments: • Dato-DXd versus ICC (ITT population) Secondary analysis using Investigator assessment: • Dato-DXd versus ICC (ITT population) Sensitivity analysis for the PFS dual primary analysis (ITT population): • Evaluation-time bias • Attrition bias • Ascertainment bias • Subsequent anticancer therapy

Table 10 Pre-planned Statistical and Sensitivity Analyses to be Conducted for Primary Endpoints

Endpoints analyzed	Notes
Overall survival	Stratified log-rank test for: Dual primary analysis: • Dato-DXd versus ICC (ITT population)

9.4.2.1.1 Calculation or Derivation of Tumor Response Variables

Investigator RECIST 1.1-based assessments

All RECIST 1.1 assessments, whether scheduled or unscheduled, will be included in the calculations. This is also 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 the 28 days prior to randomization. The tumor response endpoints (PFS, ORR, DoR, and DCR) will then be derived from the scan dates and overall visit responses.

BICR

A BICR of radiological scans will be performed on all participants to confirm the robustness of the investigator-assessed PFS, ORR, and DoR endpoints.

All images will be collected centrally, until PFS analysis. Additionally, following RECIST 1.1-defined radiological progression by Investigator assessment, 1 additional follow-up scan should be performed as per imaging schedule (ie, either 6 weeks or 9 weeks later). This scan will be used in the PFS dual primary endpoint analysis.

The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and will be adjudicated, if required. For each participant, the BICR 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 tumor 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 (PFS, ORR, DoR, and DCR) will then be derived from the scan dates and overall visit responses.

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

9.4.2.1.2 Progression-Free Survival

Progression-free survival will be defined as the time from the date of randomization until the

date of objective PD per RECIST 1.1 (as assessed by BICR) or death (by any cause in the absence of progression), (ie, date of event or censoring – date of randomization + 1). The comparison will include all randomized participants, as randomized, regardless of whether the participant withdraws from randomized therapy, receives another anticancer 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 visits or does not have baseline data, they will be censored at the date of randomization, unless they die within 2 scheduled scans of baseline (12 weeks [+1 week] allowing for a late assessment within the visit window).

Analysis Methods

The dual primary endpoint of PFS will be based on the BICR assessment of PD by RECIST 1.1.

Progression-free survival will be analyzed using a log-rank test stratified by number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor. The hazard ratio together with its 95% CI and p-value will be presented (a hazard ratio less than 1 will favor the comparator arm). The hazard ratio and CI will be estimated from a stratified Cox proportional hazards model (with ties = Efron), and the CI will be calculated using a profile likelihood approach.

The stratification variables will be defined according to data from the IRT. If the number of events in an individual stratum are too small for a meaningful analysis, then a method will be applied that will remove stratification factors until there are meaningful number of events per strata. Details will be presented in the SAP.

Kaplan-Meier plots of PFS will be presented by treatment group. 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 primary and final analysis of PFS will be performed approximately 2 months after the last participant is randomized in the study; approximately 419 PFS BICR events across the Dato-DXd and ICC treatment groups (60% maturity) are anticipated at that time.

9.4.2.1.3 PFS Sensitivity Analyses

Details of these analyses will be presented in the SAP.

Evaluation-time Bias

A sensitivity analysis will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled time points. The midpoint between the time of progression and the previous evaluable RECIST assessment (using the final date of the assessment) will be analyzed using a stratified log-rank test, as described for the primary analysis of PFS.

Attrition Bias

Attrition bias will be assessed by repeating the PFS analysis except that the actual PFS event times, rather than the censored times, of participants who progressed or died in the absence of progression immediately following two, or more, non-evaluable tumor assessments will be included. In addition, and within the same sensitivity analysis, participants who take subsequent therapy (note that for this analysis radiotherapy is not considered a subsequent anticancer therapy) prior to their last evaluable RECIST assessment or progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy. This analysis will be supported by a Kaplan-Meier plot of the time to censoring using the PFS data from the primary analysis and where the censoring indicator of the PFS analysis is reversed.

Ascertainment bias

Ascertainment bias will be assessed by analyzing the site Investigator data which is a secondary efficacy variable (analysis methods presented in Section 9.4.2.2.3).

If there is an important discrepancy between the primary analysis using the BICR assessments and the secondary analysis using investigator assessments, the proportion of participants with site but no central confirmation of progression will be summarized; such participants have the potential to introduce bias in the central review due to informative censoring. An approach that imputes an event at the next visit in the central review analysis may help inform the most likely hazard ratio value, but only if an important discrepancy exists.

Subsequent Anticancer Therapy

PFS may be impacted for participants who are treated with a subsequent anticancer therapy. Therefore, an analysis will be performed censoring a participant at the last available tumor assessment prior to taking subsequent anticancer therapy.

Additional sensitivity analyses may be defined in the SAP.

9.4.2.1.4 Overall Survival

Overall survival is defined as the time from the date of randomization until death due to any cause. The comparison will include all randomized participants, as randomized, regardless of whether the participant withdraws from randomized therapy or receives another anticancer

therapy (ie, date of death or censoring – date of randomization + 1). Any participant not known to have died at the time of analysis will be censored based on the last recorded date on which the participant was known to be alive.

Note: Survival calls will be made following the date of DCO for the analysis (these contacts should generally occur within 7 days of the DCO). 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

Overall survival will be analyzed using the same methodology specified for PFS. The effect of Dato-DXd versus ICC will be estimated by the hazard ratio together with its corresponding CI and p-value. Kaplan-Meier plots will be presented by treatment group.

The study may continue monitoring participants for OS up to the scheduled final analysis, beyond planned interim analyses, to provide more refined estimates of treatment effects for survival.

9.4.2.1.5 Subgroup Analysis

Subgroup analyses will be conducted, comparing PFS (per RECIST 1.1 using BICR assessments) and OS between Dato-DXd and ICC in the following subgroups of the ITT (but not limited to):

- Number of previous lines of chemotherapy (1 versus 2)
- Geographic region (Region 1 [US, Canada, Europe] versus Region 2 [Rest of World])
- Prior use of CDK4/6 inhibitor (Yes versus No)
- Prior use of taxanes and/or anthracyclines (taxanes alone, anthracyclines alone, both taxanes and anthracyclines, neither taxanes nor anthracyclines)
- Age at randomization (< 65 versus ≥ 65 years of age)
- Race (Asian versus non-Asian)
- Pre-selected choice of chemotherapy (Capecitabine, Gemcitabine, Eribulin mesylate, or Vinorelbine)
- Brain metastases (Yes versus No)

Other baseline variables may also be assessed if there is clinical justification, or an imbalance is observed between the treatment groups. The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic and/or predictive factors.

A forest plot of the PFS hazard ratios (along with the 95% CIs) will be produced for each level of the subgroups listed above.

The subgroup analyses for the stratification factors will be based on the values entered into the IRT; all other factors will be based on values recorded on the eCRF, or from the third-party vendor data.

Additional subgroups of interest and analysis methods will be outlined in the SAP.

Unless there is a marked difference between the results of the statistical analyses of the PFS from the BICR data and that of the site Investigator tumor data, these subgroup analyses will only be performed on the PFS endpoint using the BICR data.

9.4.2.2 Secondary Endpoint(s)

9.4.2.2.1 Objective Response Rate

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

The analysis will include all randomized participants as randomized, with measurable disease at baseline. Data obtained from randomization up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR, regardless of whether the participant withdraws from therapy. Participants who go off treatment without a response or progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR.

Analysis Methods

The ORR will be compared between the treatment arms using a logistic regression model adjusting for the same stratification factors as the PFS as covariates in the model. The results of the analysis will be presented in terms of an adjusted odds ratio (OR) together with its associated 95% CI and p-value. If there are not enough responses for a meaningful analysis using logistic regression, then a CMH test is presented. The CMH test is stratified using the same stratification factors as PFS. The results of the analysis are presented in terms of an OR together with the 95% CI and p-value. Further details will be presented in the SAP. Comparisons between treatment groups will be made using both BICR RECIST 1.1 and investigator assessments.

Summaries will be produced that present the number and percentage of participants with a tumor response (CR/PR). For each treatment arm, BoR will be summarized by n (%) for each category (CR, PR, SD, PD, and NE).

Best objective response (BoR) is calculated based on the overall visit responses from each RECIST assessment. It is the best response a participant has had following randomization, but prior to starting any subsequent cancer therapy and up to and including RECIST progression or the last evaluable assessment in the absence of RECIST progression. Categorization of BoR will be based on RECIST using the following response categories: CR, PR, SD, PD, and NE.

Best objective response will be determined programmatically based on RECIST from the overall visit response using all BICR data up until the first progression event. It will also be determined programmatically based on RECIST using all site investigator data up until the first progression event. The denominators for each case will be consistent with those used in the ORR analysis.

9.4.2.2.2 Duration of Response

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

The analysis will include all randomized participants as randomized who have a confirmed response, regardless of whether the participant withdraws from therapy, receives another anticancer therapy or clinically progresses prior to RECIST 1.1 progression.

Analysis Methods

Duration of response will be analyzed by summary statistics and Kaplan-Meier plots. Comparisons will be presented for both BICR RECIST 1.1 and investigator assessments.

9.4.2.2.3 Progression-Free Survival by Investigator assessment

PFS by Investigator assessment will be defined as the time from the date of randomization until the date of PD per RECIST 1.1 (by Investigator assessment) or death (by any cause in the absence of progression), (ie, date of event or censoring – date of randomization + 1). The analysis will include all randomized participants as randomized regardless of whether the participant withdraws from therapy, receives another anticancer therapy, or clinically progresses prior to RECIST 1.1. However, if the participant progresses or dies immediately after two or more consecutive missed visits, the participant will be censored at the time of the latest evaluable assessment prior to the two missed visits.

Analysis Methods

This secondary endpoint of PFS based Investigator assessment will be analyzed using the same methodology described in Section 9.4.2.1.2.

9.4.2.2.4 Disease control rate

Disease control rate at 12 weeks is defined as the percentage of participants who have a confirmed CR or PR or who have SD, per RECIST 1.1, as assessed BICR/per investigator assessment and derived from the raw tumor data for at least 11 weeks after randomization.

The analysis will include all randomized participants as randomized. Data obtained from randomization up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of DCR, regardless of whether the participant withdraws from therapy. Participants who receive a subsequent therapy prior to week 11 will

not be considered to have disease control in the analysis.

Analysis Methods

Disease control rate will be analyzed using the same methodology specified for ORR.

9.4.2.2.5 Time to First Subsequent Therapy (TFST)

Time to first subsequent therapy is defined as the time from randomization until the start date of the first subsequent anticancer therapy after discontinuation of randomized treatment, or death due to any cause.

The analysis will include all randomized participants as randomized, regardless of progression status.

Analysis Methods

Time to first subsequent therapy will be analyzed using the same methodology as that used for the analysis of PFS. In addition, medians and a Kaplan-Meier plot of the time to the start of subsequent therapy will be presented by treatment arm and the time between progression and starting subsequent therapy will be summarized.

9.4.2.2.6 Time to Second Subsequent Therapy (TSST)

Time to second subsequent therapy is defined as the time from randomization to until the start date of the second subsequent anticancer therapy after discontinuation of first subsequent treatment, or death due to any cause.

The analysis will include all randomized participants as randomized, regardless of progression status on study treatment or first subsequent treatment.

Analysis Methods

Time to second subsequent therapy will be analyzed using the same methodology as that used for the analysis of TFST.

9.4.2.2.7 Time from randomization to second progression or death (PFS2)

Time to second progression of death will be defined as the time from the randomization to the earliest of the progression event (following the initial progression), subsequent to first subsequent therapy, or death. The date of second progression will be recorded by the Investigator in the eCRF and defined according to local standard clinical practice.

The analysis will include all randomized participants as randomized, regardless of progression status on study treatment or first subsequent treatment.

Analysis Methods

Time to second progression or death will be analyzed using identical methods as outlined for

PFS.

9.4.2.2.8 Clinical Outcome Assessments

The secondary PRO endpoints include:

- TTD in pain as measured by the pain scale from EORTC QLQ-C30
- TTD in physical functioning as measured by the physical functioning scale from EORTC QLQ-C30
- TTD in GHS/QoL as measured by the GHS/QoL scale from EORTC QLQ-C30.

Time to deterioration (TTD) is defined as time from the date of randomization to the date of deterioration. Deterioration is defined as change from baseline that reaches a clinically meaningful deterioration threshold. Anchor-based methods using the participant-based anchors PGIS and PGIC will be considered to define thresholds for clinically meaningful within-participant change used in the TTD endpoints. Other methods including distribution-based methods, cumulative distribution function, and probability density function curves, and methods using other anchors may also be considered.

Clinically meaningful thresholds will be estimated for the following patient-reported outcomes:

- EORTC QLQ-C30: Global health status/QoL, functioning, and select symptom subscales including pain and fatigue
- EORTC QLQ IL116: breast symptoms, arm symptoms.

The analysis to define clinically meaningful change thresholds in the TTD PRO endpoints will include all randomized participants using the pooled treatment arms data prior to database lock. These TTD PRO endpoints will be analyzed using the same time-to-event analysis methodology described in Section 9.4.2.1.2.

Details of all statistical analyses, including analyses for other exploratory PRO endpoints, will be described in full in the SAP.

9.4.2.2.9 Pharmacokinetics

Dato-DXd, total anti-TROP2 antibody, and MAAA-1181a PK concentrations will be listed and summarized by visit and scheduled time point. Non-compartment PK parameters that can be derived with sparse PK sampling, such as peak and trough concentrations, will be reported as data allows. Details of those analysis will be described in SAP. Population PK, and exploratory exposure response/safety analyses will be performed. A separate modeling analysis plan will be written before the database lock. The population PK analysis and exploratory exposure response/safety analysis will be presented separately from the main CSR.

9.4.2.2.10 Immunogenicity

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 titer and neutralizing ADA data will be listed for samples confirmed positive for the presence of anti-Dato-DXd antibodies.

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

9.4.2.3 Exploratory Endpoints

Details of all statistical analyses for exploratory endpoints (including biomarkers, PRO, and medical resource utilization) will be described in full in the SAP.

9.4.2.3.1 Biomarkers

Biomarker status will be assessed for participants in each treatment group according to pre-specified criteria that may be detailed in the SAP. The relationship of biomarker expression and, if applicable, of exploratory biomarkers to clinical outcomes (including but not restricted to) of PFS, ORR, and OS may be presented. Biomarker exploratory analyses may be described in a separate analysis plan and may be reported outside the CSR in a separate report. The results of this biomarker assessment will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

The results of this biomarker assessment may be pooled with biomarker data from other studies with the study intervention to generate hypotheses to be tested in future research.

9.4.2.3.2 Medical Resource Utilization and Health Economics

To investigate the impact of treatment and disease on health care resource use, the following variables will be captured:

- Planned and unplanned hospital attendances beyond protocol-mandated visits (including physician visits, emergency room visits, day cases, and admissions)
- Primary sign or symptom the participant presents with
- Length of hospital stay, per stay
- Length of any time spent in an intensive care unit
- Procedures and tests

Where admitted overnight, the length of hospital stay will be calculated as the difference between the date of hospital discharge (or death date) and the start date of hospitalization or start of study intervention if the start of study intervention is after start date of hospitalization (length of hospital stay = end date of hospitalization – start date of hospitalization + 1). Participants with missing discharge dates will be calculated as the difference between the last day with available data and the start date of hospitalization. The length of intensive care unit

stay will be calculated using the same method.

Analysis Methods

The potential impact of the disease and treatment on health care resource use will be analyzed for the purposes of submissions to payers. Descriptive statistics (as appropriate, including means, median, ranges or frequencies, and percentages) will be provided for each treatment group on the different types of hospital admissions, the length of stay for participants admitted to hospital for at least 1 overnight stay, and the length of stay for participants admitted to intensive care/high dependency units, as well as the primary sign or symptom the participant presents with.

9.4.3 Safety

Safety summaries will be provided using the SAS. 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

Adverse events will be coded using the most recent version of MedDRA that will be released for execution at AstraZeneca, and graded using NCI-CTCAE v5.0.

The following adverse events are considered treatment emergent:

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

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

Adverse events will be presented for each treatment group by System Organ Class, HLT and/or PT covering number and percentage of participants reporting at least one event and number of events where appropriate.

An overview of AEs will present for each treatment group the number and percentage of

participants with any AE, AEs with outcome of death, serious AEs, and AEs leading to discontinuation of study intervention, as well as AEs leading to study intervention dose interruptions, AEs leading to study intervention dose reduction and AEs leading to withdrawal from study as well as the number of individual occurrences in those categories.

Treatment emergent adverse events will be presented for each treatment group by System Organ class and/or PT covering number and percentage of participants reporting at least one event and number of events where appropriate.

Separate AE tables will be provided taken into consideration relationship as assessed by the investigator, maximum CTCAE grading, seriousness, death and events leading to discontinuation of study intervention, as well as other action taken related to study intervention, and AESIs.

Key participant information will be presented for participants with AEs with outcome of death, SAEs, and AEs leading to discontinuation of study intervention.

An AE listing for the safety analysis set will cover details for each individual AE.

Full details of AE analyses will be provided in the SAP.

Vital signs

Vital sign parameters will be presented for each treatment group.

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.

Laboratory parameters

Laboratory parameters will be presented for each treatment group.

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

Elevation in liver parameters for assessment of Hy's Law will be reported appropriately.

A shift table for urinalysis will be presented with baseline assessment against the maximum on treatment 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 endpoint analyses

Details of analyses of urinalysis, ECGs, and ECHOs/MUGAs will be specified in the SAP.

9.4.4 Other Analyses

9.4.4.1 Optional Exploratory Genetic Sample

Data will be reported outside the CSR (please see Appendix D).

9.4.4.2 Ophthalmologic Analysis

See Section 8.2.5.5. Details will be specified in the SAP.

9.5 Interim Analyses

Two interim analyses for OS are planned. The first OS interim will occur at the primary PFS analysis (approximately 40% of target OS events) and the second when approximately 80% of the target OS events have occurred. The Lan DeMets approach (Lan and DeMets 1983) that approximates the O'Brien and Fleming spending function will be used to maintain an overall 2-sided type I error across the three planned analyses of OS. If the PFS dual primary analysis crosses the efficacy threshold, the 1.0% type I error allocated to the PFS endpoint will be reallocated to the OS endpoint for a total 2-sided type I error of 5.0%. Details of the planned timing of the two interim and final analyses are provided in Table 11. Note that the actual allocation of alpha across the three analysis times will be driven by the actual information fraction associated with the analysis.

The interim analyses will be performed by an IDMC. It is expected that recruitment will have completed prior to the results of the interim analyses being available. For the interim analyses, the IDMC will review unblinded interim data and inform the sponsor whether the interim boundaries specified in Table 11 are met.

Table 11 Summary of planned timings of the interim and final OS analyses

	Interim Analysis 1		Interim Analysis 2		Primary Analysis	
Projected Timing	21 Months [b]		34 Months		44 Months	
Number of Deaths [a]	178		355		444	
Information Fraction	40%		80%		100%	
Maturity	25%		51%		63%	
Recommendation	**Continue**	**Reject Null Hypothesis**	**Continue**	**Reject Null Hypothesis**	**Do Not Reject Null Hypothesis**	**Reject Null Hypothesis**
At 4.0% 2-sided alpha [c]						
2-sided nominal p-value	≥ 0.0005	< 0.0005	≥ 0.0184	< 0.0184	≥ 0.0345	< 0.0345

Table 11 Summary of planned timings of the interim and final OS analyses

	Interim Analysis 1		Interim Analysis 2		Primary Analysis	
Estimated hazard ratio	≥ 0.591	< 0.591	≥ 0.777	< 0.777	≥ 0.817	< 0.817
At 5.0% 2-sided alpha [c]						
2-sided nominal p-value	≥ 0.0008	< 0.0008	≥ 0.0241	< 0.0241	≥ 0.0427	< 0.0427
Estimated hazard ratio	≥ 0.604	< 0.604	≥ 0.786	< 0.786	≥ 0.824	< 0.824

[a] Estimates based on exponential survival where the median OS is 19.0 months for ICC and 25.3 months for Dato-DXd. The total proportion of participants randomized at time t [t ≤ 19 months] following the start of the study is assumed to be $(t/19)^{1.5}$.
[b] Timing of first IA based on PFS. Number of deaths is an estimate.
[c] Alpha allocated to OS endpoint (4.0% or 5.0%) dependent on statistical significance of PFS.

The study may continue monitoring participants for OS up to the scheduled final analysis, beyond planned interim analyses, to provide more refined estimates of treatment effects for survival.

The first IA for OS will occur at the time of the PFS analysis. If 40% of the target OS events (178/444) are available at the time of the first OS IA, then the largest (nominal) 2-sided p-value that will cross the efficacy threshold is 0.0008. If the first interim results do not meet the criterion for rejecting the null hypothesis in the ITT population, then follow-up will continue until at the criteria are met for the second OS IA. The second OS IA is planned when approximately 80% of target OS events (355/444) are available. The largest (nominal) 2-sided p-value that will cross the efficacy threshold is 0.0241 based on the expected timing of the second IA. If the interim results do not meet the criterion for rejecting the null hypothesis in the ITT population, then follow-up will continue until the criteria is met for the for OS primary analysis. The OS primary analysis will be performed when 444 OS events are observed, and the nominal 2-sided p-value will be 0.0427 based on the expected timing of the second IA. Note that the p-value boundaries reported in this paragraph presume that 5.0% type I error is available for the OS analysis.

If the PFS primary analysis does not cross the efficacy threshold, the total 2-sided type I error allocated to the OS analyses will be 4.0%. For the 2 interim and primary analyses of OS, based on the expected number of events at each analysis, the nominal 2-sided p-values associated with the three analyses times are 0.0005, 0.0184, and 0.0345, respectively.

The SAP will describe the planned interim analyses in greater detail.

9.6 Data Monitoring Committees

9.6.1 Independent Data Monitoring Committee

An IDMC comprised of independent experts will convene and will meet approximately 6 months after the study has started. The IDMC will review unblinded safety data and make

recommendations on whether the study should continue, be amended, or stopped based on safety findings. In addition, the IDMC may be requested to review efficacy data. For the interim analyses, the IDMC will review unblinded interim data and inform the Sponsor whether the interim boundaries specified in Section 9.5 are crossed.

Full details of the IDMC communications, procedures, processes, and interim analyses will be presented in the IDMC Charter.

9.6.2 ILD Adjudication Committee

An independent ILD Adjudication Committee for the Dato-DXd program is responsible for reviewing all cases of potential ILD/pneumonitis. To ensure adequate and relevant independent evaluation, systematic additional data collection will be conducted for all cases that will be brought for adjudication. These additional data collections will cover a more in-depth relevant medical history (eg, smoking, radiation, COPD and other chronic lung conditions), diagnostic evaluation, treatment and outcome of the event. This data collection will be triggered based on a pre-defined list of PTs eligible for adjudication as described in the Event Adjudication Site Manual. Further details can be found in the ILD Adjudication Charter.

9.6.3 Ophthalmologic Data Review Committee

An independent Ophthalmologic Data Review Committee is responsible for reviewing the data from baseline, periodic and end of therapy ophthalmologic assessments. This data collection will be triggered based on a pre-defined list of PTs eligible for review. Further details will be available in the Ophthalmologic Data Review Committee Charter.

9.7 Mainland China Cohort

The global cohort will enrol approximately 1000 participants to randomize approximately 700 participants. The mainland China cohort will consist of approximately an additional 20 randomized participants in mainland China. The global cohort will consist of participants recruited by the documented date of the last participants randomized of the global cohort. Participants randomized in the mainland China cohort prior to the last participants randomized of the global cohort enrolment will be included in both the ITT and the mainland China ITT. Participants randomized in the mainland China cohort after the last participants randomized of the global cohort enrolment will be included only in the mainland China ITT. The mainland China ITT will include all participants randomized in the mainland China cohort including those who were recruited prior to the closure of the global cohort and are therefore included in the analyses of efficacy and safety for the main study. The mainland China safety analysis set will consist of all participants included in the mainland China ITT who received at least 1 dose of study treatment.

Per NMPA guidance, in addition to the evaluation of the global cohort data for primary, secondary and safety objectives, evaluation of consistency in efficacy and safety in Chinese

populations is required to facilitate the benefit-risk assessment for mainland Chinese participants. Hence, the safety and efficacy data in the mainland China cohort will be analyzed separately where the same endpoint definitions and the same analysis methods are applied.

Details of the mainland China cohort analyses will be specified in the SAP.

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 protocol 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 protocol, protocol 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 protocol 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 authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a Contract Research Organization 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 21CFR 312.120, ICH guidelines, the IRB/IEC, and the European Regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of a 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 utilizing 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 EU CT Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- 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 (email 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 1 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 authorized 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 authorized 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 center.

- 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 authorized 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 authorized representative.

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

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 which 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 authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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 protocol.

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. For additional details see Section 9.6.1.

A 6 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com, http://www.clinicaltrials.gov, and https://www.clinicaltrialsregister.eu as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 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.
- The sponsor 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 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 clinical reviews of study data from a medical perspective, and handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided 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, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized 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 protocol 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.
- 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 act of recruitment is the first site open 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 protocol, 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 Contract Research Organization(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 multicenter studies only in their entirety and not as individual site data. In this case, a coordinating 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 and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable 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 hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

AEs for **malignant tumors** 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 tumor event should be assessed and reported as a **Non-Serious** AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, 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 tumor event in question is a new malignant tumor (ie, it is *not* the tumor 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 tumor under study). Malignant tumors that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

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).

Hospitalization

Outpatient treatment in an emergency room is not in itself a 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, hospitalization, disability or incapacity but may jeopardize 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 anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Intensity rating scale:

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

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 etiology such as the underlying disease, other drugs, 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 re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized 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, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP 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 recognized that could have led to an error.

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

- Drug name confusion.
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant.
- Drug not administered as indicated, eg, 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 refrigerator when it should be at room temperature.

- Wrong participant received the medication (excluding IRT errors).
- Wrong drug administered to participant (excluding IRT errors).

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

- Errors related to or resulting from IRT - including those which 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 IMP/study intervention or AstraZeneca NIMP 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 Data Entry Site 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 drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug 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 (by a study participant) of IMP/study intervention or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs/study interventions or AstraZeneca NIMPs, outside the intended use as specified in the protocol, and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site 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 drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that they were feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug.

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 center keeps full traceability of collected biological samples from the participants while in storage at the center 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 life cycle 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 life cycle. 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 analyzed, 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 protocol.

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

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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, 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
- are to be packed in accordance with UN3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which 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/contentassets/b08040a138dc4442a4f066e6fb99fe2a/dgr-62-en-pi650.pdf).

- Biological samples transported in dry-ice require additional dangerous goods specification for the dry-ice content.

Appendix D Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant's DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on Dato-DXd continues but no longer than 15 years from the end of the study (as defined in the protocol) or other period as per local requirements.

D 2 Genetic Research Plan and Procedures

Selection of genetic research population

- All participants will be asked to participate in this genetic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion criteria

For inclusion in this genetic research, participants must fulfil all of the inclusion criteria described in the main body of the CSP and provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Previous allogeneic bone marrow transplant.
  - Transfusion of non-leukocyte depleted blood or blood component within 120 days of genetic sample collection.

Withdrawal of consent for genetic research

Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main CSP.

Collection of samples for genetic research

The blood sample for this genetic research will be obtained from the participants pre-dose at the first dosing visit. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at the first dosing visit, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and storage of DNA samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples may be stored for a maximum of 15 years from the end of the study (as defined in the protocol), after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).
- The link between the participant enrolment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed consent

The genetic component of this study is optional, and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study the participant must sign and date both the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study center. The principal investigator(s) is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant data protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, general physician, or any other third party unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca physician or an investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyze the samples.
- AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organizations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results, but they will not be able to see individual participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical methods

The number of participants that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal

statistical evaluation or whether only descriptive statistics will be generated. An SAP may be prepared where appropriate.

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

E 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.

Specific guidance on managing liver abnormalities can be found in the TMGs (see the Annex document to this CSP).

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 potential 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.

E 2 Definitions

Potential Hy's Law (PHL)

AST 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.

Hy's Law (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, 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.

E 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 E 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

E 4 Follow-up

E 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.

E 4.2 Potential Hy's Law Criteria Met

If the participant does meet PHL criteria the investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.

- Within 1 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 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 physician contacts the investigator, to provide guidance, discuss and agree an approach for the study participant's 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 etiology of the event and perform diagnostic investigations as discussed with the study physician.
  - 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 physician if there is any uncertainty.

E 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 physician 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 were 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 a 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:

- Provide 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 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 amend the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 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 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 central Study Team, then follow the subsequent process described in Section E 4.2.

E 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 E 6 of this Appendix?

If No: follow the process described in Section E 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 E 4.2 for reporting PHL as an SAE.

E 8 Laboratory Tests

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.

Tests to Further Evaluate Increases in Liver Biochemistry and Hy's Law

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
Alcoholic hepatitis	Carbohydrate-deficient transferrin [b]
Autoimmune hepatitis	Antinuclear antibody Anti-liver/kidney microsomal antibody Anti-smooth muscle antibody
Metabolic diseases	Alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin [b] 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 = immuno-globulin G; IgM = immuno-globulin M; INR = international normalized ratio; LDH = lactate dehydrogenase; RNA = ribonucleic acid.

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

[b] Carbohydrate-deficient transferrin and transferrin are not available in mainland China.

E 9 References

Aithal et al 2011
Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther 2011;89(6):806-15.

FDA Guidance 2009
Food and Drug Administration. Guidance for industry: Drug-induced liver injury:

premarketing clinical evaluation. July 2009. Available from: URL: https://www.fda.gov/downloads/guidances/UCM174090.pdf. Accessed 08 October 2019.

Appendix F Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)

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.

Additional special guidance is provided for evaluation of scans collected after a RECIST 1.1-defined radiological progression.

Imaging modalities and acquisition specifications for RECIST 1.1

A summary of the imaging modalities that can be used for tumor assessment of TLs, NTLs and NLs is provided in Table 12.

Table 12 Summary of Imaging Modalities for Tumor Assessment

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

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

Computed Tomography and Magnetic Resonance Imaging

CT 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 tumor 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, tumor assessor (eg, radiologist), and method of tumor 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/tumor assessment schedule as closely as possible (refer to the SoA; Table 1), 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 tumor evaluation are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

a. Anatomic coverage: Optimal anatomic coverage for most solid tumors is the chest-abdomen-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 tumor measurements but also identification of new disease.

Required anatomical regions to be imaged for assessment of tumor 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 (Table 1). Examples include the following:

- IV 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).
- IV contrast-enhanced CT or MRI of the head and neck.
- IV 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:

6 Chest-abdomen-pelvis CT with IV CT contrast (most preferred).
7 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.

8 Chest-abdomen-pelvis CT without IV contrast, if both IV CT and MRI contrast are medically contraindicated or the participant has compromised renal function.

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

b. IV contrast administration: Optimal visualization and measurement of metastases in solid tumors 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 tumor 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 visualize 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.

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.

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.

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.

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

^{18}F-fluoro-deoxyglucose positron emission tomography(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 on 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 tumor 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 tumor 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.

Ultrasound

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

Other tumor assessments

Clinical examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will

[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.

not be used for RECIST 1.1 assessments. Tumors identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

Endoscopy and laparoscopy

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

Histology and cytology

Histology or tumor markers on tumor biopsy samples will not be used as part of the tumor 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 tumor 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.

Measurability of tumor lesions at baseline

RECIST 1.1 measurable lesions at baseline

A tumor 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[1] 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.

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.

[1] The short axis is defined as the longest in-plane axis perpendicular to the long axis.

- 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).[1]
- Previously irradiated lesions.[2]
- Brain metastasis.

Special considerations regarding lesion measurability at baseline

- Bone lesions:
  - Bone scan, PET scan, or plain X-ray 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.

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

---

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

[2] Localized 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.

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 millimeters. 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.

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.
- Tumor 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.

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.

Evaluation of tumor response and progression

RECIST 1.1 TL assessment at follow-up

This section defines the criteria used to determine objective tumor visit response for RECIST 1.1-defined TLs. 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 millimeters. 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 1 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.
- When a TL has had any intervention (eg, definitive radiotherapy, embolization, surgery, transarterial chemoembolization, 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 13 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.

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. 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 tumor burden has increased sufficiently to merit unequivocal progression by NTLs. A modest "increase" in the size of 1 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 14 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 1 or more NTLs.
PD	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in 1 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 1 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.

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 1 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 tumor. If a NL is equivocal, for example because of its small size, the treatment and tumor 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 a NL and will indicate PD.

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 15.

Table 15 RECIST 1.1 Overall Visit Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Visit Response
CR	CR	No	CR
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	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; 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 tumor disease at baseline:

- For participants with TLs (at baseline): CR, PR, SD, PD, or NE.

Central imaging

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed imaging Contract Research Organization (iCRO) for quality control, storage, and for BICR. 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. A BICR 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 tumor assessments will not be shared with the central reviewers.

The management of participants will be based in part upon the results of the tumor assessments conducted by the investigator. Further details of the BICR will be documented in an Independent Review Charter.

F 1 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 G Contraception Requirements

Contraception requirements for this study are as follows.

G 1 Female Participants

Women not of childbearing potential are defined as those who are surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or who are post-menopausal.

Women will be considered post-menopausal if they have been amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women < 50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all hormonal replacement therapy and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution, or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
- Women ≥ 50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all hormonal replacement therapy, or had radiation-induced menopause with last menses > 1 year ago, or had chemotherapy-induced menopause with last menses > 1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

Women of childbearing 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-sterilized male partner must use at least 1 highly effective method of contraception (Table 16). They should have been stable on their chosen method of birth control starting at a minimum of 3 months before C1D1 and continue to use it throughout the total duration of the drug treatment and the drug washout period (7 months after the last dose of study intervention).

Non-sterilized male partners of a woman of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial. Female participants should refrain from breastfeeding throughout this period. Women must not donate, or retrieve for their own use, ova from the time of screening and throughout the study treatment period, and for at least 7 months after the final study drug administration. Preservation of ova should be considered prior to enrolment in this study.

G 2 Male Participants with a Female Partner of Childbearing Potential

Non-sterilized male participants (including males sterilized 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 (ie, at least 4 months after the last dose of study intervention) 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, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male participants should refrain from sperm donation or banking throughout the drug washout period. Preservation of sperm should be considered prior to enrolment in this study.

Vasectomized (ie, sterile) males are considered fertile 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 fetus from drug in ejaculate.

Female partners (of childbearing potential) of male participants must also use a highly effective method of contraception throughout this period (Table 16).

G 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 16. 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 16 Highly Effective Methods of Contraception (< 1% Failure Rate)

Non-Hormonal Methods	Hormonal Methods[b]
• Total sexual abstinence (evaluate in relation to the duration of the clinical study and the preferred and usual lifestyle choice of the participant) • Vasectomized sexual partner (with participant assurance that partner received post-vasectomy confirmation of azoospermia) • 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.
[b] Hormonal methods of contraception must not be used by female patients participating in this study; this information is meant for female partners of male participants.

For participants in the ICC (eribulin, capecitabine, vinorelbine, or gemcitabine) group: Follow the local Prescribing Information relating to contraception, the time limits for such precautions, and any additional restrictions required for the specific ICC agent.

Appendix H Patient-reported Outcomes

H 1 EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌋⌊_⌋⌊_⌋⌊_⌋
Your birthdate (Day, Month, Year): ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋
Today's date (Day, Month, Year): 31 ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

SPECIMEN

ENGLISH

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

© Copyright 1995 EORTC Quality of Life Group. All rights reserved. Version 3.0

SPECIMEN

H 2 EORTC IL116

ENGLISH

EORTC IL116

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
1.	Have you had any pain in your arm or shoulder?	1	2	3	4
2.	Have you had a swollen arm or hand?	1	2	3	4
3.	Have you had problems raising your arm or moving it sideways?	1	2	3	4
4.	Have you had any pain in the area of your affected breast?	1	2	3	4
5.	Has the area of your affected breast been swollen?	1	2	3	4
6.	Has the area of your affected breast been oversensitive?	1	2	3	4
7.	Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4

SPECIMEN

© Copyright 2021 EORTC Quality of Life Group. All rights reserved.

H 3 PRO-CTCAE

NCI PRO-CTCAE ™ ITEMS

Item Library Version 1.0

English

Form Created on 01 April 2021

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days…

1a. In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
1b. In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

2a. In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
2b. In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
O Not at all	OA little bit	O Somewhat	O Quite a bit	O Very much

3a. In the last 7 days, how OFTEN did you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
3b. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

4a. In the last 7 days, how OFTEN did you have VOMITING?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
4b. In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

5a. In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

The PRO-CTCAE™ items and information herein were developed by the Division of Cancer Control and Population Sciences in the NATIONAL CANCER INSTITUTE at the NATIONAL INSTITUTES OF HEALTH, in Bethesda, Maryland, U.S.A. Use of the PRO- CTCAE™ is subject to NCI's Terms of Use.

6a. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly

7a. In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
7b. In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
7c. In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

8a. In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
8b. In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

9a. In the last 7 days, what was the SEVERITY of your COUGH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
9b. In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

10a. In the last 7 days, did you have any RASH?	
O Yes	O No

11a. In the last 7 days, did you have any HAIR LOSS?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

12a. In the last 7 days, what was the SEVERITY of your HAND-FOOT SYNDROME (A RASH OF THE HANDS OR FEET THAT CAN CAUSE CRACKING, PEELING, REDNESS OR PAIN) at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

The PRO-CTCAE™ items and information herein were developed by the Division of Cancer Control and Population Sciences in the NATIONAL CANCER INSTITUTE at the NATIONAL INSTITUTES OF HEALTH, in Bethesda, Maryland, U.S.A. Use of the PRO- CTCAE™ is subject to NCI's Terms of Use.

13a. In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
13b. In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

14a. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
14b. In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

The PRO-CTCAE™ items and information herein were developed by the Division of Cancer Control and Population Sciences in the NATIONAL CANCER INSTITUTE at the NATIONAL INSTITUTES OF HEALTH, in Bethesda, Maryland, U.S.A. Use of the PRO- CTCAE™ is subject to NCI's Terms of Use.

H 4 EORTC IL117

ENGLISH

EORTC IL117

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
1.	Have your eyes been dry?	1	2	3	4
2.	Have you had pain in your mouth?	1	2	3	4
3.	Have you had soreness in your mouth?	1	2	3	4

SPECIMEN

© Copyright 2021 EORTC Quality of Life Group. All rights reserved.

H 5 PGI-TT

PATIENT GLOBAL IMPRESSION OF TREATMENT TOLERABILITY (PGI-TT)

In the last 7 days, how bothered were you by the side effects of your cancer treatment?

- ☐ Not at all
- ☐ A little bit
- ☐ Somewhat
- ☐ Quite a bit
- ☐ Very much

H 6 PGIS

Patient Global Impression of Severity - Cancer (PGIS-Cancer-4-Item)

Please select the response below that best describes the severity of your overall cancer symptoms over the past 7 days.

Please select one response only

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe

H 7 PGIC

PATIENT GLOBAL IMPRESSION OF CHANGE - GENERIC (PGIC-GENERIC)

Overall, how would you rate the change in your health status since starting this study?

Please select one response only

- ☐ Much better
- ☐ Moderately better
- ☐ A little better
- ☐ About the same
- ☐ A little worse
- ☐ Moderately worse
- ☐ Much worse

H 8 EQ-5D-5L

Health Questionnaire

English version for the UK

Sample

© 2009 EuroQol Research Foundation. EQ-5D™ is a trade mark of the EuroQol Research Foundation. UK (English) v1.2

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

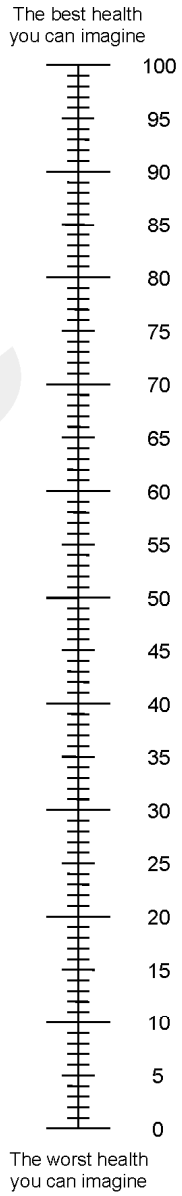
I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

© 2009 EuroQol Research Foundation. EQ-5D™ is a trade mark of the EuroQol Research Foundation. UK (English) v1.2

Sample

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Sample

3

© 2009 EuroQol Research Foundation. EQ-5D™ is a trade mark of the EuroQol Research Foundation. UK (English) v1.2

Appendix I Concomitant Medications

I 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.

I 2 Restricted, Prohibited, and Permitted Concomitant Medications/Therapies

Restricted, prohibited, and permitted concomitant medications/therapies are described in Table 17, Table 18, and Table 19. Refer also to the TMGs in the Annex document to this CSP. Participants must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

Table 17 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 should be recorded in the eCRF.
Palliative radiotherapy	Permitted for optimal symptom control or pain management. Delay Dato-DXd therapy for the duration of radiotherapy and restart at least 2 weeks after completion of radiotherapy. Curative radiotherapy is not permitted.

With the exception of medications that are under investigation in the study (ie, standard of care, comparators, or combination therapies), the medications, treatment and procedures in Table 18 will be prohibited during the treatment period. The Sponsor must be notified if a participant receives any of these during the study.

Table 18 Prohibited medications/therapies

Prohibited medication/class of drug/therapy	Usage
Chloroquine or hydroxychloroquine	Concomitant treatment with chloroquine or hydroxychloroquine is not allowed during the study treatment. If treatment with chloroquine or hydroxychloroquine treatment is absolutely required, study intervention must be interrupted. If chloroquine or hydroxychloroquine is administered, then a washout period of at least 14 days is required before restarting study intervention (see Appendix J for more details).
Any concurrent anticancer therapy, including cytotoxic, targeted agents, immunotherapy, antibody, retinoid or radiotherapy (except palliative radiotherapy to areas other than chest, after consultation with the sponsor study physician) or hormonal therapy for cancer treatment.	Must not be given concomitantly while the participant is on study intervention. Concurrent use of hormones for noncancer-related conditions (eg, insulin for diabetes and topical hormone replacement therapy) is acceptable.
Concomitant use of chronic systemic (IV or oral) corticosteroids or other immunosuppressive medications except for managing AEs; inhaled steroids, intra-articular steroid injections, and other topical steroid formulations are permitted in this study. Corticosteroid mouthwash formulations are permitted to prevent and manage certain AEs.	Dato-DXd cannot be administered when the participant is taking immunosuppressive medications, including corticosteroids with the exception of: • short-term courses (<2 weeks) • doses less than 10mg/day of prednisone or equivalent • 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. A temporary period of steroid treatment will be allowed for different indications after discussion with the sponsor study physician (eg, COPD, radiation, nausea, etc). Participants with bronchopulmonary disorders who require intermittent use of bronchodilators (eg, albuterol) will not be excluded from this study. 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 Annex document to this CSP). Immunosuppressive medications also include drugs like methotrexate, azathioprine, and tumor necrosis factor-alpha blockers.
Other investigational therapeutic agents	Must not be given concomitantly while the participant is on study intervention.

Table 19 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.
Prophylactic anti-emetic agents for Dato-DXd	Based on currently available clinical safety data, it is highly recommended that participants receive prophylactic anti-emetic agents prior to infusion of Dato-DXd and on subsequent days. Antiemetics such as 5-HT3 antagonists and steroids (eg, dexamethasone) should be considered and administered in accordance with the prescribing information or institutional guidelines. NK1 receptor antagonists can be used, if needed.
Prophylactic/supportive stomatitis/oral mucositis agents	Recommended that dexamethasone oral solution be strongly considered for prophylaxis as well as treatment of stomatitis/oral mucositis.
Bisphosphonates, denosumab	Permitted for the treatment of bone metastasis.
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive treatment and AE management, except for those medications identified as "prohibited," as listed above	As per TMGs, institutional guidelines and investigator's discretion. To be administered as prescribed by the investigator except for those medications identified as "prohibited," as listed in Table 18.
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, etc.]) 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 18.
Dietary supplements, medications not prescribed by the investigator, and alternative/complementary treatments	Concomitant use is discouraged, but not prohibited.
Intermittent use of bronchodilators (eg, albuterol)	Participants with bronchopulmonary disorders who require this medication will not be excluded from this study.
Inhaled steroids, intra-articular steroid injections, and other topical steroid formulations	Permitted.
Required for management of other medical conditions	As required except for those identified as "prohibited," as listed in Table 18.

Appendix J Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

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 SARS-CoV-2 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.

J 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 the sections below. 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.

J 2 Rescreening of Participants to Reconfirm Study Eligibility

An extended rescreening period will be allowed for participants that are affected by study disruptions, that have already screen failed and entered rescreening. 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 Table 1, the participant will be allowed to remain in screening until reconfirmation of eligibility before commencing study procedures. The procedures detailed in Table 1 must be undertaken to confirm eligibility using the same E-code as initially assigned to the participant.

J 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 clinical study protocol (CSP).

J 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 targeted physical examination to be reported and documented. Site personnel to also ensure that ePROs are being completed by participant as per SoA.

J 5 Data Capture During Telemedicine Visits (where applicable)

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP (or site delegate) from the study site or TPV service in the source documents.

Appendix K Protocol Version History

The Summary of Changes Table for the current revision is located directly before the TOC.

Amendment 3 (10 October 2022)

Overall Rationale for the Amendment:

The overall rationale for the amendment is to provide flexible language for the inclusion of a mainland China-specific recruitment tail, if required, for regulatory submission purposes, as well as alignment with the latest Dato-DXd program standards.

Other important administrative and operational clarifications have also been made.

The rationale for each of these changes is provided in the table below:

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 1.1, Synopsis, Number of Participants, Statistical Methods Section 4.1, Overall Design	Updated to include possibility of a mainland China cohort.	If required for regulatory submission purposes, the recruitment of participants in mainland China may continue beyond the close of the global cohort.	Non-Substantial
Section 1.2, Schema	Clarified requirement for patient to have progressed on **and** not be suitable for endocrine therapy, in accordance with existing eligibility criteria.	Typographical correction.	Non-substantial
Section 1.3, Schedule of Assessments, Table 1 Section 8.2.5.1, Echocardiogram/Multigated Acquisition Scan	Removed requirement to do an ECHO or MUGA scan to assess LVEF at EoT visit. Updated footnote “i” to clarify that an ECHO or MUGA may be done at EoT visit, if clinically indicated.	To align with AstraZeneca Dato-DXd program standards, the ECHO/MUGA scan is not required at EoT visit unless clinically indicated.	Non-substantial
Section 1.3, Schedule of Assessments, Table 1 Section 8.2.4, Table 7	Removed requirement to do coagulation tests at screening.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 1.3, Schedule of Assessments, Table 1	Added optional bronchoalveolar lavage and lung biopsy sample on diagnosis of suspected ILD/Pneumonitis into SoA.	Administrative clarification, as collection of this sample was previously omitted from the SoA.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 1.3, Schedule of Assessments, Table 1	Updated footnote "a" to ensure the safety follow-up visit is performed 28 (+7) days after the last study intervention administration regardless of participant starting new anticancer treatment.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 1.3, Schedule of Assessments, Table 1	Updated footnote "q" to specify prior HIV serology, HBV serology, and HCV serology test results can still be used if performed within 120 days of enrolment.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 1.3, Schedule of Assessments, Table 1	Updated footnote "r" to specify that participants must be tested for HIV if applicable by local regulations or an IRB/EC.	Administrative clarification.	Non-substantial
Section 5.2, Exclusion Criteria #5	Updated text to clarify circumstances where patients may still be eligible with respect to hepatitis B or C.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 5.2, Exclusion Criteria #6	Updated definition of well controlled HIV infection. Clarified recommendation to monitor viral RNA load and CD4+ count, and that participants must be tested for HIV if acceptable by local regulations or an IRB/EC.	To align with AstraZeneca Dato-DXd program standards.	Substantial
Section 6.5, Concomitant Therapy	Added requirement for all concomitant medications administered during the study to be recorded until the end of the safety follow up period and those administered for drug-related AESIs to be recorded in the eCRF as required.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 6.6, Dose Modification	Clarified dose delay allowance.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 8.2.4, Clinical Safety Laboratory Assessments Section 8.3.6, Hy's Law E2 Definitions, E3 Identification of Potential Hy's Law Cases	Corrected typo in Hy's Law criteria from TBL > 2 ULN to TBL ≥ 2 ULN.	Typographical correction.	Non-substantial
Section 8.3.1, Time Period and Frequency for Collecting AE and SAE Information	Added Grade ≥ 2 keratitis events to list of AEs to be reported by the investigator in eCRF within 24 hours of awareness.	To align with AstraZeneca Dato-DXd program standards.	Substantial
Section 8.3.6, Hy's Law	Removed reference to Section 8.3.11 as Hy's Law event is no longer considered an AESI.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 8.3.11, Adverse Events of Special Interest	Clarified that all AESIs must be followed until either event resolution, end of study, trial termination, withdrawal of consent, or participant death.	Administrative clarification.	Non-substantial
Section 9.3, Table 9, Population for Analysis	Updated table to specify that participants in the mainland China cohort will be excluded from ITT population. Additional changes to clarify SAS, OAS, and PAS will be comprised of participants in the ITT population.	Included as part of flexible language to allow for mainland China tail, if required.	Non-substantial
Section 9.4.2.2.9, Pharmacokinetics	Corrected substrate name from MAAA-1191a to MAAA-11**8**1a.	Typographical correction.	Non-substantial
Section 9.7, Mainland China Cohort	Summarized details of mainland China cohort.	If required for regulatory submission purposes, the recruitment of participants in mainland China may continue beyond the close of the global cohort.	Non-substantial
Appendix I, Table 19, Supportive Medications/therapies	Clarified recommendation for usage of prophylactic anti-emetic agents.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Throughout CSP	Clarified that 'China' refers to mainland China.	To align with China R&D preferred terminology.	Non-substantial

Amendment 2 (19 April 2022)

Overall Rationale for the Amendment:

The overall rationale for the amendment is to provide additional guidance for investigators after the annual update of the Dato-DXd Investigator's Brochure v6.0. The Toxicity Management Guidelines includes further details on management of ocular surface toxicities, and are now located in an Annex document. Adverse Events of Special Interest no longer include "combined elevations of aminotransferase and bilirubin", and stomatitis/mucosal inflammation have been separated into "oral mucositis/stomatitis" and "mucosal inflammation other than oral mucositis/stomatitis."

Other administrative and operational clarifications have also been made.

The rationale for each of these changes is provided in the table below:

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 1.1, Synopsis, Participant Population Section 5.1, Inclusion Criteria #1	Removed requirement for participants in Japan to be ≥ 20 years.	Update to the civil code for age of adulthood in Japan.	Substantial
Section 1.1, Synopsis, Intervention Groups and Duration Section 4.1, Overall Design Section 9.4.2.1.5, Subgroup Analysis	Added Canada as a Region 1 country.	Administrative clarification.	Non-Substantial
Section 1.1, Synopsis, Follow-up of Participants Post Discontinuation of Study Intervention	Added that the EoT assessments can function as the Safety Follow-up visit if the date of discontinuation is over 35 days from the last administration of study intervention.	Administrative clarification.	Non-substantial
Section 1.3, Schedule of Assessments, Table 1	Added ePRO training and set up.	Administrative clarification.	Non-substantial
Section 1.3, Schedule of Assessments, Table 1	Updated footnote "d" so that safety assessments do not have to be repeated if they have been performed within 72 hours prior to the day of dosing.	To allow flexibility in patient management without compromising safety.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 1.3, Schedule of Assessments, Table 1 Section 5.1, Inclusion Criteria #14	Updated footnote "p" and added clarification that a serum pregnancy test should be negative at screening and.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 1.3, Schedule of Assessments, Table 1 Section 6.3, Participant Enrolment and Randomization	Updated footnote "q" and Section 6.3.1 to be consistent with Exclusion Criterion #5.	Administrative clarification.	Non-substantial
Section 1.3, Schedule of Assessments, Table 1 Section 8.1.1, Imaging Tumor Assessments	Updated footnote "x" and added clarification of abdomen imaging.	To align with AstraZeneca program standards.	Non-substantial
Section 1.3, Schedule of Assessments	Table 2 added detailing the assessments to be performed in the event of suspected ILD/pneumonitis.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 2.2.1, HR-positive, HER2-negative, inoperable/metastatic breast cancer	Added baseline characteristics/factors which could be relevant to the target study population.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 2.2.2.1, TROPION-PanTumor01 study Section 2.3.3, Overall Benefit: Risk Conclusion	Updated safety and efficacy data from the DS1062-A-J101 study.	To align with latest Dato-DXd Investigator Brochure.	Non-substantial
Section 2.3.1.1, Dato-DXd, Table 3 Section 8.3.11, Adverse Events of Special Interest	Labeled "stomatitis/oral mucositis" as an identified risk/AESI and established "mucosal inflammation other than oral mucositis/stomatitis" as a separate identified risk/AESI. Removed anaphylaxis in relation to IRR.	To align with latest Dato-DXd safety profile information.	Substantial
Section 4.3.1, Dato-DXd	Updated to include latest available data.	To align with latest Dato-DXd Investigator Brochure.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 5.1, Inclusion Criteria #8	Limit of AST/ALT criteria extended to assess adequate organ and bone marrow function. Removed INR or PT, and either PTT or aPTT criteria.	To allow flexibility in patient enrolment without compromising safety.	Substantial
Section 5.1, Inclusion Criteria #10	Added definition for washout period of immunotherapy.	Administrative clarification.	Non-substantial
Section 5.1, Inclusion Criteria #15	Removed references to HRT in relation to female participant contraception.	HRT is contraindicated for HR-positive disease.	Substantial
Appendix G1, Female Participants	Updated contraceptive requirement to 3 months before C1D1.	Administrative clarification.	Substantial
Section 5.1, Inclusion Criteria #16	Added that female partners of male participants are allowed to use HRT for contraception. Updated that male participants should use a highly effective method of contraception.	Clarification following the change to Inclusion Criteria #15. To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 5.2, Exclusion Criteria #3	Removed allowance of study physician judgment and added examples of permitted toxicities related to previous anticancer therapy.	To provide operational flexibility without compromising safety.	Substantial
Section 5.2, Exclusion Criteria #16	Clarified to allow concurrent use of hormones for non-cancer related conditions (eg, insulin for diabetes).	To align with CSP permitted medications.	Non-substantial
Section 5.2, Exclusion Criteria #19	Removed exclusion criteria to allow for the enrolment of participants using chronic systemic corticosteroids.	To align with AstraZeneca Dato-DXd program standards.	Substantial
Section 5.3, Lifestyle Considerations	Added recommendation regarding consideration to preserve ova prior to enrolment.	Compliance with AstraZeneca program standards.	Non-substantial
Section 6.2.1.2, Administration of Dato-DXd	Added clarification regarding mandated pre-medications. Added that the IV line will be flushed following infusion.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 6.2.1.3, Monitoring of Dato-DXd Administration	Section to include Dato-DXd monitoring added.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 6.5, Concomitant Therapy	Added information regarding concomitant use of Dato-DXd and CYP3A inhibitors and drugs that inhibit OATP1B1, OATP1B3, MATE2-K, P-gp, BCRP, and MRP1. Added information regarding concomitant use of Dato-DXd and hydroxychloroquine and/or chloroquine.	To align with AstraZeneca and Dato-DXd program standards.	Non-substantial
Section 6.6, Dose Modification	Added information regarding dose delays, interruptions, and modifications.	Consequent to change in Section 6.1.1, and to align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 6.6.4, Dato-DXd Dose Modification/ Toxicity Management Guidelines	Removed Toxicity Management Guidelines (TMG) from the body of the CSP (including Appendix L) and included as an Annex.	To provide operational flexibility, as the TMG may be updated without CSP amendment.	Non-substantial
Section 6.7, Intervention after the End of the Study	Added text regarding continuation of open-label treatment and alternative supply options should they become available.	To align with AstraZeneca program standards.	Substantial
Section 8.1.1 Imaging Tumor Assessments	Added that for participants with documented bone lesion at baseline, the bone scan must have been performed no more than 28 days before randomization.	To align with AstraZeneca and Dato-DXd program standards.	Non-substantial
Section 8.1.1 Imaging Tumor Assessments	Added clarification that CT/MRI are to be collected for all participants at baseline. Removed the text regarding treatment continuation regardless of study intervention discontinuation or start of subsequent anticancer therapy.	Administrative clarification.	Non-substantial
Section 8.1.5.9, Administration of Electronic PRO (ePRO) Questionnaires	Added timing of onboarding participant onto the ePRO application.	To ensure the correct C1D1 date is registered in the ePRO system.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 8.2.2, Vital signs	Added seated assessment position.	To allow flexibility in patient management without compromising safety.	Non-substantial
Section 8.2.3, Electrocardiograms	Amended the requirement of timing of ECGs and ECG machine capabilities.	To provide operational flexibility for both timing and the ECG machine capabilities; without compromising safety.	Non-substantial
Section 8.2.4, Clinical Safety Laboratory Assessments	Added urea and calcium (ionized) to the laboratory safety variables.	To align with AstraZeneca Dato-DXd program standards and allow for operational flexibility without compromising safety.	Non-substantial
Section 8.2.5.3, ILD/Pneumonitis Investigation	Added troponin assessment to the ILD/pneumonitis investigations. Clarified that bronchoscopy and bronchoalveolar lavage are options and added optional lung biopsy to the ILD/pneumonitis investigations.	To align with AstraZeneca Dato-DXd program standards to rule out cardiac etiology.	Substantial
Section 8.2.5.3, ILD/Pneumonitis Investigation Section 8.5.1, Pharmacokinetics	Removed the requirement for a blood sample for PK in the case of suspected ILD/pneumonitis.	No longer within the scope of the study.	Non-substantial
Section 8.2.5.5, Ophthalmologic Assessments Section 8.3.11, Adverse Events of Special Interest	Added that the assessments are to be performed by an ophthalmologist, or if unavailable, another licensed eye care provider.	To align with AstraZeneca Dato-DXd program standards.	Substantial
Section 8.2.5.5, Ophthalmologic Assessments	Added alternative to fluorescein staining, ocular symptoms to be considered during assessment, reporting of assessment results and use of additional eye medications.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 8.2.5.6, Oral Care Plan Appendix I2, Restricted, Prohibited, and Permitted Concomitant Medication/Therapies, Table 18	Added details of use of prophylactic mouthwash and cryotherapy.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 8.3, Adverse Events and Serious Adverse Events	Added requirements for reporting Grade ≥ 3 ocular surface toxicity events.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 8.3.1, Time Period and Frequency for Collecting AE and SAE Information	Added specific AEs that should be reported within 24 hours of the investigator becoming aware.	To align with AstraZeneca program standards.	Substantial
Section 8.3.5, Adverse Events Based on Examinations and Tests	Added that ECOG performance status and ophthalmologic assessments will be summarized in the CSR.	To align with AstraZeneca program standards.	Non-substantial
Section 8.3.11, Adverse Events of Special Interest	Removed combined elevations of aminotransferases and bilirubin. Added the actions to be taken for ILD/pneumonitis cases. Clarified dry eye is an identified risk and keratitis is a potential risk within the ocular surface toxicity AESI.	To align with AstraZeneca Dato-DXd program standards.	Substantial
Section 8.3.14.1, Maternal Exposure	Added that AstraZeneca 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.	To align with AstraZeneca Dato-DXd program standards.	Substantial
Section 8.6.3, Other Study Related Biomarker Assessments	Added reasons for additional exploratory analyses.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 8.8, Medical Resource Utilization and Health Economics	Added variables to be captured in the HOSPAD eCRF module.	To align with AstraZeneca program standards.	Non-substantial
Appendix A7, Data Quality Assurance	Increased the record and document retention time to 25 years.	To align with updated AstraZeneca Global Retention and Destruction standards.	Substantial
Appendix A7, Data Quality Assurance	Added medical oversight responsibility.	To align with AstraZeneca program standards.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Appendix I2, Guidance Regarding Potential Interactions with Concomitant Medications	Added information regarding concomitant use of Dato-DXd and CYP3A inhibitors and drugs that inhibit OATP1B1, OATP1B3, MATE2-K, P-gp, BCRP, and MRP1.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Appendix I2, Restricted, Prohibited, and Permitted Concomitant Medication/Therapies, Table 17	Added palliative radiotherapy.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Appendix I2, Restricted, Prohibited, and Permitted Concomitant Medication/Therapies, Table 18	Added other investigational therapeutic agents.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Appendix I2, Restricted, Prohibited, and Permitted Concomitant Medication/Therapies, Table 19	Added additional supportive medications/therapies.	To align with AstraZeneca program standards.	Non-substantial
Appendix J, Instructions Related to COVID-19	Added requirement if PCR testing is not available.	To align with AstraZeneca program standards.	Non-substantial
Appendix K2, Rescreening of Participants to Reconfirm Study Eligibility	Rescreening period extended for those participants who have entered rescreening. Updated to allow for participants to remain in screening until reconfirmation of eligibility.	To accommodate enrolment of participants during periods of study disruption, in alignment with established study processes already in place.	Substantial
Throughout	Minor changes to protocol wording, tables and figures, and editorial and document formatting revisions.	To align with project standard or to provide clarification.	Non-substantial

Amendment 1 (27 August 2021)

Overall Rationale for the Amendment:

The overall rationale for the amendment is to provide additional guidance for investigators on the monitoring and management of ocular surface toxicities potentially associated with Dato-DXd, the management of Grade 3 non-hematologic toxicities, as well as clarifying the Oral Care Protocol (OCP) to be used on this study. Furthermore, the schedule of assessments and inclusion/exclusion criteria were updated.

The rationale for each of these changes is provided in the table below:

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Title Page	Added EudraCT number.	Added EudraCT number as it has become available.	Non-substantial
Section 1.1, Synopsis, Overall Design Section 9.2, Sample Size Determination	Updated number of participants to be enrolled from 900 to 1000.	Updated number of participants enrolled based on available feasibility recruitment data. The number of participants to be randomized remains unchanged.	Non-substantial
1.2 Schema	Removed PARP inhibitors from being considered a prior line of chemotherapy.	To ensure that enrolled participants have received at least one prior line of chemotherapy.	Substantial
Section 1.3, Schedule of Assessments, Table 1 Section 8.2.5.5, Ophthalmologic Assessments	**Ophthalmological Assessment:** Updated SoA for ophthalmologic assessments to occur every 3 cycles from C1D1(within 14 days prior to scheduled cycle Day 1 visit), in addition to as clinically indicated; updated footnote "l" to provide additional clarifications around the ophthalmologic assessments. Section 8.2.5.5 has additional details around ophthalmologic assessments and care.	To help prevent ocular surface toxicities, and to monitor and treat these events should they arise.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 1.3, Schedule of Assessments, Table 1 Section 8.2.5.6, Oral Care Plan	**Oral Care Plan:** Oral Care Plan added to SoA; updated footnote "m" and created section 8.2.5.6 to provide additional details and guidance around daily oral care.	The Oral Care Plan is designed to mitigate the risk of oral mucositis/stomatitis. This was previously listed in section 6.6.1, Table 5, but has been moved to SoA and new section created (8.2.5.6) to ensure introduction of this plan for participants at the appropriate time.	Substantial
Section 2.3.1.1, Risk Assessment – Dato-DXd Section 8.3.11, Adverse Events of Special Interest	Ocular surface toxicity was added to the list of AESIs, and mitigations were added.	For participant safety, as ocular surface toxicity has been noted in some participants treated with Dato-DXd. Associated monitoring by ophthalmologic assessments and a dedicated safety review will be performed.	Substantial
Section 5.1, Inclusion Criteria #3	Removed PARP inhibitors from being considered a prior line of chemotherapy.	To ensure that enrolled participants have received at least one prior line of chemotherapy.	Substantial
Section 5.1, Inclusion Criteria #8	Hemoglobin level unit of measurement corrected to g/dL.	Correction of incorrect unit of measurement listed in initial version of CSP.	Non-substantial
Section 5.2, Exclusion Criteria #9	Additional note added to Exclusion Criteria #9 regarding ineligibility of participants found to have ILD/pneumonitis on baseline screening chest CT.	To ensure participants enrolled do not have active ILD.	Substantial
Section 6.2.1.2, Administration of Dato-DXd	Updated total cumulative time from dilution start time until end of infusion for Dato-DXd.	To align with updated handling instructions.	Non-substantial
Section 6.2.1.2, Administration of Dato-DXd	Added guidance around dose re-calculation if participant's weight changes during the study.	Original wording is lacking information important for correct dose re-calculation.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 6.6.1, Table 5: Dose Modifications for Non-hematologic and Hematologic Toxicity Related to Dato-DXd	Amended dose reduction thresholds and added guidance around optimizing use of prophylactic and supportive medications.	For participant safety, emphasis has been placed on providing prophylactic/supportive medications (when appropriate); in addition, dose reductions for Grade 3 toxicities (regardless of time of resolution) have been added for most non-hematologic toxicities.	Substantial
Section 7.1.3, Follow-up for Survival	Specified that local death registries may be used to obtain survival status information.	To clarify options for gathering survival data, in line with AZ standards.	Non-substantial
Section 8.2.4, Table 7	Updated list of acceptable values for leukocyte differential count to now include percentages.	To accommodate sites only able to provide a percentage value, as absolute count is not key.	Non-substantial
Section 9.3, Populations for Analysis	Added Ophthalmologic Analysis Set (OAS).	Added analysis for potential risk of ocular surface toxicity, and terminology clarification.	Substantial
Section 9.4.2.1, Efficacy, Primary Endpoints, Table 10	Added 'subsequent anticancer therapy' to list of sensitivity analyses.	Additional sensitivity analysis to assess robustness of PFS dual primary analysis.	Substantial
Section 9.4.2.1.3, PFS Sensitivity Analyses	Added language regarding subsequent anticancer therapy.	Additional sensitivity analysis to assess robustness of PFS dual primary analysis.	Substantial
Section 9.4.2.1.5, Subgroup Analysis	Added two additional subgroups: prior use of taxanes and/or anthracyclines, and pre-selected choice of chemotherapy. Clarified that forest plot of the PFS hazard ratios will be produced for each level of the subgroups.	More detailed subgroup analysis to provide additional data, and terminology clarification.	Substantial
Section 9.4.2.2.8, Clinical Outcome Assessments	Updated analysis language.	To clarify that clinically meaningful change thresholds will be based on pooled data, not the actual TTD endpoint analyses.	Non-substantial
Section 9.6.3, Ophthalmologic Data Review Committee	Added details around the independent Ophthalmologic Data Review Committee.	Data review of participant safety with regard to ophthalmologic assessments.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Appendix I, Table 19, Supportive Medications/Therapies	Updated details around prophylactic/supportive stomatitis/oral mucositis agents.	To mitigate risk of stomatitis for participant safety.	Non-substantial
Throughout	Minor changes to protocol wording, tables and figures.	To align with project standard or to provide clarification.	Non-substantial
Throughout	Minor editorial and document formatting revisions.	To further clarify.	Non-substantial

Appendix L Country-Specific Addendums to the Protocol

L 1 Country-specific Requirements for Brazil

Table L20 Country-specific Requirements for Brazil (Effective 15 September 2022)

Section # and Name	Description of Change with Reason
▪ **Table 1: Informed consent: genetic sample and analysis (optional)** ▪ **Item 5.1 – Inclusion Criteria #16: "**Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of sample for optional genetic research that supports Genomic Initiative**"** ▪ **Item 6.3.1 – Participant Enrolment ("**Obtain signed informed consent for the optional Genomics Initiative") ▪ **Item 8.7 – Optional Genomics Initiative Sample** ▪ **Item 9.4.4.1 - Optional Exploratory Genetic Sample** ▪ **Appendix D – Optional Genomics Initiative Sample**	AZ clarifies that the information related to the Optional Genetic Research described in the items/appendix is not applicable for the Brazilian Research Participants since Brazil will not take part in the Optional Genetic Research (Genomic Initiative).
▪ **Item 5.1 – Inclusion Criteria - #13:** "(…) Contraceptive use by men or women should be consistent with local regulations (…)". ▪ **Item 5.1 – Inclusion Criteria – #15: "(…)** Female participants must be post-menopausal for at least 1 year, surgically sterile, or using one highly effective form of birth control **(…)"** ▪ **Item 5.1 – Inclusion Criteria – #16: "**Male participants who intend to be sexually active with a female partner of childbearing potential must be surgically sterile or using an acceptable method of contraception **(…)"** ▪ **Item 5.3 – Lifestyle Considerations: "**Participants must follow the contraception requirements outlined in Appendix G."	AZ clarifies that the research participant will receive the contraceptive method chosen in common agreement with the Study Doctor, with no costs for her/his health insurance and public health system. Additionally, AZ clarifies that, according to Brazilian Resolution 466/12, item III.2.t, if the research participant has sexual relationship only with partner(s) with the same gender, there is no need to use contraceptive methods to participate in this study.

Section # and Name	Description of Change with Reason
▪ **Appendix G- Contraception Requirements**	
▪ **Item 5.2 - Exclusion Criteria - #21:** **"**Participation in another clinical study with a study intervention or investigational medicinal device administered in the last 4 weeks prior to first dosing (…)"	AZ clarifies that, according to Brazilian Resolution CNS/MS 251/97, item III.2.j, the study doctor should recommend that no individual be selected as research participant before a year has passed from her participation in another research, unless that individual were to directly benefit from it.
▪ **Item 1.1 – Synopsis - Intervention Groups and Duration: "**Continued treatment with the same study drug post-progression may be allowed, based on prior discussion with study physician on case-by-case basis" ▪ **Item 4.1 – Overall Design** ▪ **Item 6.1.1.1 – Duration of Treatment**	AZ clarifies that after the end of the research participant participation in the study, in accordance with the Resolutions of Health National Council, AstraZeneca is committed to guarantee the free and indefinite access to the study medication, if it has been shown effective (for example, until disease progression – worsening of your cancer – or toxicity) and indicated by the Doctor.
▪ **Item 8.5 – Human Biological Samples –** This item states the following: "Samples may be stored for a maximum of 15 years from the end of the study (as defined in Section 4.4) in line with consent and local requirements, after which they will be destroyed/repatriated. PK and ADA samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses. Samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR. Remaining sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years from the end of the study (as defined in Section 4.4). Additional use includes, but is not limited to, further characterization of any ADAs, evaluation of novel and emerging biomarkers, confirmation and/or requalification of the assay,	AZ clarifies that the information described on these items are not applicable for the samples collected from Brazilian research participants. For Brazil, the biological samples (tumor and blood) will be used as stated in the attached document "Sample Receipt and Storage Process". We confirm that there will be no future additional analysis different from those detailed on this document. After processing the biological samples and receiving the results, the remaining biological samples will be stored only during the execution of this specific project for repetition and/or confirmation of the tests previously performed when needed and, after that, discarded. AZ also clarifies that from CSP v2.0 and CSP v3.0 implementation, Brazil will no longer participate in the exploratory analyses. The samples collected under CSP v1.0 will be analyzed and destroyed after the end of the study. For tumor samples (biopsies), the remaining samples will be repatriated (sent back to the hospital department who provided it) immediately after all study analysis has been completed.

Section # and Name	Description of Change with Reason
and/or diagnostic assay development. The results from future analysis will not be reported in the CSR.**"** ▪ **Item 8.6 - Human Biological Sample Biomarkers:** "(…) Samples may be retained in all regions to allow for potential diagnostic development (…)" ▪ **Appendix A – Item A3 - Informed consent process: "(…)** The investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. (..)" ▪ **Appendix C – Item C1 – Chain of custody of biological samples** ("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 life cycle"). ▪ **Appendix J - Instructions Related to SARS-COV-2 (COVID-19) -** If the participant consents, the remaining serum samples will also be stored for future analysis.	
▪ **Item 8.5 – Human Biological Samples;** ▪ **Items 8.5.1 – Pharmacokinetics;** ▪ **Item 8.5.2 – Immunogenicity Assessments;** ▪ **Item 8.6 – Human Biological Sample Biomarkers;** ▪ **Item 8.6.1 – Collection of Mandatory Samples for Biomarker analysis;** ▪ **Item 8.6.2 – Collection of Optional Biomarker Samples;** ▪ **Item 8.6.3 – Other Study-related Biomarker Assessments**	Related to the tests described on these items, AZ clarifies that all tests which may be done with biological samples during the study (tumor and blood) are listed on the attached document "Sample Receipt and Storage Process". No additional tests will be performed with the samples provided by Brazilian research participants. AZ clarifies that from CSP v2.0 and CSP v3.0 implementation, the information related to Exploratory Analysis described in the items/appendix listed are also not applicable for the Brazilian Research Participants since Brazil will no longer participate in the any exploratory analysis (biomarker and genetic). The samples collected under CSP v1.0 will be analyzed and destroyed after the end of the study.
▪ **Appendix A – Item A3 - Informed consent process**	This item points that a copy of the signed ICF is given to each patient or his/her legal representative. We clarify that, according to the Brazilian Resolution

Section # and Name	Description of Change with Reason
	CNS/MS 466/12, item IV.3.f, the principal investigator must ensure that another original of the signed ICF is given to each research participant.

Moreover, the FDA has mandated that for additional study participant safety, dose reductions by 1 level for Grade 3 toxicities (regardless of time to resolution) be added for most non-hematologic toxicities.

<table>
<tr><th>Section # and Name</th><th>Description of Change with Reason</th></tr>
<tr><td>▪ Section 6.6.1, Table 5: Dose Modifications for Non-hematologic and Hematologic Toxicity Related to Dato-DXd</td><td>The following sections do not specify dose reduction by 1 level for Grade 3 toxicities:
<table>
<tr><th colspan="2">Other Laboratory Adverse Events</th></tr>
<tr><td>Grade 3</td><td>Delay dose until resolved to ≤ Grade 1 or baseline level, if determined by the investigator to be clinically significant.</td></tr>
<tr><td>Grade 4</td><td>Discontinue participant from study treatment.</td></tr>
<tr><th colspan="2">Other Non-laboratory Adverse Events</th></tr>
<tr><td>Grade 3</td><td>Delay dose until resolved to ≤ Grade 1 or baseline, if determined by the investigator to be clinically significant.</td></tr>
<tr><td>Grade 4</td><td>Discontinue participant from study treatment.</td></tr>
</table>
The text should read as follows:
<table>
<tr><th colspan="2">Other Laboratory Adverse Events</th></tr>
<tr><td>Grade 3</td><td>Delay dose until resolved to ≤ Grade 1 ~~or baseline level~~ and then reduce by 1 level, if determined by the investigator to be clinically significant.</td></tr>
<tr><td>Grade 4</td><td>Discontinue participant from study treatment.</td></tr>
<tr><th colspan="2">Other Non-laboratory Adverse Events</th></tr>
<tr><td>Grade 3</td><td>Delay dose until resolved to ≤ Grade 1 ~~or baseline~~ and then reduce by 1 level, if determined by the investigator to be clinically significant.</td></tr>
<tr><td>Grade 4</td><td>Discontinue participant from study treatment.</td></tr>
</table></td></tr>
</table>

L 2 Country-specific Requirements for Canada

Table L21 Country-specific Requirements for Canada (Effective 13 December 2022)

Section # and Name	Description of Change with Reason
A7 – Data Quality Assurance	Prior text: Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years from the end of the study (as defined in the protocol) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. Modified text: Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years from the end of the study (as defined in the protocol) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. *Rationale: Health Canada reduced the retention period for clinical trial records for drugs and natural health products from 25 years to 15 years under the Food and Drug Regulations and Natural Health Products Regulations.*

L 3 Country-specific Requirements for France

Table L22 Country-specific Requirements for France (Effective 10 November 2022)

Section # and Name	Description of Change with Reason
Section 1.3, Schedule of Activities: Table 1	Change: Addition of Footnote 'cc' to clarify that Clinical Outcome Assessments are not applicable to date to participants in France. **Clinical Outcome Assessments** EORTC QLQ-C30, EORTC IL116, PGIS, EQ-5D-5L[cc] | | C1D1, Q3W from C1D1 for the first 48 weeks, and Q6W thereafter until EoT | At EoT visit, then Q6W (relative to C1D1) after EoT until 18 weeks after PD | | | | Section 8.1.5 PRO-CTCAE, EORTC IL117, PGI-TT[cc] | | C1D1, every week from C1D1 for the first 12 weeks, and Q3W thereafter until EoT | X | | | | Section 8.1.5 PGIC[cc] | | Q6W from C1D1 for the first 12 weeks (ie, 6 weeks and 12 weeks from C1D1) | | | | | Section 8.1.5 [bb] Only applicable to participants who are required to attend study visits on Day 8 of each cycle (ie, those randomized to receive Investigators Choice of Chemotherapy which are administered by IV infusion). [cc] **Not applicable to participants in France.** Note: All assessments on treatment days are to be performed prior to study intervention administration, unless otherwise indicated. Following the DCO for the primary analysis, PK assessments will be discontinued. Data collection following final study analysis until the end of the study is described in Section 8. Reason: Electronic Patient Reported Outcomes (ePROs) will not be collected from participants in France at this time until further notice. This is due to ePRO vendor (Medable) non-compliance to date with French CNIL regulations which require processing of directly identifying data and health data by the same vendor to remain excluded.
Section 8.1.5, Clinical Outcome Assessments (COA)	Change: Addition of note to clarify that PROs will not be collected to date from participants in France. The following PRO instruments will be administered in this study (see Appendix H): • EORTC QLQ-C30 (see Section 8.1.5.1) • EORTC IL116: selected breast and arm symptom scales from EORTC QLQ-BR45/IL (see Section 8.1.5.2) • Selected items from PRO-CTCAE (see Section 8.1.5.3) • EORTC IL117: selected symptomatic AE items from EORTC IL (see Section 8.1.5.4) • PGI-TT (see Section 8.1.5.5) • PGIS (see Section 8.1.5.6) • PGIC (see Section 8.1.5.7) • EQ-5D-5L (see Section 8.1.5.8) **Note : PROs will not be collected to date from participants in France**

	Reason: Electronic Patient Reported Outcomes (ePROs) will not be collected from participants in France at this time until further notice. This is due to ePRO vendor (Medable) non-compliance with French CNIL regulations which require processing of directly identifying data and health data by the same vendor to remain excluded.

Table L23 Country-specific Requirements for France (Effective 21 January 2022)

Section # and Name	Description of Change with Reason
Section 5.1, Inclusion Criteria: *Criterion #3*	Change: Progressed on or not suitable for endocrine therapy per investigator assessment, and treated with 1 to 2 lines of prior standard of care chemotherapy in the inoperable/metastatic setting. Participant must have documented progression on their most recent line of chemotherapy. Note: • If a chemotherapy drug is changed within 28 days of use to another drug in the same class (ie, antimetabolite to antimetabolite) for any reason, the first drug is not counted as a line (Flatiron 2019). Targeted agents (such as mTOR inhibitors, PD-1/PD-L1 inhibitors, PARP inhibitors), endocrine therapies, and CDK4/6 inhibitors on their own do not contribute to the count of prior lines of chemotherapy; however, regimens with such agents in combination with metastatic chemotherapy should be classified as one line of chemotherapy. • **Patients must have been treated with (neo)adjuvant anthracycline and/or taxane, if they received systemic treatment in the (neo)adjuvant setting, unless anthracycline and/or taxane was contraindicated or not considered the best treatment option for the subject in the opinion of the treating physician.** Reason: The French Regulatory Authority (ANSM) request to precise the standard of care chemotherapy that patients should have received prior to ennrolment. According to the ESMO guidelines, in the absence of medical contraindications or patient concerns, anthracycline- or taxane-based regimens, preferably as single agents, would usually be considered as first-line chemotherapy for HER2-negative advanced breast cancer in those patients who have not received these regimens as (neo)adjuvant treatment. Moreover, capecitabine, vinorelbine or eribulin (and gemcitabine as additional choice) are recommended for patients pre-treated with an anthracycline and a taxane. Thus, the sponsor should ensure that patients have had the opportunity to receive taxanes and anthracyclines (if not contraindicated) along the course of their disease. This request is in line with the EMA scientific advice EMA/SA/0000060979 (22/07/2021).
Section: 6.6.1, Dato-	Change:

<table>
<tr><td>DXd Dose Modification/Toxicity Management Guidelines: Table 5</td><td>
<table>
<tr><th colspan="2"><u>Anemia</u></th></tr>
<tr><td>Grade 3
(Hemoglobin < 8.0 g/dL; transfusion indicated)</td><td>Delay dose until resolved to ≤ Grade 2, then maintain dose.</td></tr>
<tr><td>Grade 4
Life-threatening consequences; urgent intervention indicated</td><td>Delay dose until resolved to ≤ Grade 2, then reduce dose by 1 level.
Permanently discontinue Dato-DXd, if recurrent grade 4/life-threatening anemia occurs after dose reduction by 1 level.</td></tr>
</table>
<u>Reason:</u>

The French Regulatory Authority (ANSM) request to modify the protocol so as to permanently discontinue Dato-DXd in case of recurrent life-threatening Grade 4 anemia after one level dose reduction.
</td></tr>
<tr><td>Section 6.4, Concomitant Therapy</td><td>
<u>Change:</u>

Any concomitant treatment, procedure, vaccine, or other medication considered necessary by the investigator for the participant’s safety and wellbeing (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 28 (+7) day safety follow-up period following the last dose of study intervention must be recorded in the eCRF along with:

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

The Study Clinical Lead 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.
</td></tr>
</table>

	Restricted, prohibited, and permitted concomitant medications/therapies are described in more detail in Appendix I2. For participants randomized to receive ICC, refer to the local Prescribing Information with regard to warnings, precautions, and contraindications. Guidance regarding potential interactions with concomitant medications is provided in Appendix I1. **For management of patients receiving capecitabine, gemcitabine, eribulin mesylate and vinorelbine, investigators must refer to local prescribing information and to the SmPC website (https://base-donnees-publique.medicaments.gouv.fr/), especially for information concerning contraindications, special warnings and precautions, posology adaptation in case of toxicity, monitoring, as well as medications that are contraindicated or that must be used with caution.** Reason: The French Regulatory Authority (ANSM) request to modify the protocol in order to inform the investigators that they must refer to the SmPC of capecitabine, gemcitabine, eribulin mesylate and vinorelbine for the management of patients, especially concerning contraindications, special warnings and precautions, posology adaptation in case of toxicity, monitoring, as well as medications that are contraindicated or that must be used with caution, and, enclose the SmPC or refer to the website: http://base-donnees-publique.medicaments.gouv.fr which presents the updated version of the SmPCs of medications.
Section 1.3, Schedule of Activities: *Table 1, Footnote 'P'*	Change: Within 72 hours before randomization for all female subjects of childbearing potential; a positive urine pregnancy test result must immediately be confirmed using a serum test. Perform repeat pregnancy tests (urine or serum test per institutional guideline) within 72 hours before each cycle of study intervention and at end of treatment. **Pregnancy testing is to be repeated monthly during 7 months after treatment discontinuation.** Reason: The French Regulatory Authority (ANSM) request to modify the Table 1 Schedule of Activities and correspondent sections so as to extend the duration for monthly pregnancy testing to 7 months after treatment

	discontinuation, in order to align with post-treatment contraception duration.
Section 8.2.4, Clinical Safety Laboratory Assessments	Change: A negative result from a serum pregnancy test (which must have a sensitivity of at least 25 mIU/mL) must be available at the screening visit. Pregnancy tests should be conducted within 72 hours prior to randomization for all female participants of childbearing potential. Repeat pregnancy tests (urine beta-human chorionic gonadotropin or serum test per institutional guideline) should be performed 72 hours before infusion of each cycle and at the EoT visit. **Pregnancy testing is to be repeated monthly during 7 months after treatment discontinuation.** If a positive urine pregnancy test result is confirmed using a serum test in a female participant of childbearing potential, then the participant should not be treated. Reason: The French Regulatory Authority (ANSM) request to modify the Table 1 Schedule of Activities and correspondent sections so as to extend the duration for monthly pregnancy testing to 7 months after treatment discontinuation, in order to align with post-treatment contraception duration.

L 4 Country-specific Requirements for Germany

Table L24 Country-specific Requirements for Germany (Effective 15 November 2022)

Section # and Name	Description of Change with Reason
N/A	Editorial change: adaption of the referenced CSP version
N/A	According to AstraZeneca's procedures the Clinical Study Protocol (CSP) version 4.0 from 10 October 2022 was signed by the sponsor electronically only. This Addendum to the CSP contains the signature of the National Coordinating Investigator as requested by local regulatory authority. The protocol version 4.0 has no further impact on the German addendum and therefore no additional changes were made.
N/A	According to AstraZeneca's procedures the Clinical Study Protocol (CSP) version 3.0 from 19 April 2022 was signed by the sponsor electronically only.
Overall study conduct, tumor sampling	No invasive sampling for fresh tumor specimen for the purpose of testing with companion diagnostics will be done for study participants. Therefore, no fresh biopsies will be taken during the study and only archived residual tumor material will be used at Screening. No optional paired tumor biopsy and no optional fresh tumor biopsy at progression will be conducted. Study participants will be informed in ICF accordingly.
2.3.2 Benefit assessment	"Additionally, at the time of disease progression, participants will be offered an optional tumor biopsy, which will provide real-time next-generation sequencing results from the FoundationOne®CDx, that may help guide next treatment options." Is deleted from section 2.3.2
8.6.2 Collection of Optional Biomarker Samples	"Optional tumor tissue samples for exploratory biomarker research • Paired tumor biopsy: A baseline biopsy will be taken (where the participant has provided informed consent) before initial dosing of study intervention (at screening or pre-dose on C1D1), and a paired (second) biopsy will be taken on-treatment. The paired on-treatment biopsy can be collected C2D1 and C2D7. On-treatment sample may also be collected outside of this specified timepoint with prior agreement from the Sponsor. Paired preclinical treatment and on-treatment tumor samples must be obtained from the same lesion where clinically feasible to maximize the utility for assessment of pharmacodynamic changes. These optional paired tumor samples will be mandatory at select sites. • Tumor biopsy on disease progression: An additional tumor biopsy sample should be obtained at termination of treatment/documented RECIST 1.1 disease progression in participants that have signed the additional optional

Section # and Name	Description of Change with Reason
Table 1	consent. These samples will be used to explore mechanisms of resistance. The on-study provision of tumor tissue is encouraged only if clinically appropriate and not considered detrimental to participant care. Biopsies at study entry, on treatment, and progression are optional for the majority of participants in this study, and participants will not be excluded from the study if these samples are not collected. These optional biopsy samples will be mandatory at select sites." Is deleted from Section 8.6.2 "Optional tumor biopsy (FFPE/FF) at Progression" and "Optional paired tumor biopsy (FFPE/FF)" is deleted from Table 1
Section 7.1 Discontinuation of Study Intervention	The wording in this section is changed from Participants may be discontinued from study intervention in the following situations: to Participants ***must*** be discontinued from study intervention in the following situations: • RECIST 1.1-defined radiological progression (refer to Section 8.1.1 and Appendix F). • An AE that, in the opinion of the investigator or AstraZeneca, contraindicates further dosing. • Any AE that meets criteria for discontinuation defined in the TMGs (see the Annex document to this CSP), or as defined in the local Prescribing Information for the ICC agents. • 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 (refer to Appendix G and Section 8.3.14). • Initiation of subsequent anticancer therapy, including another investigational agent. Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study. Crossover within the study is not permitted.
Appendix G Contraception Requirements	Women of childbearing potential who are not totally sexually abstinent (ie, refraining from heterosexual intercourse during the entire period of risk

Section # and Name	Description of Change with Reason
G1 Female participants	associated with study interventions) and intend to be sexually active with a non-sterilized male partner must use at least 1 highly effective method of contraception (Table 16). Is changed to: Women of childbearing 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-sterilized male partner must use at least 1 highly effective non-hormonal method of contraception (Table 16). Hormonal methods of contraception must not be used by female patients participating in this study.

L 5 Country-specific Requirements for India

Table L25 Country-specific Requirements for India (Effective 02 November 2021)

<table>
<tr><th>Section # and Name</th><th>Description of Change with Reason</th></tr>
<tr><td>Section 6.6.1, Table 5: Dose Modifications for Non-hematologic and Hematologic Toxicity Related to Dato-DXd</td><td>The following sections do not specify dose reduction by 1 level for Grade 3 toxicities:
<table>
<tr><th colspan="2">Other Laboratory Adverse Events</th></tr>
<tr><td>Grade 3</td><td>Delay dose until resolved to ≤ Grade 1 or baseline level, if determined by the investigator to be clinically significant.</td></tr>
<tr><td>Grade 4</td><td>Discontinue participant from study treatment.</td></tr>
<tr><th colspan="2">Other Non-laboratory Adverse Events</th></tr>
<tr><td>Grade 3</td><td>Delay dose until resolved to ≤ Grade 1 or baseline, if determined by the investigator to be clinically significant.</td></tr>
<tr><td>Grade 4</td><td>Discontinue participant from study treatment.</td></tr>
</table>
The text should read as follows:
<table>
<tr><th colspan="2">Other Laboratory Adverse Events</th></tr>
<tr><td>Grade 3</td><td>Delay dose until resolved to ≤ Grade 1 ~~or baseline level~~ and then reduce by 1 level, if determined by the investigator to be clinically significant.</td></tr>
<tr><td>Grade 4</td><td>Discontinue participant from study treatment.</td></tr>
<tr><th colspan="2">Other Non-laboratory Adverse Events</th></tr>
<tr><td>Grade 3</td><td>Delay dose until resolved to ≤ Grade 1 ~~or baseline~~ and then reduce by 1 level, if determined by the investigator to be clinically significant.</td></tr>
<tr><td>Grade 4</td><td>Discontinue participant from study treatment.</td></tr>
</table></td></tr>
</table>

The global clinical study protocol and its amendments (as applicable) for the study is to be read as follows:

<table>
<tr><th>Section # and Name</th><th>Description of Change with Reason</th></tr>
<tr><td>8.3.5 Adverse Events Based on Examinations andTests</td><td>Previous Text:
The results from the CSP-mandated laboratory tests, vital signs, physical examinations, ECGs, and echocardiogram/MUGA scans will be summarized in the CSR.
Deterioration as compared with baseline in protocol-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 not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, e.g., dose adjustment or study intervention interruption).
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 (e.g., anemia versus low hemoglobin value). In the absence of clinical signs</td></tr>
</table>

Section # and Name	Description of Change with Reason
	or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s). Deterioration of a laboratory value, which 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. **Revised Text:** The results from the CSP-mandated laboratory tests, vital signs, physical examinations, ECGs, and echocardiogram/MUGA scans will be summarized in the CSR. Deterioration as compared with baseline in protocol-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 not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, e.g., dose adjustment or study intervention interruption). 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 (e.g., anemia versus low hemoglobin 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, which 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. However, all the events occurring at the Indian sites (the reason whatsoever) that meet the criteria for seriousness (SAEs) from the time of signing the ICF, throughout the treatment period, including the safety follow up period (28 [+7] days after the discontinuation of study intervention) and if an event that starts after the defined safety follow-up period noted above and is considered to be due to a late onset toxicity to the study intervention, should be reported as an SAE per local regulatory requirements to the Sponsor (appropriate AstraZeneca representatives), Indian regulatory authority and the concerned Ethics Committees in accordance with New Drugs and Clinical Trials Rules, 2019.

Section # and Name	Description of Change with Reason
	Reason for change: Per Indian regulatory requirements, all the events that meet criteria for seriousness have to be reported expeditiously to the Sponsor, Indian regulatory authority and the concerned Ethics Committees.
8.3.7 Disease Progression	**Previous Text:** 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 metastases or progression of existing metastasis to the primary cancer under study should be considered as PD and not an AE. Events, which are unequivocally due to PD, should not be reported as an AE during the study. Death due to disease progression should be recorded on the Death eCRF. **Revised Text:** 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 metastases or progression of existing metastasis to the primary cancer under study should be considered as PD and not an AE. Events, which are unequivocally due to PD, should not be reported as an AE during the study. Death due to disease progression should be recorded on the Death eCRF. However, all the events occurring at the Indian sites (the reason whatsoever) that meet the criteria for seriousness (SAEs) from the time of signing the ICF, throughout the treatment period, including the safety follow up period (28 [+7] days after the discontinuation of study intervention) and if an event that starts after the defined safety follow-up period noted above and is considered to be due to a late onset toxicity to the study intervention, should be reported as an SAE per local regulatory requirements to the Sponsor (appropriate AstraZeneca representatives), Indian regulatory authority and the concerned Ethics Committees in accordance with New Drugs and Clinical Trials Rules, 2019. **Reason for change:** Per Indian regulatory requirements, all the events that meet criteria for seriousness have to be reported expeditiously to the Sponsor, Indian regulatory authority and the concerned Ethics Committees.
8.3.10 Deaths	**Previous Texts:** All deaths that occur during the study intervention period, or within the protocol-defined 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.

Section # and Name	Description of Change with Reason
	• 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 protocol-defined 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 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. **Revised Text:** All deaths that occur during the study intervention period, or within the protocol-defined 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 protocol-defined 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 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. However, all the events occurring at the Indian sites (the reason whatsoever) that meet the criteria for seriousness (SAEs) from the time of signing the ICF, throughout the treatment period, including the safety follow up period (28 [+7] days after the discontinuation of study intervention) and if an event that starts

Section # and Name	Description of Change with Reason
	after the defined safety follow-up period noted above and is considered to be due to a late onset toxicity to the study intervention, should be reported as an SAE per local regulatory requirements to the Sponsor (appropriate AstraZeneca representatives), Indian regulatory authority and the concerned Ethics Committees in accordance with New Drugs and Clinical Trials Rules, 2019. **Reason for change:** Per Indian regulatory requirements, all the events that meet criteria for seriousness have to be reported expeditiously to the Sponsor, Indian regulatory authority and the concerned Ethics Committees.

Study sites affected by this addendum:

This Clinical Study Protocol - Addendum affects all the study sites in India and will prevail if in conflict with any other section in the Clinical Study Protocol (CSP) (including its appendices).

L 6 Country-specific Requirements for United Kingdom

Table L26 Country-specific Requirements for United Kingdom (Effective 19 May 2022)

Section # and Name	Description of Change with Reason
Section 5.1 Inclusion Criteria #16	**Inclusion #16 states** - "Male participants who intend to be sexually active with a female partner of childbearing potential must be surgically sterile or using an acceptable method of contraception (see Appendix G) from the time of screening throughout the total duration of the study and the drug washout period (at least 4 months after the last dose of study intervention) to prevent pregnancy in a partner. Male participants must not donate or bank sperm during this same time period. Not engaging in heterosexual activity (sexual abstinence) for the duration of the study and drug washout period is an acceptable practice if this is the preferred usual lifestyle of the participant; however, periodic or occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception." **To clarify for the UK:** If administered with either Gemcitabine or Vinorelbine, non-sterilized male participants must use an acceptable method of contraception and refrain from donating or banking sperm from the time of screening throughout the total duration of the study and the drug washout period (i.e., at least 6 months after the last dose of study intervention).
Section 8.3.14.2 Paternal Exposure	To clarify specifically for non-sterilized male participants administered either Gemcitabine or Vinorelbine who intend to be sexually active with a female partner of childbearing potential, that they must use an acceptable method of contraception and refrain from donating or banking sperm from the time of screening throughout the duration of the study and the drug washout period (i.e., at least 6 months after the last dose of study intervention).
Appendix G, G2 Male Participants with a Female Partner of Childbearing Potential	To clarify specifically for non-sterilized male participants administered either Gemcitabine or Vinorelbine who intend to be sexually active with a female partner of childbearing potential, that they must use an acceptable method of contraception and refrain from donating or banking sperm from the time of screening throughout the duration of the study and the drug washout period (i.e., at least 6 months after the last dose of study intervention).

Appendix M Abbreviations

Abbreviation or Special Term	Explanation
5-HT3	5-hydroxytryptamine receptor
ADA	antidrug antibody
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
AxMP	auxiliary medicinal product
BCRP	breast cancer resistance protein
BICR	Blinded Independent Central Review
BID	twice daily
BoR	best objective response
CAP	College of American Pathologists
CD	cluster of differentiation
CHF	congestive heart failure
CI	confidence interval
ClinRO	clinician-reported outcome
C_{max}	maximum observed concentration
CNS	central nervous system
COA	clinical outcome assessment
COPD	chronic obstructive pulmonary disorder
COVID-19	coronavirus 2019-nCoV
CR	complete response
CRF	case report form
CrCl	calculated creatinine clearance
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation or Special Term	Explanation
ctDNA	circulating tumor DNA
CTIS	Clinical Trial Information System (EU)
CTR	Clinical Trial Regulation
CYP	cytochrome P450
Dato-DXd	Datopotamab deruxtecan (DS-1062a)
DCO	data cutoff
DCR	disease control rate
DILI	drug-induced liver injury
DLCO	diffusion capacity of the lungs for carbon monoxide
DNA	deoxyribonucleic acid
DoR	duration of response
DXd	MAAA-1181a
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
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EoT	end of treatment
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQoL 5-dimension, 5-level health state utility index
ER	estrogen receptor
EU	European Union
FDA	Food and Drug Administration
FEV1	forced expiratory volume – 1 second
FEV6	forced expiratory volume – 6 seconds
FF	fresh-frozen
FFPE	formalin fixed and paraffin embedded
FIH	first-in-human
FU	follow up
FVC	forced vital capacity
GCP	Good Clinical Practice

Abbreviation or Special Term	Explanation
GHS	global health status
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCP	health care professional
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HL	Hy's Law
HLT	High Level Term (MedDRA)
HOSPAD	Hospital Admission form
HR	hormone receptor
HRCT	high-resolution computed tomography
HRQoL	health-related quality of life
HRT	hormone replacement therapy
5-HT3	5-hydroxytryptamine 3
IA	interim analysis
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICC	Investigator's Choice Chemotherapy
ICF	informed consent form
ICH	International Council for Harmonisation
iCRO	imaging Contract Research Organization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	immunohistochemical
IL	item library
ILD	interstitial lung disease
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	Interactive Response Technology
ITT	intent-to-treat

Abbreviation or Special Term	Explanation
IV	intravenous
LVEF	left ventricular ejection fraction
MATE2-K	multidrug and toxin extrusion protein 2
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRP1	multidrug resistance-associated protein 1
mTOR	mammalian target of rapamycin
MTP	multiple testing procedure
MUGA	multigated acquisition
NCI	National Cancer Institute
NE	not evaluable
NIMP	non-investigational medicinal product
NK1	Neurokinin 1
NL	new lesion
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
NTL	non-target lesion
OAS	Ophthalmologic Analysis Set
OATP	organic anion transporting polypeptide
ObsRO	observer-reported outcome
ORR	objective response rate
OS	overall survival
PARP	poly (ADP-ribose) polymerase
PAS	pharmacokinetic analysis set
PD	progression of disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PEF	peak expiratory flow
PET	positron emission tomography
PFS	progression-free survival
PFS (Inv)	progression-free survival (as per investigator assessment)
PFS2	time to second progression or death
PGIC	Patients' Global Impression of Change
PGIS	Patients' Global Impression of Severity

Abbreviation or Special Term	Explanation
PGI-TT	Patient's Global Impression of Treatment Tolerability
P-gp	p-glycoprotein
PgR	progesterone receptor
PHL	potential Hy's Law
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
PS	Performance Status
PT	Preferred Term (MedDRA)
PTT	partial thromboplastin time
Q3W	every 3 weeks
Q6W	every 6 weeks
Q9W	every 9 weeks
QLQ-C30	30-item core quality of life questionnaire
QoL	quality of life
QTcF	QT interval corrected by Fridericia's formula
RANKL	receptor activator of nuclear factor-κB ligand
RECIST 1.1	Response Evaluation Criteria in Solid Tumours, Version 1.1
RNA	ribonucleic acid
RV	residual volume
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	safety analysis set
SD	stable disease
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SoC	standard of care
SpO_2	peripheral capillary oxygen saturation
TBL	total bilirubin
T-DXd	trastuzumab deruxtecan
TEAE	treatment emergent adverse event
TFST	time to first subsequent therapy
TL	target lesion
TLC	total lung capacity

Abbreviation or Special Term	Explanation
TMG	toxicity management guideline
TNBC	triple-negative breast cancer
TPV	third-party vendor
TROP2	trophoblast cell surface antigen 2
TSST	time to second subsequent therapy
TTD	time from the date of randomization to the date of deterioration
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
WBC	white blood cell
WOCBP	women of childbearing potential
w/v	weight per volume

11 REFERENCES

Aaronson et al 1993
Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.

Alberti et al 1992
Alberti S, Miotti S, Stella M, Klein CE, Fornaro M, Menard S, et al. Biochemical characterization of Trop-2, a cell surface molecule expressed by human carcinomas: formal proof that the monoclonal antibodies T16 and MOv-16 recognize Trop-2. Hybridoma 1992; 11(5): 539-45.

Allison et al 2020
Allison KH, Hammond MEH, Dowsett M, McKernin SE, Carey LA, Fitzgibbons PL, et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Guideline Update. Arch Pathol Lab Med;144(5):545-563. doi: 10.5858/arpa.2019-0904-SA. Epub 2020 Jan 13. PMID: 31928354.

André et al 2019
André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, et al; SOLAR-1 Study Group. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med 2019; 380(20): 1929-1940.

Bardia et al 2020
Bardia A, Tolaney SM, Loirat D, Punie K, Oliveira M, Rugo HS, et al. LBA17 ASCENT: A randomized Phase III study of Sacituzumab Govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC). Annals of Oncology 2020; 31(Suppl. 4): S1142-S1215.

Bardia et al 2021
Bardia A, Juric D, Shimizu T, et al. Datopotamab deruxtecan (Dato-DXd), a TROP2-directed antibody-drug conjugate (ADC), for triple-negative breast cancer (TNBC): Preliminary results from an ongoing phase 1 trial. Presented at: ESMO Breast Cancer Virtual Congress 2021; May 5-8, 2021; Virtual. Abstract LBA4. Accessed at: https://www.annalsofoncology.org/action/showPdf?pii=S0923-7534%2821%2901141-8. Last accessed 19 May 2021.

Barrios 2010
Barrios, C.H, Liu, MC, Lee, S.C, et al. Phase III randomized trial of sunitinib versus capecitabine in patients with previously treated HER2-negative advanced breast cancer. Breast Cancer Res Treat 2010; 121, 121–131.

Basch et al 2014
Basch E, Reeve BB, Mitchell SA, Clauser SB, Minasian LM, Dueck AC, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst. 2014 Sep 29;106(9):dju244. doi: 10.1093/jnci/dju244. PMID: 25265940; PMCID: PMC4200059.

Bjelic-Radisic et al 2020
Bjelic-Radisic V, Cardoso F, Cameron D, Brain E, Kuljanic K, da Costa RA, et al. An international update of the EORTC questionnaire for assessing quality of life in breast cancer patients: EORTC QLQ-BR45. Ann Oncol. 2020 Feb;31(2):283-288. doi: 10.1016/j.annonc.2019.10.027. Epub 2019 Dec 18. Erratum in: Ann Oncol. 2020 Apr;31(4):552. PMID: 31959345.

Blum et al 1999
Blum JL, Jones SE, Buzdar AU, LoRusso PM, Kuter I, Vogel C, et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. J Clin Oncol 1999; 17(2): 485-93.

Brufsky 2011
Brufsky AM, Mayer M, Rugo HS, Kaufman PA, Tan-Chiu E, Tripathy D, et al. Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence, treatment, and survival in patients from registHER. Clin Cancer Res 2011; 17(14):4834-43.

Burman et al 2009
Burman CF, Sonesson C, Guilbaud O. A recycling framework for the construction of Bonferroni based multiple tests. Stat Med 2009;28:739-61.

Capecitabine USPI 2015
Capecitabine USPI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020896s037lbl.pdf. Last accessed 27 April 2021.

Cardoso et al 2018
Cardoso F, Spence D, Mertz S, Corneliussen-James D, Sabelko K, Gralow J, et al. Global analysis of advanced/metastatic breast cancer: Decade report (2005-2015). Breast 2018; 39: 131-138.

Cardoso et al 2020
Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020 Dec;31(12):1623-1649.

Cortes et al 2011
Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet 2011; 377(9769): 914-23.

Domenech and Vogel 2001
Domenech GH, Vogel CL. A review of vinorelbine in the treatment of breast cancer. Clin Breast Cancer 2001; 2(2): 113-28.

Dueck et al 2015
Dueck AC, Mendoza TR, Mitchell SA, Reeve BB, Castro KM, Rogak LJ, et al. Validity and Reliability of the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). JAMA Oncol. 2015 Nov;1(8):1051-9. doi: 10.1001/jamaoncol.2015.2639. Erratum in: JAMA Oncol. 2016 Jan;2(1):146. PMID: 26270597; PMCID: PMC4857599.

EMA 2017
EMA. Guideline on the evaluation of anticancer medicinal products in man, September 2017. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-anticancer-medicinal-products-man-revision-5_en.pdf. Last accessed 28 April 2021.

EuroQol 2019
EuroQol Group. EQ-5D-5L User Guide: Basic information on how to use the EQ-5D-5L instrument, Version 3.0, September 2019. Available from: URL: https://euroqol.org/wp-content/uploads/2019/09/EQ-5D-5L-English-User-Guide_version-3.0-Sept-2019-secured.pdf. Accessed 18 December 2019.

FDA 2018
FDA. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. Guidance for Industry, December 2018. Available at: https://www.fda.gov/media/71195/download. Last accessed 28 April 2021.

FDA-NIH BEST Resource
FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016. Glossary. 2016 Jan 28 [Updated 2018 May 2]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK338448. Co-published by National Institutes of Health (US), Bethesda (MD).

Fornaro et al 1995
Fornaro M, Dell'Arciprete R, Stella M, Bucci C, Nutini M, Capri MG, et al. Cloning of the gene encoding Trop-2, a cell-surface glycoprotein expressed by human carcinomas. Int J Cancer 1995; 62(5): 610-8.

Gradishar et al 2005
Gradishar WJ, Tjulandin S, Davidson N, Shaw H, Desai N, Bhar P, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol 2005; 23(31): 7794-803.

Gridelli et al 1999
Gridelli C, Perrone F, Gallo C, et al. Single-agent gemcitabine as second-line treatment in patients with advanced non small cell lung cancer (NSCLC): a phase II trial. Anticancer Res 1999; 19:4535.

Harbeck et al 2019
Harbeck N, Penault-Llorca F, Cortes J, et al. Breast cancer. Nat Rev Dis Primers 2019; 5: 66.

Hay et al 2014
Hay JL, Atkinson TM, Reeve BB, Mitchell SA, Mendoza TR, Willis G, et al. Cognitive interviewing of the US National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Qual Life Res. 2014 Feb;23(1):257-69. doi: 10.1007/s11136-013-0470-1. Epub 2013 Jul 20. PMID: 23868457; PMCID: PMC3896507.

Howlader et al 2014
Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LA, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status, JNCI J Natl Cancer Inst 2014; 106(5): dju055.

Jerusalem et al 2018
Jerusalem G, de Boer RH, Hurvitz S, et al. Everolimus Plus Exemestane vs Everolimus or Capecitabine Monotherapy for Estrogen Receptor–Positive, HER2-Negative Advanced Breast Cancer: The BOLERO-6 Randomized Clinical Trial. JAMA Oncol 2018; 4(10): 1367–1374.

Kalinsky et al 2020
Kalinsky K, Diamond JR, Vahdat LT, Tolaney SM, Juric D, O'Shaughnessy J, et al. Sacituzumab govitecan in previously treated hormone receptor-positive/HER2-negative metastatic breast cancer: final results from a phase I/II, single-arm, basket trial. Ann Oncol 2020; 31(12): 1709-1718.

Kaufman et al 2015
Kaufman PA, Awada A, Twelves C, Yelle L, Perez EA, Velikova G, et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally

advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol 2015; 33(6): 594-601.

Kluetz et al 2018
Kluetz PG, O'Connor DJ, Soltys K. Incorporating the patient experience into regulatory decision making in the USA, Europe, and Canada. Lancet Oncol 2018;19(5):e267-74.

Lan and DeMets 1983
Lan KKG and DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983; 70659–663.

Lipinski et al 1981
Lipinski M, Parks DR, Rouse RV, Herzenberg LA. Human trophoblast cell-surface antigens defined by monoclonal antibodies. Proc Natl Acad Sci USA 1981; 78(8): 5147-50.

Martín et al 2007
Martín M, Ruiz A, Munoz M, et al. Gemcitabine plus vinorelbine versus vinorelbine monotherapy in participants with metastatic breast cancer previously treated with anthracyclines and taxanes: final results of the phase III Spanish Breast Cancer Research Group (GEICAM) trial. Lancet Oncol. 2007;8: 219–25.

Matutino et al 2018
Matutino A, Joy AA, Brezden-Masley C, Chia S, Verma S. Hormone receptor-positive, HER2-negative metastatic breast cancer: redrawing the lines. Curr Oncol 2018; 25(Suppl. 1): S131-S141.

Midgley and Kerr 2008
Midgley R, and Kerr DJ. Capecitabine: have we got the dose right? Nat Clin Pract Oncol 2008; 6: 17–24.

Miller et al 2005
Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbacher L, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol 2005; 23(4): 792-9.

Miller et al 2007
Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007; 357(26): 2666-76.

Modi et al 2020
Modi S, Saura C, Yamashita T, Park YH, Kim S-B, Kenji Tamura K, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. N Engl J Med 2020; 382: 610-621.

NCCN Guidelines 2020
NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. Version 3 2020. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx. Last accessed 28 April 2021.

O'Shaughnessy 2005
O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. Oncologist 2005; 10(Suppl. 3): 20-9.

Pau Ni et al 2010
Pau Ni IB, Zakaria Z, Muhammad R, Abdullah N, Ibrahim N, Aina Emran N, et al. Gene expression patterns distinguish breast carcinomas from normal breast tissues: the Malaysian context. Pathol Res Pract. 2010; 206(4): 223-8.

Piccart-Gebhart et al 2008
Piccart-Gebhart MJ, Burzykowski T, Buyse M, Sledge G, Carmichael J, Lück HJ, et al. Taxanes alone or in combination with anthracyclines as first-line therapy of patients with metastatic breast cancer. J Clin Oncol 2008; 26(12): 1980-6.

Possinger et al 1999
Possinger K, Kaufman M, Coleman R et al. Phase II study of gemcitabine as firstline chemotherapy in patients with advanced or metastatic breast cancer. Anticancer Drugs 1999; 10: 155–162.

Schott 2021
Schott AF. Chemotherapy in patients with hormone receptor-positive, HER2-negative advanced breast cancer. Available at: https://www.uptodate.com/contents/chemotherapy-in-patients-with-hormone-receptor-positive-her2-negative-advanced-breast-cancer/print. Last accessed 27 April 2021.

Seidman et al 2018
Seidman A, Bordeleau L, Fehrenbache Lr, Barlow W, Perlmutter J, Rubinstein L, et al. National Cancer Institute Breast Cancer Steering Committee Working Group Report on Meaningful and Appropriate End Points for Clinical Trials in Metastatic Breast Cancer. Journal of Clinical Oncology 2018; 36(32): 3259-3268.

Sprangers et al 1996
Sprangers MA, Groenvold M, Arraras JI, Franklin J, te Velde A, Muller M, Franzini L, Williams A, de Haes HC, Hopwood P, Cull A, Aaronson NK. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol. 1996 Oct;14(10):2756-68. doi: 10.1200/JCO.1996.14.10.2756. PMID: 8874337.

Sparano et al 2010
Sparano JA, Vrdoljak E, Rixe O, Xu B, Manikhas A, Medina C, et al. Randomized phase III trial of ixabepilone plus capecitabine versus capecitabine in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2010; 28(20): 3256-63.

Sung et al 2021
Sung H, Ferlay J, Siegel SL, Laversanne L, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Ca Cancer J Clin 2021; 0: 1–41.

Thomas et al 2007
Thomas ES, Gomez HL, Li RK, Chung HC, Fein LE, Chan VF, et al. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. J Clin Oncol. 2007 Nov 20;25(33):5210-7.

Twelves et al 2016
Twelves C, Awada A, Cortes J, Yelle L, Velikova G, Olivo MS, et al. Subgroup Analyses from a Phase 3, Open-Label, Randomized Study of Eribulin Mesylate Versus Capecitabine in Pre-treated Patients with Advanced or Metastatic Breast Cancer. Breast Cancer (Auckl). 2016;10: 77-84.

Von Minckwitz et al 2019
von Minckwitz G, Huang C-S, Mano MS, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med 2019; 380:617-628.

Wolff et al 2018
Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. Arch Pathol Lab Med 2018;142(11):1364-1382. doi: 10.5858/arpa.2018-0902-SA. Epub 2018 May 30. PMID: 29846104.

Yang et al 2021
Yang F, Rizvi Y, Yuca E, Zhao M, Evans K, Zheng X, et al. Abstract PS18-37: Loss of Trop2 protein in metaplastic carcinoma of breast by IHC. Cancer Res 2021; 81(Suppl. 4): PS18-37.

Yardley et al 2013
Yardley DA, Ismail-Khan RR, Melichar B, Lichinitser M, Munster PN, Klein PM, et al. Randomized phase II, double-blind, placebo-controlled study of exemestane with or without entinostat in postmenopausal women with locally recurrent or metastatic estrogen receptor-positive breast cancer progressing on treatment with a nonsteroidal aromatase inhibitor. J Clin Oncol. 2013; 31(17): 2128-35.

Youlden et al 2012
Youlden D.R, Cramb S.M, Dunn N.A, Muller J.M, Pyke C.M, Baade P.D. The descriptive epidemiology of female breast cancer: An international comparison of screening, incidence, survival and mortality. Cancer Epidemiol. 2012; 36: 237–248.

Yuan et al 2019
Yuan P, Hu X, Sun T, Li W, Zhang Q, Cui S, et al. Eribulin mesilate versus vinorelbine in women with locally recurrent or metastatic breast cancer: A randomised clinical trial. Eur J Cancer. 2019; 112: 57-65.

Zhao et al 2018
Zhao W, Kuai X, Zhou X, Jia L, Wang J, Yang X, et al. Trop2 is a potential biomarker for the promotion of EMT in human breast cancer. Oncology Reports 2018; 40: 759-766.

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d9268c00001-oncology-late-phase-master-csp-v5		
Document Title:	D9268C00001 Oncology Late Phase Master Clinical Study Protocol version 5	
Document ID:	Doc ID-004464097	
Version Label:	5.0 CURRENT LATEST APPROVED	
Server Date (dd-MMM-yyyy HH:mm 'UTC'Z)	**Signed by**	**Meaning of Signature**
28-Dec-2023 04:22 UTC	PPD	Content Approval
13-Dec-2023 20:53 UTC	PPD	Content Approval
13-Dec-2023 13:07 UTC	PPD	Content Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.

Clinical Study Protocol	
Study Intervention	Datopotamab deruxtecan (Dato-DXd, DS-1062a)
Study Code	D9268C00001
Version	1.0 European Union (Local Amendment 1 European Union)
Date	22 April 2024
EudraCT Number	2020-005620-12
EU CT Number	2023-509631-37

A Phase 3, Open-label, Randomized Study of Dato-DXd Versus Investigator's Choice of Chemotherapy in Participants With Inoperable or Metastatic Hormone Receptor-Positive, HER2-Negative Breast Cancer Who Have Been Treated With One or Two Prior Lines of Systemic Chemotherapy (TROPION-Breast01)

Sponsor Name: AstraZeneca

Legal Registered Address: AstraZeneca AB, 151 85 Södertälje, Sweden.

Regulatory Agency Identifier Number(s):
EudraCT Number: 2020-005620-12; EU CT number: 2023-509631-37; IND Number: 155696

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: D9268C00001

Local Amendment Number: 1 European Union

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

Study Phase: Phase 3

Short Title: A Study of Dato-DXd Versus Investigator's Choice Chemotherapy in Inoperable or Metastatic Hormone Receptor-positive, HER2-negative Breast Cancer

Acronym: TROPION-Breast01

Study Clinical Lead Name and Contact Information will be provided separately.

International Co-ordinating Investigator:

PPD

Massachusetts General Hospital Cancer Center
55 Fruit Street, Boston, MA 02114-2696.

VERSION HISTORY

DOCUMENT HISTORY	
Document	**Date**
Local Amendment 1, European Union (Version 1.0 European Union)	22 April 2024
Amendment 3 (Version 4.0)	10 October 2022
Amendment 2 (Version 3.0)	19 April 2022
Amendment 1 (Version 2.0)	27 August 2021
Original Protocol (Version 1.0)	01 July 2021

Local Amendment 1, European Union (22 April 2024)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the EU and in the EU CT Regulation Article 2, 2 (13).

Overall Rationale for the Amendment:

The overall rationale for the amendment is to update the protocol for EU CTR requirements and to align with the latest Dato-DXd program standards.

Other important administrative and operational clarifications have also been made.

The rationale for each of these changes is provided in the table below:

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Title page	EU CT number added	To meet EU CTR requirements.	Non-substantial
Synopsis	Regulatory Agency Identifiers added	For completeness of the Synopsis and to meet EU CTR requirements.	Non-substantial
1.3 Schedule of Activities Table 1 and Table 2, 8.2.5.3 ILD/Pneumonitis Investigation, 8.6.2 Collection of Optional Biomarker Samples	Optional lung biopsy specimen removed	To reflect that lung biopsy is no longer an optional biomarker sample.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
1.3 Schedule of Activities Table 1	Reference to the Dato-DXd Site Ophthalmologic Assessment Manual was added.	To clarify that the Ophthalmologic Assessment form is now included in the Dato-DXd Site Ophthalmologic Assessment Manual.	Non-substantial
1.3 Schedule of Activities Table 1	Oral care plan row, arrow from Cycle 1 through Safety FU assessment was replaced with wording “Daily before dosing, throughout treatment, and up to the first follow-up visit”.	To ensure clarity of the oral care protocol and avoid footnote details being missed.	Non-substantial
1.3 Schedule of Activities Table 1, 8.6.2 Collection of Optional Biomarker Samples	Optional bronchoalveolar lavage and lung biopsy sample on suspected ILD/diagnosis of ILD row was deleted.	The lung biopsy will not be collected. The lavage sample will not be collected centrally anymore and is specified in Table 2.	Non-substantial
1.3 Schedule of Activities Table 2	Table for assessments to be performed if ILD/pneumonitis suspected during the intervention period was updated to match the corresponding Section 8.2.5.3 for clarity and consistency eg, physical examination including auscultation of lung field, arterial blood gases if clinically indicated were added to Table 2.	To clarify assessments in case of suspected and/or confirmed ILD/pneumonitis and ensure consistency across protocol sections.	Non-substantial
2.3.1.1 Dato-DXd Table 3 Risk Assessment, 2.3.3 Overall Benefit: Risk Conclusion	IRR was downgraded from important identified risk to the identified risk category. A sentence was added to clarify that Dato-DXd has not been studied in participants with renal or hepatic impairment. The Summary of Data/Rationale for Risk was updated with the latest safety data from the IB. The Mitigation Strategy was updated to list out the AESIs.	To reflect clinical data for Dato-DXd in alignment with Dato-DXd IB Edition 7.0.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
2.3.3 Overall Benefit: Risk Conclusion, 6.5 Concomitant Therapy, 6.6 Dose Modification, 8.3 Adverse Events and Serious Adverse Events, 8.6.1 Collection of Mandatory Samples for Biomarker Analysis, 8.6.3 Other Study Related Biomarker Assessments, 9.4.1 General Considerations, Appendix I2 (Table 18), Appendix J	COVID-19 specific text was deleted throughout the protocol.	No specific safety concerns have been identified in patients with COVID-19 who have been treated with Dato-DXd.	Non-substantial
4.1 Overall Design, 5 Study Population	A reference for country-specific study requirements provided in Appendix L was added.	Country-specific addendums were added to the appendices to create one global protocol for EU CTR submission.	Non-substantial
4.4 End of Study Definition	The end of study definition was updated to distinguish between end of study (EU definition) and study completion (FDA definition).	To provide a clear definition of end of the study for results disclosure purposes.	Non-substantial
6.1.1 Investigational Products	In Table 5, AxMP was added to the IMP and NIMP row. For the unit dose strength row, ‘vial’ was deleted from ‘100 mg vial’. Reference to GMP Annex 13 was removed from labelling information.	To ensure all interventions are designated as an investigational medicinal product or a non-investigational medicinal product/auxiliary medicinal product. To omit repetition of packaging details in dose unit dose strength information. To ensure country-specific labelling requirements are followed.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
6.2.1 Dato-DXd	Density of Dato-DXd was added. Reference to the Pharmacy Manual was moved to Section 6.2.1.1 and corrected.	To ensure the latest available information is reflected in the protocol and to align with the Pharmacy Manual.	Non-substantial
6.2.1.1 Preparation of Dato-DXd	Guidance for preparation of Dato-DXd has been updated with additional details. A reference to the Pharmacy Manual for administration details provided separately was added.	To ensure the latest available information is reflected in the protocol and to align with the Pharmacy Manual.	Non-substantial
6.2.1.2 Administration of Dato-DXd	Guidance for administration of Dato-DXd has been updated additional details.	To ensure the latest available information is reflected in the protocol and to align with the Pharmacy Manual.	Non-substantial
6.6 Dose Modification	Subheadings were added: 6.6.1 Dose Delays, 6.6.2 Dose Delays for Reasons Other than Treatment-related Toxicity, 6.6.3 Dose Reductions and the text restructured accordingly. Clarification was added around doses delayed for up to 3 consecutive cycles (63 days) from the planned date of administration (ie, 84 days from the last infusion date). Figure 3 Dose Delay Schema for Dato-DXd was added. Section 6.6.2 Dose Delays for Reasons Other Than Treatment-related Toxicity guidance as included.	To clarify dose modification guidance.	Non-substantial
6.7 Intervention after the End of the Study	Section heading was updated to Continued Access to Study Intervention after the End of the Study. Language was added to describe methods of providing participants with access to treatment after data collection in the study has ended.	To clarify intervention available to participants after the end of the study.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
8.2.2 Vital Signs	End of infusion vital signs collection window restriction of ±5 minutes was removed.	To avoid unnecessary protocol deviations since vital signs measurements timing can be more flexible.	Non-substantial
8.2.5.3 ILD/Pneumonitis Investigation	ILD/pneumonitis investigation paragraph was updated for clarity. Signs and symptoms entry was deleted from the list of evaluations. Optional bronchoscopy and bronchoalveolar lavage if clinically indicated text was updated for clarity. Acceptable CT scan was clarified to include non-contrast chest CT with 1 to 2 mm slice thickness recommended. Differential white blood cell count was specified with blood tests for clarification. The additional blood sample for exploratory biomarker analysis was clarified as an optional serum sample when ILD/pneumonitis is suspected and/or diagnosed. An example of other tests that may be needed was added. Text was updated to match the corresponding Section 8.2.5.3 for clarity and consistency.	To clarify ILD/pneumonitis investigations. Signs and symptoms are not assessments and covered under adverse events reporting. To clarify what constitutes an acceptable CT and biomarker sample requirements.	Non-substantial
8.2.5.5 Ophthalmologic Assessments, 8.3.11 Adverse Events of Special Interest	A reference to the Dato-DXd Ophthalmologic Assessment Manual was added. The frequency of use of artificial tears was specified as 4 times daily as preventative measures and up to 8 times daily as clinically needed.	To clarify the frequency of use of artificial tears.	Non-substantial
8.2.5.6 Oral Care Plan	Oral care guidance for participants was updated to state participants receiving ICC are recommended daily use of alcohol-free mouthwash while participants receiving Dato-DXd are recommended to use a steroid-containing mouthwash. A reference to the Dato-DXd TMGs was added.	To specify the recommended mouthwash for oral care with study treatments. To direct reader to TMGs should oral mucosal toxicity arise despite prophylaxis measures.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
8.3 Adverse Events and Serious Adverse Events	The section title was updated to Adverse Events, Serious Adverse Events, and Other Safety Reporting.	To clarify that other safety reporting is also captured in this section.	Non-substantial
8.3.1 Time Period and Frequency for Collecting AE and SAE Information	The reporting period for ILD/pneumonitis events was clarified to extend beyond the 28 + 7 day safety follow-up period. The reporting period for all AESIs was clarified. Reporting instructions for pre-existing medical conditions was included. Clarification was provided for reporting details of hepatic events.	To ensure appropriate data collection on ILD/pneumonitis events and all other AEs and SAEs.	Non-substantial
8.3.11 Adverse Events of Special Interest	Reporting requirements for concomitant medication administered as treatment for drug-related AESIs was specified. IRR was changed from important identified risk to identified risk.	To ensure that concomitant medications for drug-related AESIs are appropriately recorded.	Non-substantial
8.3.15 Medication Error	Section heading was updated to Medication Error, Drug Abuse, and Drug Misuse. Subsections including relevant definitions were added for Medication Error, Drug Abuse, Drug Misuse. A reference to Appendix B4 was added.	To clarify what constitutes a medication error, drug abuse, and drug misuse in the study.	Non-substantial
8.5 Human Biological Samples	For PK and ADA samples retention, the wording “unless consented for future analysis” was deleted. It was clarified that remaining ADA sample aliquots will be retained for a maximum of 5 years after CSR publication. Wording was added to clarify ADA samples collected in China will be disposed of 1 year after CSR publication.	The samples will be used for study analysis only. To clarify sample retention periods.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
8.6.1 Collection of Mandatory Samples for Biomarker Analysis, 1.3 Schedule of Activities Table 1	Additional blood samples for exploratory biomarker analysis to be collected as soon as ILD/pneumonitis is suspected, if feasible was moved to Section 8.6.2 since these are optional samples. In Table 1, It was clarified that the additional exploratory biomarker blood samples are optional. The retention time for residual tumor samples collected for TROP2 IHC testing from Chinese participants was corrected to state samples will be destroyed or repatriated within 1 year after CSR completion.	To clarify that the additional exploratory biomarker samples are optional. To correct residual tumor sample retention for Chinese participants.	Non-substantial
9.3 Populations for Analyses Table 9	ITT and Safety Analysis Set descriptions were updated to specify clinical outcomes assessments included in each set.	To clarify the populations definitions and align with objectives and endpoints.	Non-substantial
Appendix A1 Regulatory and Ethical Considerations	Investigator oversight of the conduct of the study and adherence to regulatory requirements was clarified. A subsection for Regulatory Reporting Requirements of Serious Breaches was added.	To clarify investigator responsibilities and include guidance on reporting serious breaches during study conduct.	Non-substantial
Appendix A6 Dissemination of Clinical Study Data	The timeframe for submitting results summaries to EU CTIS was included. The AstraZeneca website for a description of the study was updated.	To clarify study result submission timelines and include the current AstraZeneca website.	Non-substantial
Appendix A7 Data Quality Assurance	It was clarified that clinical reviews of data from a medical perspective form part of the monitoring strategy. The record and document retention period was clarified.	To clarify the monitoring process and record retention policy.	Non-substantial
Appendix B4 Medication Error	Section heading was updated to Medication Error, Drug Abuse, and Drug Misuse. Subheading for Medication Error as well as a range for dose error was added. Subsections for Drug Abuse and Drug Misuse were added.	To clarify what constitutes a medication error, drug abuse, and drug misuse in the study.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Appendix I2 Restricted, Prohibited, and Permitted Concomitant Medications/Therapies	In Table 17 was updated to include instructions regarding Dato-DXd therapy when palliative radiotherapy is given. It was clarified that curative radiotherapy prohibited.	To clarify Dato-DXd therapy delays in the case of palliative radiotherapy.	Non-substantial
Appendix I2 Supportive Medications/Therapies	Table 19: 'Antihistamines and acetaminophen' was re-labeled as 'pre-medications for prevention of IRR or as supportive treatment of Dato-DXd'. Examples of prophylactic anti-emetic agents was deleted from text in the supportive medication column.	Text was updated to mention examples in the Usage column instead of in the medications/class of drug/therapy column.	Non-substantial
Appendix K Protocol Version History	Previous protocol amendments were moved to Appendix K.	To focus protocol text on current information with additional information provided in appendices.	Non-substantial
Appendix L	Country-specific addendums to the protocol were added in Appendix L.	Country-specific addendums were added to the appendices to create one global protocol for EU CTR submission.	Non-substantial
Throughout	Minor editorial and formatting revisions.	To further clarify.	Non-substantial

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Open-label, Randomized Study of Dato-DXd Versus Investigator's Choice of Chemotherapy in Participants With Inoperable or Metastatic Hormone Receptor-Positive, HER2-Negative Breast Cancer Who Have Been Treated With One or Two Prior Lines of Systemic Chemotherapy (TROPION-Breast01).

Short Title: A Study of Dato-DXd Versus Investigator's Choice Chemotherapy in Inoperable or Metastatic Hormone Receptor-positive, HER2-negative Breast Cancer.

Regulatory Agency Identifier Number(s):

EudraCT Number: 2020-005620-12; IND Number: 155696; EU CT number: 2023-509631-37

Rationale:

Single agent chemotherapy remains the cornerstone of therapy for patients with HR-positive, HER2-negative metastatic breast cancer who have exhausted endocrine therapy options. However, patient prognosis is poor, and durable antineoplastic therapy options are necessary to improve outcomes in this patient population.

Dato-DXd is a TROP2 antibody-drug conjugate (administered via IV infusion, Q3W). Within the Dato-DXd clinical development program, preliminary data supporting the use of Dato-DXd in participants with HR-positive, HER2-negative breast cancer are available from an ongoing phase 1 first-in-human study, TROPION-PanTumor01 (NCT03401385), which is evaluating Dato-DXd in participants with advanced non-small cell lung cancer and triple-negative breast cancer, relapsed or refractory to standard-of-care therapy. These data have demonstrated highly encouraging efficacy across dose groups, with tumor responses observed at doses of 4, 6, and 8 mg/kg and an acceptable and manageable toxicity profile.

Given these encouraging preliminary safety and efficacy data, the current study is designed to provide a robust and detailed understanding of the efficacy and safety of Dato-DXd when compared with Investigator's choice of standard-of-care single-agent chemotherapy (eribulin, capecitabine, vinorelbine, or gemcitabine; henceforth referred to as ICC) in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with one or two prior lines of systemic chemotherapy, for which an unmet medical need remains.

Objectives and Endpoints

Objectives	Endpoints
Dual Primary	
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of PFS in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer, who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting, per BICR.	• PFS is defined as time from randomization until progression per RECIST 1.1, as assessed by BICR, or death due to any cause. The analysis will include all randomized participants as randomized regardless of whether the participant withdraws from therapy, receives another anticancer therapy, or clinically progresses prior to RECIST 1.1. The measure of interest is the hazard ratio of PFS.
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of OS in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer, who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting.	• OS is defined as time from randomization until the date of death due to any cause. The comparison will include all randomized participants as randomized, regardless of whether the participant withdraws from therapy or receives another anticancer therapy. The measure of interest is the hazard ratio of OS.
Secondary	
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of ORR in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer, who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting, per BICR and per investigator assessment.	• ORR is defined as the proportion of participants who have a confirmed CR or PR, as determined by the BICR/Investigator assessment, per RECIST 1.1. The analysis will include all randomized participants as randomized. Data obtained from randomization up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR, regardless of whether the participant withdraws from therapy. Participants who go off treatment without a response or progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR. The measure of interest is the odds ratio of the ORR.
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of DoR in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting.	• DoR is defined as the time from the date of first documented confirmed response until date of documented progression per RECIST 1.1, as assessed by BICR/Investigator assessment or death due to any cause. The analysis will include all randomized participants as randomized who have a confirmed response, regardless of whether the participant withdraws from therapy, receives another anticancer therapy or clinically progresses prior to RECIST 1.1 progression. The measure of interest is the median of DoR.
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of PFS in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting, per investigator assessment.	• PFS is defined as time from randomization until progression per RECIST 1.1, as assessed by investigator assessment, or death due to any cause. The analysis will include all randomized participants as randomized regardless of whether the participant withdraws from therapy, receives another anticancer therapy, or clinically progresses prior to RECIST 1.1. The measure of interest is the hazard ratio of PFS.

Objectives	Endpoints
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of DCR in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer, who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting, per BICR and per investigator assessment.	• DCR at 12 weeks is defined as the percentage of participants who have a confirmed CR or PR or who have SD, per RECIST 1.1, as assessed BICR/per investigator assessment and derived from the raw tumor data for at least 11 weeks after randomization. Data obtained from randomization up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of DCR, regardless of whether the participant withdraws from therapy. Participants who receive a subsequent therapy prior to week 11 will not be considered to have disease control in the analysis. The analysis will include all randomized participants as randomized. The measure of interest is the odds ratio of the DCR.
To assess pain in participants treated with Dato-DXd compared to ICC.	• TTD in pain as measured by the pain scale from EORTC QLQ-C30 TTD is defined as time from the date of randomization to the date of deterioration. Deterioration is defined as change from baseline that reaches a clinically meaningful deterioration threshold. The analysis will include all randomized participants. The measure of interest is the hazard ratio of TTD in pain.
To assess physical functioning in participants treated with Dato-DXd compared to ICC.	• TTD in physical functioning as measured by the physical functioning scale from EORTC QLQ-C30 TTD is defined as time from the date of randomization to the date of deterioration. Deterioration is defined as change from baseline that reaches a clinically meaningful deterioration threshold. The analysis will include all randomized participants. The measure of interest is the hazard ratio of TTD in physical functioning.
To assess global health status/quality of life (GHS/QoL) in participants treated with Dato-DXd compared to ICC.	• TTD in GHS/QoL as measured by the GHS/QoL scale from EORTC QLQ-C30 TTD is defined as time from the date of randomization to the date of deterioration. Deterioration is defined as change from baseline that reaches a clinically meaningful deterioration threshold. The analysis will include all randomized participants. The measure of interest is the hazard ratio of TTD in GHS/QoL.
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of TFST in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting.	• TFST is defined as the time from randomization until the start date of the first subsequent anticancer therapy after discontinuation of randomized treatment, or death due to any cause. The analysis will include all randomized participants as randomized, regardless of progression status. The measure of interest is the hazard ratio of TFST.

Objectives	Endpoints
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of TSST in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting.	• TSST is defined as the time from randomization to until the start date of the second subsequent anticancer therapy after discontinuation of first subsequent treatment, or death due to any cause. The analysis will include all randomized participants as randomized, regardless of progression status on study treatment or first subsequent treatment. The measure of interest is the hazard ratio of TSST.
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of PFS2 in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting.	• PFS2 will be defined as the time from the randomization to the earliest of the progression event (following the initial progression), subsequent to first subsequent therapy, or death. The date of second progression will be recorded by the Investigator in the eCRF and defined according to local standard clinical practice. The comparison will include all randomized participants as randomized regardless of whether the participant withdraws from subsequent therapy and regardless of missed visits. The measure of interest is the hazard ratio of PFS2.
To assess the PK of Dato-DXd 6mg/kg IV Q3W.	• Plasma concentrations of Dato-DXd, total anti-TROP2 antibody, and MAAA-1181a (payload).
To investigate the immunogenicity of Dato-DXd 6mg/kg IV Q3W.	• Presence of ADA.
Safety	
To assess the safety and tolerability profile of Dato-DXd compared to ICC.	Safety and tolerability will be evaluated in terms of adverse events (graded by CTCAE version 5.0), and also in terms of: • ECOG PS • Vital signs, body weight, physical examination • Clinical chemistry, hematology, and urinalysis assessments • ECG, ECHO/MUGA and Ophthalmologic assessments

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

Overall Design

Disclosure Statement: This is a Phase 3, randomized, open-label, 2 arm, multicenter, international study assessing the efficacy and safety of Dato-DXd compared with ICC in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with one or two prior lines of systemic chemotherapy in the inoperable or metastatic setting.

Participant Population: The target population of interest in this study is male or female adult (≥ 18 years participants with inoperable or metastatic HR-positive, HER2 negative breast cancer (per ASCO/CAP guidelines, on local laboratory results) who have progressed on and are not suitable for endocrine therapy per investigator assessment, and have been treated with 1 to 2 lines of prior chemotherapy in the inoperable/metastatic setting. Participants must have documented progression on their most recent line of chemotherapy, and be eligible for one of

the chemotherapy options listed as ICC (eribulin, capecitabine, vinorelbine, gemcitabine), per investigator assessment.

To be eligible for randomization, availability of a FFPE tumor sample (block preferred, or a minimum of 20 freshly cut slides) is required, at the time of screening. This sample can be from either the primary disease setting (surgical resection or diagnostic sample), or from a metastatic lesion (excluding bone). If neither an adequate FFPE block nor the minimum of 20 slides are available, a patient may still be considered eligible. In this situation, approval by the Study Team for patient's entry into the study is required. If there is no written confirmation of the availability of an appropriate tumor sample prior to enrolment, the participant will not be eligible for the study. At the time of enrolment all participants must have an ECOG PS of 0 or 1, and have at least 1 measurable lesion not previously irradiated that qualifies as a RECIST 1.1 target lesion. Participants with clinically inactive brain metastases may be included in the study.

Number of Participants: Approximately 1000 participants will be enrolled to achieve approximately 700 randomly assigned participants to study intervention. If required for regulatory submission purposes, the recruitment of participants in mainland China may continue beyond the close of the global cohort, to include approximately an additional 20 randomized participants in the mainland China cohort. The mainland China cohort is defined as all participants from sites in mainland China randomized into the study. A participant randomized in the mainland China cohort prior to the last participant randomized in the global cohort will be included in both the global and mainland China cohorts. A participant randomized in mainland China after the last participant was randomized in the global cohort will be included only in the mainland China cohort.

Note: "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. Potential participants who are screened for the purpose of determining eligibility for the study, but are not randomly assigned in the study, are considered "screen failures", unless otherwise specified by the protocol.

Intervention Groups and Duration: Participants will be randomized in a 1:1 ratio to one of the following intervention groups:

- **Arm 1:** Dato-DXd (6 mg/kg IV on Day 1, Q3W)
- **Arm 2:** ICC:
  - Capecitabine (1000 or 1250 mg/m^2 oral BID on Days 1 to 14, Q3W); choice between the 2 doses will be determined by standard institutional practice.
  - Gemcitabine (1000 mg/m^2 IV on Day 1 and Day 8, Q3W)

- Eribulin mesylate (1.4 mg/m^2 IV on Days 1 and 8, Q3W)
- Vinorelbine (25 mg/m^2 IV on Days 1 and 8, Q3W)

Randomization will be stratified by the following prognostic and/or predictive factors:

- Number of previous lines of chemotherapy (1 versus 2)
- Geographic region (Region 1 [US, Canada, Europe] versus Region 2 [Rest of World])
- Prior use of CDK4/6 inhibitor (Yes versus No)

A 50% cap will be applied to participants who have had 2 prior lines of chemotherapy in the inoperable/metastatic setting, while a 49% cap will be applied to participants who have not received prior CDK4/6 inhibitor therapy.

All participants will receive study intervention until Investigator-defined disease progression according to RECIST 1.1, or until unacceptable toxicity, withdrawal of consent, or another criterion for discontinuation is met. Continued treatment with the same study drug post-progression may be allowed, based on prior discussion with study physician on case-by-case basis. No crossover between study treatment arms will be allowed.

Follow-up of participants post discontinuation of study intervention

After study intervention discontinuation, all participants will undergo an end-of-treatment visit (to be conducted +7 days of the decision to discontinue treatment) and will be followed up for safety assessments 28 (+7) days after their last dose of study intervention (ie, the safety follow-up visit). If the date of discontinuation is over 35 days from last study intervention administration, then the EoT assessments can also function as the Safety Follow-up visit.

Participants who have discontinued study intervention in the absence of RECIST 1.1-defined radiological progression (by investigator assessment) will be followed up with tumor assessments according to the Schedule of Activities (SoA) until RECIST 1.1-defined PD (as assessed by the Investigator) or death regardless of whether or not the participant started a subsequent anticancer therapy, unless they have withdrawn all consent to study related assessments. Following disease progression, 1 additional follow-up scan should also be performed as per imaging schedule (ie, either 6 weeks or 9 weeks later). In the event the investigator identified progression does not match with the BICR evaluation, this additional scan may identify progression by BICR.

In addition, all participants will be followed up for survival status after intervention discontinuation every 3 months (±14 days) from the date of the date of the Safety Follow-up Visit until death, withdrawal of consent, or the end of the study (ie, progression/survival follow-up), as per the SoA. Participants will be followed up for time to second progression or death (PFS2) and subsequent anticancer therapy use after intervention discontinuation every

3 months (±14 days) from the date of randomization until death, withdrawal of consent, or the end of the study (ie, progression/survival follow-up), as per SoA. The study may continue monitoring participants for OS up to the scheduled final analysis, beyond planned interim analyses, to provide more refined estimates of treatment effects for survival.

See Section 6.7 for a description of assessments following study DCOs.

Independent Data Monitoring Committee (IDMC): An IDMC comprised of independent experts will be convened to review unblinded safety data and make recommendations to continue, amend, or stop the study based on safety findings. In addition, the IDMC may be requested to review efficacy data. For the interim analyses, the IDMC will review unblinded interim data and inform the Sponsor whether the interim boundaries specified in Section 9.5 are crossed. Full details of the IDMC procedures, processes, and interim analyses can be found in the IDMC Charter.

Statistical methods

The study is sized for dual primary endpoints to characterize the PFS and OS benefit of Dato-DXd versus ICC in intent-to-treat (ITT) population. This comprises all participants randomized into the study, excluding participants randomized in mainland China after the global cohort last participant randomized, and will be analyzed according to randomized treatment regardless of the treatment received (ITT principle). The study will be considered positive (a success) if either the PFS analysis results and/or the OS analysis results are statistically significant.

The primary, final analysis of PFS will be performed when approximately 419 PFS BICR events occur, approximately 2 months after the last participant is randomized in the study; 419 PFS BICR events from the ITT population across the Dato-DXd and ICC treatment groups will represent 60% maturity of data. Assuming the true PFS hazard ratio is 0.55 for Dato-DXd versus ICC, the study will have a greater than 99% power to demonstrate statistical significance at the 1.0% level (using a 2-sided test). This assumes median PFS times of 4.7 months and 8.5 months in ICC and Dato-DXd, respectively when the PFS times are exponentially distributed. The smallest treatment difference that could be statistically significant at the final analysis is a hazard ratio of 0.775.

The final analysis of OS will be performed when approximately 444 OS events have occurred across the Dato-DXd and ICC treatment groups (63% maturity). Assuming the true OS hazard ratio is 0.75 for Dato-DXd versus ICC, the study will have 85% power to demonstrate statistical significance at the 5.0% level (using a 2-sided test). This assumes the PFS primary analysis crosses the efficacy threshold, and allowing 2 interim analyses to be conducted at information fractions of approximately 40% and 80% of the target events, respectively (per the O’Brien and Fleming approach). The smallest treatment difference that could be

statistically significant at the final analysis is a hazard ratio of 0.824. If the PFS primary analysis does not cross the efficacy threshold, the OS analysis will have 83% power to demonstrate statistical significance at the 4.0% level (using a 2-sided test). The smallest treatment difference that could be statistically significant at the final analysis is a hazard ratio of 0.817. Calculations assume median OS times of 19.0 months and 25.3 months in ICC and Dato-DXd, respectively when the survival times are exponentially distributed.

The study may continue monitoring participants for OS up to the scheduled final analysis, beyond planned interim analyses, to provide more refined estimates of treatment effects for survival.

A nonuniform accrual of participants (with k = 1.5) is assumed when estimating the analysis times. The total proportion of participants randomized at time t [t ≤ 19 months] following the start of the study is assumed to be $(t/19)^k$.

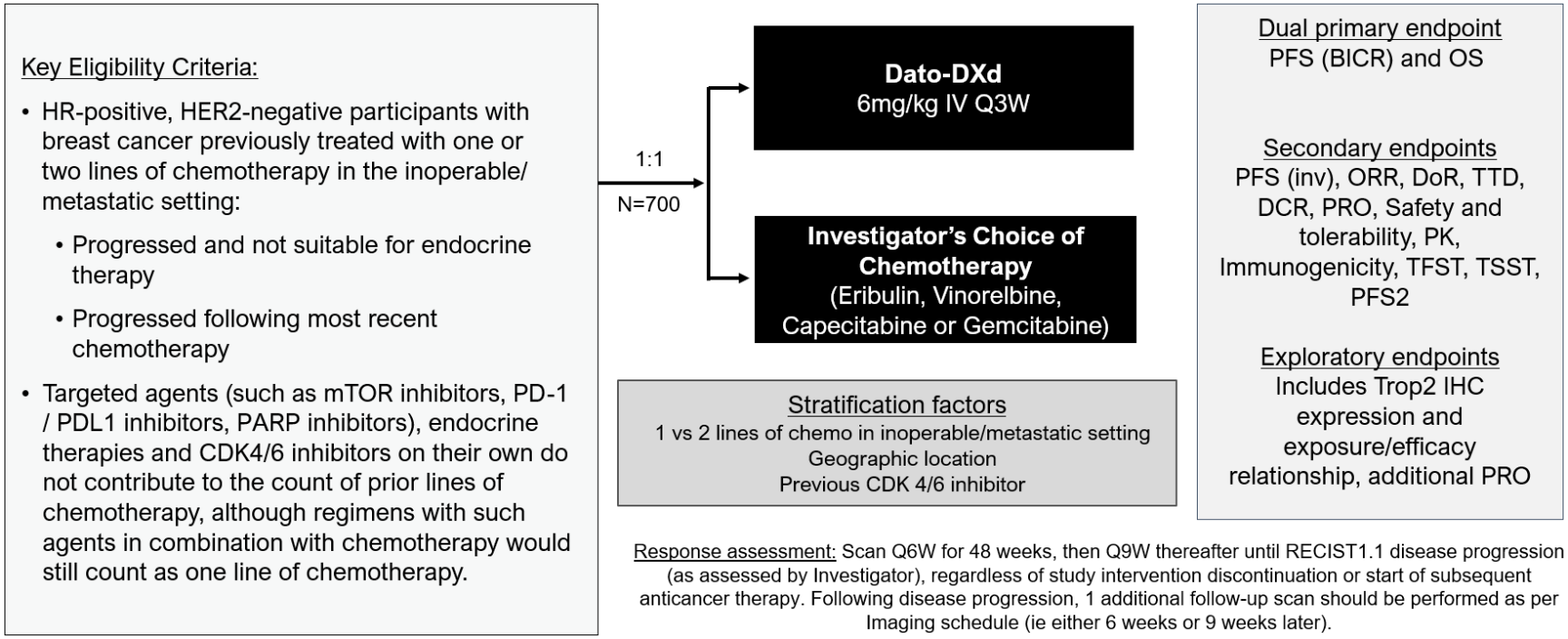
Hypotheses will be tested using a multiple testing procedure (MTP) with an alpha-exhaustive recycling strategy. To strongly control the familywise type I error rate at the 5.0% level (2-sided), an alpha level of 1.0% will be allocated to the PFS dual primary analysis and the remaining 4.0% alpha level will be allocated to the OS analyses. If the PFS dual primary analysis crosses the efficacy threshold, the 1.0% type I error allocated to the PFS endpoint will be reallocated to the OS endpoint for a total 2-sided type I error of 5.0%.

Safety data will be summarized descriptively and will not be formally analyzed unless otherwise specified.

1.2 Schema

The study schema is presented in Figure 1.

Figure 1 Study Design



1.3 Schedule of Activities

The procedures for this study are presented in the SoA (Table 1). Assessments in the event of suspected ILD/pneumonitis are presented separately in Table 2.

Table 1 Schedule of Activities

Procedure	Screening (up to 28 days before C1D1)	Intervention Period				Post-intervention Follow-up Period				Details in CSP Section or Appendix
		Cycle 1		Cycle 2 +		EoT (within 7 days of decision to stop treatment)	Safety FU (28 days after last dose [+7 days]) [a]	At PD	Survival FU (Every 3 months [±14 days]) relative to the date of Safety FU Visit	
		Day 1	Day 8 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)					
Informed consent: main study [b]	X									Section 5.1 and Appendix A 3
Informed consent: genetic sample and analysis (optional)	X									Section 5.1 and Appendix A 3
Study Procedures and Assessments										
Inclusion and exclusion criteria	X									Sections 5.1 & 5.2
Randomization		X [c]								Section 6.3
Demography	X									Section 5.1
Full physical examination (including weight and height)	X									Section 8.2.1
Targeted physical examination (including weight)		X [d]		X [e, f]		X	X			Section 8.2.1
Medical history [g]	X									Sections 5.1 & 5.2
Past and current medical conditions and prior anticancer therapy use	X									Sections 5.1 & 5.2
ECOG performance status	X	X [d]		X [f]		X	X			Section 8.2.5.4
12-lead ECG [h]	X	As clinically indicated				X				Section 8.2.3
Echocardiogram or MUGA (LVEF) [i]	X	As clinically indicated								Section 8.2.5.1
Vital signs including SpO_2 [j]	X	X		X [e]		X	X			Section 8.2.2
Pulmonary function tests [k]	X	If ILD/pneumonitis is suspected								Section 8.2.5.2
ILD/pneumonitis investigation, including HRCT		If ILD/pneumonitis is suspected								Section 8.2.5.3

Table 1 Schedule of Activities

Procedure	Screening (up to 28 days before C1D1)	Intervention Period				Post-intervention Follow-up Period				Details in CSP Section or Appendix
		Cycle 1		Cycle 2 +		EoT (within 7 days of decision to stop treatment)	Safety FU (28 days after last dose [+7 days]) [a]	At PD	Survival FU (Every 3 months [±14 days]) relative to the date of Safety FU Visit	
		Day 1	Day 8 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)					
Ophthalmologic assessments [l]	X	<-------every 3 cycles from C1D1 onwards (eg, C4D1, C7D1, C10D1 etc) within 14 days prior to scheduled cycle Day 1 visit (but not after the scheduled visit) and as clinically indicated---------->				X				Section 8.2.5.5
Oral care plan [m]	X	Daily before dosing, throughout treatment, and up to the first follow-up visit								Section 8.2.5.6
AE [n, o]	X	<---------->				X	X			Section 8.3
Prior and concomitant medication [o]	X	<---------->				X	X			Section 6.5
Subsequent anticancer therapy							X		X	
Clinical Safety Laboratory Assessments										
Serum/urine pregnancy test (WOCBP only) [p]	X	X		X		X	X			Sections 5.1, 5.2 & 8.2.4
Hepatitis B and C serology [q]	X									Sections 5.2 & 8.2.4
HIV antibody test (as required by local regulations or IRB/EC) [q, r]	X									Sections 5.2 & Section 8.2.4
Clinical safety laboratory assessments (clinical chemistry and hematology)	X	X [d]		X [d, e]		X	X			Section 8.2.4
Urinalysis	X	As clinically indicated								Section 8.2.4
Pharmacokinetics Assessments (for participants randomized to Dato-DXd only)										
PK blood sampling (before infusion) [s]		X		X (C2, C4, C6, C8, and C12, then every 4 cycles)		X				Section 8.5.1

Table 1 Schedule of Activities

Procedure	Screening (up to 28 days before C1D1)	Intervention Period				Post-intervention Follow-up Period				Details in CSP Section or Appendix
		Cycle 1		Cycle 2 +		EoT (within 7 days of decision to stop treatment)	Safety FU (28 days after last dose [+7 days]) [a]	At PD	Survival FU (Every 3 months [±14 days]) relative to the date of Safety FU Visit	
		Day 1	Day 8 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)					
PK blood sampling (end of infusion) [t]		X [u]		X (C2, C4, C6, C8)						Section 8.5.1
Immunogenicity Assessments (for participants randomized to Dato-DXd only)										
Blood sample for immunogenicity testing (ADA)		X [s]		X [s] (C2, C4, C6, C8, and C12; then every 4 cycles)		X	X			Section 8.5.2
Biomarker Assessments										
Mandatory tumor sample available (FFPE)	X									Section 8.6.1
Optional tumor biopsy (FFPE/FF) at progression [v]								X		Section 8.6.2
Optional paired tumor biopsy (FFPE/FF) [v]	X			X (C2D1 to C2D7 only)						Section 8.6.2
Plasma samples for biomarker analysis [v]	X	X		X (C2, C4)		X		X		Section 8.6.1
Serum samples for biomarker analysis [v]	X	X		X (C2, C4)		X		X		Section 8.6.1
Optional plasma samples for biomarker analysis on suspected ILD/diagnosis of ILD		As clinically indicated								Section 8.6.1

Table 1 Schedule of Activities

Procedure	Screening (up to 28 days before C1D1)	Intervention Period				Post-intervention Follow-up Period				Details in CSP Section or Appendix
		Cycle 1		Cycle 2 +		EoT (within 7 days of decision to stop treatment)	Safety FU (28 days after last dose [+7 days]) [a]	At PD	Survival FU (Every 3 months [±14 days]) relative to the date of Safety FU Visit	
		Day 1	Day 8 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)					
Optional serum samples for biomarker analysis on suspected ILD/diagnosis of ILD		As clinically indicated								Section 8.6.1
Whole blood sample for gene expression analysis (RNA) [v]	X	X		X (C2, C4)				X		Section 8.6.1
Whole blood sample for gene expression analysis (DNA) [v]	X	X		X (C2, C4)				X		Section 8.6.1
Plasma samples for ctDNA analysis [v]	X	X		X (C2-C6; then Q6W)		X		X		Section 8.6.1
Genomics Initiative (optional)										
Optional exploratory genetic blood sample for Genomics Initiative [v, w]		X								Section 8.7 & Appendix D
Efficacy Assessments										
Tumor imaging (RECIST 1.1) [x]	X	Every 6 weeks (±7 days) from randomization for 48 weeks, then every 9 weeks (±7 days) thereafter until RECIST 1.1 disease progression (as assessed by the Investigator), regardless of study intervention discontinuation or start of subsequent anticancer therapy. Following disease progression, 1 additional follow-up scan should be performed as per imaging schedule (ie, either 6 weeks or 9 weeks later).								Section 8.1.1
Brain MRI/CT imaging [y]	X	Mandated for participants who had brain metastases documented at baseline, per RECIST 1.1 schedule.								Section 8.1.1
Whole body bone scan [z]	X	As clinically indicated								Section 8.1.1
Survival status									X	Section 7.1.3 & 8.1.4
Time to second progression or death (PFS2)							X		X	Section 8.1.3

Table 1 Schedule of Activities

Procedure	Screening (up to 28 days before C1D1)	Intervention Period				Post-intervention Follow-up Period				Details in CSP Section or Appendix
		Cycle 1		Cycle 2 +		EoT (within 7 days of decision to stop treatment)	Safety FU (28 days after last dose [+7 days]) [a]	At PD	Survival FU (Every 3 months [±14 days]) relative to the date of Safety FU Visit	
		Day 1	Day 8 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)					
Clinical Outcome Assessments										
ePRO training and setup		X								Section 8.1.5
EORTC QLQ-C30, EORTC IL116, PGIS, EQ-5D-5L		C1D1, Q3W from C1D1 for the first 48 weeks, and Q6W thereafter until EoT				At EoT visit, then Q6W (relative to C1D1) after EoT until 18 weeks after PD				Section 8.1.5
PRO-CTCAE, EORTC IL117, PGI-TT		C1D1, every week from C1D1 for the first 12 weeks, and Q3W thereafter until EoT				X				Section 8.1.5
PGIC		Q6W from C1D1 for the first 12 weeks (ie, 6 weeks and 12 weeks from C1D1)								Section 8.1.5
Medical Resource Utilization										
HOSPAD [aa]		X	X [bb]	X	X [bb]	X				Section 8.8
Study Intervention Administration										
Dato-DXd administration (IV)		X		X						Section 6
Capecitabine administration (oral)		Days 1 to 14 only, BID		Days 1 to 14 only, BID						Section 6
Eribulin administration (IV)		X	X	X	X					Section 6
Vinorelbine administration (IV)		X	X	X	X					Section 6
Gemcitabine administration (IV)		X	X	X	X					Section 6

[a] The safety follow-up visit will be performed 28 (+7) days after the last study intervention administration. If the date of discontinuation is over 35 days from last study intervention administration, then the EoT assessments can also function as the Safety FU visit.

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

[c] Every effort should be made to minimize the time between randomization and starting treatment (ie, no more than 3 days from the date of randomization).

[d] If safety assessments have been performed within 72 hours prior to starting Day 1 of a cycle, they do not have to be repeated, if the participant's condition has not changed.

[e] For participants randomized to Investigator's Choice of Chemotherapy (ICC), routine clinical care should be performed in accordance with local practice.

[f] Within 3 days prior to administration of study intervention.

[g] Includes ocular history (since prior ocular events may predispose to or cause dry eye/keratitis), as well as history, type and frequency of tobacco use, e-cigarette use, vaping (including dates).

[h] Triplicate ECGs will be taken at screening and EoT. Triplicate ECGs will be taken in close succession, while in a supine/semi-recumbent position. Single ECGs should be taken during treatment as clinically indicated.

[i] The same test must be used for the participant throughout the study. ECHO/MUGA not required at EoT unless clinically indicated.

[j] Vital signs and SpO_2 should be performed both before and after study intervention administration (where applicable), and as clinically indicated during treatment. Participant should remain at the site for at least 1-hour post-infusion (where applicable) for close observation for IRRs.

[k] Pulmonary function tests at a minimum should include spirometry (minimum requirement of: FVC [L], FVC % predicted, FEV1 [L], FEV1 % predicted, FEV1/FVC %). DLCO will be performed (when feasible); however, for participants with prior severe and/or clinically significant pulmonary disorders, DLCO is a requirement.

[l] Ophthalmologic assessments (by a licensed eye care provider) including but not limited to visual acuity testing, fluorescein staining, intraocular pressure, slit-lamp examination and fundoscopy will be performed at screening, and then every 3 cycles from C1D1 onwards (eg, C4D1, C7D1, C10D1 etc) within 14 days prior to scheduled cycle Day 1 visit (but not after the scheduled visit), in addition to as clinically indicated while on trial, and at EoT. (see Section 8.2.5.5 for additional information). Please refer to the Dato-DXd Site Ophthalmologic Assessment Manual for further details.

[m] A daily Oral Care Protocol (OCP) will be started before study drug initiation, and it must be maintained throughout the study until 28 days after last dose. An oral care kit will be provided at study enrolment and monthly thereafter until the safety FU visit, which will include a toothbrush, toothpaste, dental floss, and an alcohol-free mouthwash. An oral care plan participant information guide should be given to each randomized participant before study drug initiation. Strongly consider initiation of dexamethasone oral solution (see Section 8.2.5.6 for details).

[n] Data collection may be conducted by phone if not tied to a visit.

[o] All AEs occurring after the participant signs the ICF and up to 28 (+7) days after the last dose of study drug (ie, the safety follow-up period), whether observed by the Investigator or reported by the participant, will be recorded on the AE eCRF page (see Section 8.3 for additional information).

[p] Negative serum pregnancy test performed within 72 hours before study intervention at screening and repeat urine or serum pregnancy tests (per institutional guideline) performed within 72 hours before infusion of each cycle and at EoT and during safety follow-up. A positive urine pregnancy test result must immediately be confirmed using a serum test.

[q] 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 enrolment. In this case, there is no need for a repeat test during the 28-day screening period.

[r] Participants must be tested for HIV if acceptable by local regulations or an IRB/EC. If an HIV infection meets the criteria outlined in Section 5.2, monitoring of the participants' viral RNA load and CD4+ cell count should be monitored per local SoC (eg, every 3 months).

[s] To be performed within 8 hours prior to the start of Dato-DXd infusion, except for the EoT visit, during which samples can be collected anytime during this visit.

[t] To be performed within 1 hour after the end of Dato-DXd infusion.

[u] An additional PK sample should be taken 5 hours (±1 hour) from the start of Dato-DXd infusion on C1D1.

[v] Not applicable to participants in mainland China.

[w] The sample for genetic research will be obtained at Day 1 pre-dose. If, for any reason, the sample is not drawn at Day 1, it may be taken at any visit until the last study visit. Only 1 sample should be collected per participant for genetics during the study.

[x] The baseline tumor assessment must be performed within 28 days before randomization and as close as possible to the start of treatment. The assessment should include CT (preferred) or MRI, with IV contrast, of the chest, abdomen (including the entire liver and both adrenal glands), and pelvis. Any other areas of disease involvement should be additionally imaged at screening based on known metastasis sites or by the signs and symptoms of individual participants. The follow-up assessments should include CT/MRI with IV contrast of the chest, abdomen and pelvis and any other area where disease was identified at baseline. The assessment must continue until **1 visit (per original schedule)** after radiographic disease progression (as assessed by Investigator), whether or not the participant is still on treatment. The same imaging technique (CT or MRI) used to characterize each identified and reported lesion at baseline will be used in the subsequent tumor assessments.

[y] Participants with brain metastases at baseline must have the lesions recorded as part of the RECIST assessment and must have a brain scan performed per the tumor imaging schedule until radiological progression per RECIST. For participants in whom CNS metastases are first discovered at the time of screening, the treating investigator should consider delay of randomization and study intervention to document stability of CNS metastases with repeat imaging at least 4 weeks later (in which case, repeat of all screening activity may be required).

[z] 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.

[aa] The site should complete the “Hospital Admission (HOSPAD)” form at the site at every scheduled clinic visit up to and including the post study treatment discontinuation follow up visit. If the participant discontinues study treatment for reasons other than RECIST progression, the HOSPAD form should continue to be administered until progression has been confirmed. Study mandated visits should not be included as a hospital admission.

[bb] Only applicable to participants who are required to attend study visits on Day 8 of each cycle (ie, those randomized to receive Investigators Choice of Chemotherapy which are administered by IV infusion).

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

Table 2 Assessments if ILD/Pneumonitis is Suspected during the Intervention Period

Procedure	Details in CSP Section
ILD/pneumonitis investigation	Section 8.2.5.3
Detailed past medical history and concomitant medications	Section 8.2.5.3
Physical examination, including auscultation of lung field	Section 8.2.5.3
HRCT of the chest if feasible (otherwise non-contrast chest CT is acceptable)	Section 8.2.5.3
Arterial blood gases if clinically indicated	Section 8.2.5.3
Pulmonary function tests and pulse oximetry (SpO_2)	Sections 8.2.5.2 and 8.2.5.3
Bronchoscopy and bronchoalveolar lavage should be considered if clinically indicated and feasible	Sections 8.2.5.3
Pulmonologist consultation (infectious diseases consultation, as clinically indicated)	Section 8.2.5.3
Blood culture, complete blood count, and differential white blood cell count; other blood tests could be considered as needed	Section 8.2.5.3
Troponin measurements to rule out cardiac etiology	Section 8.2.5.3
Additional optional blood sample for plasma exploratory ILD/pneumonitis analysis as soon as ILD/pneumonitis is suspected and/or diagnosed [a]	Sections 8.2.5.3 and 8.6.1
Additional optional blood sample for serum exploratory ILD/pneumonitis analysis as soon as ILD/pneumonitis is suspected and/or diagnosed [a]	Sections 8.2.5.3 and 8.6.1

Note: Other tests could be considered, as needed (eg, COVID-19 test).

[a] Whenever ECGs, vital signs and blood draws are scheduled for the same day, the assessments should occur in the following order: ECG, vital signs and then blood draws. The timing of the ECG and vital signs assessments must allow for the blood draw (eg, PK blood sample) to occur at the scheduled time points specified in Table 1. Pulse oximetry (SpO_2) will be performed at the same time as vital signs.

2 INTRODUCTION

Datopotamab deruxtecan (Dato-DXd, DS-1062a) is an antibody-drug conjugate (ADC) that comprises a recombinant humanized anti-TROP2 IgG1 monoclonal antibody, which is covalently conjugated to a drug linker via thioether bonds.

Antibody-drug conjugates are targeted anticancer medicines that deliver cytotoxic chemotherapy (‘payload’) to cancer cells via a linker attached to a monoclonal antibody that binds to a specific target expressed on cancer cells. Antibody-drug conjugates provide a unique opportunity to deliver drugs to tumor cells while minimizing toxicity to normal tissue.

Dato-DXd binds to trophoblast cell surface protein 2 (TROP2), also known as tumor-associated calcium signal transducer 2. Dato-DXd is in development as a candidate therapy for cancer.

2.1 Study Rationale

Single agent chemotherapy remains the cornerstone of therapy for patients with HR-positive, HER2-negative metastatic breast cancer who have exhausted endocrine therapy options. However, patient prognosis is poor, and durable antineoplastic therapy options are necessary to improve outcomes in this patient population (see Section 2.2.1 for further details).

TROP2 is a type I transmembrane glycoprotein originally identified in human trophoblast cells (Fornaro et al 1995, Alberti et al 1992, Lipinski et al 1981). TROP2 is highly expressed in a number of normal tissues and several cancers and has been recognized as a novel promising antigen for ADCs due to its high expression in breast tumors (Pau Ni et al 2010). Furthermore, increased TROP2 mRNA in breast cancer has been shown to be a predictor of lymph node involvement, distant metastasis, and poor OS (Zhao et al 2018).

The potential for TROP2 ADCs in the treatment of breast cancer has been demonstrated with the FDA approval of sacituzumab govitecan (TRODELVY; IMMU-132; Gilead Sciences, Inc.) for patients with locally advanced and metastatic TNBC who have received at least 2 prior systemic therapies, at least one of them for metastatic disease. Most recent data in HR-positive, HER2-negative metastatic breast cancer population treated with sacituzumab govitecan, who have received at least 2 prior lines of therapy, with a median follow-up of 11.5 months, has shown that the ORR was 31.5% (95% CI: 19.5, 45.6; 17 partial responses); median DoR was 8.7 months (95% CI: 3.7, 12.7), median PFS was 5.5 months (95% CI: 3.6, 7.6), and median OS was 12 months (95% CI: 9.0, 18.2) (Kalinsky et al 2020). Of note, significant toxicities in sacituzumab govitecan treated participants have been reported, which include myelosuppression and diarrhea (Bardia et al 2020). Furthermore, the efficacy of ADCs in breast cancer has been demonstrated from the approval of ENHERTU (T-DXd) and KADCYLA (T-DM1), two HER2-targeted ADCs indicated for HER2-positive breast cancer (Modi et al 2020, Von Minckwitz et al 2019).

Dato-DXd is a TROP2 ADC (administered via IV infusion, Q3W) that binds to TROP2, is internalized, and after enzymatic processing, the topoisomerase I inhibitor, MAAA-1181a, is released, leading to inhibition of tumor growth, DNA damage, and apoptosis of target cells. The cytotoxic payload of Dato-DXd is the same as T-DXd. Preclinical data has demonstrated that Dato-DXd exerts specific cell growth inhibitory activity against TROP2-expressing cells, but it does not have cell growth inhibitory against TROP2-negative cells.

Within the Dato-DXd clinical development program, preliminary data supporting the use of Dato-DXd in participants with HR-positive, HER2-negative breast cancer are available from an ongoing phase 1 FIH study, TROPION-PanTumor01 (NCT03401385), which is evaluating escalating doses of Dato-DXd (0.27 mg/kg to 10 mg/kg) in participants with advanced NSCLC and TNBC, relapsed or refractory to SoC therapy. These data have demonstrated highly encouraging efficacy across dose groups, with tumor responses observed at doses of 4,

6, and 8 mg/kg and an acceptable and manageable toxicity profile (see Section 2.2.2.1). An additional cohort of participants with HR-positive, HER2-negative breast cancer is currently recruiting as of March 2021.

Given the biological rationale and encouraging preliminary safety and efficacy data obtained from the TROPION-PanTumor01 study, the current study is designed to provide a robust and detailed understanding of the efficacy and safety of Dato-DXd when compared with Investigator's choice of standard-of-care single-agent chemotherapy (eribulin, capecitabine, vinorelbine, or gemcitabine; henceforth referred to as ICC) in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with one or two prior lines of systemic chemotherapy, for which an unmet medical need remains.

2.2 Background

2.2.1 HR-positive, HER2-negative, inoperable/metastatic breast cancer

Breast cancer is the most common cancer in the world, with an estimated 2.2 million new cases in 2020 globally (11.7% of all new cancers). Breast cancer is also the fifth most common cause of death from cancer, with an estimated 684000 deaths in 2020 (Sung et al 2021). In Europe, an estimated 531000 patients were diagnosed with breast cancer in 2020, and 141000 died from the disease. Despite advances in the diagnosis and treatment of breast cancer, around 6% of women diagnosed with breast cancer in the US have metastatic disease at time of diagnosis, and up to 30% of women with early-stage non-metastatic breast cancer will develop metastatic disease (O'Shaughnessy 2005). Although treatable, metastatic breast cancer remains virtually incurable, with a median survival of approximately 3 years and a 5-year survival rate of approximately 25% (Cardoso et al 2018).

Currently, clinical practice typically uses a surrogate classification of three breast cancer subtypes, based on molecular characteristics: HER2-positive, HR-positive but HER2-negative, and triple-negative. Tumors expressing ER and/or PR are considered HR-positive breast cancers, whereas tumors that do not express ER, PR or HER2 are defined as TNBC (Harbeck et al 2019). Approximately 70% of all breast cancers are HR-positive, HER2-negative (Howlader et al 2014).

In patients with metastatic HR-positive, HER2-negative breast cancer, the preferred initial treatment of choice is endocrine therapy, given either alone or in combination with targeted therapies such as CDK4/6 inhibitors, PI3-K, and mTOR inhibitors (Matutino et al 2018, André et al 2019). Within these, CDK4/6 as a class has shown to improve both PFS and OS in a meta-analysis (Cardoso et al 2018); however, the optimal sequence and integration of the agents is not fully established and is largely determined by geographic availability, which treatments were previously administered, the response obtained, and individual patient and disease characteristics.

In patients with metastatic HR-positive, HER2-negative breast cancer, who have exhausted or are not suitable for endocrine therapy, first-line chemotherapy is the SoC, with sequential single-agent chemotherapy (such as eribulin, capecitabine, gemcitabine, vinorelbine) generally preferred over combination therapy due to lack of consistent OS benefit and poor tolerability with combination therapy (Cardoso et al 2020, NCCN Guidelines 2020).

The following baseline clinico-pathological characteristics/factors could be clinically relevant to the targeted study population of interest for this study:

- Proportion of patients with 1 versus 2 prior lines of chemotherapy in the metastatic or inoperable setting
- Prior CDK4/6 inhibitor use (yes versus no)
- History of brain metastasis (yes versus no).

These and other factors may be recorded in IRT and could be included as part of routine monitoring throughout enrolment of the study. Unexpected variations could be evaluated by the Sponsor (see Appendix A).

2.2.1.1 Unmet medical need

The SoC of single agent chemotherapy in the HR-positive, HER2-negative metastatic breast cancer population has led to reported response rates of approximately 23%, a median PFS of 7 to 10 months, and a median OS of 26 to 36 months (Jerusalem et al 2018, Kaufman et al 2015, Twelves et al 2016). After two prior lines of chemotherapy, a median PFS of between 4 and 5 months and a median OS of between 14 and 24 months has been reported (Twelves et al 2016, Brufsky 2011, Miller et al 2005, Sparano et al 2010, Barrios 2010, Thomas et al 2007). Data after three lines of chemotherapy report a median PFS of approximately 3 to 4 months and median OS of between 11 to 16 months (Cortes et al 2011, Yardley et al 2013, Martín et al 2007, Yuan et al 2019). These data indicate that patients who are not suitable for, or who have exhausted, endocrine treatment options have an increasingly poor prognosis, with the greatest unmet medical need arising in patients who have received two or three prior lines of chemotherapy, for whom median survival is currently less than 2 years.

Chemotherapy is also associated with significant toxicities, including hematologic adverse effects, gastrointestinal toxicities including diarrhea, nausea, vomiting, alopecia, and skin reactions (Gradishar et al 2005, Miller et al 2007, Piccart-Gebhart et al 2008), which can have a significant impact on patient quality of life. Consequently, new and novel treatments for participants with HR-positive, HER2-negative advanced breast cancer are still needed to improve prognosis, control disease and prevent symptoms while minimizing toxicity, and therefore represents an area of considerable unmet medical need. A new class of therapy with better efficacy and relatively fewer side effects would therefore be a preferred option in this

treatment setting, to offer an alternative after traditional standard chemotherapies.

2.2.2 Dato-DXd

Dato-DXd is being co-developed by Daiichi Sankyo and AstraZeneca as an anticancer agent.

To date, clinical (preliminary safety and efficacy) data is currently available from one ongoing study (TROPION-PanTumor01; sponsored by Daiichi Sankyo). A summary of recent data from this study is presented in Section 2.2.2.1. Please refer to the Dato-DXd IB for a list of all studies in the Dato-DXd clinical development program, including participant exposure.

A detailed description of the chemistry, pharmacology, mechanism of action, efficacy, and safety of Dato-DXd is provided in the IB.

2.2.2.1 TROPION-PanTumor01 study

This ongoing Phase I FIH study evaluated escalating doses (0.27 to 10 mg/kg) of Dato-DXd in advanced solid tumors in participants with unresectable advanced NSCLC, and is currently in the dose expansion phase evaluating selected doses of Dato-DXd in participants with NSCLC, TNBC, and ER-positive, HER2-negative breast cancer who have been refractory to or relapsed on standard treatment or for which no standard treatment is available.

At the efficacy DCO date, 30 July 2021, preliminary efficacy data from the ongoing DS1062-A-J101 study were available. A total of 254 participants were evaluable for response assessments (210 with NSCLC and 44 with TNBC), defined as participants who received at least 1 dose of Dato-DXd and had pre-treatment and at least 1 post-treatment tumor assessment or discontinued from study drug. For participants with TNBC, the DCR was 76.2% (13 PRs and 16 SDs in 42 participants) in the 6 mg/kg dose group and 100% (1 PR and 1 SD in 2 participants) in the 8 mg/kg dose group.

Preliminary safety summary, as of 30 July 2021, in participants with breast cancer (TNBC and HR+/HER2-breast cancer) are summarized below. A total of 75 (93.8%) participants experienced at least 1 TEAE. The most frequently (≥ 15% of participants) reported TEAEs were nausea (45 [56.3%] participants), stomatitis (37 [46.3%] participants), alopecia (24 [30.0%] participants), fatigue (24 [30.0%] participants), vomiting (22 [27.5%] participants), constipation (16 [20.0%] participants), mucosal inflammation (18 [22.5%] participants), and headache (17 [21.3%] participants).

A total of 28 (35.0%) participants experienced ≥ Grade 3 TEAEs. The most commonly (> 2.5% of participants) reported ≥Grade 3 events by investigator-reported PT were lymphocyte count decreased (4 [5.0%] participants), stomatitis (4 [5.0%] participants), fatigue (3 [3.8%] participants), and lymphopenia (3 [3.8%] participants). A total of 1 (1.3%) participant had TEAEs associated with study treatment discontinuation due to investigator-reported PT of pneumonitis. A total of 1 (1.3%) participant experienced TEAEs

associated with an outcome of death due to investigator-reported PT of dyspnea. A total of 12 participants experienced serious TEAEs.

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 expected benefits and risks and the overall efficacy and safety profiles of Dato-DXd are found below and in the IB.

2.3.1 Risk Assessment

2.3.1.1 Dato-DXd

Based on safety data from nonclinical toxicology studies and clinical data available to date, the risks associated with Dato-DXd are presented in Table 3.

Table 3 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Dato-DXd		
• *Important identified risks:* ILD/pneumonitis. • *Identified risks*: IRR, anemia, fatigue, nausea, vomiting, diarrhea, decreased appetite, dry eye, alopecia, stomatitis/oral mucositis, mucosal inflammation other than oral mucositis/stomatitis, and rash/maculopapular rash. • *Potential risks*: Keratitis, skin pigmentation, increased ALT, increased AST, and constipation. • *AESIs*: ILD/pneumonitis, IRRs, oral mucositis/stomatitis, mucosal inflammation other than oral mucositis/stomatitis, and ocular surface toxicity. Dato-DXd has not been studied in participants with renal or hepatic impairment.	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 ILD/pneumonitis. No confirmed cases of Hy's Law or DILI have been observed. Please see the current version of the IB for a	Clinical experience in the Dato-DXd clinical development program to date has demonstrated that these identified and potential risks have been manageable through dose modification and routine clinical practice. However, specific inclusion/exclusion criteria (see Section 5) and monitoring/management guidelines (see Section 6.6) are currently in place to mitigate the important identified risks and AESIs (ILD/pneumonitis, IRR, oral mucositis/stomatitis, mucosal inflammation other than oral mucositis/stomatitis, and ocular surface toxicity). To specifically mitigate the incidence of pulmonary toxicities, inclusion/exclusion criteria are included prohibiting participants with relevant pre-existing pulmonary co-morbidities from entering the study. In addition, baseline pulmonary function tests will be performed for all participants. Potential ILD cases will be monitored closely for confirmatory signs and symptoms of ILD

Table 3 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Information on AEs is presented in Section 8.3.	detailed and up to date summary of data including AEs, SAEs, and CTCAE Grade 3 to 5 events reported across the Dato-DXd program.	and reviewed by an independent, blinded, ILD Adjudication Committee, which has been established for the Dato-DXd program to ensure adequate evaluation of events of interest (see Section 9.6.2). To mitigate the risk of IRRs, participants with a history of hypersensitivity reactions to any of the Dato-DXd excipients are excluded from participation in the study. Guidance on required pre-medication for the prevention of IRRs is also provided (see Section 6.6). To mitigate the risk of ocular surface toxicity, participants with clinically significant corneal disease are excluded from participation in the study. In addition, baseline, periodic and EoT ophthalmologic assessments will be performed by a licensed eye care provider. Ophthalmologic assessment data will be reviewed by an independent Ophthalmologic Data Review Committee (see Section 9.6.3). Guidance on prevention and management of ocular surface toxicity is provided (see Sections 8.2.5.5 and 6.6).

2.3.2 Benefit Assessment

Dato-DXd is under development for the treatment of lung, breast, and other advanced solid tumors. Data from the ongoing TROPION-PanTumor01 study demonstrate efficacy across dose groups, with tumor responses observed at starting doses of 4, 6, and 8 mg/kg and an acceptable and manageable toxicity profile across doses of Dato-DXd (see Section 2.2.2.1). Consequently, it is hypothesized that participants randomized to receive Dato-DXd may derive benefit from a potentially efficacious agent, whilst participants randomized to receive ICC will be treated in accordance with the current SoC for HR-positive, HER2-negative inoperable or metastatic breast cancer. Furthermore, compared to the toxicities of the comparator ICC agents, Dato-DXd appears to have a more favorable safety profile.

Other participant benefits include the less frequent infusions of Dato-DXd (Q3W) compared to comparator ICC schedules, making Dato-DXd treatment potentially more convenient. Additionally, at the time of disease progression, participants will be offered an optional tumor

biopsy, which will provide real-time next-generation sequencing results from the FoundationOne®CDx, that may help guide next treatment options.

Overall, participants enrolling onto this study will have a 1:1 chance of the receiving either the experimental drug Dato-DXd, or a standard chemotherapy agent. All participants will be contributing to the process of developing new therapies in an area of great unmet medical need.

2.3.3 Overall Benefit: Risk Conclusion

There is an unmet medical need for efficacious and safe therapies in treatment of HR-positive, HER2-negative inoperable or metastatic breast cancer in order to improve clinical outcomes. The extensive expression of TROP2 in breast cancers and the proof-of-concept shown by sacituzumab govitecan in HR-positive, HER2-negative (and TNBC) metastatic breast cancer has demonstrated the strong rationale of using an anti-TROP2-ADC in the HR-positive, HER2-negative population (Bardia et al 2021, Kalinsky et al 2020).

Preliminary results from the TNBC cohort of the TROPION-PanTumor01 study have shown promising efficacy of Dato-DXd at a dose of 6 mg/kg Q3W and support the further evaluation of Dato-DXd in the HR-positive, HER2-negative breast cancer population. In this cohort, the most common TEAEs were nausea, stomatitis, alopecia, fatigue, vomiting, constipation, mucosal inflammation, and headache. The most common Grade ≥ 3 TEAEs were lymphocyte count decreased, stomatitis, fatigue, and lymphopenia. One participant had TEAEs associated with study treatment discontinuation and one participant experienced TEAEs associated with an outcome of death.

The 2 most relevant risks considered for the benefit/risk assessment are the important identified risk of ILD/pneumonitis and the identified risk of IRR. Both of these risks can be fatal. Several measures have been put into place within the CSP to mitigate the incidence of pulmonary toxicities, including eligibility criteria that prohibit participants with pre-existing pulmonary co-morbidities from entering the study. In addition, baseline pulmonary function tests will be performed for all participants. Participants will be monitored closely throughout the study and clinical and laboratory assessments will be performed before every cycle. Toxicity Management Guidelines are also provided to assist with the management of the most commonly reported AEs and AESIs (see the Annex document to this CSP).

Consequently, compared to the safety profile of SoC chemotherapies, Dato-DXd is a potent anticancer therapy with the potential to provide an improved meaningful clinical benefit and a more favorable safety profile. Furthermore, the long half-life of Dato-DXd also enables a single IV, Q3W regimen, providing convenience to patients. It is therefore of key importance to evaluate the role of Dato-DXd in the HR-positive, HER2-negative inoperable or metastatic breast cancer population who have had progression of disease on 1 or 2 lines of chemotherapy,

and considering the measures to minimize risks to participants, the benefit/risk assessment supports the proposed study.

3 OBJECTIVES AND ENDPOINTS

Table 4 Objectives and Endpoints

Objectives	Endpoints
Dual Primary	
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of PFS in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer, who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting, per BICR.	• PFS is defined as time from randomization until progression per RECIST 1.1, as assessed by BICR, or death due to any cause. The analysis will include all randomized participants as randomized regardless of whether the participant withdraws from therapy, receives another anticancer therapy, or clinically progresses prior to RECIST 1.1. The measure of interest is the hazard ratio of PFS.
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of OS in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer, who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting.	• OS is defined as time from randomization until the date of death due to any cause. The comparison will include all randomized participants as randomized, regardless of whether the participant withdraws from therapy or receives another anticancer therapy. The measure of interest is the hazard ratio of OS.
Secondary	
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of ORR in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer, who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting, per BICR and per investigator assessment.	• ORR is defined as the proportion of participants who have a confirmed CR or PR, as determined by the BICR/Investigator assessment, per RECIST 1.1. The analysis will include all randomized participants as randomized. Data obtained from randomization up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR, regardless of whether the participant withdraws from therapy. Participants who go off treatment without a response or progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR. The measure of interest is the odds ratio of the ORR.
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of DoR in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting.	• DoR is defined as the time from the date of first documented confirmed response until date of documented progression per RECIST 1.1, as assessed by BICR/Investigator assessment or death due to any cause. The analysis will include all randomized participants as randomized who have a confirmed response, regardless of whether the participant withdraws from therapy, receives another anticancer therapy or clinically progresses prior to RECIST 1.1 progression. The measure of interest is the median of DoR.

Objectives	Endpoints
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of PFS in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting, per investigator assessment.	• PFS is defined as time from randomization until progression per RECIST 1.1, as assessed by investigator assessment, or death due to any cause. The analysis will include all randomized participants as randomized regardless of whether the participant withdraws from therapy, receives another anticancer therapy, or clinically progresses prior to RECIST 1.1. The measure of interest is the hazard ratio of PFS.
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of DCR in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer, who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting, per BICR and per investigator assessment.	• DCR at 12 weeks is defined as the percentage of participants who have a confirmed CR or PR or who have SD, per RECIST 1.1, as assessed BICR/per investigator assessment and derived from the raw tumor data for at least 11 weeks after randomization. Data obtained from randomization up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of DCR, regardless of whether the participant withdraws from therapy. Participants who receive a subsequent therapy prior to week 11 will not be considered to have disease control in the analysis. The analysis will include all randomized participants as randomized. The measure of interest is the odds ratio of the DCR.
To assess pain in participants treated with Dato-DXd compared to ICC.	• TTD in pain as measured by the pain scale from EORTC QLQ-C30 TTD is defined as time from the date of randomization to the date of deterioration. Deterioration is defined as change from baseline that reaches a clinically meaningful deterioration threshold. The analysis will include all randomized participants. The measure of interest is the hazard ratio of TTD in pain.
To assess physical functioning in participants treated with Dato-DXd compared to ICC.	• TTD in physical functioning as measured by the physical functioning scale from EORTC QLQ-C30 TTD is defined as time from the date of randomization to the date of deterioration. Deterioration is defined as change from baseline that reaches a clinically meaningful deterioration threshold. The analysis will include all randomized participants. The measure of interest is the hazard ratio of TTD in physical functioning.
To assess global health status/quality of life (GHS/QoL) in participants treated with Dato-DXd compared to ICC.	• TTD in GHS/QoL as measured by the GHS/QoL scale from EORTC QLQ-C30 TTD is defined as time from the date of randomization to the date of deterioration. Deterioration is defined as change from baseline that reaches a clinically meaningful deterioration threshold. The analysis will include all randomized participants. The measure of interest is the hazard ratio of TTD in GHS/QoL.

Objectives	Endpoints
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of TFST in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting.	• TFST is defined as the time from randomization until the start date of the first subsequent anticancer therapy after discontinuation of randomized treatment, or death due to any cause. The analysis will include all randomized participants as randomized, regardless of progression status. The measure of interest is the hazard ratio of TFST.
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of TSST in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting.	• TSST is defined as the time from randomization to until the start date of the second subsequent anticancer therapy after discontinuation of first subsequent treatment, or death due to any cause. The analysis will include all randomized participants as randomized, regardless of progression status on study treatment or first subsequent treatment. The measure of interest is the hazard ratio of TSST.
To demonstrate the superiority of Dato-DXd compared to ICC by assessment of PFS2 in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with 1 or 2 lines of chemotherapy in the inoperable/metastatic setting.	• PFS2 will be defined as the time from the randomization to the earliest of the progression event (following the initial progression), subsequent to first subsequent therapy, or death. The date of second progression will be recorded by the Investigator in the eCRF and defined according to local standard clinical practice. The comparison will include all randomized participants as randomized regardless of whether the participant withdraws from subsequent therapy and regardless of missed visits. The measure of interest is the hazard ratio of PFS2.
To assess the PK of Dato-DXd 6mg/kg IV Q3W.	• Plasma concentrations of Dato-DXd, total anti-TROP2 antibody, and MAAA-1181a (payload).
To investigate the immunogenicity of Dato-DXd 6mg/kg IV Q3W.	• Presence of ADA.
Safety	
To assess the safety and tolerability profile of Dato-DXd compared to ICC.	Safety and tolerability will be evaluated in terms of adverse events (graded by CTCAE version 5.0), and also in terms of: • ECOG PS • Vital signs, body weight, physical examination • Clinical chemistry, hematology, and urinalysis assessments • ECG, ECHO/MUGA and Ophthalmologic assessments
Exploratory	
To assess participant-reported symptomatic AEs and treatment tolerability.	Proportion of participants experiencing different levels of symptomatic AEs as measured by selected items from the PRO-CTCAE and EORTC Item Library (IL; ie, EORTC IL117) and reporting different levels of overall tolerability as measured by the PGI-TT. The analysis will include all dosed participants. The measure of interest will be proportion of participants reporting different levels of symptomatic AEs and overall tolerability.

Objectives	Endpoints
To assess participant-reported global impression of the severity of overall cancer symptoms.	Proportion of participants reporting different levels of global impression of the severity of overall cancer symptoms as measured by PGIS. The analysis will include all randomized participants. The measure of interest will be proportion of participants reporting different levels of global impression of the severity of overall cancer symptoms.
To assess participant-reported global impression of change in health status.	Proportion of participants reporting different levels of global impression of change in health status as measured by PGIC. The analysis will include all randomized participants. The measure of interest will be proportion of participants reporting different levels of global impression of change in health status.
To assess participant-reported symptoms, functioning and health-related QoL.	• TTD in fatigue and other symptoms as measured by EORTC QLQ-C30 • TTD in other functioning as measured by EORTC QLQ-C30 • Change from baseline of symptom, functioning and GHS/QoL scores as measured by EORTC QLQ-C30 The analysis will include all randomized participants. The measure of interest will be hazard ratio of TTD in fatigue and other symptoms, TTD in other functioning, and mean change from baseline of symptom, functioning and GHS/QoL scores.
To assess breast and arm symptoms in participants treated with Dato-DXd compared to ICC.	• TTD in breast symptoms as measured by the breast symptoms scale from EORTC QLQ-BR45/IL116 • TTD in arm symptoms as measured by the arm symptoms scale from EORTC QLQ-BR45/IL116 TTD is defined as time from the date of randomization to the date of deterioration. Deterioration is defined as change from baseline that reaches a clinically meaningful deterioration threshold. The analysis will include all randomized participants. • The measure of interest is the hazard ratio of TTD in breast symptoms/arm symptoms.
To assess participant-reported health status.	• VAS score, its change from baseline and 5-dimension scores as measured by EQ-5D-5L The analysis will include all randomized participants. The measure of interest will be mean and mean change from baseline of VAS score, and proportion of participants reporting different levels of each of 5-dimension scores.
Association of TROP2 or other tumor derived biomarkers with response and tolerability to Dato-DXd and ICC. [a]	• Correlation of biomarkers with clinical response (BoR, DoR, PFS, OS and other relevant efficacy endpoints) and/or development of cancer • Correlation of biomarkers with safety and tolerability endpoints Analysis may include, but is not limited to, the analysis of tumor biomarkers which include DNA, RNA, proteins or metabolite analysis

Objectives	Endpoints
Association of exploratory biomarkers in tumor, plasma, whole blood, or serum collected before, during treatment or at disease progression with disease status and/or response and tolerability to Dato-DXd. [a]	• Correlation of biomarkers with clinical response (BoR, DoR, PFS, OS and other relevant efficacy endpoints) and/or development of cancer • Correlation of biomarkers with safety and tolerability endpoints Analysis may include, but is not limited to, the analysis of tumor biomarkers which include DNA, RNA, proteins or metabolite analysis
Assessment of ctDNA mutational profile and dynamic changes as an indicator for early response and/or relapse on Dato-DXd, and assessment of molecular and genomic determinants of response to Dato-DXd in tumor and blood. [a]	• Assessment of ctDNA levels and mutational status of cancer-associated genes in ctDNA, including dynamic changes on treatment and correlation with clinical response on Dato-DXd and ICC, and correlation of gene expression and cancer gene mutational profile with clinical response.
To explore the impact of treatment and disease on health care resource use.	• The HOSPAD module will be used to collect information on key health care resource use beyond study mandated visits.

[a] Optional biomarker samples will not be collected in mainland China.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, open-label, randomized study of Dato-DXd versus ICC in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with one or two prior lines of systemic chemotherapy in the inoperable or metastatic setting. For an overview of the study design, see Figure 1.

Approximately 700 participants will be randomized in a 1:1 ratio to one of 2 intervention arms. If required for regulatory submission purposes, the recruitment of participants in mainland China may continue beyond the close of the global cohort, to include approximately an additional 20 randomized participants in the mainland China cohort. The mainland China cohort is defined as all participants from sites in mainland China randomized into the study. A participant randomized in the mainland China cohort prior to the last participant randomized in the global cohort will be included in both the global and mainland China cohorts. A participant randomized in mainland China after the last participant was randomized in the global cohort will be included only in the mainland China cohort.

Randomization will be stratified by the following prognostic and/or predictive factors:

- Number of previous lines of chemotherapy (1 versus 2)
- Geographic region (Region 1 [US, Canada, Europe] versus Region 2 [Rest of World])
- Prior use of CDK4/6 inhibitor (Yes versus No)

A 50% cap will be applied to participants who have had 2 prior lines of chemotherapy in the inoperable/metastatic setting.

CDK4/6 inhibitors are being increasingly utilized as part of standard of care for patients with HR+ breast cancer. To ensure that majority of participants have received prior CDK4/6 inhibitor therapy in the HER2 negative, HR-positive population, a cap of 49% will be applied to participants who have NOT received prior CDK4/6 inhibitor therapy.

The study intervention arms are:

- **Arm 1:** Dato-DXd (6 mg/kg IV on Day 1, Q3W)
- **Arm 2:** ICC:
  - Capecitabine (1000 or 1250 mg/m^2 oral BID on Days 1 to 14, Q3W); choice between the 2 doses will be determined by standard institutional practice.
  - Gemcitabine (1000 mg/m^2 IV on Day 1 and Day 8, Q3W)
  - Eribulin mesylate (1.4 mg/m^2 IV on Days 1 and 8, Q3W)
  - Vinorelbine (25 mg/m^2 IV on Days 1 and 8, Q3W)

Further details of all study interventions are provided in Section 6. All participants will receive study intervention until Investigator-defined disease progression according to RECIST 1.1, or until unacceptable toxicity, withdrawal of consent, or another criterion for discontinuation is met (see Section 7 for further details). Continued treatment with the same study drug post-progression may be allowed, based on prior discussion with study physician on case-by-case basis. No crossover between study treatment arms will be allowed.

The study is powered to assess the efficacy of Dato-DXd compared to ICC for the dual primary objectives of PFS (per RECIST 1.1, as assessed by BICR) and OS. Other measures of efficacy (ORR, DoR, DCR, TFST, TSST, PFS2) and HRQoL will also be evaluated during the study, in addition to the safety and tolerability profile of Dato-DXd, PK parameters, and immunogenicity. Details of all study objectives and corresponding endpoints are provided in Section 3.

All participants must have available a FFPE tumor sample (block preferred, or minimum of 20 freshly cut slides), at the time of screening. This can be from either the primary disease setting (surgical resection or diagnostic sample), or from a metastatic lesion (excluding bone) for tissue-based analysis (including but not restricted/limited to IHC staining of potential predictive biomarkers as well as tumor mutational analysis). The mandatory FFPE tumor sample submitted for analysis should be obtained as close to the time of diagnosis of metastatic or inoperable disease as possible.

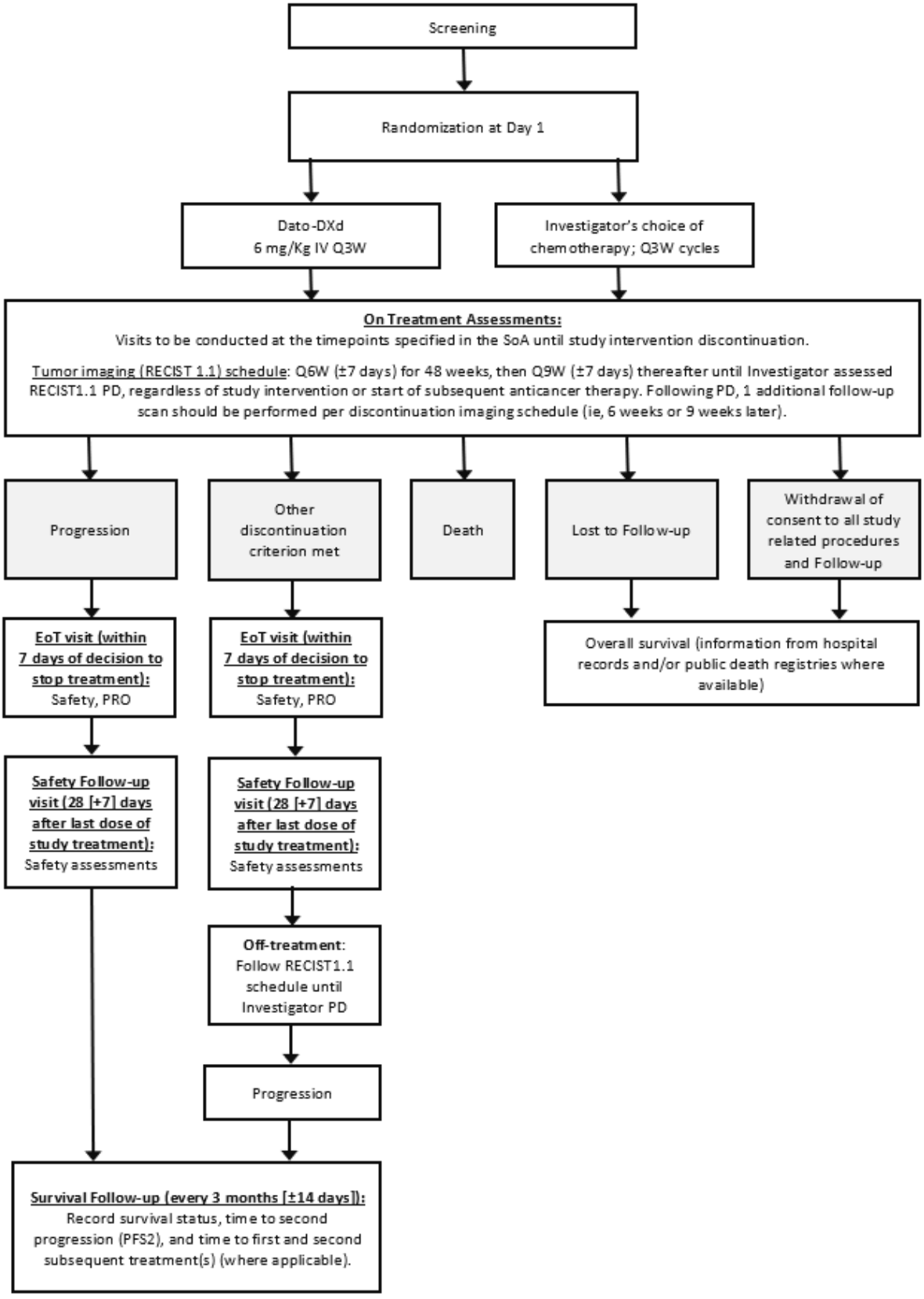
If neither an adequate FFPE block nor the minimum of 20 slides are available, a patient may still be considered eligible. In this situation, approval by the Study Team for patient's entry into the study is required. If there is no written confirmation of the availability of an appropriate tumor sample prior to enrolment, the participant will not be eligible for the study. At the time of enrolment all participants must have an ECOG PS of 0 or 1.

Note: Sample collection in mainland China will follow local regulatory approval.

A summary of the study periods and timings of study visits and main efficacy assessments is provided in Figure 2.

Country-specific study requirements are provided in Appendix L.

Figure 2 Study Flow Chart



4.1.1 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 SARS-CoV-2 or 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 minimize risks to study integrity. Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the ICF should be signed at the participant's next contact with the study site).
- Rescreening: Extended rescreening period 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 Health Care Professional (HCP) or HCP provided by a third-party vendor (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 J.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Design

This randomized, open-label, 2-arm study will investigate Dato-DXd monotherapy versus ICC (eribulin, vinorelbine, capecitabine, or gemcitabine). The open-label design was chosen due to the differing dosing schedules of the ICC treatments; however, the trial will be conducted as "sponsor-blind" and the specific study intervention (Dato-DXd or ICC) to be taken by a participant will be assigned in a randomized manner. To maintain the integrity of the study, Sponsor personnel directly involved in the study conduct will not undertake or have access to efficacy data aggregated by treatment arm prior to final data readout for the dual primary

endpoint of PFS. At Sponsor discretion, the sponsor blind may be dropped if the dual primary endpoint of PFS achieves statistical significance at its primary analysis.

4.2.2 Rationale for Choice of Comparator Treatments

Chemotherapy (single agent or doublet) is considered the main treatment option for patients who have exhausted or are not suitable for endocrine therapy in the metastatic setting. Combination chemotherapy has shown higher ORR, however, could not clearly show an OS benefit (Schott 2021). In addition, to balance the OS benefits with the toxicities between single agent and combination therapy, single agent sequential chemotherapies are recommended. Preferred agents in this setting include capecitabine, gemcitabine, vinorelbine, and eribulin (NCCN Guidelines 2020, Cardoso et al 2020).

Capecitabine is frequently the first choice because of oral administration and low risk of alopecia and myelotoxicity. In the large phase 2 study in participants with metastatic breast cancer, capecitabine monotherapy achieved an ORR of 20% and median OS of 12.6 months (Blum et al 1999). Gastrointestinal side effects and hand-foot syndrome were the most commonly occurring adverse events.

Eribulin has demonstrated anti-tumor activity as single-agent in metastatic breast cancer participants. In the EMBRACE trial, eribulin significantly improved OS in heavily pre-treated metastatic breast cancer participants as compared to SoC (median OS of 13.1 months versus 10.6 months). The primary toxicity with eribulin was neutropenia whereas peripheral neuropathy was the most common adverse event leading to discontinuation of eribulin (Cortes et al 2011).

Vinorelbine has demonstrated activity even in heavily pre-treated participants with metastatic breast cancer. In a Phase 3 study of vinorelbine monotherapy versus gemcitabine plus vinorelbine, median PFS in the single-agent vinorelbine arm was 4.0 months and OS was 16.4 months (Martín et al 2007). Vinorelbine rarely induces total alopecia or severe gastrointestinal events or symptomatic cardiac events. The major dose-limiting hematological toxicity associated with vinorelbine is neutropenia (Domenech and Vogel 2001).

Gemcitabine is active in metastatic breast cancer, with a response rate of approximately 25% and a median DoR of 13.5 months. A median OS of 15.2 months has also been reported (Possinger et al 1999). The drug is relatively well tolerated; alopecia and gastrointestinal toxicity are mild, and its use is not associated with significant neuropathy. Thrombocytopenia can be a dose-limiting toxicity. Gemcitabine appears to cross the blood brain barrier and may be a good option in participants with a history of CNS metastases (Gridelli et al 1999).

4.2.3 Rationale for Stratification Factors

4.2.3.1 Stratification based on previous lines of chemotherapy

The proposed dual primary endpoints of this study are PFS and OS, which are expected to differ in their magnitude dependent on whether a participant has received 1 or 2 lines of prior chemotherapy (see Section 2.2.1.1 for further details). Therefore, stratification by lines of chemotherapy (1 versus 2) has been chosen. Additionally, the study will also cap enrolment at 50% for participants who have received 2 prior lines of chemotherapy.

4.2.3.2 Stratification based on prior CDK4/6 inhibitor use

Differences in the magnitude of benefit in PFS and OS are also expected in participants receiving TROP2 inhibitors, dependent on whether treatment with a prior CDK4/6 inhibitor has been received. In HR-positive, HER2-negative participants treated with sacituzumab govitecan (a TROP2 ADC approved for use in metastatic TNBC by in the US), a subgroup analysis performed on prior CDK4/6 inhibitor use (no prior use versus prior use) demonstrated notable differences in median PFS, OS, and ORR (Kalinsky et al 2020). It is expected that the majority of study participants will have received CDK4/6 inhibitors. There are however global regions where CDK4/6 inhibitors are not yet adopted, and as such patients may be enrolled, stratification based on prior CDK4/6 inhibitor use are proposed.

4.2.3.3 Stratification based on geographical region

Mortality rates from breast cancer vary by geographic region, due to regional differences in drug availability and medical practice. In many western countries, mortality rates due to breast cancer are decreasing, which has been attributed to a combination of early detection using mammographic screening and improved treatment options. In contrast, mortality rates in many South American, African, and Asian countries increased (Youlden et al 2012). Given these examples of differences in outcomes in various regions, stratification based on geographical region is proposed.

4.2.4 Rationale for Primary Efficacy Endpoints

The primary dual endpoints of the study are OS and PFS by BICR, according to RECIST 1.1 in the ITT. These endpoints are in line with the guidelines outlined by the NCI Breast Cancer Steering Committee Working Group Report (Seidman et al 2018), which recommends OS to be a primary endpoint in poor prognosis disease settings, and PFS to be a most robust and appropriate endpoint in HR-positive, HER2-negative disease, which has longer post-progression survival.

Overall survival is a clinically meaningful and direct measure of overall efficacy in metastatic breast cancer disease, and both the EMA (EMA 2017) and FDA (FDA 2018) advice consider OS as the most persuasive and reliable endpoint. However, both Agencies also consider PFS as an acceptable endpoint, dependent on the disease under study and other factors. For a randomized Phase 3 study, PFS is a relevant measure of clinical benefit that demonstrates

superiority of a new antineoplastic therapy, particularly in a setting where patients may frequently change chemotherapy agents due to side effects or progressive disease. Progression-free survival is an objective endpoint and is potentially less affected by post discontinuation therapies (as opposed to OS). A sufficiently prolonged PFS may therefore be considered in itself a clinically relevant effect, provided detriments on other important endpoints can be excluded, particularly if the magnitude of effect is large and the therapy has an acceptable risk/benefit profile. When rigorously tested, a robust treatment effect based on PFS complemented by no detriment in OS, can offer treatments to be made available early for patients with limited options especially in studies with long OS.

Given these factors, and in recognizing the value of both PFS and OS as measures of overall efficacy, both are planned as dual primary endpoints.

4.2.5 Rationale for Other Study Endpoints

The secondary endpoints of this study are in line with the recommendations outlined in the NCI Breast Cancer Steering Committee Working Group Report (Seidman et al 2018).

The secondary participant-reported pain, physical functioning and global health status/quality of life endpoints, assessed using EORTC QLQ-C30, as well as participant-reported symptomatic AEs measured by selected items from the PRO-CTCAE/EORTC IL117 will show the overall influence of the benefits and toxicity of the treatment from the participant's perspective and will aid in understanding the benefit/risk evaluation. These PRO questionnaires are well-established instruments that have been previously included in cancer clinical studies.

Biological samples will be used to explore potential biomarkers in tumor, plasma, and/or serum, which may predict the progression of cancer (and associated clinical characteristics) and/or tumor response. By mandating tumor sample collection as part of the study design, TROP2 expression will be tested retrospectively by IHC, to explore correlation with treatment response. Increased TROP2 mRNA in breast cancer has been shown to be a predictor of lymph node involvement, distant metastasis, and poor OS (Zhao et al 2018). In one heterogenous breast cancer series, TROP2 analysis by IHC showed 92.6% (38/42) of tumors expressed TROP2 (Yang et al 2021). Internal AstraZeneca analysis of TROP2 expression also shows broad levels of expression in > 90% of HR-positive breast cancer clinical samples (unpublished data).

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.

4.3 Justification for Dose

4.3.1 Dato-DXd

The 6.0 mg/kg IV dose of Dato-DXd was selected based on preliminary results of the ongoing Phase 1, 2-part (dose escalation and dose expansion), multicenter, nonrandomized, open-label, multiple dose, first-in-human study (Study DS1062-A-J101) in participants with solid tumors. 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 8.0 mg/kg. During the dose escalation phase, the non-tolerated dose for Dato-DXd was 10.0 mg/kg, where 2 participants had Grade 3 dose-limiting toxicities of mucosal inflammation and stomatitis. One participant at 6.0 mg/kg had a dose-limiting toxicity of Grade 3 maculopapular rash. The maximum tolerated dose (8.0 mg/kg) was determined during the dose escalation phase.

However, an ongoing review of emerging Phase 1 study data has allowed a closer evaluation of the benefit/risk balance by dose. Based on these data, the Dato-DXd 6 mg/kg dose has a more favorable benefit/risk balance than the 8 mg/kg dose; thus, the 6 mg/kg is the optimal monotherapy dose for further development of Dato-DXd in clinical studies.

Based on review of the safety data as of 16 November 2021, Dato-DXd exhibited an acceptable safety profile with established risk monitoring and risk mitigation measures for the important identified risks of ILD/pneumonitis and IRR as well as the AESIs of ILD/pneumonitis, IRR, oral mucositis/stomatitis, mucosal inflammation other than oral mucositis/stomatitis, and ocular surface toxicity.

Overall, the safety and tolerability profile of Dato-DXd 6 mg/kg remains acceptable and manageable. The 6 mg/kg dose has a better benefit/risk profile than the 8 mg/kg dose and thus supports continued clinical development of Dato-DXd at this dose.

The mean terminal half-life of Dato-DXd was 4.82 days at the 6.0 mg/kg dose, thus supporting a Q3W dosing schedule.

For information on dose modifications for Dato-DXd, see Section 6.6.

4.3.2 Investigator Choice of Chemotherapy (ICC)

The dosages of the ICC agents (capecitabine, gemcitabine, vinorelbine, eribulin) to be used in the current study are based on recommendations in the Prescribing Information for each agent, and are in accordance with current international breast cancer treatment guidelines (NCCN Guidelines 2020, Cardoso et al 2020).

In specific relation to capecitabine, 2 dose options have been selected for use (to be determined by standard institutional practice), as dose tolerance is different between some patients due to pharmacogenetic differences (Midgley and Kerr 2008). For example, in the FDA label for capecitabine, Japanese patients had a lower concentration (C_{max}) of drug at the

same dose given to Caucasian patients (Capecitabine USPI 2015).

4.4 End of Study Definition

For the purpose of Clinical Trial Transparency, the definition of the end of the study differs under FDA and EU regulatory requirements:

- European Union requirements define study completion as the last visit of the last subject for any protocol related activity.
- United States FDA requirements defines 2 completion dates:
  - Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all the primary outcomes.
  - Study Completion Date – is defined as the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measure and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if they have 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.

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

5 STUDY POPULATION

The target population of interest in this study is participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with one or two prior lines of systemic chemotherapy in the inoperable/metastatic setting.

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

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

Country-specific study requirements are provided in Appendix L.

5.1 Inclusion Criteria

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

Age

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

Type of Participant and Disease Characteristics

2 Inoperable or metastatic HR-positive, HER2-negative breast cancer (per ASCO/CAP guidelines, on local laboratory results); ie, is documented as HR-positive (either ER and/or PgR positive [ER or PgR ≥ 1%]) and HER2-negative. If a participant had multiple results after metastatic disease, the most recent local test result will be used to confirm eligibility (Allison et al 2020, Wolff et al 2018).

3 Progressed on and not suitable for endocrine therapy per investigator assessment, and treated with 1 to 2 lines of prior standard of care chemotherapy in the inoperable/metastatic setting. Participant must have documented progression on their most recent line of chemotherapy.

Note: If a chemotherapy drug is changed within 28 days of use to another drug in the same class (ie, antimetabolite to antimetabolite) for any reason, the first drug is not counted as a line.

Targeted agents (such as mTOR inhibitors, PD-1/PD-L1 inhibitors, PARP inhibitors), endocrine therapies, and CDK4/6 inhibitors on their own do not contribute to the count of prior lines of chemotherapy; however, regimens with such agents in combination with metastatic chemotherapy should be classified as one line of chemotherapy.

4 Eligible for one of the chemotherapy options listed as ICC (eribulin, capecitabine, vinorelbine, gemcitabine), per investigator assessment.

Note: Participants who previously received any of these agents are eligible for enrolment to another ICC agent in this study.

5 ECOG PS of 0 or 1, with no deterioration over the previous 2 weeks prior to day of first dosing.

6 At least 1 measurable 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, which is suitable for accurate repeated measurements.

Note: Participants with bone-only metastases are not permitted.

7 Participants with a history of previously treated neoplastic spinal cord compression, or clinically inactive brain metastases, who require no treatment with corticosteroids or anticonvulsants, may be included in the study, if they have recovered from the acute toxic

effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of radiotherapy and study enrolment.

8 Adequate organ and bone marrow function within 7 days before day of first dosing as follows:

- *Hemoglobin*: ≥ 9.0 g/dL. Red blood cell/plasma transfusion is not permitted within 1 week prior to screening assessment.
- *Absolute neutrophil count*: ≥ 1500/mm^3. Granulocyte colony-stimulating factor administration is not permitted within 1 week prior to screening assessment.
- *Platelet count*: ≥ 100000/mm^3. Platelet transfusion is not permitted within 1 week prior to screening assessment.
- *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.
- *ALT and AST*: ≤ 3 × ULN for AST/ALT; however, if elevation is due to liver metastases, ≤ 5.0 × ULN is allowed.
- *Calculated creatinine clearance*: ≥ 30 mL/min as calculated using the Cockcroft-Gault equation (using actual body weight):

$$\textit{Female}: \quad \text{CrCl (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

$$\textit{Male}: \quad \text{CrCl (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

9 LVEF ≥ 50% by either an echocardiogram or MUGA within 28 days of first dosing.

10 Has had an adequate treatment washout period before Cycle 1 Day 1, defined as:

- Major surgery: ≥ 3 weeks.
- Radiation therapy including palliative radiation to chest: ≥ 4 weeks (palliative radiation therapy to other areas ≥ 2 weeks).
- Anticancer therapy including hormonal therapy: ≥ 3 weeks (for small molecule targeted agents: ≥ 2 weeks or 5 half-lives, whichever is longer).
- Antibody-based anticancer therapy: ≥ 4 weeks with the exception of receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors (eg, denosumab for the treatment of bone metastases).
- Immunotherapy (non-antibody-based therapy): ≥ 2 weeks or 5 times the terminal elimination T½ of the agent, whichever is longer.

- Chloroquine/hydroxychloroquine: ≥ 14 days.

11 All participants must have available a FFPE tumor sample (block preferred, or a minimum of 20 freshly cut slides), at the time of screening. This can be from either the primary disease setting (surgical resection or diagnostic sample), or from a metastatic lesion (excluding bone) for tissue-based analysis (including but not restricted/limited to IHC staining of potential predictive biomarkers as well as tumor mutational analysis). The mandatory FFPE tumor sample submitted for analysis should be obtained as close to the time of diagnosis of metastatic or inoperable disease as possible. If neither an adequate FFPE block nor the minimum of 20 slides are available, a patient may still be considered eligible. In this situation, approval by the Study Team for patient's entry into the study is required.

Note: Sample collection in mainland China will comply with local regulatory approval.

12 Minimum life expectancy of 12 weeks at screening.

Sex

13 Male 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; however, oral estrogens are not permitted.

Reproduction

14 Negative pregnancy test (serum) for women of childbearing potential.

15 Female participants must be post-menopausal for at least 1 year, surgically sterile, or using one highly effective form of birth control (a highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly). For female contraception, please refer to Appendix G. Women of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control. They should have been stable on their chosen method of birth control starting at a minimum of 3 months before C1D1 to at least 7 months after the last dose (see Appendix G for complete list of highly effective birth control methods). Female participants must refrain from egg cell donation and breastfeeding while on study and for at least 7 months after the last dose of study intervention. Non-sterilized male partners of a woman of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) throughout this period.

16 Male participants who intend to be sexually active with a female partner of childbearing potential must be surgically sterile or using a highly effective method of contraception

(see Appendix G) from the time of screening throughout the total duration of the study and the drug washout period (at least 4 months after the last dose of study intervention) to prevent pregnancy in a partner. Male participants must not donate or bank sperm during this same time period. Not engaging in heterosexual activity (sexual abstinence) for the duration of the study and drug washout period is an acceptable practice if this is the preferred usual lifestyle of the participant; however, periodic or occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female partners of male participants are allowed to use HRT for contraception.

Informed Consent

17 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 protocol.

18 Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of sample for optional genetic research that supports Genomic Initiative.

5.2 Exclusion Criteria

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

Medical Conditions

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

2 History of another primary malignancy except for malignancy treated with curative intent with no known active disease within 3 years before the first dose of study intervention and of low potential risk for recurrence. Exceptions include basal cell carcinoma of the skin and squamous cell carcinoma of the skin that has undergone potentially curative therapy, adequately resected non-melanoma skin cancer, curatively treated in situ disease, or other solid tumors curatively treated.

3 Persistent toxicities caused by previous anticancer therapy (excluding alopecia), not yet improved to CTCAE Version 5.0 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 first dosing 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 I diabetes.
    - Hyperglycaemia.
    - Adrenal insufficiency
  - Adrenalitis.
- Skin hypopigmentation (vitiligo).

4 Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals; suspected infections (eg, prodromal symptoms); or inability to rule out infections.

Note: Participants with localized fungal infections of skin or nails are eligible.

5 Known active or uncontrolled hepatitis B or C infection. 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+ (i.e., those who have cleared HBV after infection) and meet conditions i-iii below:

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

i. HBV DNA viral load < 2000 IU/mL

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

6 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, CD4+ count > 350 cells/mm^3, no history of AIDs-defining opportunistic infection within the past 12 months, and stable for at least 4 weeks on same anti-HIV retroviral medications (meaning there are no expected further changes in that time to the number or type of antiretroviral drugs in the regimen). If an HIV infection meets the above criteria, 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.

7 Uncontrolled or significant cardiac disease, including myocardial infarction or uncontrolled/unstable angina within 6 months prior to C1D1, CHF (New York Heart Association Class II to IV), uncontrolled or significant cardiac arrhythmia, or uncontrolled hypertension (resting systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg).

8 Investigator judgment of 1 or more of the following:

- Mean resting corrected QTcF interval > 470 ms, obtained from triplicate ECGs performed at screening.
- 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.

9 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.
Note: Participants found to have ILD/pneumonitis on baseline screening chest CT are not eligible.

10 Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (ie, pulmonary emboli within three months of first dosing, severe asthma, severe COPD, restrictive lung disease, pleural effusion etc), or any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (ie, Rheumatoid arthritis, Sjogren's, sarcoidosis etc), or prior pneumonectomy.

11 Leptomeningeal carcinomatosis.

12 Clinically significant corneal disease.

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

Prior/Concomitant Therapy

14 Any of the following prior anticancer therapies:

- Any treatment (including ADC) containing a chemotherapeutic agent targeting topoisomerase I
- TROP2-targeted therapy
- Prior treatment with same ICC agent

(**Note**: Participants are eligible for enrolment into this study if they able to receive treatment with another ICC agent not previously received; see Inclusion Criterion 4)

15 Any concurrent anticancer treatment, with the exception of bisphosphonates, denosumab, for the treatment of bone metastases.

16 Concurrent use of systemic hormonal replacement therapy (eg, estrogen). However, concurrent use of hormones for non-cancer related conditions (eg, insulin for diabetes) is acceptable.

17 Major surgical procedure (excluding placement of vascular access) or significant traumatic injury within 3 weeks of the first dose of study intervention or an anticipated need for major surgery during the study.

18 Receipt of live, attenuated vaccine within 30 days prior to the first dose of study treatment.

19 Criterion removed in Protocol version 3.0.

Prior/Concurrent Clinical Study Experience

20 Previous treatment in the present study.

21 Participation in another clinical study with a study intervention or investigational medicinal device administered in the last 4 weeks prior to first dosing, randomization into a prior Dato-DXd or T-DXd (trastuzumab deruxtecan) study regardless of treatment assignment, or concurrent enrolment in another clinical study, unless it is an observational (noninterventional) clinical study or during the follow-up period of an interventional study.

22 Participants with a known hypersensitivity to Dato-DXd, or any of the excipients of the product (including, but not limited to, polysorbate 80).

23 Known history of severe hypersensitivity reactions to other monoclonal antibodies.

Other Exclusions

24 Involvement 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 women only, currently pregnant (confirmed with positive pregnancy test) or breastfeeding, or who are planning to become pregnant.

5.3 Lifestyle Considerations

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

- Participants must follow the contraception requirements outlined in Appendix G.
- Participants should not donate blood or blood components while participating in this study and through 28 (+7) days after the last dose of study intervention. Preservation of ova and sperm should be considered prior to enrolment in this study.
- 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.

Restrictions relating to concomitant therapies are described in Appendix I 2.

5.4 Screen Failures

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

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 any effect on study results can be assessed.

All assessments must be repeated for rescreening unless they are within 28 days of randomization.

Screen failure 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 randomized).

Participant enrolment and randomization is described in Section 6.3.

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

6.1.1 Investigational Products

AstraZeneca will supply datopotamab deruxtecan (Dato-DXd). Investigator's Choice of Chemotherapy agents (capecitabine, gemcitabine, eribulin, or vinorelbine) will be supplied locally. Under certain circumstances, when local sourcing is not feasible, these agents may be supplied centrally through AstraZeneca.

Dose modifications are described in Section 6.6.

A summary of study treatments is provided in Table 5.

Table 5 Investigational Products

Arm name / Intervention Name	Arm 1: Dato-DXd	Arm 2: Investigator's Choice of Chemotherapy			
		Capecitabine	Gemcitabine	Eribulin mesylate	Vinorelbine
Type	Drug	Drug	Drug	Drug	Drug
Dose Formulation	Lyophilized powder for concentrate for solution for infusion	Tablet	Injection	Solution for injection	Injection
Unit Dose Strength(s)	100 mg	As sourced locally [a]	As sourced locally [a]	As sourced locally [a]	As sourced locally [a]
Dosage Level(s)	6 mg/kg on Day 1 of each 21-day cycle	1000 or 1250 mg/m^2 BID on Days 1 to 14 of a 21-day cycle [b]	1000 mg/m^2 on Days 1 and 8 of a 21-day cycle	1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle [c]	25 mg/m^2 on Day 1 and 8 of a 21-day cycle [d]
Route of Administration	IV infusion	Oral	IV infusion	IV infusion	IV infusion
Use	Experimental	Active comparator	Active comparator	Active comparator	Active comparator
IMP/ NIMP/ AxMP	IMP	IMP	IMP	IMP	IMP

Table 5 Investigational Products

Arm name / Intervention Name	Arm 1: Dato-DXd	Arm 2: Investigator's Choice of Chemotherapy			
		Capecitabine	Gemcitabine	Eribulin mesylate	Vinorelbine
Sourcing	Central	As sourced locally [a]	As sourced locally [a]	As sourced locally [a]	As sourced locally [a]
Packaging and Labelling	Dato-DXd will be provided in 100 mg vials in a carton. Each vial and carton will be labelled as required per country regulatory requirements [e]	As sourced locally [a]	As sourced locally [a]	As sourced locally [a]	As sourced locally [a]
Current/ Former Name or Alias	DS-1062a	Not applicable	Not applicable	Not applicable	Not applicable

[a] Under certain circumstances when local sourcing is not feasible, an ICC treatment may be supplied centrally through AstraZeneca.
[b] The choice of dose will be determined by standard institutional practice. Reduce the dose by 25% in participants with moderate (CrCl 30-49 mL/min) renal impairment.
[c] A lower starting dose of 1.1 mg/m^2 is recommended for participants with moderate (CrCl 30-49 mL/min) renal impairment, or mild hepatic impairment (Child-Pugh A).
[d] Exercise caution in participants currently taking drugs known to inhibit CYP3A. Concurrent administration of vinorelbine with a CYP3A inhibitor may cause an earlier onset and/or an increased severity of adverse reactions.
[e] Label text for Dato-DXd (DS-1062a) may show "DS-1062a" depending on the agreed product name used in the respective approved study master label document. All naming conventions for these compounds are correct during the transitional period.

6.1.1.1 Duration of Treatment

All study treatments are to be administered until RECIST 1.1-defined radiological progression (as determined by the Investigator) or until meeting any other reason to discontinue study intervention (see Section 7.1). Continued treatment with the same study drug post-progression may be allowed, based on prior discussion with study physician on case-by-case basis. No crossover between study treatment arms will be allowed.

6.1.2 Medical Devices

Not applicable.

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 authorization is provided for on-site destruction or removal of the study intervention, reflecting completion of the study. In the event that a

temperature excursion is 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 authorized 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 authorized 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. The investigator (or designee) is responsible for ensuring that the participant has returned all unused study intervention.

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

6.2.1 Dato-DXd

Dato-DXd will be supplied as a 100 mg lyophilized powder for concentrate for solution for infusion. The reconstituted solution contains 20 mg/mL Dato-DXd in CCI mM histidine/histidine HCl, CCI % (w/v) sucrose, CCI % (w/v) polysorbate 80; it has a pH of 6.0 and density of 1.04 g/mL. The post-reconstitution volume is 5 mL. The reconstituted drug product is a clear to slightly opalescent, colorless to slightly yellow liquid and practically free from visible particles.

6.2.1.1 Preparation of Dato-DXd

The dose of Dato-DXd for administration must be prepared by the pharmacy staff members (or an appropriate designee trained in study drug preparation), using aseptic technique in compliance with local regulations and site requirements.

Dato-DXd should be handled in accordance with practices required for hazardous drugs (i.e., chemotherapy).

Incompatibilities have been identified with 0.9% sodium chloride for injection and **must not** be used for dose preparation.

The total time from needle puncture of the Dato-DXd vial to the start of administration must not exceed 24 hours at 2 °C to 8 °C (36 °F to 46 °F), otherwise a new dose must be prepared from new vials.

Following preparation and during administration, the prepared IV bag must be covered by a light protection cover; the cover must be applied immediately after dose preparation and

remain on throughout the administration time.

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

6.2.1.2 Administration of Dato-DXd

Pre-medication is required prior to any dose of Dato-DXd and must include antihistamines and acetaminophen, with or without glucocorticoids. Participants should remain at the site for at least 1-hour post-infusion of every dose of Dato-DXd for close observation for possible IRRs.

It is also highly recommended that participants receive prophylactic anti-emetic agents prior to infusion of Dato-DXd and on subsequent days as needed. Antiemetics such as 5-HT3 receptor antagonists, NK1 receptor antagonists and steroids (eg, dexamethasone) should be considered and administered in accordance with the prescribing information or institutional guidelines.

Dato-DXd must reach room temperature prior to administration.

Incompatibilities have been observed with 0.9% sodium chloride for injection and must not be used for drug administration; additionally these solutions must not be co-infused in the same IV line as Dato-DXd.

Dato-DXd will be administered using an IV bag containing 5% dextrose injection through an IV administration set, using local practices. Do not shake the prepared IV bag.

The infusion must be administered with a 0.2- or 0.22-µm filter; acceptable configurations include an IV set containing an in-line filter or the attachment of a separate filter to the distal end of the IV tubing.

Dato-DXd infusion time is approximately 90 minutes (±10 minutes) for the first infusion. If the first infusion is well tolerated and the participant does not experience an infusion-related reaction, then the minimum infusion time for subsequent cycles is 30 minutes.

In case of interruptions, the total cumulative time from needle puncture of the Dato-DXd vial to the end of infusion must not exceed 4.5 hours with the IV bag kept at room temperature, otherwise a new dose must be prepared from new vials to complete the dose.

Do not co-administer other drugs through the same IV line.

After the content of the IV bag is administered, the IV line will be flushed with a volume of 5% dextrose for injection equal to the IV-line volume, at the same rate as infusion according to local practices, to ensure the full dose is administered.

The total infusion time recorded in the EDC system reflects when the infusion IV bag is empty; this time does not include the post-infusion flush.

If an IRR (such as fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnea, hypotension) is observed during administration, the infusion speed should be reduced by 50% and participants should be closely monitored.

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 ≥ ±10%, the participant's dose will be recalculated based on the participant's updated weight. After the re-calculation, the participant's updated weight will be used as the new baseline weight. The site may follow local institutional policy for recalculating dose based on weight changes less than 10%.

6.2.1.3 Monitoring of Dato-DXd Administration

Participants will be monitored during and after infusion of Dato-DXd. Vital signs will be measured according to the SoA and Section 8.2.2.

Management of study intervention-related toxicities are described in the TMGs for Dato-DXd, (see the Annex document to this CSP). As with any biologic product, IRRs 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 recognize and treat anaphylaxis.

6.2.1.4 Storage of Dato-DXd

The investigator, or an appropriate delegate, will ensure that all study intervention is stored in a secured 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.

Investigational product vials are stored at 2 °C to 8 °C (36 °F to 46 °F) and must not be frozen. Investigational product must be kept in original packaging until use to prevent prolonged light exposure.

6.2.2 Investigator's Choice of Chemotherapy

Participants will receive ICC (eribulin, capecitabine, vinorelbine and gemcitabine) at the doses specified in Table 5. The choice of chemotherapy must be pre-defined prior to randomization. The number of treatment cycles for ICC is not fixed. Refer to the local label for details on handling.

The ICC agents will either be locally sourced by the study site or centrally supplied by AstraZeneca and will be administered according to Prescribing Information or treatment guidance in general use by the investigating site. Under certain circumstances when local sourcing by the study site is not feasible, AstraZeneca will centrally supply the drug, which will be labelled with local language translated text in accordance with regulatory guidelines.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Participant Enrolment and Randomization

All participants will be centrally assigned to randomized study intervention using an IRT. Before the study is initiated, the call/log-in directions and user guides for the IRT will be provided to each site.

If a participant withdraws from the study, then their enrolment 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 (up to 28 days before C1D1), the investigators (or suitably trained delegate) will:

- 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 randomization except for virus antibody test results and hepatitis B virus surface antigen, which can be used if performed within 120 days before screening.
- Participants will be identified to the IRT per country regulations. Obtain a unique 7-digit enrolment number (E-code) through the IRT in the following format: PPD PPD . 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).
- Obtain signed informed consent for the optional Genomics Initiative. Participants who decide not to sign the specific genetic ICF, but the general study ICF, are eligible for study enrolment and all other study procedures.

At randomization, once the participant is confirmed to be eligible, the investigator (or suitably trained delegate) will:

- Select the ICC treatment (based on the most appropriate option for the participant) that the participant would receive if randomized to the ICC group prior to randomization of the participant. This must be completed for all participants. The selection will be recorded in the IRT system.
- Assign a randomized treatment group via the IRT. Randomization codes will be assigned strictly sequentially within each stratum and site/country/region as participants become eligible for randomization. The system will randomize the eligible participant to one of the 2 treatment groups.

If the participant is ineligible and not randomized, the IRT should be accessed to terminate the participant in the system.

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

6.3.2 Procedures for Handling Incorrectly Enrolled or Randomized Participants

Participants who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. 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 randomized or started on study intervention and must be withdrawn from the study.

Where a participant does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the participant from treatment. The AstraZeneca study physician 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

The actual treatment given to participants will be determined by the randomization scheme in the IRT. The randomization scheme will be produced by a computer software program that incorporates a standard procedure for generating randomization numbers. One randomization list will be produced for each of the randomization strata. A blocked randomization will be generated, and all centers will use the same list in order to minimize any imbalance in the number of participants randomized to each treatment group.

Randomization codes will be assigned strictly sequentially (refer to the 3 stratification factors in Section 4.1), as participants become eligible for randomization. When study intervention is provided centrally by AstraZeneca, the IRT will provide the kit identification number to be allocated to the participant at the randomization visit and subsequent treatment visits. If

medication is provided locally, IRT will not provide kit numbers.

6.3.4 Methods for Ensuring Blinding

This is an open-label study for the personnel at study sites; however, the trial will be conducted as "sponsor-blind" and the specific study intervention (Dato-DXd or ICC) to be taken by a participant will be assigned using an IRT. To maintain the integrity of the study, AstraZeneca personnel directly involved in the study conduct will not undertake or have access to efficacy data aggregated by treatment arm prior to final data readout for the primary endpoint. Before the first participant is randomized, a Study Integrity Plan document will be generated, in which data access levels for relevant AstraZeneca personnel will be pre-specified.

6.4 Study Intervention Compliance

When participants are dosed at the study site (applicable to Dato-DXd and ICC agents gemcitabine, eribulin and vinorelbine), 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.

When participants self-administer study intervention(s) at home (as applicable to the ICC agent capecitabine), compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned tablets, as well as by the review of participant completed dosing diaries during the site visits and documented in the source documents and eCRF. A record of the number of capecitabine tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

The Investigational Product Storage Manager is responsible for managing the study intervention from receipt by the study site until the destruction or return of all unused study intervention.

6.5 Concomitant Therapy

Any concomitant treatment, procedure, vaccine, or other medication considered necessary by the investigator for the participant's safety and wellbeing (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 28 (+7) day safety follow-up period following the last dose of study

intervention must be recorded in the eCRF along with:

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

The Study Clinical Lead 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 I 2.

For participants randomized to receive ICC, refer to the local Prescribing Information with regard to warnings, precautions, and contraindications.

Guidance regarding potential interactions with concomitant medications is provided in Appendix I 1.

All concomitant medications administered during the study should be recorded until the end of the safety follow-up period. Concomitant medications administered as treatment for drug-related AESIs should be recorded in eCRF until either event resolution, end of study, trial termination, withdrawal of consent, or subject death.

Drug-drug Interactions

Nonclinical PK studies have indicated that MAAA 1181a (payload: deruxtecan) is primarily metabolized by CYP3A4 and is a substrate for OATP1B1, OATP1B3, MATE2-K, P-gp, BCRP, and MRP1.

No formal drug-drug interaction studies with Dato-DXd have been conducted in humans. Since drug-drug interactions are primarily driven by MAAA-1181a, the drug component of Dato-DXd, a drug-drug interaction study of trastuzumab deruxtecan, which has the same payload, is considered of relevance. Recent results from a clinical drug-drug interaction study of trastuzumab deruxtecan (Study NCT03383692) showed that co-administration of a dual inhibitor of OATP1B/CYP3A, ritonavir, and a strong CYP3A inhibitor, itraconazole, increased MAAA-1181a AUC17d by 22% and 18%, respectively. Therefore, the effect of the CYP3A/OATP1B inhibitors on MAAA-1181a is not considered clinically meaningful and as a

result, concomitant use of CYP3A/OATP1B inhibitors with Dato-DXd is allowed. However, caution must be followed by the investigator in case of concomitant use of Dato-DXd and CYP3A inhibitors, or drugs that inhibit OATP1B1, OATP1B3, MATE2-K, P-gp, BCRP, and MRP1. Patients must be closely monitored in these cases.

Concomitant use of drugs that inhibit MATE2-K, P-gp, BCRP, and MRP1 is allowed, although participants should be closely monitored for adverse reactions. Because the urinary excretion of MAAA-1181a 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 MAAA-1181a. In addition, multiple efflux transporters such as P-gp and BCRP are involved in the excretion of MAAA-1181a; 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.

Concomitant use of drugs that are substrates of OAT1 and OATP1B1 is allowed. Because the exposure of MAAA-1181a is expected to be low with Dato-DXd at doses administered in clinical studies, the inhibition of OAT1 and OATP1B1 by MAAA-1181a 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 ≥14 days is required before restarting study intervention.

Guidance regarding potential interactions with concomitant medications is provided in Appendix I 1.

6.6 Dose Modification

Dosing modification guidelines and TMGs are included in the Annex document to this CSP. Dose delays are permitted for Dato-DXd. Dose reductions are permitted for Dato-DXd. All dose reductions and delays (including any missed doses), and the reasons for the reductions/delays are to be recorded in the eCRF.

Refer to Section 4.3.1for the justification for dose for Dato-DXd.

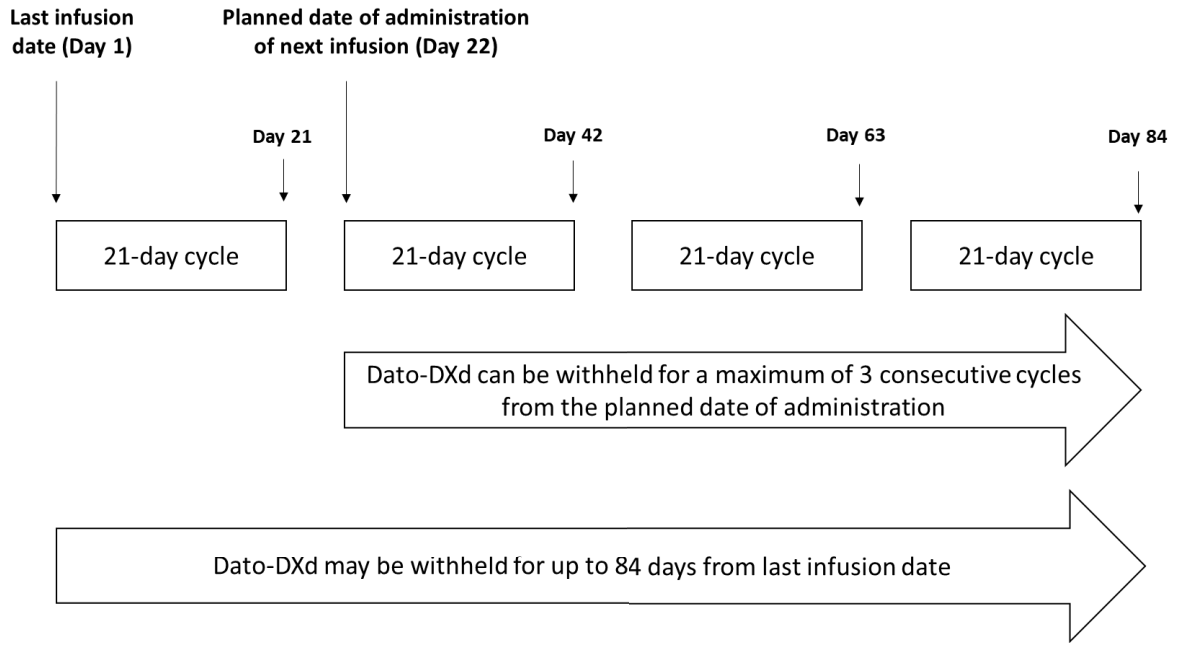
6.6.1 Dose Delays

Dose delays are permitted for Dato-DXd treatment and the dosing interval for the next Dato-DXd cycle may be shortened, as clinically feasible to gradually align with the schedule

of tumor efficacy assessment. Two consecutive doses must be administered at least 19 days apart.

Study treatment dose delay for conditions other than toxicity resolution should be kept as short as possible. A dose can be delayed for up to 3 consecutive cycles (63 days) from the planned date of administration (ie, 84 days from the last infusion date). If a participant is assessed as requiring a dose delay longer than 3 consecutive cycles (ie, > 84 days from last infusion date to the planned date of administration on a Q3W schedule), the subject/participant must discontinue study treatment (see Figure 3).

Figure 3 Dose Delay Schema for Dato-DXd



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.

In the event of a dose interruption occurring prior to completion of PK/pharmacodynamic 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. If a participant cannot restart study treatment within 84 days from the last infusion date for resolution of intercurrent conditions not related to PD or toxicity, the case should be discussed with the Study Clinical Lead.

6.6.3 Dose Reductions

In case a dose reduction is necessary, Dato-DXd will be modified as follows.

Up to 2 dose reductions will be permitted for participants receiving Dato-DXd (see Table 6 for dosing levels). Once the dose of Dato-DXd has been reduced, no dose re-escalation is permitted. After the permitted dose reductions, if further toxicity meeting the requirement for dose reduction occurs, the participant will be withdrawn from the study intervention.

In a rare circumstance, one additional dose reduction may be possible on a case-by-case basis only after discussion and agreement between the Investigator and Sponsor.

Table 6 Dose Reduction Levels of Dato-DXd

Starting Dose (Dose Level 1)	Dose Level -1	Dose Level -2
6.0 mg/kg IV, Q3W	4.0 mg/kg IV, Q3W	3.0 mg/kg IV, Q3W

Investigators should consider dose reductions or discontinuations of Dato-DXd according to the participant's condition and after discussion with the study clinical lead or designee (see the Annex document to this CSP for details of when dose reductions may be required).

Refer to Section 4.3 for the justification of dose for Dato-DXd.

6.6.4 Management of Toxicities

Full TMGs for Dato-DXd are included in the Annex document to this CSP. 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. Please refer to the Annex document to this CSP for the management of drug-induced ILD/pneumonitis.

Specific criteria for 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.

On improvement of an AE for which Dato-DXd was temporarily interrupted, 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 interruption, or if a different AE subsequently requires dose interruption, Dato-DXd may be restarted at a 1 dose level reduction on improvement of the AE or discontinued if the participant is receiving the lowest protocol-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 interrupted or permanently discontinued in accordance with the TMGs and supportive therapy administered as required.

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

For management of toxicities due to ICC, refer to the locally approved Prescribing Information or manage in accordance with institutional guidelines.

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 all participants have discontinued study intervention and completed their last expected visit/contact. No intervention is planned after the end of the study.

After the final DCO for this study, AstraZeneca will continue to supply open-label treatment in the continued access phase of this study and after completion of this study to participants who received Dato-DXd or centrally supplied ICC while, in the opinion of the investigator, the participant is benefiting until PD occurs (as judged by the investigator), or until meeting any other discontinuation criteria as defined in Section 7.1.

Participants should be followed according to the institution's SoC assessments. No further data collection is required, except for reporting of SAEs.

Participants who were randomized to receive other study interventions (ie, locally supplied ICC), or who discontinue from the study, should continue appropriate treatment at the discretion of the investigator.

Where possible, if commercial supply of Dato-DXd is available in the local market then this route should be used. 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 a roll-over or safety extension study is available at the time of the final DCO and database closure, participants currently receiving treatment with Dato-DXd may be transitioned to such a study. The roll-over or extension study would ensure treatment continuation with visit assessments per its protocol, as applicable. Any participant who would

be proposed to move to such a study would be given a new informed consent, as applicable.

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 PFS (if the participant has not progressed according to RECIST 1.1), PFS2, OS, TFST and TSST. 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. All study intervention should be returned by the participant at their next on-site study visit or unscheduled visit.

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

- RECIST 1.1-defined radiological progression (refer to Section 8.1.1 and Appendix F).
- An AE that, in the opinion of the investigator or AstraZeneca, contraindicates further dosing.
- Any AE that meets criteria for discontinuation defined in the TMGs (see the Annex document to this CSP), or as defined in the local Prescribing Information for the ICC agents.
- 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 (refer to Appendix G and Section 8.3.14).
- Initiation of subsequent anticancer therapy, including another investigational agent.

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

Crossover within the study is not permitted.

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 28 (+7) days after their last dose of study intervention. Additional assessments to be performed at the time of the safety follow-up visit are detailed in the SoA (Table 1). For ILD/pneumonitis, safety follow-up will continue until the resolution of ILD/pneumonitis.

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 tumor and survival assessments as indicated in the SoA (Table 1) until one visit after investigator-defined PD according to RECIST 1.1, or death regardless of whether or not the participant started a subsequent anticancer therapy, unless they have withdrawn all consent to study-related assessments.

See the SoA (Table 1) for data to be collected at the time of intervention discontinuation (ie, the end-of-treatment visit) and follow-up and for any further evaluations that need to be completed.

7.1.2 Follow-up of Participants to PFS2

Following objective progression, participants will have their subsequent progression status recorded every 3 months (±14 days) per local standard clinical practice to assess PFS2. Assessments will be performed according to the local practice, and formal RECIST 1.1 measurements will not be collected for assessment of PFS2. See Section 8.1.3 for additional information.

7.1.3 Follow-up for Survival

Participants will be followed up for survival status as indicated in the SoA (Table 1) 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, by contact with the participant's current physician, or local death registries (if allowed by local regulations). Additional assessments to be performed at the time of survival follow-up are detailed in the SoA (Table 1). The study may continue monitoring participants for OS up to the scheduled final analysis, beyond planned interim analyses, to provide more refined estimates of treatment effects for survival.

Telephone calls to assess survival 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 the 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.

7.2 Participant 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, behavioral, 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 of any ongoing AEs and concomitant medications (eg, telephone contact 28 [+7] days 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 EoT visit and a safety follow-up visit should be conducted, as shown in the SoA (Table 1). 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 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 Global Study Team.

7.3 Lost 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 protocol.

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 randomized, including those who did not get study intervention. Public sources may be searched for vital status information. 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 key efficacy endpoints of PFS and OS, the survival status of all participants in the ITT population and the Safety 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 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 summarized in the SoA (Table 1). Data collection following study analysis until the end of the study is described below.

- 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 (Table 1), 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 utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 1).

Data Collection Following Study Analysis until the End of the Study

Following the DCO for the primary PFS efficacy endpoint, assessments for PK will be discontinued. Participants will continue with all other assessments as indicated in the SoA (Table 1).

For SAE reporting and laboratory assessment collection after final analysis, see Section 8.3.12. After the final DCO and database closure, only SAEs will be reported for the purposes of this study (see Section 8.3.12).

8.1 Efficacy Assessments

Efficacy assessments of PFS, ORR, DoR, and DCR will be evaluated based on RECIST 1.1 tumor assessments.

8.1.1 Imaging Tumor Assessments

Tumor assessments use images from CT (preferred) or MRI, with IV contrast, of the chest, abdomen (including the entire liver and both adrenal glands), and pelvis, collected during screening/baseline and at regular (follow-up) intervals during study intervention as defined in the SoA (Table 1).

An MRI (preferred) or CT of the brain will also be collected for all participants at baseline. Follow-up brain scans are subsequently mandatory for all participants randomized with stable brain metastases at baseline, whilst participants without brain metastases do not need additional brain scans for subsequent tumor assessments, unless clinically indicated.

All participants should have a baseline whole body bone scan or skeletal survey. For participants with no bone lesion, a historical bone scan documenting absence of bone lesions

performed no more than 12 weeks before randomization could be provided. For participants with documented bone lesion at baseline, the bone scan must be performed no more than 28 days before randomization. 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 less than 28 days before randomization, it may be utilized as screening scan to document bone disease. Bone lesions identified on bone scan at baseline must be confirmed by CT, MRI, or X-ray to be recorded as NTLs and followed by the same method (CT, MRI, or X-ray), as indicated in the SoA (Table 1).

Any other areas of disease involvement should be additionally imaged at screening based on known metastasis sites or by the signs and symptoms of individual participants.

The imaging modality used for baseline tumor assessment, CT/MRI for chest and abdomen and MRI for brain, should be kept the same consistently at each subsequent follow-up assessment throughout the study if possible. It is important to follow the tumor assessment schedule as closely as possible (refer to the SoA [Table 1]) relative to randomization.

New lesions may also be identified by fluorodeoxyglucose-PET scans, X-ray, bone (scintigraphy) scans. If an unscheduled assessment was performed (eg, to investigate clinical signs/symptoms of progression) and the disease has not progressed, every attempt should be made to perform the subsequent imaging at the next regularly scheduled visit. Digital copies of all scans should be maintained at the site as source documents.

Screening/baseline imaging should be performed no more than 28 days before randomization and ideally should be performed as close as possible to and prior randomization.

Treatment continues until RECIST 1.1-defined radiological progression by Investigator assessment (refer to Appendix F). Following disease progression, 1 additional follow-up scan should be performed as per imaging schedule (ie, either 6 weeks or 9 weeks later). In the event the investigator identified progression does not match with the BICR evaluation, this additional scan may identify progression by BICR.

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 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).

8.1.2 Central Reading of Scans

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed iCRO for quality control, storage, and for BICR. 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. A BICR 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 tumor assessments will not be shared with the central reviewers.

The management of participants will be based upon the results of RECIST 1.1 assessments conducted by the Investigator. After the primary PFS analysis, central review of scans will no longer be required, and investigators will be advised when to stop sending copies of the scans to the iCRO conducting the central review; however, digital copies of all original scans should continue to be stored at the investigator site as source documents.

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

8.1.3 Time to Second Progression or Death

Following objective progression, participants will have their subsequent progression status recorded every 3 months (±14 days) per local standard clinical practice to assess PFS2.

A participant's PFS2 status is defined according to the local practice and may involve any of:

- objective radiological progression (preferred),
- symptomatic progression, or
- death.

Scans will be performed according to the local practice and formal RECIST 1.1 measurements will not be collected for assessment of PFS2. The second progression event must have occurred during or after anticancer treatment with a subsequent treatment after the progression event used for the primary variable PFS or death. The date of PFS2 assessment and investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the source documents and the eCRF.

8.1.4 Overall Survival

Assessments for survival will be conducted every 3 months (±14 days) following objective PD or treatment discontinuation until 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 as described in Section 7.2. The study may continue monitoring participants for OS up to the scheduled final analysis, beyond

planned interim analyses, to provide more refined estimates of treatment effects for survival.

8.1.5 Clinical Outcome Assessments (COA)

A COA is any assessment that may be influenced by human choices, judgment, or motivation and may support either direct or indirect evidence of treatment benefit. COAs can be reported by a participant (PRO), a clinician (ClinRO), an observer (ObsRO), or through a performance-based assessment (FDA-NIH BEST Resource). A COA may be used in clinical studies to provide either direct or indirect evidence of treatment benefit. It is important to examine the impact of therapy on symptoms, function, and other health-related QoL of the participant to aid understanding of the risk-benefit profile.

Patient Reported Outcome (PRO) assessment is one type of COA and is a general term referring to all outcomes and symptoms that are directly reported by the participant. Patient Reported Outcomes have become important in evaluating the efficacy and tolerability of study interventions in clinical studies and will aid in understanding of the benefit/risk evaluation (Kluetz et al 2018).

The following PRO instruments will be administered in this study (see Appendix H):

- EORTC QLQ-C30 (see Section 8.1.5.1)
- EORTC IL116: selected breast and arm symptom scales from EORTC QLQ-BR45/IL (see Section 8.1.5.2)
- Selected items from PRO-CTCAE (see Section 8.1.5.3)
- EORTC IL117: selected symptomatic AE items from EORTC IL (see Section 8.1.5.4)
- PGI-TT (see Section 8.1.5.5)
- PGIS (see Section 8.1.5.6)
- PGIC (see Section 8.1.5.7)
- EQ-5D-5L (see Section 8.1.5.8)

Patient Reported Outcome questionnaires will be administered according to the SoA (Table 1). The PRO questionnaires will be completed by participants if a linguistically validated version is available in their language for the country in which they live.

8.1.5.1 EORTC QLQ-C30

The EORTC QLQ-C30 was developed by the EORTC QoL Group 1993. It consists of 30 item and measures symptoms, functioning, and global health status/QoL (Aaronson et al 1993) for all cancer types. Questions are grouped into 5 multi-item functional scales (physical, role, emotional, cognitive, and social), 3 multi-item symptom scales (fatigue, pain, and nausea/vomiting), a 2-item global QoL scale, 5 single items assessing additional symptoms

commonly reported by cancer participants (dyspnea, loss of appetite, insomnia, constipation, and diarrhea), and 1 item on the financial impact of the disease. The EORTC QLQ-C30 is a valid and reliable PRO instrument in this participant population.

8.1.5.2 EORTC IL116: selected breast and arm symptom scales from EORTC QLQ-BR45/IL

The EORTC QLQ-BR45 is an updated version of the BR23, a validated breast cancer-specific module used in conjunction with the core QLQ-C30 to assess breast cancer-specific HRQoL (Bjelic-Radisic et al 2020; Sprangers et al 1996). New breast cancer treatments and diagnostics prompted the update of the QLQ-BR23 to include an additional 22 items. Items are scored on a 4-point verbal rating scale: “Not at All,” “A Little,” “Quite a Bit,” and “Very Much”. Scores are transformed to a 0 to 100 scale, where higher scores for functioning scales or items indicate better functioning, whereas higher scores for symptom scales or items represent a worse level of symptoms.

The current study will only include the breast symptoms and arm symptoms scales (7 items) from the BR45, ie, EORTC IL116.

8.1.5.3 PRO-CTCAE

The PRO-CTCAE was developed to evaluate symptomatic toxicity in participants in cancer trials. The PRO-CTCAE will only be administered in those countries where a linguistically validated version is available. PRO-CTCAE is an item library of symptoms experienced by participants while undergoing treatment of their cancer. It has been carefully and systematically developed based on the NCI-CTCAE to provide participant-reported assessment of common adverse effects of cancer treatments, including a library of 124 items, representing 78 symptomatic toxicities. The items have previously undergone extensive qualitative and quantitative evaluation to support their validity and reliability (Basch et al 2014, Dueck et al 2015, Hay et al 2014). For each symptomatic AE (eg, headache), there are up to three questions related to key symptom attributes, including the symptom frequency, severity, and interference with daily activities. Each question uses a 7-day recall with a 5-point ordinal response scale.

The items pre-selected for this study include mouth/throat sores, decreased appetite, nausea, vomiting, constipation, diarrhea, abdominal pain, shortness of breath, cough, rash, hair loss, hand-foot syndrome, numbness/tingling, and fatigue. These items are based on a review of the core symptom set from NCI, expected treatment-related symptoms, and in consideration of symptoms that are already captured in the other PRO instruments with a view to minimize participant burden. The free text item in the PRO-CTCAE instrument is not included in the study, as the utility of this information and the analysis method have not been established.

8.1.5.4 EORTC IL117: selected symptomatic AE items from EORTC IL

The EORTC IL is an online platform comprised of more than 900 individual items from over

60 EORTC questionnaires. As the static questionnaires might not always be sufficient to meet the demands of quickly evolving treatment modalities, selecting items from EORTC IL offers new opportunities to leverage existing EORTC items for capturing the additional symptoms that are relevant to a given study.

The pre-selected items for this study will include dry eyes, mouth pain, and sore mouth (ie, EORTC IL117). These items were selected using the same methodologies as described in Section 8.1.5.3 (PRO-CTCAE) to measure additional participant-reported symptomatic AEs which are not captured in the PRO-CTCAE. The recall period is during the past week. Items are scored on a 4-point verbal rating scale: "Not at all", "A little", "Quite a bit", and "Very much".

8.1.5.5 PGI-TT

The PGI-TT item is included to assess how a participant perceives the overall burden of treatment-related side effects of cancer treatment over the past 1 week. Participants will be asked to choose the response that best describes the level of burden by the side effect of their cancer treatment over the past week. The response options are: “not at all”, “a little bit”, “somewhat”, “quite a bit”, and “very much”. This item is included to aid in the interpretation of other PRO measures and to evaluate the overall impact of treatment-related side effects.

8.1.5.6 PGIS

The PGIS item is included to assess how a participant perceives the overall severity of cancer symptoms over the past 1 week. Participants will be asked to choose the response that best describes the severity of their overall cancer symptoms over the past week. The response options are: “none”, “mild”, “moderate”, and “severe”. This item is included to aid in the interpretation of other PRO measures and to evaluate the overall impact of treatment on the global severity of cancer symptoms.

8.1.5.7 PGIC

The PGIC item is included to assess how a participant perceives their overall change in health status since the start of study treatment. This is single-item questionnaire and participants will choose from response options ranging from “Much better” to “Much worse”.

8.1.5.8 EQ-5D-5L

The EQ-5D-5L will be used to explore the impact of treatment and disease state on health state utility.

The EQ-5D-5L, developed by the EuroQoL Group, is a generic questionnaire that provides a simple descriptive profile of health and a single index value for health status for economic appraisal (EuroQol 2019). The EQ-5D-5L questionnaire comprises 6 questions that cover 5 dimensions of health (eg, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Respondents also assess their health today using the EQ-VAS, which

ranges from 0 (worst imaginable health) to 100 (best imaginable health) (see Appendix H).

8.1.5.9 Administration of Electronic PRO (ePRO) Questionnaires

Patient Reported Outcome questionnaires will be self-administered electronically at home by the participants using an application installed on their personal mobile device, or a handheld device (if their personal device is not compatible or preferred) at the time points indicated in the SoA (Table 1). Participants should complete the ePROs prior to or at the sites if the assessment time point coincides with a scheduled site visit. Participants must be instructed to bring their device to all visits.

Each site must allocate the responsibility for the administration of the ePRO instruments to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a back-up person to cover if that individual is absent.

A web back-up may be available to answer the questionnaires if there are technical problems with the device.

Approximately 10 to 20 minutes is required for participants to complete the questionnaires.

The below instructions should be followed when collecting PRO data:

- The research nurse or appointed site staff should explain to participants the value and relevance of these data, so they are motivated to comply with questionnaire completion. Inform the participant that these questions are being asked to find out, directly from them, how they feel.
- Participants must not be onboarded onto the ePRO application (ie, must not have their account set up or invitation email sent) until the actual day of their C1D1 visit. This is required to ensure that the correct C1D1 date is registered in the ePRO system.
- It is vital that the ePRO reporting is initiated prior to dosing or any other study procedure on C1D1, as specified in the SoA (Table 1) to capture the effect of the study intervention. The ePRO device must be charged and fully functional at the beginning of the baseline (ie, C1D1) visit to ensure that the PROs can be completed at the start of the visit.
- The participant should bring their device to each site visit so the research nurse or appointed site staff can check if there are available PRO questionnaire to be completed and that the device is functioning properly.
- Patient Reported Outcome questionnaires completed at the sites must be completed prior to treatment administration or any other study procedures performed at the site and ideally before any discussions of health status (following informed consent), including medication treatments, and before discussion of PD to avoid biasing the participant's responses to the questions. As feasible, site staff should also ensure PRO questionnaires

are completed prior to other study procedures, such as collection of laboratory samples, to further minimize bias.

- On completion of the questionnaire at the site, the device should be handed back to the research nurse or appointed staff, who should check that all questionnaires were completed.
- When each instrument is due to be completed, the following order must be observed (however although the order will be pre-programmed into the ePRO):
  - EORTC QLQ-C30
  - EORTC IL116
  - PRO-CTCAE
  - EORTC IL117
  - PGI-TT
  - PGIS
  - PGIC
  - EQ-5D-5L
- Patient Reported Outcome questionnaires should be completed by the participant in a quiet and private location.
- The participant should be given sufficient time to complete the PRO questionnaires at their own speed.
- The research nurse or appointed site staff should stress that the information is not routinely shared with study staff. Therefore, if the participant has any medical problems, he/she should discuss them with the doctor or research nurse separately from the ePRO assessment.
- The research nurse or appointed site staff must train the participant on how to use the ePRO device/application using the materials and training provided by the ePRO vendor.
- The research nurse or appointed site staff must provide guidance on whom to call if there are problems with the device when the participant is completing the ePRO at home.
- All PRO questionnaires are to be completed using the ePRO application and/or assigned device. If technical or other device-related issues prohibit completion on the device, an appropriate back-up option may be considered with prior approval from AstraZeneca.
- The research nurse or appointed site staff must remind the participant that there are no right or wrong answers and avoid introducing bias by not clarifying items.
- The participant must not receive help from relatives, friends, or clinic staff deciding on answers to the ePRO questionnaires. The responses are the participant's alone.

- If a participant uses visual aids (eg, glasses or contact lenses) for reading and does not have them when he or she attends the site visit, the participant may be exempted from completing the PRO questionnaires at that site visit.
- Site staff must not read or complete the ePRO questionnaires on behalf of the participant. If the participant is unable to read the questionnaire (eg, is blind or illiterate or not fluent in the available language), that participant is exempted from completing PRO questionnaires but may still participate in the study. If the participant cannot complete the PRO questionnaires due to reasons other than being blind, illiterate, or not fluent in an available language, the AstraZeneca study team must be contacted to determine if they can be exempted. Participants exempted in any regard should be flagged appropriately by the site staff in the source documents and in the designated eCRF.
- Questions must not be translated from an available language in the device into the language for the participant speaks.
- Reminders should be provided to participants as needed to ensure compliance with the assessment schedules.
- The research nurse or appointed site staff must monitor compliance since minimizing missing data is a key aspect of the study success.
- Finally, the research nurse or appointed site staff will review the completion status of questionnaires during site visits and document the reason(s) why a participant could not complete assessments, in the source documents and in the designated eCRF. If the site receives an email notification regarding the participant's compliance, appropriate action will be taken (eg, discussion with participant to improve compliance, a check in call from the site to ask the participant if they have any difficulties in completing questionnaires on schedule, etc). A solution to enhance/resolve compliance should be discussed with the participant. Discussion and compliance review should be reflected in source documents.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1).

8.2.1 Physical Examinations

Physical examination, as well as assessment of height and weight, will be performed at the timings specified in the SoA (Table 1); investigators should pay special attention to clinical signs related to previous serious illnesses, as new or worsening abnormalities may qualify as AEs; see Section 8.3.5 for details.

A full physical examination includes assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), oral (mouth), lymph nodes, thyroid, musculoskeletal (including spine and extremities), urogenital, dermatological, gastrointestinal, endocrine, hematologic/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 includes at a minimum, assessments of the skin, lungs, oral, cardiovascular system, and abdomen (liver and spleen).

8.2.2 Vital Signs

Vital signs will be performed at timelines as specified in the SoA (Table 1). Temperature, pulse rate, respiratory rate, pulse oximetry (SpO_2), and blood pressure will be assessed. The participant should remain at the site for at least 1-hour post-infusion for close observation for possible IRRs (for participants receiving Dato-DXd only).

Blood pressure and pulse measurements will be assessed in a supine, semi-recumbent, or seated position with a completely automated device, whenever possible. 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, cell phones).

Vital signs will be evaluated and recorded in eCRF.

Where applicable, blood pressure and pulse rate should be collected prior to the beginning of study intervention infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion]) and at the end of the infusion. These measurements may also be taken more frequently if clinically indicated.

Situations in which vital signs results should be reported as AEs are described in Section 8.3.5.

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

8.2.3 Electrocardiograms

Triplicate 12-lead ECGs will be performed at screening and at the EoT visit. The 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.

Electrocardiograms will be performed at timelines as specified in the SoA (Table 1) after the participant has been resting supine/semi-recumbent for at least 5 minutes and recorded while the participant remains in that position using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals, as possible.

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.

Situations in which ECG results should be reported as AEs are described in Section 8.3.5.

Whenever ECGs, vital signs, and blood draws are scheduled for the same nominal time, ECG assessments should occur first, then vital signs assessments, and then blood draws; the timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in the SoA (Table 1).

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, hematology, coagulation, and urinalysis will be taken at the visits indicated in the SoA (Table 1).

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. Laboratory assessments for off-schedule study drug dosing may be entered in the eCRF as unscheduled visits.

The clinical chemistry, hematology and urinalysis will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample volumes may vary depending on laboratory method used and routine practice at the site.

Other safety laboratory tests include assessment for pregnancy (serum at screening and urine at all other time points), and hepatitis B and C serology, and HIV antibody test.

Pregnancy tests may be performed at the site using a licensed test. A negative result from a serum pregnancy test (which must have a sensitivity of at least 25 mIU/mL) must be available at the screening visit. Pregnancy tests should be conducted within 72 hours prior to randomization for all female participants of childbearing potential. Repeat pregnancy tests (urine beta-human chorionic gonadotropin or serum test per institutional guideline) should be performed 72 hours before infusion of each cycle and at the EoT visit. If a positive urine pregnancy test result is confirmed using a serum test in a female participant of childbearing potential, then the participant should not be treated.

Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

The laboratory variables to be measured are presented in Table 7.

Table 7 Laboratory Safety Variables

Hematology/Haemostasis (Whole Blood)	Clinical Chemistry (Serum or Plasma)
Hemoglobin	Creatinine
White blood cell count	Bilirubin, total
Leukocyte differential count (absolute count and/or %; neutrophils, lymphocytes, monocytes, eosinophils, basophils)	Alkaline phosphatase
	AST
Platelet count	ALT
Hematocrit	Albumin
Red blood cell count	Potassium
Urinalysis	Calcium (total) or Calcium (ionized)
Hemoglobin/Erythrocytes/Blood	Sodium
Protein/Albumin	Lactate dehydrogenase
Glucose	Protein, total
	Urea nitrogen or blood urea nitrogen or urea
	Magnesium
	Chloride

The investigator should assess the available results with regard to clinically relevant abnormalities in documentation. Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 8.3.5.

All participants with Grade 3 or 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 2, unless these values are not likely to improve because of the underlying disease.

NB. If a participant has an AST **or** ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN, refer to Appendix E for further instructions.

8.2.5 Other Safety Assessments

8.2.5.1 Echocardiogram/Multigated Acquisition Scan

An echocardiogram or MUGA scan to assess LVEF will be performed at the visits indicated in SoA (Table 1). The modality of the cardiac function assessments must be consistent for a given participant (ie, if echocardiogram is used for the screening assessment for a given participant, then echocardiogram 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%).

The EoT echocardiogram/MUGA scan is not required unless clinically indicated. If a participant has any clinically significant decrease in LVEF (greater than 10 percentage points to below 50%), there should be follow-up within 4 weeks until resolution.

Situations in which echocardiogram or MUGA results should be reported as AEs are described in Section 8.3.5.

8.2.5.2 Pulmonary Function Tests

Pulse oximetry (SpO_2) should be evaluated by the investigator or the delegate physician at the time points outlined in the SoA and as clinically indicated. The SpO_2 should be measured at the same time as vital signs.

Pulmonary function tests should include basic spirometry at a minimum with optional additional components as mentioned in Table 8.

Table 8 Spirometry Component

Required spirometry components	Optional spirometry components
FVC (L)	PEF
FVC % predicted	DLCO
FEV1 (L)	FEV6
FEV1 % predicted	TLC
FEV1/FVC %	RV

Diffusion capacity of the lungs for carbon monoxide will be performed/encouraged if feasible, but for participants with prior severe and/or prior clinically significant pulmonary disorders, DLCO is a requirement. In event of suspected ILD/pneumonitis, refer to Section 8.2.5.3 additional pulmonary assessments.

8.2.5.3 ILD/Pneumonitis Investigation

For suspected ILD/pneumonitis (ie, if new or worsening pulmonary symptoms [eg, dyspnea, 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 Annex document to this CSP).

Evaluations should include:

- Detailed past medical history (including concomitant medications, ocular history, and previous use of tobacco, e-cigarettes, and/or vaping, etc.)
- Physical examination, including auscultation of lung field

- Arterial blood gases (if clinically indicated)
- Pulmonary function tests (see Section 8.2.5.2) and pulse oximetry (SpO_2)
- Bronchoscopy and bronchoalveolar lavage should be considered if clinically indicated and feasible.
- HRCT of the chest (if feasible, otherwise non-contrast chest CT is acceptable [1 to 2 mm slice thickness recommended]). If both a non-contrast chest HRCT scan for assessment of ILD/pneumonitis and a diagnostic IV contrast enhanced chest CT scan for tumor response assessment (as part of chest-abdomen-pelvis imaging) are to be acquired in the same imaging session, HRCT should be performed first.
- Pulmonologist consultation (infectious disease consultation as clinically indicated)
- Blood culture, complete blood count, and differential white blood cell count; other blood tests could be considered as needed.
- Troponin measurements will be done to rule out cardiac etiology.
- Additional optional blood samples for serum exploratory ILD/pneumonitis biomarker analysis as soon as ILD/pneumonitis is suspected and/or diagnosed (see Section 8.6.1)
- Additional optional blood sample for plasma exploratory ILD/pneumonitis biomarker analysis as soon as ILD/pneumonitis is suspected and/or diagnosed (see Section 8.6.1).

Other tests may be considered, as needed (eg, COVID-19 test).

The results of the full diagnostic workup (including HRCT, blood and sputum culture, hematological parameters, etc) is to be captured in the eCRF. A full diagnostic workup is strongly recommended to exclude alternative causes, such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of ILD/pneumonitis should be considered and the TMGs should be followed (see the Annex document to this CSP).

When ILD/pneumonitis is suspected during study treatment, the following markers should be collected where possible:

- Interstitial lung disease/pneumonitis markers: KL-6, SP-D, and β-D-glucan
- Tumor markers: particular tumor markers that are related to disease progression (carcinoembryonic antigen)
- Additional clinical chemistry: C-reactive protein, lactate dehydrogenase

8.2.5.4 ECOG Performance Status

Eastern Cooperative Oncology Group performance status will be assessed at the times specified in the SoA (Table 1) 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.

8.2.5.5 Ophthalmologic Assessments

Ophthalmologic assessments by a licensed eye care provider, including but not limited to visual acuity testing, fluorescein staining, intraocular pressure, slit-lamp examination, and fundoscopy, will be performed as specified in the SoA (Table 1) by an ophthalmologist, or if unavailable, another licensed eye care provider. This will be done at screening, and then every 3 cycles from C1D1 onwards (eg, C4D1, C7D1, C10D1 etc) within 14 days prior to scheduled cycle Day 1 visit (but not after scheduled visit), in addition to being done as clinically indicated while on trial, and at EoT. 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 ophthalmologic assessments should be entered into the eCRF and copies of all consultation reports should be filed in source notes. Please refer to the Dato-DXd Site Ophthalmologic Assessment Manual for further details.

It should be strongly considered for all participants to avoid the use of contact lenses and to use artificial tears 4 times daily as preventative measure and up to 8 times daily as clinically needed while participating in the trial, starting at C1D1. 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. Data from the ophthalmologic assessments on the first 100 randomized participants (approximately 50 in each arm, Dato-DXd and ICC) will be reviewed by a dedicated Ophthalmologic Data Review Committee (Section 9.6.3). The proposed data cutoff will be after completion of the last ophthalmologic assessment and a minimum of 2 assessments per participant for the first approximately 100 randomized participants. Until data collection has been completed and reviewed on the first approximately 100 participants, ophthalmologic assessments will continue for enrolled participants, and participants should continue to be advised to strongly consider using artificial tears and avoiding use of contact lenses. Data from these ophthalmologic assessments on the first

approximately 100 randomized participants will be reviewed by an Ophthalmologic Data Review Committee (Section 9.6.3). Review of the Ophthalmologic Data Review Committee findings will further inform the ophthalmologic assessment and monitoring plan.

The Dato-DXd Site Ophthalmologic Assessment Manual will be supplied by AZ, which provides assistance to the licensed eye care provider to assess any ocular surface toxicity.

Any significant change from baseline must be reported as an AE (see Section 8.3.5).

8.2.5.6 Oral Care Plan

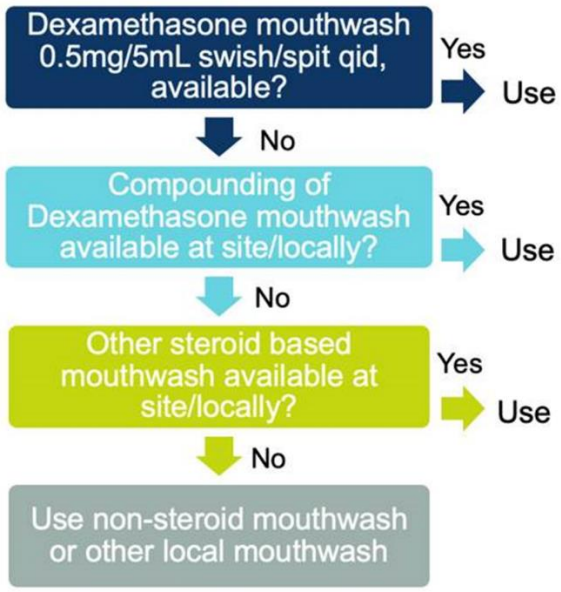
A daily Oral Care Protocol (OCP) will be started before study drug initiation for all randomized participants (both Dato-DXd and ICC arms), and it must be maintained throughout the study as specified in the SoA (Table 1). An oral care kit will be provided at study enrolment and monthly thereafter until the safety FU visit, which will include a toothbrush, toothpaste, dental floss, and an alcohol-free mouthwash, as well as an oral care plan participant information guide will be provided to each randomized participant before study drug initiation.

Participants should adhere to the following guidance:

- Gently brush their teeth after meals and at bedtime using a soft or ultra-soft toothbrush (or swab) and a bland-flavored fluoride-containing toothpaste.
- Floss their teeth every day, if able to do so without pain or causing gingival bleeding.
- For participants receiving ICC, daily use of alcohol-free mouthwash is recommended.
- For participants receiving Dato-DXd:
  Daily use of prophylaxis with a steroid-containing mouthwash (eg, dexamethasone oral solution 0.1 mg/mL 10 mL 4 times daily swish for 1 to 2 minutes then spit out; or a similar mouthwash regimen using an alternative steroid advocated by institutional/local guidelines) is highly recommended.
  - Note: Participants are allowed to take oral nystatin suspension or other topical antifungal agents after the steroid-containing mouthwash according to clinician preference based on institutional/local guidelines.
- In the absence of a prophylactic steroid-containing mouthwash, daily use of inert, bland mouth rinses (eg, with a non-alcoholic and/or bicarbonate-containing mouthwash, 4 to 6 times a day).
  - Prophylactic cryotherapy (ice chips or ice water held in the mouth throughout the infusion) should also be considered.

The algorithm in Figure 4 may be used as a guidance to select an appropriate prophylaxis mouthwash:

Figure 4 Prophylactic Mouthwash Algorithm



As per Investigator judgment, a professional dental evaluation before study drug initiation and dental treatment if indicated, may reduce the risk of local and systemic infections from odontogenic sources.

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

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

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 authorized representative).

Grade ≥ 3 ocular surface toxicity events should be reported in the EDC system within 24 hours of awareness.

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

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events and SAEs (other than ILD/pneumonitis) will be collected from the time of signature of the ICF, throughout the treatment period and including the safety follow-up

period (28 [+7] days) after the discontinuation of study intervention). All ILD/pneumonitis events regardless of severity should be reported beyond the 28 + 7-day 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 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 AE or SAE as applicable.

Collection and reporting of AEs and SAEs after the final DCO is described in Section 8.3.12.

Pre-existing medical conditions that may have been identified by mandatory screening procedures (eg, cataract on baseline ophthalmologic assessment, 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 should be reported by the investigator in eCRF EDC AE page(s) in the clinical study database/paper SAE report form within 24 hours of becoming aware:

- SAEs (see Section 8.3.2).
- All potential ILD/pneumonitis cases, including both serious and non-serious potential ILD/pneumonitis cases (potential ILD/pneumonitis is described by the Event Adjudication Site Manual).
- 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 either at different time points or simultaneously at any time during this study 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. If the participant discontinues study intervention due to liver enzyme abnormalities, the participant will have additional clinical and laboratory evaluations as described in Appendix E in order to determine the nature and severity of the potential liver injury.
- Grade ≥ 3 IRR.
- Grade ≥ 3 ocular surface toxicity events.
- Grade ≥ 2 keratitis events (includes keratitis, punctate keratitis, and ulcerative keratitis).
- Overdose (see Section 8.4).

Additional relevant information regarding the AESIs, regardless of seriousness, is to be collected through targeted questionnaires within the clinical study database (see

Section 8.3.11).

8.3.2 Follow-up of AEs and SAEs

Any AE that is unresolved at the participant's last AE assessment in the study should be 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).
- The date when the AE started and stopped.
- CTCAE grade/changes in CTCAE grade (report only the maximum CTCAE grade for a calendar day).
- 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 hospitalization.
- 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 NCI-CTCAE Version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into

CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.3.3 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 investigational product?"

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 to the CSP.

8.3.4 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.

8.3.5 Adverse Events Based on Examinations and Tests

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

Deterioration as compared with baseline in protocol-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 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 interruption).

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, anemia versus low hemoglobin 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, which 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.

8.3.6 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. A targeted questionnaire in the eCRF needs to be filled out for every case that meets these pre-specified laboratory criteria.

8.3.7 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 metastases or progression of existing metastasis to the primary cancer under study should be considered as PD and not an AE. Events, which are unequivocally due to PD, should not be reported as an AE during the study. Death due to disease progression should be recorded on the Death eCRF.

8.3.8 Disease Under Study

Symptoms of disease under study are those which might be expected to occur as a direct result of breast cancer. Events which are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the study intervention.

8.3.9 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.

8.3.10 Deaths

All deaths that occur during the study intervention period, or within the protocol-defined 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 protocol-defined 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 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.

8.3.11 Adverse Events of Special Interest

Adverse events of special interest are events of scientific and medical interest specific to the further understanding of the Dato-DXd safety profile and require close monitoring and rapid communication by investigators to AstraZeneca. An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF using a recognized medical term or diagnosis that accurately reflects the event. Serious AESIs will be recorded and reported as per Section 8.3.13.

For the Dato-DXd clinical program, based on the available preclinical data, review of the cumulative literature, reported toxicities for drugs with a similar monoclonal antibody and payload of Dato-DXd, and biological plausibility, the following are considered AESIs:

- ILD/pneumonitis
- IRR
- Oral mucositis/stomatitis
- Mucosal inflammation other than oral mucositis/stomatitis
- Ocular surface toxicity

All AESIs, regardless of severity or seriousness, must be followed until either event resolution, end of study, 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.

ILD/pneumonitis

Interstitial lung disease/pneumonitis is considered an important identified risk for Dato-DXd 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 payload as Dato-DXd. Refer to the current IB for a summary of preliminary clinical study data.

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 targeted questionnaire is built within the eCRF to collect relevant additional information for these potential cases regardless of seriousness.

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 dyspnea, cough or fever. For further guidance on the management of suspected ILD/pneumonitis events, refer to Section 8.2.5.3 and the Annex document to this CSP.

If the AE is suspected to be ILD/pneumonitis, treatment with study intervention should be interrupted pending further evaluations. Evaluations should include those outlined in Section 8.2.5.3. If the AE is confirmed to be ILD/pneumonitis, follow the management guidance outlined in the TMGs (see the Annex document to this CSP). All events of ILD/pneumonitis, regardless of severity or seriousness, will be followed until resolution including after Dato-DXd discontinuation. An autopsy in cases of Grade 5 ILD/pneumonitis is encouraged. An independent ILD Adjudication Committee for the Dato-DXd program is responsible for reviewing all cases of potential ILD/pneumonitis. See Section 9.6.2 for further details.

IRR

Infusion-related reaction is an identified risk for Dato-DXd. A Grade 3 IRR was reported and was assessed by an external consultant as anaphylaxis. A targeted questionnaire for ≥ Grade 3 IRR will be available as an eCRF to collect relevant additional information for these potential cases. All grade ≥ 3 events of IRR, regardless of seriousness, must be reported in EDC within 24 hours. Refer to the current IB for a summary of preliminary clinical study data.

Pre-medication is required prior to any dose of Dato-DXd and must include antihistamines and acetaminophen with or without glucocorticoids. If there are any signs or symptoms of a grade 1 or 2 IRR, the infusion of Dato-DXd must be either slowed down or interrupted based on severity of the infusion-related reaction (see Section 6.2.1.2). If the IRR is grade 3 or 4, or if there are any signs of anaphylaxis, the infusion of Dato-DXd must be discontinued. Please refer to the IRR management guidance outlined in the TMGs (see the Annex document to this CSP).

Oral Mucositis/Stomatitis

Oral mucositis/stomatitis AEs are considered as identified risks and AESIs associated with Dato-DXd treatment. Oral mucositis/stomatitis is considered as a separate AESI from mucosal inflammation other than oral mucositis/stomatitis. Recommendations for preventing and treating oral mucositis/stomatitis are outlined in the SoA (Table 1), Section 8.2.5.6, and the TMGs (see the Annex document to this CSP).

Mucosal Inflammation other than Oral Mucositis/Stomatitis

Mucosal inflammation AEs are considered as identified risks associated with Dato-DXd treatment and as a separate AESI from oral mucositis/stomatitis.

Ocular Surface Toxicity

Ocular surface toxicity (eg, dry eye, keratitis) is considered an AESI associated with Dato-DXd. Dry eye is considered as an identified risk and keratitis as a potential risk within this AESI. Participants are advised to use artificial tears daily and to avoid contact lenses. Recommendations for preventing and treating ocular surface toxicity are available in the SoA (Table 1), Section 8.2.5.5 and the TMGs (see the Annex document to this CSP).

The Dato-DXd Site Ophthalmologic Assessment Manual will be supplied by AstraZeneca to provide assistance to the licensed eye care provider to assess any ocular surface toxicity.

8.3.12 Safety Data to be Collected Following the Final Data Cutoff of the Study

For participants continuing to receive study intervention after the final DCO, AEs and SAEs will be collected, but only SAEs will be reported. In addition, it is recommended that investigators monitor all participant's safety laboratory results periodically during treatment with study intervention in order to manage AEs, consistent with the TMGs (see the Annex document to this CSP). 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 study intervention (or within the 28 [+7] days following the last dose of study intervention) after the final DCO must be

reported as detailed in Section 8.3.13.

8.3.13 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. For further guidance on the definition of an SAE, see Appendix B.

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 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 1 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 1 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.

The reference document for definition of expectedness is the IB for Dato-DXd, and respective EU SmPCs for the active comparator products.

8.3.14 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.

Female participants must not donate, or retrieve for their own use, ova from the time of Screening and throughout the study treatment period, and for at least 7 months after the final study drug administration.

8.3.14.1 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 female 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 abnormalities/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 during the course of the study, the investigator or other site personnel must inform the appropriate AstraZeneca representatives within 1 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 1 or 5 calendar days for SAEs (see Section 8.3.13) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

8.3.14.2 Paternal Exposure

Non-sterilized male participants who intend to be sexually active with a female partner of childbearing potential 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 study intervention.

Participants in the ICC (capecitabine, eribulin, vinorelbine or gemcitabine) arm should follow the local Prescribing Information relating to contraception, the time limits for such precautions, and any additional restrictions for ICC agents.

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 7 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 local 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.

8.3.15 Medication Error, Drug Abuse, and Drug Misuse

8.3.15.1.1 Timelines

If an event of medication error, drug abuse **or** drug misuse occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar 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 **1** (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 medication error (see Section 8.3.13) and **within 30 days** for all other medication errors.

8.3.15.2 Medication Error

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

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

8.3.15.3 Drug Abuse

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

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

8.3.15.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP/study intervention or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs/study intervention(s) or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

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

8.3.16 Medical Device Deficiencies

This section is not applicable.

8.4 Overdose

The use of Dato-DXd in doses exceeding that specified in the protocol 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. An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules 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 1 or 5 calendar days for overdoses associated with an SAE (see Section 8.3.13) and within 30 days for all other overdoses.

For participants receiving ICC (capecitabine, eribulin, vinorelbine or gemcitabine), refer to the local Prescribing Information for treatment of cases of overdose. If any overdose is associated with an AE or SAE, record the AE/SAE diagnosis or symptoms in the relevant AE modules only of the eCRF.

8.5 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 may be stored for a maximum of 15 years from the end of the study (as defined in the Section 4.4) in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier).

  - Samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
  - Samples collected in mainland China will be stored and disposed of according to local laws and regulations. PK samples collected in mainland China will be destroyed after finalization of Bioanalytical Report or completion of CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 5 years from the CSR publication. ADA samples collected in China will be disposed of within 1 year of CSR publication. Additional use includes, but is not limited to, further characterization of any ADAs, evaluation of novel and emerging biomarkers, confirmation and/or requalification of the assay, and/or diagnostic assay development. The results from future analysis will not be reported in the CSR.

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

8.5.1 Pharmacokinetics

Whole blood samples will be collected for participants receiving Dato-DXd treatment for measurement of plasma concentrations of Dato-DXd, total anti-TROP2 antibody, and MAAA-1181a, per the schedule specified in the SoA (Table 1). The actual date and time (24-hour clock time) of each sample should be recorded.

Samples may also be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor (eg, for safety reasons). The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

8.5.1.1 Determination of Drug Concentration

Samples for determination of Dato-DXd, total anti-TROP2 antibody, and MAAA-1181a 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.

8.5.2 Immunogenicity Assessments

Whole blood samples for determination of ADA for Dato-DXd in plasma will be collected from participants receiving Dato-DXd per the schedule specified in the SoA (Table 1). The

ADA samples may also be further tested for characterization of the ADA response. The ADA titer, and the presence of neutralizing ADA will be tested for positive ADA samples.

Samples will be 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.

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

Participant consent to the study includes participation in the mandatory biomarker assessment components of the study.

Samples for biomarker assessment are required and will be collected from all participants in this study as specified in the SoA (Table 1). In mainland China, tumor sample collection and tests will follow local regulatory requirements.

The following mandatory samples will be collected from all randomized participants:

Tumor tissue

Tumor samples are mandatory for all participants in this study and must be available at the time of screening. This can be from either the primary disease setting (surgical resection or diagnostic sample), or from a metastatic lesion (excluding bone). The mandatory FFPE tumor sample submitted for analysis should be obtained as close to the time of diagnosis of metastatic or inoperable disease as possible.

If neither an adequate FFPE block nor the minimum of 20 slides are available, a patient may still be considered eligible. In this situation, approval by the Global Study Team for patient's entry into the study is required.

If a block is not available, a minimum of 20 slides of freshly prepared, unstained, 4 to 5-micron sections from the archival tumor block. As uncontrolled oxidation processes affect tumor sections, tumor tissue blocks are preferred.

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

In mainland China, tumor sample collection and testing will follow local regulatory approval.

Samples may be tested for biomarkers including (but not limited to) TROP2 protein and gene

expression, TROP2-interacting proteins and TOPO-1 expression, and tumor mutational profile to evaluate their association with the observed clinical responses to Dato-DXd (including but not limited to PFS and OS, as well as key safety endpoints).

Based on availability of tissue, further additional exploratory biomarkers may be evaluated, which may include (but are not limited to), cell death and immunological biomarkers such as PD-L1 expression and tumor infiltrating lymphocyte, and gene-expression based tumor subtyping.

Blood-borne Biomarkers

- Blood samples to perform exploratory circulating biomarker, safety or clinical analyses on plasma and serum to identify candidate factors that may correlate with drug response, likelihood of clinical benefit and tolerability.

  These analyses may include, but are not limited to, cytokines and chemokines, to assess a range of oncology, immunological and safety biomarkers, the detection of the presence of viruses. Plasma may also be used for the detection/quantification of autoantibodies (against tumor-associated antigens).
- Blood sample for the isolation of plasma and buffy coat to enable analysis and interpretation of ctDNA, to characterize changes in mutational profile (single nucleotide variant and copy number alteration) and allele frequency, between baseline and on-treatment as a predictive marker for clinical outcomes as exploratory endpoints.

  The buffy coat layer obtained during the plasma isolation process of the baseline sample will be taken, to enable assessment, analysis and interpretation of ctDNA:
  - ctDNA samples will be analyzed for predictive biomarkers of response to treatment. The sample is requested prior to treatment in order to maximize the probability of detecting ctDNA where the tumor burden is relatively high.
  - ctDNA samples taken during treatment and a final sample taken at disease progression will be used for additional exploratory research which may include but is not limited to interrogation of changes in genetic alterations, ctDNA levels as well as the dynamics changes of the biomarkers on treatment and potential mechanisms of resistance to treatment.
- Whole blood sample for RNA and DNA to conduct gene expression and mutational analyses to understand immunological changes following treatment with Dato-DXd and to assess gene signatures that may predict treatment response.

These samples will be taken at multiple timepoints and analyzed for a range of oncology and immunological biomarkers that may correlate with drug response. These biomarkers may include but are not limited to T-cell receptor repertoire analysis and analysis of gene expression biomarkers associated with immunomodulatory effects.

Samples may be retained in all regions to allow for potential diagnostic development, while mainland China sample usage will still follow local regulatory approval.

Test residual tumor samples collected for TROP2 IHC testing from Chinese participants will be destroyed or repatriated within 1 year after CSR completion.

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

8.6.2 Collection of Optional Biomarker Samples

Collection of optional samples for biomarker assessment is also part of this study (as specified in the SoA; Table 1) and is subject to agreement to optional consent. Collection of some optional samples will be mandated at select sites.

Note: Optional biomarker samples will not be collected in mainland China.

Optional tumor tissue samples for exploratory biomarker research

- *Paired tumor biopsy*: A baseline biopsy will be taken (where the participant has provided informed consent) before initial dosing of study intervention (at screening or pre-dose on C1D1), and a paired (second) biopsy will be taken on-treatment. The paired on-treatment biopsy can be collected C2D1 and C2D7. On-treatment sample may also be collected outside of this specified timepoint with prior agreement from the Sponsor. Paired pre-treatment and on-treatment tumor samples must be obtained from the same lesion where clinically feasible to maximize the utility for assessment of pharmacodynamic changes. These optional paired tumor samples will be mandatory at select sites.
- *Tumor biopsy on disease progression:* An additional tumor biopsy sample should be obtained at termination of treatment/documented RECIST 1.1 disease progression in participants that have signed the additional optional consent. These samples will be used to explore mechanisms of resistance. The on-study provision of tumor tissue is encouraged only if clinically appropriate and not considered detrimental to participant care.

Biopsies at study entry, on treatment, and progression are optional for the majority of participants in this study, and participants will not be excluded from the study if these samples are not collected. These optional biopsy samples will be mandatory at select sites.

ILD related samples

Participants will sign an informed consent for optional tissue samples to be taken in the event of suspected or diagnosed ILD.

Additional optional blood samples (serum and plasma) will be collected for exploratory biomarker analysis as soon as ILD/pneumonitis is suspected and/or diagnosed, if feasible (see Section 8.2.5.3).

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

8.6.3 Other Study Related Biomarker Assessments

Already collected samples may be analyzed on different biomarkers thought to play a role in efficacy and safety outcomes including, but not limited to, serum analytes, or tissue biomarkers and/or specific candidate genes/genome-wide analysis for RNA, to evaluate their association with observed clinical responses to Dato-DXd. The presence of viruses may also be investigated.

Additional exploratory analyses may be undertaken on participants' samples to identify other biomarkers of sensitivity and resistance to study interventions and our understanding of cancer. These studies would extend the search for other potential biomarkers relevant to the effects of Dato-DXd, cancer and/or the response/resistance to the study intervention. This may include the development of ways to detect, monitor or treat cancer. These additional investigations would be dependent upon clinical outcome, reagent, and sample availability.

Samples collected in China will not be used for additional exploratory biomarker analyses beyond initial TROP2 IHC testing.

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

8.7 Optional Genomics Initiative Sample

Collection of optional samples for genomics initiative research is also part of this study as specified in the SoA (Table 1) and is subject to agreement in the ICF addendum. Samples will be collected according to local regulatory approval.

Blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

See Appendix D for information regarding the storage and destruction of Genomics Initiative genetic sample. Details on processes for collection, shipment and destruction of these samples can be found in the Laboratory Manual.

Note: These samples will not be collected in mainland China.

8.8 Medical Resource Utilization and Health Economics

Health care resource use data associated with medical encounters, will be collected in the eCRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The assessment of health care resource use will increase the understanding regarding the relationship between treatment and tumor-related cancer symptoms on resource use. This will be captured and analyzed to inform submissions to payers.

The HOSPAD eCRF module will be used to collect information on key health care resource use beyond study mandated visits. To investigate the impact of treatment and disease on health care resource use and to conduct exploratory economic analyses, the following variables will be captured:

- Planned and unplanned hospital attendances beyond trial protocol-mandated visits (including inpatient or outpatient physician visits, emergency room visits, surgeries, day cases and admissions)
- Primary sign or symptom the participant presents with
- Length of hospital stay
- Length of any time spent in an intensive care unit
- Number and type of diagnostic and therapeutic tests and procedures
- Any other medical encounters and interventions (including physician or emergency room visits, tests and procedures, and medications).

9 STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by AstraZeneca or its representatives.

A comprehensive SAP will be prepared prior to 3 months post-FSI, with final amendments completed prior to database lock.

9.1 Statistical Hypotheses

The hypotheses of interest with regards to the efficacy for the dual primary endpoints are:

- H0: No differences between Dato-DXd and ICC for PFS and OS.
- H1: Differences between Dato-DXd and ICC for PFS and/or OS.

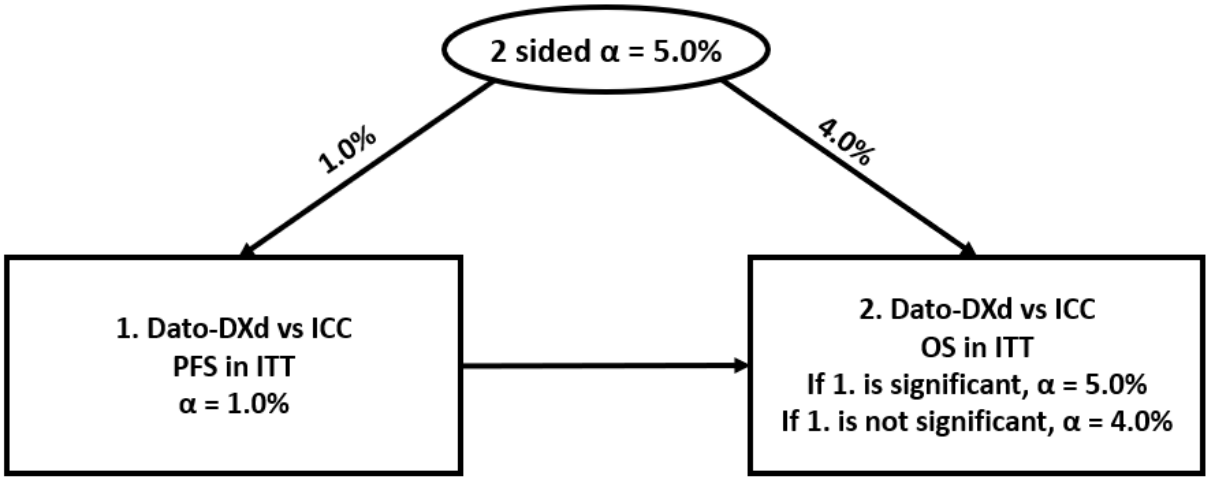
The MTP will define which significance levels should be applied to the interpretation of the raw p-values for the dual primary endpoints of PFS and OS. Hypotheses will be tested using a MTP with an alpha-exhaustive recycling strategy (Burman et al 2009).

To strongly control the familywise type I error rate at the 5.0% level (2-sided), an alpha level of 1.0% will be allocated to the PFS dual primary analysis and the remaining 4.0% alpha level will be allocated to the OS analyses. If the PFS dual primary analysis crosses the efficacy threshold, the 1.0% type I error allocated to the PFS endpoint will be reallocated (Burman et al 2009) to the OS endpoint for a total 2-sided type I error of 5.0%.

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

To preserve the overall type I error (familywise error rate) in the strong sense, an MTP including the dual primary endpoints will be implemented. The MTP will be fully specified in the SAP. The MTP for the dual primary endpoints is described in Figure 5.

Figure 5 Multiple Testing Procedure



9.2 Sample Size Determination

Approximately 1000 participants will be enrolled to achieve approximately 700 participants randomly assigned to study intervention.

Note: "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. Potential participants who are screened for the purpose of determining eligibility for the study but are not randomly assigned/assigned in the study, are considered "screen failures", unless otherwise specified by the protocol.

The study is sized for dual primary endpoints to characterize the PFS and OS benefit of Dato-DXd versus ICC in the participants with HR-positive, HER2-negative breast cancer who

have been treated with one or two prior lines of systemic chemotherapy in the inoperable/metastatic setting. The study will be considered positive (a success) if either the PFS analysis results and/or the OS analysis results are statistically significant.

The primary, final analysis of PFS will be performed when approximately 419 PFS BICR events occur, approximately 2 months after the last participant is randomized in the study; 419 PFS BICR events from the ITT population across the Dato-DXd and ICC treatment groups will represent 60% maturity of data. Assuming the true PFS hazard ratio is 0.55 for Dato-DXd versus ICC, the study will have a greater than 99% power to demonstrate statistical significance at the 1.0% level (using a 2-sided test). This assumes median PFS times of 4.7 months and 8.5 months in ICC and Dato-DXd, respectively when the PFS times are exponentially distributed. The smallest treatment difference that could be statistically significant at the final analysis is a hazard ratio of 0.775.

The final analysis of OS will be performed when approximately 444 OS events have occurred across the Dato-DXd and ICC treatment groups (63% maturity). Assuming the true OS hazard ratio is 0.75 for Dato-DXd versus ICC, the study will have 85% power to demonstrate statistical significance at the 5.0% level (using a 2-sided test). This assumes the PFS primary analysis crosses the efficacy threshold, and allowing 2 interim analyses to be conducted at information fractions of approximately 40% and 80% of the target events, respectively (per the O'Brien and Fleming approach [Lan and DeMets 1983]). The smallest treatment difference that could be statistically significant at the final analysis is a hazard ratio of 0.824. If the PFS primary analysis does not cross the efficacy threshold, the OS analysis will have 83% power to demonstrate statistical significance at the 4.0% level (using a 2-sided test). The smallest treatment difference that could be statistically significant at the final analysis is a hazard ratio of 0.817. Calculations assume median OS times of 19.0 months and 25.3 months in ICC and Dato-DXd, respectively when the survival times are exponentially distributed. The study may continue monitoring participants for OS up to the scheduled final analysis, beyond planned interim analyses, to provide more refined estimates of treatment effects for survival. Further details of the interim analyses are presented in Section 9.5.

A nonuniform accrual of participants (with $k = 1.5$) is assumed when estimating the analysis times. The total proportion of participants randomized at time t [$t \leq 19$ months] following the start of the study is assumed to be $(t/19)^k$.

Dual Primary Endpoints

- ***Dato-DXd versus ICC (PFS in the ITT):***

  Assuming the true PFS treatment effect under the alternative hypothesis is a hazard ratio of 0.55 for Dato-DXd versus ICC, and the median PFS in ICC is 4.7 months, 419 PFS events from the ITT population (60% maturity) will provide greater than 99% power to demonstrate statistical significance at the 2-sided alpha level of 1.0%. The smallest

treatment difference that is statistically significant will be a hazard ratio of 0.775. Assuming a recruitment period of 19 months, this analysis is anticipated to be 21 months after the first participant has been randomized.

- ***Dato-DXd versus ICC (OS in the ITT):***

  Assuming the true OS treatment effect under the alternative hypothesis is a hazard ratio of 0.75 for Dato-DXd versus ICC, and the median OS in ICC is 19.0 months, 444 OS events from the ITT population (63% maturity) will provide approximately 83% power to demonstrate statistical significance at the 2-sided alpha level of 4.0%. The smallest treatment difference that is statistically significant will be a hazard ratio of 0.817. If the PFS dual primary analysis crosses the efficacy threshold, OS will be tested at the 2-sided alpha level of 5.0% and the analysis will have 85% power to demonstrate statistical significance. The smallest treatment difference that is statistically significant will be a hazard ratio of 0.824. With a recruitment period of approximately 19 months it is anticipated that the primary/final OS analysis will occur approximately 44 months after the first participant has been randomized.

9.3 Populations for Analyses

The populations for analysis are defined in Table 9.

Table 9 Populations for Analysis

Population/Analysis Set	Description
Enrolled	All participants who sign the ICF.
Intent-to-treat (ITT) population	All participants who are randomized in the study, excluding participants randomized in mainland China after the global cohort last participant randomized, if applicable. The ITT will be used for all the efficacy analyses (including PROs: EORTC QLQ-C30, EORTC IL116, EQ-5D-5L, PGIS, PGIC). Treatment groups will be compared on the basis of randomized study intervention, regardless of the intervention actually received. Participants who were randomized but did not subsequently receive study intervention are included in the analysis in the intervention group to which they were randomized.

Table 9 Populations for Analysis

Population/Analysis Set	Description
Safety Analysis Set (SAS)	Participants in the ITT who have received at least 1 dose of study intervention. Safety data will not be formally analyzed but summarized using the SAS according to actual study intervention received (including PROs: PGI-TT, PRO-CTCAE, EORTC IL117).
Ophthalmologic Analysis Set (OAS)	Approximately the first 100 randomized participants (approximately 50 per arm, Dato-DXd and ICC) in the ITT. See section 8.2.5.5 for details.
Pharmacokinetic Analysis Set (PAS)	All participants in the ITT randomly assigned to study intervention who received at least 1 dose of study intervention for whom any post-dose PK data are available and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses. The population will be defined by the sponsor Study Physician, Pharmacokineticist, and Statistician prior to any analyses being performed.

9.4 Statistical Analyses

The SAP will be finalized prior to 3 months post-FSI of the first randomized participant, and 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 key secondary endpoints.

9.4.1 General Considerations

More detail will be provided in the SAP.

9.4.2 Efficacy

9.4.2.1 Primary Endpoints

Table 10 Pre-planned Statistical and Sensitivity Analyses to be Conducted for Primary Endpoints

Endpoints analyzed	Notes
Progression-free survival	Stratified log-rank test for: Dual primary analysis using BICR RECIST 1.1 assessments: • Dato-DXd versus ICC (ITT population) Secondary analysis using Investigator assessment: • Dato-DXd versus ICC (ITT population) Sensitivity analysis for the PFS dual primary analysis (ITT population): • Evaluation-time bias • Attrition bias • Ascertainment bias • Subsequent anticancer therapy

Table 10 Pre-planned Statistical and Sensitivity Analyses to be Conducted for Primary Endpoints

Endpoints analyzed	Notes
Overall survival	Stratified log-rank test for: Dual primary analysis: • Dato-DXd versus ICC (ITT population)

9.4.2.1.1 Calculation or Derivation of Tumor Response Variables

Investigator RECIST 1.1-based assessments

All RECIST 1.1 assessments, whether scheduled or unscheduled, will be included in the calculations. This is also 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 the 28 days prior to randomization. The tumor response endpoints (PFS, ORR, DoR, and DCR) will then be derived from the scan dates and overall visit responses.

BICR

A BICR of radiological scans will be performed on all participants to confirm the robustness of the investigator-assessed PFS, ORR, and DoR endpoints.

All images will be collected centrally, until PFS analysis. Additionally, following RECIST 1.1-defined radiological progression by Investigator assessment, 1 additional follow-up scan should be performed as per imaging schedule (ie, either 6 weeks or 9 weeks later). This scan will be used in the PFS dual primary endpoint analysis.

The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and will be adjudicated, if required. For each participant, the BICR 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 tumor 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 (PFS, ORR, DoR, and DCR) will then be derived from the scan dates and overall visit responses.

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

9.4.2.1.2 Progression-Free Survival

Progression-free survival will be defined as the time from the date of randomization until the

date of objective PD per RECIST 1.1 (as assessed by BICR) or death (by any cause in the absence of progression), (ie, date of event or censoring – date of randomization + 1). The comparison will include all randomized participants, as randomized, regardless of whether the participant withdraws from randomized therapy, receives another anticancer 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 visits or does not have baseline data, they will be censored at the date of randomization, unless they die within 2 scheduled scans of baseline (12 weeks [+1 week] allowing for a late assessment within the visit window).

Analysis Methods

The dual primary endpoint of PFS will be based on the BICR assessment of PD by RECIST 1.1.

Progression-free survival will be analyzed using a log-rank test stratified by number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor. The hazard ratio together with its 95% CI and p-value will be presented (a hazard ratio less than 1 will favor the comparator arm). The hazard ratio and CI will be estimated from a stratified Cox proportional hazards model (with ties = Efron), and the CI will be calculated using a profile likelihood approach.

The stratification variables will be defined according to data from the IRT. If the number of events in an individual stratum are too small for a meaningful analysis, then a method will be applied that will remove stratification factors until there are meaningful number of events per strata. Details will be presented in the SAP.

Kaplan-Meier plots of PFS will be presented by treatment group. 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 primary and final analysis of PFS will be performed approximately 2 months after the last participant is randomized in the study; approximately 419 PFS BICR events across the Dato-DXd and ICC treatment groups (60% maturity) are anticipated at that time.

9.4.2.1.3 PFS Sensitivity Analyses

Details of these analyses will be presented in the SAP.

Evaluation-time Bias

A sensitivity analysis will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled time points. The midpoint between the time of progression and the previous evaluable RECIST assessment (using the final date of the assessment) will be analyzed using a stratified log-rank test, as described for the primary analysis of PFS.

Attrition Bias

Attrition bias will be assessed by repeating the PFS analysis except that the actual PFS event times, rather than the censored times, of participants who progressed or died in the absence of progression immediately following two, or more, non-evaluable tumor assessments will be included. In addition, and within the same sensitivity analysis, participants who take subsequent therapy (note that for this analysis radiotherapy is not considered a subsequent anticancer therapy) prior to their last evaluable RECIST assessment or progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy. This analysis will be supported by a Kaplan-Meier plot of the time to censoring using the PFS data from the primary analysis and where the censoring indicator of the PFS analysis is reversed.

Ascertainment bias

Ascertainment bias will be assessed by analyzing the site Investigator data which is a secondary efficacy variable (analysis methods presented in Section 9.4.2.2.3).

If there is an important discrepancy between the primary analysis using the BICR assessments and the secondary analysis using investigator assessments, the proportion of participants with site but no central confirmation of progression will be summarized; such participants have the potential to introduce bias in the central review due to informative censoring. An approach that imputes an event at the next visit in the central review analysis may help inform the most likely hazard ratio value, but only if an important discrepancy exists.

Subsequent Anticancer Therapy

PFS may be impacted for participants who are treated with a subsequent anticancer therapy. Therefore, an analysis will be performed censoring a participant at the last available tumor assessment prior to taking subsequent anticancer therapy.

Additional sensitivity analyses may be defined in the SAP.

9.4.2.1.4 Overall Survival

Overall survival is defined as the time from the date of randomization until death due to any cause. The comparison will include all randomized participants, as randomized, regardless of whether the participant withdraws from randomized therapy or receives another anticancer

therapy (ie, date of death or censoring – date of randomization + 1). Any participant not known to have died at the time of analysis will be censored based on the last recorded date on which the participant was known to be alive.

Note: Survival calls will be made following the date of DCO for the analysis (these contacts should generally occur within 7 days of the DCO). 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

Overall survival will be analyzed using the same methodology specified for PFS. The effect of Dato-DXd versus ICC will be estimated by the hazard ratio together with its corresponding CI and p-value. Kaplan-Meier plots will be presented by treatment group.

The study may continue monitoring participants for OS up to the scheduled final analysis, beyond planned interim analyses, to provide more refined estimates of treatment effects for survival.

9.4.2.1.5 Subgroup Analysis

Subgroup analyses will be conducted, comparing PFS (per RECIST 1.1 using BICR assessments) and OS between Dato-DXd and ICC in the following subgroups of the ITT (but not limited to):

- Number of previous lines of chemotherapy (1 versus 2)
- Geographic region (Region 1 [US, Canada, Europe] versus Region 2 [Rest of World])
- Prior use of CDK4/6 inhibitor (Yes versus No)
- Prior use of taxanes and/or anthracyclines (taxanes alone, anthracyclines alone, both taxanes and anthracyclines, neither taxanes nor anthracyclines)
- Age at randomization (< 65 versus ≥ 65 years of age)
- Race (Asian versus non-Asian)
- Pre-selected choice of chemotherapy (Capecitabine, Gemcitabine, Eribulin mesylate, or Vinorelbine)
- Brain metastases (Yes versus No)

Other baseline variables may also be assessed if there is clinical justification, or an imbalance is observed between the treatment groups. The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic and/or predictive factors.

A forest plot of the PFS hazard ratios (along with the 95% CIs) will be produced for each level of the subgroups listed above.

The subgroup analyses for the stratification factors will be based on the values entered into the IRT; all other factors will be based on values recorded on the eCRF, or from the third-party vendor data.

Additional subgroups of interest and analysis methods will be outlined in the SAP.

Unless there is a marked difference between the results of the statistical analyses of the PFS from the BICR data and that of the site Investigator tumor data, these subgroup analyses will only be performed on the PFS endpoint using the BICR data.

9.4.2.2 Secondary Endpoint(s)

9.4.2.2.1 Objective Response Rate

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

The analysis will include all randomized participants as randomized, with measurable disease at baseline. Data obtained from randomization up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR, regardless of whether the participant withdraws from therapy. Participants who go off treatment without a response or progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR.

Analysis Methods

The ORR will be compared between the treatment arms using a logistic regression model adjusting for the same stratification factors as the PFS as covariates in the model. The results of the analysis will be presented in terms of an adjusted odds ratio (OR) together with its associated 95% CI and p-value. If there are not enough responses for a meaningful analysis using logistic regression, then a CMH test is presented. The CMH test is stratified using the same stratification factors as PFS. The results of the analysis are presented in terms of an OR together with the 95% CI and p-value. Further details will be presented in the SAP. Comparisons between treatment groups will be made using both BICR RECIST 1.1 and investigator assessments.

Summaries will be produced that present the number and percentage of participants with a tumor response (CR/PR). For each treatment arm, BoR will be summarized by n (%) for each category (CR, PR, SD, PD, and NE).

Best objective response (BoR) is calculated based on the overall visit responses from each RECIST assessment. It is the best response a participant has had following randomization, but prior to starting any subsequent cancer therapy and up to and including RECIST progression or the last evaluable assessment in the absence of RECIST progression. Categorization of BoR will be based on RECIST using the following response categories: CR, PR, SD, PD, and NE.

Best objective response will be determined programmatically based on RECIST from the overall visit response using all BICR data up until the first progression event. It will also be determined programmatically based on RECIST using all site investigator data up until the first progression event. The denominators for each case will be consistent with those used in the ORR analysis.

9.4.2.2.2 Duration of Response

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

The analysis will include all randomized participants as randomized who have a confirmed response, regardless of whether the participant withdraws from therapy, receives another anticancer therapy or clinically progresses prior to RECIST 1.1 progression.

Analysis Methods

Duration of response will be analyzed by summary statistics and Kaplan-Meier plots. Comparisons will be presented for both BICR RECIST 1.1 and investigator assessments.

9.4.2.2.3 Progression-Free Survival by Investigator assessment

PFS by Investigator assessment will be defined as the time from the date of randomization until the date of PD per RECIST 1.1 (by Investigator assessment) or death (by any cause in the absence of progression), (ie, date of event or censoring – date of randomization + 1). The analysis will include all randomized participants as randomized regardless of whether the participant withdraws from therapy, receives another anticancer therapy, or clinically progresses prior to RECIST 1.1. However, if the participant progresses or dies immediately after two or more consecutive missed visits, the participant will be censored at the time of the latest evaluable assessment prior to the two missed visits.

Analysis Methods

This secondary endpoint of PFS based Investigator assessment will be analyzed using the same methodology described in Section 9.4.2.1.2.

9.4.2.2.4 Disease control rate

Disease control rate at 12 weeks is defined as the percentage of participants who have a confirmed CR or PR or who have SD, per RECIST 1.1, as assessed BICR/per investigator assessment and derived from the raw tumor data for at least 11 weeks after randomization.

The analysis will include all randomized participants as randomized. Data obtained from randomization up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of DCR, regardless of whether the participant withdraws from therapy. Participants who receive a subsequent therapy prior to week 11 will

not be considered to have disease control in the analysis.

Analysis Methods

Disease control rate will be analyzed using the same methodology specified for ORR.

9.4.2.2.5 Time to First Subsequent Therapy (TFST)

Time to first subsequent therapy is defined as the time from randomization until the start date of the first subsequent anticancer therapy after discontinuation of randomized treatment, or death due to any cause.

The analysis will include all randomized participants as randomized, regardless of progression status.

Analysis Methods

Time to first subsequent therapy will be analyzed using the same methodology as that used for the analysis of PFS. In addition, medians and a Kaplan-Meier plot of the time to the start of subsequent therapy will be presented by treatment arm and the time between progression and starting subsequent therapy will be summarized.

9.4.2.2.6 Time to Second Subsequent Therapy (TSST)

Time to second subsequent therapy is defined as the time from randomization to until the start date of the second subsequent anticancer therapy after discontinuation of first subsequent treatment, or death due to any cause.

The analysis will include all randomized participants as randomized, regardless of progression status on study treatment or first subsequent treatment.

Analysis Methods

Time to second subsequent therapy will be analyzed using the same methodology as that used for the analysis of TFST.

9.4.2.2.7 Time from randomization to second progression or death (PFS2)

Time to second progression of death will be defined as the time from the randomization to the earliest of the progression event (following the initial progression), subsequent to first subsequent therapy, or death. The date of second progression will be recorded by the Investigator in the eCRF and defined according to local standard clinical practice.

The analysis will include all randomized participants as randomized, regardless of progression status on study treatment or first subsequent treatment.

Analysis Methods

Time to second progression or death will be analyzed using identical methods as outlined for

PFS.

9.4.2.2.8 Clinical Outcome Assessments

The secondary PRO endpoints include:

- TTD in pain as measured by the pain scale from EORTC QLQ-C30
- TTD in physical functioning as measured by the physical functioning scale from EORTC QLQ-C30
- TTD in GHS/QoL as measured by the GHS/QoL scale from EORTC QLQ-C30.

Time to deterioration (TTD) is defined as time from the date of randomization to the date of deterioration. Deterioration is defined as change from baseline that reaches a clinically meaningful deterioration threshold. Anchor-based methods using the participant-based anchors PGIS and PGIC will be considered to define thresholds for clinically meaningful within-participant change used in the TTD endpoints. Other methods including distribution-based methods, cumulative distribution function, and probability density function curves, and methods using other anchors may also be considered.

Clinically meaningful thresholds will be estimated for the following patient-reported outcomes:

- EORTC QLQ-C30: Global health status/QoL, functioning, and select symptom subscales including pain and fatigue
- EORTC QLQ IL116: breast symptoms, arm symptoms.

The analysis to define clinically meaningful change thresholds in the TTD PRO endpoints will include all randomized participants using the pooled treatment arms data prior to database lock. These TTD PRO endpoints will be analyzed using the same time-to-event analysis methodology described in Section 9.4.2.1.2.

Details of all statistical analyses, including analyses for other exploratory PRO endpoints, will be described in full in the SAP.

9.4.2.2.9 Pharmacokinetics

Dato-DXd, total anti-TROP2 antibody, and MAAA-1181a PK concentrations will be listed and summarized by visit and scheduled time point. Non-compartment PK parameters that can be derived with sparse PK sampling, such as peak and trough concentrations, will be reported as data allows. Details of those analysis will be described in SAP. Population PK, and exploratory exposure response/safety analyses will be performed. A separate modeling analysis plan will be written before the database lock. The population PK analysis and exploratory exposure response/safety analysis will be presented separately from the main CSR.

9.4.2.2.10 Immunogenicity

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 titer and neutralizing ADA data will be listed for samples confirmed positive for the presence of anti-Dato-DXd antibodies.

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

9.4.2.3 Exploratory Endpoints

Details of all statistical analyses for exploratory endpoints (including biomarkers, PRO, and medical resource utilization) will be described in full in the SAP.

9.4.2.3.1 Biomarkers

Biomarker status will be assessed for participants in each treatment group according to pre-specified criteria that may be detailed in the SAP. The relationship of biomarker expression and, if applicable, of exploratory biomarkers to clinical outcomes (including but not restricted to) of PFS, ORR, and OS may be presented. Biomarker exploratory analyses may be described in a separate analysis plan and may be reported outside the CSR in a separate report. The results of this biomarker assessment will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

The results of this biomarker assessment may be pooled with biomarker data from other studies with the study intervention to generate hypotheses to be tested in future research.

9.4.2.3.2 Medical Resource Utilization and Health Economics

To investigate the impact of treatment and disease on health care resource use, the following variables will be captured:

- Planned and unplanned hospital attendances beyond protocol-mandated visits (including physician visits, emergency room visits, day cases, and admissions)
- Primary sign or symptom the participant presents with
- Length of hospital stay, per stay
- Length of any time spent in an intensive care unit
- Procedures and tests

Where admitted overnight, the length of hospital stay will be calculated as the difference between the date of hospital discharge (or death date) and the start date of hospitalization or start of study intervention if the start of study intervention is after start date of hospitalization (length of hospital stay = end date of hospitalization – start date of hospitalization + 1). Participants with missing discharge dates will be calculated as the difference between the last day with available data and the start date of hospitalization. The length of intensive care unit

stay will be calculated using the same method.

Analysis Methods

The potential impact of the disease and treatment on health care resource use will be analyzed for the purposes of submissions to payers. Descriptive statistics (as appropriate, including means, median, ranges or frequencies, and percentages) will be provided for each treatment group on the different types of hospital admissions, the length of stay for participants admitted to hospital for at least 1 overnight stay, and the length of stay for participants admitted to intensive care/high dependency units, as well as the primary sign or symptom the participant presents with.

9.4.3 Safety

Safety summaries will be provided using the SAS. 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

Adverse events will be coded using the most recent version of MedDRA that will be released for execution at AstraZeneca, and graded using NCI-CTCAE v5.0.

The following adverse events are considered treatment emergent:

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

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

Adverse events will be presented for each treatment group by System Organ Class, HLT and/or PT covering number and percentage of participants reporting at least one event and number of events where appropriate.

An overview of AEs will present for each treatment group the number and percentage of

participants with any AE, AEs with outcome of death, serious AEs, and AEs leading to discontinuation of study intervention, as well as AEs leading to study intervention dose interruptions, AEs leading to study intervention dose reduction and AEs leading to withdrawal from study as well as the number of individual occurrences in those categories.

Treatment emergent adverse events will be presented for each treatment group by System Organ class and/or PT covering number and percentage of participants reporting at least one event and number of events where appropriate.

Separate AE tables will be provided taken into consideration relationship as assessed by the investigator, maximum CTCAE grading, seriousness, death and events leading to discontinuation of study intervention, as well as other action taken related to study intervention, and AESIs.

Key participant information will be presented for participants with AEs with outcome of death, SAEs, and AEs leading to discontinuation of study intervention.

An AE listing for the safety analysis set will cover details for each individual AE.

Full details of AE analyses will be provided in the SAP.

Vital signs

Vital sign parameters will be presented for each treatment group.

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.

Laboratory parameters

Laboratory parameters will be presented for each treatment group.

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

Elevation in liver parameters for assessment of Hy’s Law will be reported appropriately.

A shift table for urinalysis will be presented with baseline assessment against the maximum on treatment 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 endpoint analyses

Details of analyses of urinalysis, ECGs, and ECHOs/MUGAs will be specified in the SAP.

9.4.4 Other Analyses

9.4.4.1 Optional Exploratory Genetic Sample

Data will be reported outside the CSR (please see Appendix D).

9.4.4.2 Ophthalmologic Analysis

See Section 8.2.5.5. Details will be specified in the SAP.

9.5 Interim Analyses

Two interim analyses for OS are planned. The first OS interim will occur at the primary PFS analysis (approximately 40% of target OS events) and the second when approximately 80% of the target OS events have occurred. The Lan DeMets approach (Lan and DeMets 1983) that approximates the O'Brien and Fleming spending function will be used to maintain an overall 2-sided type I error across the three planned analyses of OS. If the PFS dual primary analysis crosses the efficacy threshold, the 1.0% type I error allocated to the PFS endpoint will be reallocated to the OS endpoint for a total 2-sided type I error of 5.0%. Details of the planned timing of the two interim and final analyses are provided in Table 11. Note that the actual allocation of alpha across the three analysis times will be driven by the actual information fraction associated with the analysis.

The interim analyses will be performed by an IDMC. It is expected that recruitment will have completed prior to the results of the interim analyses being available. For the interim analyses, the IDMC will review unblinded interim data and inform the sponsor whether the interim boundaries specified in Table 11 are met.

Table 11 Summary of planned timings of the interim and final OS analyses

	Interim Analysis 1		**Interim Analysis 2**		**Primary Analysis**	
Projected Timing	21 Months [b]		34 Months		44 Months	
Number of Deaths [a]	178		355		444	
Information Fraction	40%		80%		100%	
Maturity	25%		51%		63%	
Recommendation	**Continue**	**Reject Null Hypothesis**	**Continue**	**Reject Null Hypothesis**	**Do Not Reject Null Hypothesis**	**Reject Null Hypothesis**
At 4.0% 2-sided alpha [c]						
2-sided nominal p-value	≥ 0.0005	< 0.0005	≥ 0.0184	< 0.0184	≥ 0.0345	< 0.0345

Table 11 Summary of planned timings of the interim and final OS analyses

	Interim Analysis 1		Interim Analysis 2		Primary Analysis	
Estimated hazard ratio	≥ 0.591	< 0.591	≥ 0.777	< 0.777	≥ 0.817	< 0.817
At 5.0% 2-sided alpha [c]						
2-sided nominal p-value	≥ 0.0008	< 0.0008	≥ 0.0241	< 0.0241	≥ 0.0427	< 0.0427
Estimated hazard ratio	≥ 0.604	< 0.604	≥ 0.786	< 0.786	≥ 0.824	< 0.824

[a] Estimates based on exponential survival where the median OS is 19.0 months for ICC and 25.3 months for Dato-DXd. The total proportion of participants randomized at time t [t ≤ 19 months] following the start of the study is assumed to be $(t/19)^{1.5}$.
[b] Timing of first IA based on PFS. Number of deaths is an estimate.
[c] Alpha allocated to OS endpoint (4.0% or 5.0%) dependent on statistical significance of PFS.

The study may continue monitoring participants for OS up to the scheduled final analysis, beyond planned interim analyses, to provide more refined estimates of treatment effects for survival.

The first IA for OS will occur at the time of the PFS analysis. If 40% of the target OS events (178/444) are available at the time of the first OS IA, then the largest (nominal) 2-sided p-value that will cross the efficacy threshold is 0.0008. If the first interim results do not meet the criterion for rejecting the null hypothesis in the ITT population, then follow-up will continue until at the criteria are met for the second OS IA. The second OS IA is planned when approximately 80% of target OS events (355/444) are available. The largest (nominal) 2-sided p-value that will cross the efficacy threshold is 0.0241 based on the expected timing of the second IA. If the interim results do not meet the criterion for rejecting the null hypothesis in the ITT population, then follow-up will continue until the criteria is met for the for OS primary analysis. The OS primary analysis will be performed when 444 OS events are observed, and the nominal 2-sided p-value will be 0.0427 based on the expected timing of the second IA. Note that the p-value boundaries reported in this paragraph presume that 5.0% type I error is available for the OS analysis.

If the PFS primary analysis does not cross the efficacy threshold, the total 2-sided type I error allocated to the OS analyses will be 4.0%. For the 2 interim and primary analyses of OS, based on the expected number of events at each analysis, the nominal 2-sided p-values associated with the three analyses times are 0.0005, 0.0184, and 0.0345, respectively.

The SAP will describe the planned interim analyses in greater detail.

9.6 Data Monitoring Committees

9.6.1 Independent Data Monitoring Committee

An IDMC comprised of independent experts will convene and will meet approximately 6 months after the study has started. The IDMC will review unblinded safety data and make

recommendations on whether the study should continue, be amended, or stopped based on safety findings. In addition, the IDMC may be requested to review efficacy data. For the interim analyses, the IDMC will review unblinded interim data and inform the Sponsor whether the interim boundaries specified in Section 9.5 are crossed.

Full details of the IDMC communications, procedures, processes, and interim analyses will be presented in the IDMC Charter.

9.6.2 ILD Adjudication Committee

An independent ILD Adjudication Committee for the Dato-DXd program is responsible for reviewing all cases of potential ILD/pneumonitis. To ensure adequate and relevant independent evaluation, systematic additional data collection will be conducted for all cases that will be brought for adjudication. These additional data collections will cover a more in-depth relevant medical history (eg, smoking, radiation, COPD and other chronic lung conditions), diagnostic evaluation, treatment and outcome of the event. This data collection will be triggered based on a pre-defined list of PTs eligible for adjudication as described in the Event Adjudication Site Manual. Further details can be found in the ILD Adjudication Charter.

9.6.3 Ophthalmologic Data Review Committee

An independent Ophthalmologic Data Review Committee is responsible for reviewing the data from baseline, periodic and end of therapy ophthalmologic assessments. This data collection will be triggered based on a pre-defined list of PTs eligible for review. Further details will be available in the Ophthalmologic Data Review Committee Charter.

9.7 Mainland China Cohort

The global cohort will enrol approximately 1000 participants to randomize approximately 700 participants. The mainland China cohort will consist of approximately an additional 20 randomized participants in mainland China. The global cohort will consist of participants recruited by the documented date of the last participants randomized of the global cohort. Participants randomized in the mainland China cohort prior to the last participants randomized of the global cohort enrolment will be included in both the ITT and the mainland China ITT. Participants randomized in the mainland China cohort after the last participants randomized of the global cohort enrolment will be included only in the mainland China ITT. The mainland China ITT will include all participants randomized in the mainland China cohort including those who were recruited prior to the closure of the global cohort and are therefore included in the analyses of efficacy and safety for the main study. The mainland China safety analysis set will consist of all participants included in the mainland China ITT who received at least 1 dose of study treatment.

Per NMPA guidance, in addition to the evaluation of the global cohort data for primary, secondary and safety objectives, evaluation of consistency in efficacy and safety in Chinese

populations is required to facilitate the benefit-risk assessment for mainland Chinese participants. Hence, the safety and efficacy data in the mainland China cohort will be analyzed separately where the same endpoint definitions and the same analysis methods are applied.

Details of the mainland China cohort analyses will be specified in the SAP.

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 protocol 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 protocol, protocol 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 protocol 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 authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a Contract Research Organization 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 21CFR 312.120, ICH guidelines, the IRB/IEC, and the European Regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of a 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 utilizing 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 EU CT Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- 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 (email 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 1 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 authorized 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 authorized 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 center.

- 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 authorized 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 authorized representative.

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

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 which 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 authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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 protocol.

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. For additional details see Section 9.6.1.

A 6 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com, http://www.clinicaltrials.gov, and https://www.clinicaltrialsregister.eu as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 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.
- The sponsor 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 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 clinical reviews of study data from a medical perspective, and handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided 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, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized 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 protocol 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.
- 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 act of recruitment is the first site open 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 protocol, 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 Contract Research Organization(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 multicenter studies only in their entirety and not as individual site data. In this case, a coordinating 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 and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable 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 hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

AEs for **malignant tumors** 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 tumor event should be assessed and reported as a **Non-Serious** AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, 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 tumor event in question is a new malignant tumor (ie, it is *not* the tumor 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 tumor under study). Malignant tumors that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

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).

Hospitalization

Outpatient treatment in an emergency room is not in itself a 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, hospitalization, disability or incapacity but may jeopardize 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 anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Intensity rating scale:

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

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 etiology such as the underlying disease, other drugs, 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 re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized 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, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP 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 recognized that could have led to an error.

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

- Drug name confusion.
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant.
- Drug not administered as indicated, eg, 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 refrigerator when it should be at room temperature.

- Wrong participant received the medication (excluding IRT errors).
- Wrong drug administered to participant (excluding IRT errors).

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

- Errors related to or resulting from IRT - including those which 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 IMP/study intervention or AstraZeneca NIMP 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 Data Entry Site 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 drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug 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 (by a study participant) of IMP/study intervention or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs/study interventions or AstraZeneca NIMPs, outside the intended use as specified in the protocol, and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site 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 drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that they were feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug.

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 center keeps full traceability of collected biological samples from the participants while in storage at the center 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 life cycle 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 life cycle. 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 analyzed, 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 protocol.

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

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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, 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
- are to be packed in accordance with UN3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which 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/contentassets/b08040a138dc4442a4f066e6fb99fe2a/dgr-62-en-pi650.pdf).

- Biological samples transported in dry-ice require additional dangerous goods specification for the dry-ice content.

Appendix D Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant's DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on Dato-DXd continues but no longer than 15 years from the end of the study (as defined in the protocol) or other period as per local requirements.

D 2 Genetic Research Plan and Procedures

Selection of genetic research population

- All participants will be asked to participate in this genetic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion criteria

For inclusion in this genetic research, participants must fulfil all of the inclusion criteria described in the main body of the CSP and provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Previous allogeneic bone marrow transplant.
  - Transfusion of non-leukocyte depleted blood or blood component within 120 days of genetic sample collection.

Withdrawal of consent for genetic research

Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main CSP.

Collection of samples for genetic research

The blood sample for this genetic research will be obtained from the participants pre-dose at the first dosing visit. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at the first dosing visit, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and storage of DNA samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples may be stored for a maximum of 15 years from the end of the study (as defined in the protocol), after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).
- The link between the participant enrolment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed consent

The genetic component of this study is optional, and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study the participant must sign and date both the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study center. The principal investigator(s) is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant data protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, general physician, or any other third party unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca physician or an investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyze the samples.
- AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organizations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results, but they will not be able to see individual participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical methods

The number of participants that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal

statistical evaluation or whether only descriptive statistics will be generated. An SAP may be prepared where appropriate.

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

E 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.

Specific guidance on managing liver abnormalities can be found in the TMGs (see the Annex document to this CSP).

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 potential 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.

E 2 Definitions

Potential Hy's Law (PHL)

AST 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.

Hy's Law (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, 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.

E 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 E 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

E 4 Follow-up

E 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.

E 4.2 Potential Hy's Law Criteria Met

If the participant does meet PHL criteria the investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.

- Within 1 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 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 physician contacts the investigator, to provide guidance, discuss and agree an approach for the study participant's 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 etiology of the event and perform diagnostic investigations as discussed with the study physician.
  - 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 physician if there is any uncertainty.

E 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 physician 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 were 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 a 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:

- Provide 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 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 amend the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 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 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 central Study Team, then follow the subsequent process described in Section E 4.2.

E 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 E 6 of this Appendix?

If No: follow the process described in Section E 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 E 4.2 for reporting PHL as an SAE.

E 8 Laboratory Tests

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.

Tests to Further Evaluate Increases in Liver Biochemistry and Hy's Law

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
Alcoholic hepatitis	Carbohydrate-deficient transferrin [b]
Autoimmune hepatitis	Antinuclear antibody Anti-liver/kidney microsomal antibody Anti-smooth muscle antibody
Metabolic diseases	Alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin [b] 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 = immuno-globulin G; IgM = immuno-globulin M; INR = international normalized ratio; LDH = lactate dehydrogenase; RNA = ribonucleic acid.

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

[b] Carbohydrate-deficient transferrin and transferrin are not available in mainland China.

E 9 References

Aithal et al 2011
Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther 2011;89(6):806-15.

FDA Guidance 2009
Food and Drug Administration. Guidance for industry: Drug-induced liver injury:

premarketing clinical evaluation. July 2009. Available from: URL: https://www.fda.gov/downloads/guidances/UCM174090.pdf. Accessed 08 October 2019.

Appendix F Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)

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.

Additional special guidance is provided for evaluation of scans collected after a RECIST 1.1-defined radiological progression.

Imaging modalities and acquisition specifications for RECIST 1.1

A summary of the imaging modalities that can be used for tumor assessment of TLs, NTLs and NLs is provided in Table 12.

Table 12 Summary of Imaging Modalities for Tumor Assessment

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

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

Computed Tomography and Magnetic Resonance Imaging

CT 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 tumor 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, tumor assessor (eg, radiologist), and method of tumor 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/tumor assessment schedule as closely as possible (refer to the SoA; Table 1), 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 tumor evaluation are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

a. Anatomic coverage: Optimal anatomic coverage for most solid tumors is the chest-abdomen-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 tumor measurements but also identification of new disease.

Required anatomical regions to be imaged for assessment of tumor 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 (Table 1). Examples include the following:

- IV 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).
- IV contrast-enhanced CT or MRI of the head and neck.
- IV 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:

6 Chest-abdomen-pelvis CT with IV CT contrast (most preferred).

7 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.

8 Chest-abdomen-pelvis CT without IV contrast, if both IV CT and MRI contrast are medically contraindicated or the participant has compromised renal function.

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

b. IV contrast administration: Optimal visualization and measurement of metastases in solid tumors 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 tumor 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 visualize 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.

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.

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.

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.

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

^{18}F-fluoro-deoxyglucose positron emission tomography(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 on 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 tumor 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 tumor 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.

Ultrasound

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

Other tumor assessments

Clinical examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will

[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.

not be used for RECIST 1.1 assessments. Tumors identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

Endoscopy and laparoscopy

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

Histology and cytology

Histology or tumor markers on tumor biopsy samples will not be used as part of the tumor 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 tumor 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.

Measurability of tumor lesions at baseline

RECIST 1.1 measurable lesions at baseline

A tumor 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[1] 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.

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.

[1] The short axis is defined as the longest in-plane axis perpendicular to the long axis.

- 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).[1]
- Previously irradiated lesions.[2]
- Brain metastasis.

Special considerations regarding lesion measurability at baseline

- Bone lesions:
  - Bone scan, PET scan, or plain X-ray 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.

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

---

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

[2] Localized 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.

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 millimeters. 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.

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.
- Tumor 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.

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.

Evaluation of tumor response and progression

RECIST 1.1 TL assessment at follow-up

This section defines the criteria used to determine objective tumor visit response for RECIST 1.1-defined TLs. 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 millimeters. 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 1 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.
- When a TL has had any intervention (eg, definitive radiotherapy, embolization, surgery, transarterial chemoembolization, 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 13 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.

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. 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 tumor burden has increased sufficiently to merit unequivocal progression by NTLs. A modest "increase" in the size of 1 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 14 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 1 or more NTLs.
PD	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in 1 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 1 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.

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 1 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 tumor. If a NL is equivocal, for example because of its small size, the treatment and tumor 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 a NL and will indicate PD.

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 15.

Table 15 RECIST 1.1 Overall Visit Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Visit Response
CR	CR	No	CR
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	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; 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 tumor disease at baseline:

- For participants with TLs (at baseline): CR, PR, SD, PD, or NE.

Central imaging

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed imaging Contract Research Organization (iCRO) for quality control, storage, and for BICR. 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. A BICR 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 tumor assessments will not be shared with the central reviewers.

The management of participants will be based in part upon the results of the tumor assessments conducted by the investigator. Further details of the BICR will be documented in an Independent Review Charter.

F 1 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 G Contraception Requirements

Contraception requirements for this study are as follows.

G 1 Female Participants

Women not of childbearing potential are defined as those who are surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or who are post-menopausal.

Women will be considered post-menopausal if they have been amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women < 50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all hormonal replacement therapy and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution, or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
- Women ≥ 50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all hormonal replacement therapy, or had radiation-induced menopause with last menses > 1 year ago, or had chemotherapy-induced menopause with last menses > 1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

Women of childbearing 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-sterilized male partner must use at least 1 highly effective method of contraception (Table 16). They should have been stable on their chosen method of birth control starting at a minimum of 3 months before C1D1 and continue to use it throughout the total duration of the drug treatment and the drug washout period (7 months after the last dose of study intervention).

Non-sterilized male partners of a woman of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial. Female participants should refrain from breastfeeding throughout this period. Women must not donate, or retrieve for their own use, ova from the time of screening and throughout the study treatment period, and for at least 7 months after the final study drug administration. Preservation of ova should be considered prior to enrolment in this study.

G 2 Male Participants with a Female Partner of Childbearing Potential

Non-sterilized male participants (including males sterilized 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 (ie, at least 4 months after the last dose of study intervention) 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, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male participants should refrain from sperm donation or banking throughout the drug washout period. Preservation of sperm should be considered prior to enrolment in this study.

Vasectomized (ie, sterile) males are considered fertile 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 fetus from drug in ejaculate.

Female partners (of childbearing potential) of male participants must also use a highly effective method of contraception throughout this period (Table 16).

G 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 16. 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 16 Highly Effective Methods of Contraception (< 1% Failure Rate)

Non-Hormonal Methods	Hormonal Methods[b]
• Total sexual abstinence (evaluate in relation to the duration of the clinical study and the preferred and usual lifestyle choice of the participant) • Vasectomized sexual partner (with participant assurance that partner received post-vasectomy confirmation of azoospermia) • 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.
[b] Hormonal methods of contraception must not be used by female patients participating in this study; this information is meant for female partners of male participants.

For participants in the ICC (eribulin, capecitabine, vinorelbine, or gemcitabine) group: Follow the local Prescribing Information relating to contraception, the time limits for such precautions, and any additional restrictions required for the specific ICC agent.

Appendix H Patient-reported Outcomes

H 1 EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

SPECIMEN

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

© Copyright 1995 EORTC Quality of Life Group. All rights reserved. Version 3.0

SPECIMEN

H 2 EORTC IL116

ENGLISH

EORTC IL116

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
1.	Have you had any pain in your arm or shoulder?	1	2	3	4
2.	Have you had a swollen arm or hand?	1	2	3	4
3.	Have you had problems raising your arm or moving it sideways?	1	2	3	4
4.	Have you had any pain in the area of your affected breast?	1	2	3	4
5.	Has the area of your affected breast been swollen?	1	2	3	4
6.	Has the area of your affected breast been oversensitive?	1	2	3	4
7.	Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4

SPECIMEN

© Copyright 2021 EORTC Quality of Life Group. All rights reserved.

H 3 PRO-CTCAE

NCI PRO-CTCAE ™ ITEMS

Item Library Version 1.0

English

Form Created on 01 April 2021

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days…

1a. In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
1b. In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

2a. In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
2b. In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
O Not at all	OA little bit	O Somewhat	O Quite a bit	O Very much

3a. In the last 7 days, how OFTEN did you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
3b. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

4a. In the last 7 days, how OFTEN did you have VOMITING?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
4b. In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

5a. In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

The PRO-CTCAE™ items and information herein were developed by the Division of Cancer Control and Population Sciences in the NATIONAL CANCER INSTITUTE at the NATIONAL INSTITUTES OF HEALTH, in Bethesda, Maryland, U.S.A. Use of the PRO- CTCAE™ is subject to NCI's Terms of Use.

6a. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly

7a. In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
7b. In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
7c. In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

8a. In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
8b. In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

9a. In the last 7 days, what was the SEVERITY of your COUGH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
9b. In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

10a. In the last 7 days, did you have any RASH?	
O Yes	O No

11a. In the last 7 days, did you have any HAIR LOSS?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

12a. In the last 7 days, what was the SEVERITY of your HAND-FOOT SYNDROME (A RASH OF THE HANDS OR FEET THAT CAN CAUSE CRACKING, PEELING, REDNESS OR PAIN) at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

The PRO-CTCAE™ items and information herein were developed by the Division of Cancer Control and Population Sciences in the NATIONAL CANCER INSTITUTE at the NATIONAL INSTITUTES OF HEALTH, in Bethesda, Maryland, U.S.A. Use of the PRO- CTCAE™ is subject to NCI's Terms of Use.

13a. In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
13b. In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

14a. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
14b. In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

The PRO-CTCAE™ items and information herein were developed by the Division of Cancer Control and Population Sciences in the NATIONAL CANCER INSTITUTE at the NATIONAL INSTITUTES OF HEALTH, in Bethesda, Maryland, U.S.A. Use of the PRO- CTCAE™ is subject to NCI's Terms of Use.

H 4 EORTC IL117

ENGLISH

EORTC IL117

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
1.	Have your eyes been dry?	1	2	3	4
2.	Have you had pain in your mouth?	1	2	3	4
3.	Have you had soreness in your mouth?	1	2	3	4

SPECIMEN

© Copyright 2021 EORTC Quality of Life Group. All rights reserved.

H 5 PGI-TT

PATIENT GLOBAL IMPRESSION OF TREATMENT TOLERABILITY (PGI-TT)

In the last 7 days, how bothered were you by the side effects of your cancer treatment?
☐ Not at all
☐ A little bit
☐ Somewhat
☐ Quite a bit
☐ Very much

H 6 PGIS

Patient Global Impression of Severity - Cancer (PGIS-Cancer-4-Item)

Please select the response below that best describes the severity of your overall cancer symptoms over the past 7 days.

Please select one response only

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe

H 7 PGIC

PATIENT GLOBAL IMPRESSION OF CHANGE - GENERIC (PGIC-GENERIC)

Overall, how would you rate the change in your health status since starting this study?

Please select one response only

- ☐ Much better
- ☐ Moderately better
- ☐ A little better
- ☐ About the same
- ☐ A little worse
- ☐ Moderately worse
- ☐ Much worse

H 8 EQ-5D-5L

Health Questionnaire

English version for the UK

Sample

© 2009 EuroQol Research Foundation. EQ-5D™ is a trade mark of the EuroQol Research Foundation. UK (English) v1.2

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

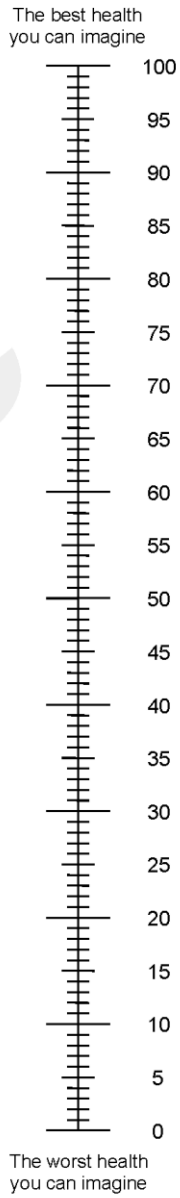
I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

© 2009 EuroQol Research Foundation. EQ-5D™ is a trade mark of the EuroQol Research Foundation. UK (English) v1.2

Sample

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Sample

3

© 2009 EuroQol Research Foundation. EQ-5D™ is a trade mark of the EuroQol Research Foundation. UK (English) v1.2

Appendix I Concomitant Medications

I 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.

I 2 Restricted, Prohibited, and Permitted Concomitant Medications/Therapies

Restricted, prohibited, and permitted concomitant medications/therapies are described in Table 17, Table 18, and Table 19. Refer also to the TMGs in the Annex document to this CSP. Participants must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

Table 17 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 should be recorded in the eCRF.
Palliative radiotherapy	Permitted for optimal symptom control or pain management. Delay Dato-DXd therapy for the duration of radiotherapy and restart at least 2 weeks after completion of radiotherapy. Curative radiotherapy is not permitted.

With the exception of medications that are under investigation in the study (ie, standard of care, comparators, or combination therapies), the medications, treatment and procedures in Table 18 will be prohibited during the treatment period. The Sponsor must be notified if a participant receives any of these during the study.

Table 18 Prohibited medications/therapies

Prohibited medication/class of drug/therapy	Usage
Chloroquine or hydroxychloroquine	Concomitant treatment with chloroquine or hydroxychloroquine is not allowed during the study treatment. If treatment with chloroquine or hydroxychloroquine treatment is absolutely required, study intervention must be interrupted. If chloroquine or hydroxychloroquine is administered, then a washout period of at least 14 days is required before restarting study intervention (see Appendix J for more details).
Any concurrent anticancer therapy, including cytotoxic, targeted agents, immunotherapy, antibody, retinoid or radiotherapy (except palliative radiotherapy to areas other than chest, after consultation with the sponsor study physician) or hormonal therapy for cancer treatment.	Must not be given concomitantly while the participant is on study intervention. Concurrent use of hormones for noncancer-related conditions (eg, insulin for diabetes and topical hormone replacement therapy) is acceptable.
Concomitant use of chronic systemic (IV or oral) corticosteroids or other immunosuppressive medications except for managing AEs; inhaled steroids, intra-articular steroid injections, and other topical steroid formulations are permitted in this study. Corticosteroid mouthwash formulations are permitted to prevent and manage certain AEs.	Dato-DXd cannot be administered when the participant is taking immunosuppressive medications, including corticosteroids with the exception of: • short-term courses (<2 weeks) • doses less than 10mg/day of prednisone or equivalent • 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. A temporary period of steroid treatment will be allowed for different indications after discussion with the sponsor study physician (eg, COPD, radiation, nausea, etc). Participants with bronchopulmonary disorders who require intermittent use of bronchodilators (eg, albuterol) will not be excluded from this study. 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 Annex document to this CSP). Immunosuppressive medications also include drugs like methotrexate, azathioprine, and tumor necrosis factor-alpha blockers.
Other investigational therapeutic agents	Must not be given concomitantly while the participant is on study intervention.

Table 19 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.
Prophylactic anti-emetic agents for Dato-DXd	Based on currently available clinical safety data, it is highly recommended that participants receive prophylactic anti-emetic agents prior to infusion of Dato-DXd and on subsequent days. Antiemetics such as 5-HT3 antagonists and steroids (eg, dexamethasone) should be considered and administered in accordance with the prescribing information or institutional guidelines. NK1 receptor antagonists can be used, if needed.
Prophylactic/supportive stomatitis/oral mucositis agents	Recommended that dexamethasone oral solution be strongly considered for prophylaxis as well as treatment of stomatitis/oral mucositis.
Bisphosphonates, denosumab	Permitted for the treatment of bone metastasis.
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive treatment and AE management, except for those medications identified as "prohibited," as listed above	As per TMGs, institutional guidelines and investigator's discretion. To be administered as prescribed by the investigator except for those medications identified as "prohibited," as listed in Table 18.
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, etc.]) 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 18.
Dietary supplements, medications not prescribed by the investigator, and alternative/complementary treatments	Concomitant use is discouraged, but not prohibited.
Intermittent use of bronchodilators (eg, albuterol)	Participants with bronchopulmonary disorders who require this medication will not be excluded from this study.
Inhaled steroids, intra-articular steroid injections, and other topical steroid formulations	Permitted.
Required for management of other medical conditions	As required except for those identified as "prohibited," as listed in Table 18.

Appendix J Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

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 SARS-CoV-2 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.

J 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 the sections below. 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.

J 2 Rescreening of Participants to Reconfirm Study Eligibility

An extended rescreening period will be allowed for participants that are affected by study disruptions, that have already screen failed and entered rescreening. 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 Table 1**,** the participant will be allowed to remain in screening until reconfirmation of eligibility before commencing study procedures. The procedures detailed in Table 1 must be undertaken to confirm eligibility using the same E-code as initially assigned to the participant.

J 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 clinical study protocol (CSP).

J 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 targeted physical examination to be reported and documented. Site personnel to also ensure that ePROs are being completed by participant as per SoA.

J 5 Data Capture During Telemedicine Visits (where applicable)

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP (or site delegate) from the study site or TPV service in the source documents.

Appendix K Protocol Version History

The Summary of Changes Table for the current revision is located directly before the TOC.

Amendment 3 (10 October 2022)

Overall Rationale for the Amendment:

The overall rationale for the amendment is to provide flexible language for the inclusion of a mainland China-specific recruitment tail, if required, for regulatory submission purposes, as well as alignment with the latest Dato-DXd program standards.

Other important administrative and operational clarifications have also been made.

The rationale for each of these changes is provided in the table below:

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 1.1, Synopsis, Number of Participants, Statistical Methods Section 4.1, Overall Design	Updated to include possibility of a mainland China cohort.	If required for regulatory submission purposes, the recruitment of participants in mainland China may continue beyond the close of the global cohort.	Non-Substantial
Section 1.2, Schema	Clarified requirement for patient to have progressed on **and** not be suitable for endocrine therapy, in accordance with existing eligibility criteria.	Typographical correction.	Non-substantial
Section 1.3, Schedule of Assessments, Table 1 Section 8.2.5.1, Echocardiogram/Multigated Acquisition Scan	Removed requirement to do an ECHO or MUGA scan to assess LVEF at EoT visit. Updated footnote “i” to clarify that an ECHO or MUGA may be done at EoT visit, if clinically indicated.	To align with AstraZeneca Dato-DXd program standards, the ECHO/MUGA scan is not required at EoT visit unless clinically indicated.	Non-substantial
Section 1.3, Schedule of Assessments, Table 1 Section 8.2.4, Table 7	Removed requirement to do coagulation tests at screening.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 1.3, Schedule of Assessments, Table 1	Added optional bronchoalveolar lavage and lung biopsy sample on diagnosis of suspected ILD/Pneumonitis into SoA.	Administrative clarification, as collection of this sample was previously omitted from the SoA.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 1.3, Schedule of Assessments, Table 1	Updated footnote "a" to ensure the safety follow-up visit is performed 28 (+7) days after the last study intervention administration regardless of participant starting new anticancer treatment.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 1.3, Schedule of Assessments, Table 1	Updated footnote "q" to specify prior HIV serology, HBV serology, and HCV serology test results can still be used if performed within 120 days of enrolment.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 1.3, Schedule of Assessments, Table 1	Updated footnote "r" to specify that participants must be tested for HIV if applicable by local regulations or an IRB/EC.	Administrative clarification.	Non-substantial
Section 5.2, Exclusion Criteria #5	Updated text to clarify circumstances where patients may still be eligible with respect to hepatitis B or C.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 5.2, Exclusion Criteria #6	Updated definition of well controlled HIV infection. Clarified recommendation to monitor viral RNA load and CD4+ count, and that participants must be tested for HIV if acceptable by local regulations or an IRB/EC.	To align with AstraZeneca Dato-DXd program standards.	Substantial
Section 6.5, Concomitant Therapy	Added requirement for all concomitant medications administered during the study to be recorded until the end of the safety follow up period and those administered for drug-related AESIs to be recorded in the eCRF as required.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 6.6, Dose Modification	Clarified dose delay allowance.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 8.2.4, Clinical Safety Laboratory Assessments Section 8.3.6, Hy's Law E2 Definitions, E3 Identification of Potential Hy's Law Cases	Corrected typo in Hy's Law criteria from TBL > 2 ULN to TBL ≥ 2 ULN.	Typographical correction.	Non-substantial
Section 8.3.1, Time Period and Frequency for Collecting AE and SAE Information	Added Grade ≥ 2 keratitis events to list of AEs to be reported by the investigator in eCRF within 24 hours of awareness.	To align with AstraZeneca Dato-DXd program standards.	Substantial
Section 8.3.6, Hy's Law	Removed reference to Section 8.3.11 as Hy's Law event is no longer considered an AESI.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 8.3.11, Adverse Events of Special Interest	Clarified that all AESIs must be followed until either event resolution, end of study, trial termination, withdrawal of consent, or participant death.	Administrative clarification.	Non-substantial
Section 9.3, Table 9, Population for Analysis	Updated table to specify that participants in the mainland China cohort will be excluded from ITT population. Additional changes to clarify SAS, OAS, and PAS will be comprised of participants in the ITT population.	Included as part of flexible language to allow for mainland China tail, if required.	Non-substantial
Section 9.4.2.2.9, Pharmacokinetics	Corrected substrate name from MAAA-1191a to MAAA-11**8**1a.	Typographical correction.	Non-substantial
Section 9.7, Mainland China Cohort	Summarized details of mainland China cohort.	If required for regulatory submission purposes, the recruitment of participants in mainland China may continue beyond the close of the global cohort.	Non-substantial
Appendix I, Table 19, Supportive Medications/therapies	Clarified recommendation for usage of prophylactic anti-emetic agents.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Throughout CSP	Clarified that 'China' refers to mainland China.	To align with China R&D preferred terminology.	Non-substantial

Amendment 2 (19 April 2022)

Overall Rationale for the Amendment:

The overall rationale for the amendment is to provide additional guidance for investigators after the annual update of the Dato-DXd Investigator's Brochure v6.0. The Toxicity Management Guidelines includes further details on management of ocular surface toxicities, and are now located in an Annex document. Adverse Events of Special Interest no longer include "combined elevations of aminotransferase and bilirubin", and stomatitis/mucosal inflammation have been separated into "oral mucositis/stomatitis" and "mucosal inflammation other than oral mucositis/stomatitis."

Other administrative and operational clarifications have also been made.

The rationale for each of these changes is provided in the table below:

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 1.1, Synopsis, Participant Population Section 5.1, Inclusion Criteria #1	Removed requirement for participants in Japan to be ≥ 20 years.	Update to the civil code for age of adulthood in Japan.	Substantial
Section 1.1, Synopsis, Intervention Groups and Duration Section 4.1, Overall Design Section 9.4.2.1.5, Subgroup Analysis	Added Canada as a Region 1 country.	Administrative clarification.	Non-Substantial
Section 1.1, Synopsis, Follow-up of Participants Post Discontinuation of Study Intervention	Added that the EoT assessments can function as the Safety Follow-up visit if the date of discontinuation is over 35 days from the last administration of study intervention.	Administrative clarification.	Non-substantial
Section 1.3, Schedule of Assessments, Table 1	Added ePRO training and set up.	Administrative clarification.	Non-substantial
Section 1.3, Schedule of Assessments, Table 1	Updated footnote "d" so that safety assessments do not have to be repeated if they have been performed within 72 hours prior to the day of dosing.	To allow flexibility in patient management without compromising safety.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 1.3, Schedule of Assessments, Table 1 Section 5.1, Inclusion Criteria #14	Updated footnote "p" and added clarification that a serum pregnancy test should be negative at screening and.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 1.3, Schedule of Assessments, Table 1 Section 6.3, Participant Enrolment and Randomization	Updated footnote "q" and Section 6.3.1 to be consistent with Exclusion Criterion #5.	Administrative clarification.	Non-substantial
Section 1.3, Schedule of Assessments, Table 1 Section 8.1.1, Imaging Tumor Assessments	Updated footnote "x" and added clarification of abdomen imaging.	To align with AstraZeneca program standards.	Non-substantial
Section 1.3, Schedule of Assessments	Table 2 added detailing the assessments to be performed in the event of suspected ILD/pneumonitis.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 2.2.1, HR-positive, HER2-negative, inoperable/metastatic breast cancer	Added baseline characteristics/factors which could be relevant to the target study population.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 2.2.2.1, TROPION-PanTumor01 study Section 2.3.3, Overall Benefit: Risk Conclusion	Updated safety and efficacy data from the DS1062-A-J101 study.	To align with latest Dato-DXd Investigator Brochure.	Non-substantial
Section 2.3.1.1, Dato-DXd, Table 3 Section 8.3.11, Adverse Events of Special Interest	Labeled "stomatitis/oral mucositis" as an identified risk/AESI and established "mucosal inflammation other than oral mucositis/stomatitis" as a separate identified risk/AESI. Removed anaphylaxis in relation to IRR.	To align with latest Dato-DXd safety profile information.	Substantial
Section 4.3.1, Dato-DXd	Updated to include latest available data.	To align with latest Dato-DXd Investigator Brochure.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 5.1, Inclusion Criteria #8	Limit of AST/ALT criteria extended to assess adequate organ and bone marrow function. Removed INR or PT, and either PTT or aPTT criteria.	To allow flexibility in patient enrolment without compromising safety.	Substantial
Section 5.1, Inclusion Criteria #10	Added definition for washout period of immunotherapy.	Administrative clarification.	Non-substantial
Section 5.1, Inclusion Criteria #15	Removed references to HRT in relation to female participant contraception.	HRT is contraindicated for HR-positive disease.	Substantial
Appendix G1, Female Participants	Updated contraceptive requirement to 3 months before C1D1.	Administrative clarification.	Substantial
Section 5.1, Inclusion Criteria #16	Added that female partners of male participants are allowed to use HRT for contraception. Updated that male participants should use a highly effective method of contraception.	Clarification following the change to Inclusion Criteria #15. To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 5.2, Exclusion Criteria #3	Removed allowance of study physician judgment and added examples of permitted toxicities related to previous anticancer therapy.	To provide operational flexibility without compromising safety.	Substantial
Section 5.2, Exclusion Criteria #16	Clarified to allow concurrent use of hormones for non-cancer related conditions (eg, insulin for diabetes).	To align with CSP permitted medications.	Non-substantial
Section 5.2, Exclusion Criteria #19	Removed exclusion criteria to allow for the enrolment of participants using chronic systemic corticosteroids.	To align with AstraZeneca Dato-DXd program standards.	Substantial
Section 5.3, Lifestyle Considerations	Added recommendation regarding consideration to preserve ova prior to enrolment.	Compliance with AstraZeneca program standards.	Non-substantial
Section 6.2.1.2, Administration of Dato-DXd	Added clarification regarding mandated pre-medications. Added that the IV line will be flushed following infusion.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 6.2.1.3, Monitoring of Dato-DXd Administration	Section to include Dato-DXd monitoring added.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 6.5, Concomitant Therapy	Added information regarding concomitant use of Dato-DXd and CYP3A inhibitors and drugs that inhibit OATP1B1, OATP1B3, MATE2-K, P-gp, BCRP, and MRP1. Added information regarding concomitant use of Dato-DXd and hydroxychloroquine and/or chloroquine.	To align with AstraZeneca and Dato-DXd program standards.	Non-substantial
Section 6.6, Dose Modification	Added information regarding dose delays, interruptions, and modifications.	Consequent to change in Section 6.1.1, and to align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 6.6.4, Dato-DXd Dose Modification/ Toxicity Management Guidelines	Removed Toxicity Management Guidelines (TMG) from the body of the CSP (including Appendix L) and included as an Annex.	To provide operational flexibility, as the TMG may be updated without CSP amendment.	Non-substantial
Section 6.7, Intervention after the End of the Study	Added text regarding continuation of open-label treatment and alternative supply options should they become available.	To align with AstraZeneca program standards.	Substantial
Section 8.1.1 Imaging Tumor Assessments	Added that for participants with documented bone lesion at baseline, the bone scan must have been performed no more than 28 days before randomization.	To align with AstraZeneca and Dato-DXd program standards.	Non-substantial
Section 8.1.1 Imaging Tumor Assessments	Added clarification that CT/MRI are to be collected for all participants at baseline. Removed the text regarding treatment continuation regardless of study intervention discontinuation or start of subsequent anticancer therapy.	Administrative clarification.	Non-substantial
Section 8.1.5.9, Administration of Electronic PRO (ePRO) Questionnaires	Added timing of onboarding participant onto the ePRO application.	To ensure the correct C1D1 date is registered in the ePRO system.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 8.2.2, Vital signs	Added seated assessment position.	To allow flexibility in patient management without compromising safety.	Non-substantial
Section 8.2.3, Electrocardiograms	Amended the requirement of timing of ECGs and ECG machine capabilities.	To provide operational flexibility for both timing and the ECG machine capabilities; without compromising safety.	Non-substantial
Section 8.2.4, Clinical Safety Laboratory Assessments	Added urea and calcium (ionized) to the laboratory safety variables.	To align with AstraZeneca Dato-DXd program standards and allow for operational flexibility without compromising safety.	Non-substantial
Section 8.2.5.3, ILD/Pneumonitis Investigation	Added troponin assessment to the ILD/pneumonitis investigations. Clarified that bronchoscopy and bronchoalveolar lavage are options and added optional lung biopsy to the ILD/pneumonitis investigations.	To align with AstraZeneca Dato-DXd program standards to rule out cardiac etiology.	Substantial
Section 8.2.5.3, ILD/Pneumonitis Investigation Section 8.5.1, Pharmacokinetics	Removed the requirement for a blood sample for PK in the case of suspected ILD/pneumonitis.	No longer within the scope of the study.	Non-substantial
Section 8.2.5.5, Ophthalmologic Assessments Section 8.3.11, Adverse Events of Special Interest	Added that the assessments are to be performed by an ophthalmologist, or if unavailable, another licensed eye care provider.	To align with AstraZeneca Dato-DXd program standards.	Substantial
Section 8.2.5.5, Ophthalmologic Assessments	Added alternative to fluorescein staining, ocular symptoms to be considered during assessment, reporting of assessment results and use of additional eye medications.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 8.2.5.6, Oral Care Plan Appendix I2, Restricted, Prohibited, and Permitted Concomitant Medication/Therapies, Table 18	Added details of use of prophylactic mouthwash and cryotherapy.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 8.3, Adverse Events and Serious Adverse Events	Added requirements for reporting Grade ≥ 3 ocular surface toxicity events.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 8.3.1, Time Period and Frequency for Collecting AE and SAE Information	Added specific AEs that should be reported within 24 hours of the investigator becoming aware.	To align with AstraZeneca program standards.	Substantial
Section 8.3.5, Adverse Events Based on Examinations and Tests	Added that ECOG performance status and ophthalmologic assessments will be summarized in the CSR.	To align with AstraZeneca program standards.	Non-substantial
Section 8.3.11, Adverse Events of Special Interest	Removed combined elevations of aminotransferases and bilirubin. Added the actions to be taken for ILD/pneumonitis cases. Clarified dry eye is an identified risk and keratitis is a potential risk within the ocular surface toxicity AESI.	To align with AstraZeneca Dato-DXd program standards.	Substantial
Section 8.3.14.1, Maternal Exposure	Added that AstraZeneca 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.	To align with AstraZeneca Dato-DXd program standards.	Substantial
Section 8.6.3, Other Study Related Biomarker Assessments	Added reasons for additional exploratory analyses.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Section 8.8, Medical Resource Utilization and Health Economics	Added variables to be captured in the HOSPAD eCRF module.	To align with AstraZeneca program standards.	Non-substantial
Appendix A7, Data Quality Assurance	Increased the record and document retention time to 25 years.	To align with updated AstraZeneca Global Retention and Destruction standards.	Substantial
Appendix A7, Data Quality Assurance	Added medical oversight responsibility.	To align with AstraZeneca program standards.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Appendix I2, Guidance Regarding Potential Interactions with Concomitant Medications	Added information regarding concomitant use of Dato-DXd and CYP3A inhibitors and drugs that inhibit OATP1B1, OATP1B3, MATE2-K, P-gp, BCRP, and MRP1.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Appendix I2, Restricted, Prohibited, and Permitted Concomitant Medication/Therapies, Table 17	Added palliative radiotherapy.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Appendix I2, Restricted, Prohibited, and Permitted Concomitant Medication/Therapies, Table 18	Added other investigational therapeutic agents.	To align with AstraZeneca Dato-DXd program standards.	Non-substantial
Appendix I2, Restricted, Prohibited, and Permitted Concomitant Medication/Therapies, Table 19	Added additional supportive medications/therapies.	To align with AstraZeneca program standards.	Non-substantial
Appendix J, Instructions Related to COVID-19	Added requirement if PCR testing is not available.	To align with AstraZeneca program standards.	Non-substantial
Appendix K2, Rescreening of Participants to Reconfirm Study Eligibility	Rescreening period extended for those participants who have entered rescreening. Updated to allow for participants to remain in screening until reconfirmation of eligibility.	To accommodate enrolment of participants during periods of study disruption, in alignment with established study processes already in place.	Substantial
Throughout	Minor changes to protocol wording, tables and figures, and editorial and document formatting revisions.	To align with project standard or to provide clarification.	Non-substantial

Amendment 1 (27 August 2021)

Overall Rationale for the Amendment:

The overall rationale for the amendment is to provide additional guidance for investigators on the monitoring and management of ocular surface toxicities potentially associated with Dato-DXd, the management of Grade 3 non-hematologic toxicities, as well as clarifying the Oral Care Protocol (OCP) to be used on this study. Furthermore, the schedule of assessments and inclusion/exclusion criteria were updated.

The rationale for each of these changes is provided in the table below:

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Title Page	Added EudraCT number.	Added EudraCT number as it has become available.	Non-substantial
Section 1.1, Synopsis, Overall Design Section 9.2, Sample Size Determination	Updated number of participants to be enrolled from 900 to 1000.	Updated number of participants enrolled based on available feasibility recruitment data. The number of participants to be randomized remains unchanged.	Non-substantial
1.2 Schema	Removed PARP inhibitors from being considered a prior line of chemotherapy.	To ensure that enrolled participants have received at least one prior line of chemotherapy.	Substantial
Section 1.3, Schedule of Assessments, Table 1 Section 8.2.5.5, Ophthalmologic Assessments	**Ophthalmological Assessment:** Updated SoA for ophthalmologic assessments to occur every 3 cycles from C1D1(within 14 days prior to scheduled cycle Day 1 visit), in addition to as clinically indicated; updated footnote "l" to provide additional clarifications around the ophthalmologic assessments. Section 8.2.5.5 has additional details around ophthalmologic assessments and care.	To help prevent ocular surface toxicities, and to monitor and treat these events should they arise.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 1.3, Schedule of Assessments, Table 1 Section 8.2.5.6, Oral Care Plan	**Oral Care Plan:** Oral Care Plan added to SoA; updated footnote "m" and created section 8.2.5.6 to provide additional details and guidance around daily oral care.	The Oral Care Plan is designed to mitigate the risk of oral mucositis/stomatitis. This was previously listed in section 6.6.1, Table 5, but has been moved to SoA and new section created (8.2.5.6) to ensure introduction of this plan for participants at the appropriate time.	Substantial
Section 2.3.1.1, Risk Assessment – Dato-DXd Section 8.3.11, Adverse Events of Special Interest	Ocular surface toxicity was added to the list of AESIs, and mitigations were added.	For participant safety, as ocular surface toxicity has been noted in some participants treated with Dato-DXd. Associated monitoring by ophthalmologic assessments and a dedicated safety review will be performed.	Substantial
Section 5.1, Inclusion Criteria #3	Removed PARP inhibitors from being considered a prior line of chemotherapy.	To ensure that enrolled participants have received at least one prior line of chemotherapy.	Substantial
Section 5.1, Inclusion Criteria #8	Hemoglobin level unit of measurement corrected to g/dL.	Correction of incorrect unit of measurement listed in initial version of CSP.	Non-substantial
Section 5.2, Exclusion Criteria #9	Additional note added to Exclusion Criteria #9 regarding ineligibility of participants found to have ILD/pneumonitis on baseline screening chest CT.	To ensure participants enrolled do not have active ILD.	Substantial
Section 6.2.1.2, Administration of Dato-DXd	Updated total cumulative time from dilution start time until end of infusion for Dato-DXd.	To align with updated handling instructions.	Non-substantial
Section 6.2.1.2, Administration of Dato-DXd	Added guidance around dose re-calculation if participant's weight changes during the study.	Original wording is lacking information important for correct dose re-calculation.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Section 6.6.1, Table 5: Dose Modifications for Non-hematologic and Hematologic Toxicity Related to Dato-DXd	Amended dose reduction thresholds and added guidance around optimizing use of prophylactic and supportive medications.	For participant safety, emphasis has been placed on providing prophylactic/supportive medications (when appropriate); in addition, dose reductions for Grade 3 toxicities (regardless of time of resolution) have been added for most non-hematologic toxicities.	Substantial
Section 7.1.3, Follow-up for Survival	Specified that local death registries may be used to obtain survival status information.	To clarify options for gathering survival data, in line with AZ standards.	Non-substantial
Section 8.2.4, Table 7	Updated list of acceptable values for leukocyte differential count to now include percentages.	To accommodate sites only able to provide a percentage value, as absolute count is not key.	Non-substantial
Section 9.3, Populations for Analysis	Added Ophthalmologic Analysis Set (OAS).	Added analysis for potential risk of ocular surface toxicity, and terminology clarification.	Substantial
Section 9.4.2.1, Efficacy, Primary Endpoints, Table 10	Added 'subsequent anticancer therapy' to list of sensitivity analyses.	Additional sensitivity analysis to assess robustness of PFS dual primary analysis.	Substantial
Section 9.4.2.1.3, PFS Sensitivity Analyses	Added language regarding subsequent anticancer therapy.	Additional sensitivity analysis to assess robustness of PFS dual primary analysis.	Substantial
Section 9.4.2.1.5, Subgroup Analysis	Added two additional subgroups: prior use of taxanes and/or anthracyclines, and pre-selected choice of chemotherapy. Clarified that forest plot of the PFS hazard ratios will be produced for each level of the subgroups.	More detailed subgroup analysis to provide additional data, and terminology clarification.	Substantial
Section 9.4.2.2.8, Clinical Outcome Assessments	Updated analysis language.	To clarify that clinically meaningful change thresholds will be based on pooled data, not the actual TTD endpoint analyses.	Non-substantial
Section 9.6.3, Ophthalmologic Data Review Committee	Added details around the independent Ophthalmologic Data Review Committee.	Data review of participant safety with regard to ophthalmologic assessments.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
Appendix I, Table 19, Supportive Medications/Therapies	Updated details around prophylactic/supportive stomatitis/oral mucositis agents.	To mitigate risk of stomatitis for participant safety.	Non-substantial
Throughout	Minor changes to protocol wording, tables and figures.	To align with project standard or to provide clarification.	Non-substantial
Throughout	Minor editorial and document formatting revisions.	To further clarify.	Non-substantial

Appendix L Country-Specific Addendums to the Protocol

L 1 Country-specific Requirements for Brazil

Table L20 Country-specific Requirements for Brazil (Effective 15 September 2022)

Section # and Name	Description of Change with Reason
▪ **Table 1: Informed consent: genetic sample and analysis (optional)** ▪ **Item 5.1 – Inclusion Criteria #16: "**Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of sample for optional genetic research that supports Genomic Initiative**"** ▪ **Item 6.3.1 – Participant Enrolment ("**Obtain signed informed consent for the optional Genomics Initiative") ▪ **Item 8.7 – Optional Genomics Initiative Sample** ▪ **Item 9.4.4.1 - Optional Exploratory Genetic Sample** ▪ **Appendix D – Optional Genomics Initiative Sample**	AZ clarifies that the information related to the Optional Genetic Research described in the items/appendix is not applicable for the Brazilian Research Participants since Brazil will not take part in the Optional Genetic Research (Genomic Initiative).
▪ **Item 5.1 – Inclusion Criteria - #13:** "(…) Contraceptive use by men or women should be consistent with local regulations (…)". ▪ **Item 5.1 – Inclusion Criteria – #15: "(…)** Female participants must be post-menopausal for at least 1 year, surgically sterile, or using one highly effective form of birth control **(…)"** ▪ **Item 5.1 – Inclusion Criteria – #16: "**Male participants who intend to be sexually active with a female partner of childbearing potential must be surgically sterile or using an acceptable method of contraception **(…)"** ▪ **Item 5.3 – Lifestyle Considerations: "**Participants must follow the contraception requirements outlined in Appendix G."	AZ clarifies that the research participant will receive the contraceptive method chosen in common agreement with the Study Doctor, with no costs for her/his health insurance and public health system. Additionally, AZ clarifies that, according to Brazilian Resolution 466/12, item III.2.t, if the research participant has sexual relationship only with partner(s) with the same gender, there is no need to use contraceptive methods to participate in this study.

Section # and Name	Description of Change with Reason
▪ **Appendix G- Contraception Requirements**	
▪ **Item 5.2 - Exclusion Criteria - #21:** **"**Participation in another clinical study with a study intervention or investigational medicinal device administered in the last 4 weeks prior to first dosing (…)"	AZ clarifies that, according to Brazilian Resolution CNS/MS 251/97, item III.2.j, the study doctor should recommend that no individual be selected as research participant before a year has passed from her participation in another research, unless that individual were to directly benefit from it.
▪ **Item 1.1 – Synopsis - Intervention Groups and Duration: "**Continued treatment with the same study drug post-progression may be allowed, based on prior discussion with study physician on case-by-case basis" ▪ **Item 4.1 – Overall Design** ▪ **Item 6.1.1.1 – Duration of Treatment**	AZ clarifies that after the end of the research participant participation in the study, in accordance with the Resolutions of Health National Council, AstraZeneca is committed to guarantee the free and indefinite access to the study medication, if it has been shown effective (for example, until disease progression – worsening of your cancer – or toxicity) and indicated by the Doctor.
▪ **Item 8.5 – Human Biological Samples –** This item states the following: "Samples may be stored for a maximum of 15 years from the end of the study (as defined in Section 4.4) in line with consent and local requirements, after which they will be destroyed/repatriated. PK and ADA samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses. Samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR. Remaining sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years from the end of the study (as defined in Section 4.4). Additional use includes, but is not limited to, further characterization of any ADAs, evaluation of novel and emerging biomarkers, confirmation and/or requalification of the assay,	AZ clarifies that the information described on these items are not applicable for the samples collected from Brazilian research participants. For Brazil, the biological samples (tumor and blood) will be used as stated in the attached document "Sample Receipt and Storage Process". We confirm that there will be no future additional analysis different from those detailed on this document. After processing the biological samples and receiving the results, the remaining biological samples will be stored only during the execution of this specific project for repetition and/or confirmation of the tests previously performed when needed and, after that, discarded. AZ also clarifies that from CSP v2.0 and CSP v3.0 implementation, Brazil will no longer participate in the exploratory analyses. The samples collected under CSP v1.0 will be analyzed and destroyed after the end of the study. For tumor samples (biopsies), the remaining samples will be repatriated (sent back to the hospital department who provided it) immediately after all study analysis has been completed.

Section # and Name	Description of Change with Reason
and/or diagnostic assay development. The results from future analysis will not be reported in the CSR.**"** ▪ **Item 8.6 - Human Biological Sample Biomarkers:** "(…) Samples may be retained in all regions to allow for potential diagnostic development (…)" ▪ **Appendix A – Item A3 - Informed consent process: "(…)** The investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. (..)" ▪ **Appendix C – Item C1 – Chain of custody of biological samples** ("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 life cycle"). ▪ **Appendix J - Instructions Related to SARS-COV-2 (COVID-19) -** If the participant consents, the remaining serum samples will also be stored for future analysis.	
▪ **Item 8.5 – Human Biological Samples;** ▪ **Items 8.5.1 – Pharmacokinetics;** ▪ **Item 8.5.2 – Immunogenicity Assessments;** ▪ **Item 8.6 – Human Biological Sample Biomarkers;** ▪ **Item 8.6.1 – Collection of Mandatory Samples for Biomarker analysis;** ▪ **Item 8.6.2 – Collection of Optional Biomarker Samples;** ▪ **Item 8.6.3 – Other Study-related Biomarker Assessments**	Related to the tests described on these items, AZ clarifies that all tests which may be done with biological samples during the study (tumor and blood) are listed on the attached document "Sample Receipt and Storage Process". No additional tests will be performed with the samples provided by Brazilian research participants. AZ clarifies that from CSP v2.0 and CSP v3.0 implementation, the information related to Exploratory Analysis described in the items/appendix listed are also not applicable for the Brazilian Research Participants since Brazil will no longer participate in the any exploratory analysis (biomarker and genetic). The samples collected under CSP v1.0 will be analyzed and destroyed after the end of the study.
▪ **Appendix A – Item A3 - Informed consent process**	This item points that a copy of the signed ICF is given to each patient or his/her legal representative. We clarify that, according to the Brazilian Resolution

Section # and Name	Description of Change with Reason
	CNS/MS 466/12, item IV.3.f, the principal investigator must ensure that another original of the signed ICF is given to each research participant.

Moreover, the FDA has mandated that for additional study participant safety, dose reductions by 1 level for Grade 3 toxicities (regardless of time to resolution) be added for most non-hematologic toxicities.

<table>
<tr><th>Section # and Name</th><th>Description of Change with Reason</th></tr>
<tr><td>▪ Section 6.6.1, Table 5: Dose Modifications for Non-hematologic and Hematologic Toxicity Related to Dato-DXd</td><td>The following sections do not specify dose reduction by 1 level for Grade 3 toxicities:
<table>
<tr><td colspan="2">Other Laboratory Adverse Events</td></tr>
<tr><td>Grade 3</td><td>Delay dose until resolved to ≤ Grade 1 or baseline level, if determined by the investigator to be clinically significant.</td></tr>
<tr><td>Grade 4</td><td>Discontinue participant from study treatment.</td></tr>
<tr><td colspan="2">Other Non-laboratory Adverse Events</td></tr>
<tr><td>Grade 3</td><td>Delay dose until resolved to ≤ Grade 1 or baseline, if determined by the investigator to be clinically significant.</td></tr>
<tr><td>Grade 4</td><td>Discontinue participant from study treatment.</td></tr>
</table>
The text should read as follows:
<table>
<tr><td colspan="2">Other Laboratory Adverse Events</td></tr>
<tr><td>Grade 3</td><td>Delay dose until resolved to ≤ Grade 1 <s>or baseline level</s> and then reduce by 1 level, if determined by the investigator to be clinically significant.</td></tr>
<tr><td>Grade 4</td><td>Discontinue participant from study treatment.</td></tr>
<tr><td colspan="2">Other Non-laboratory Adverse Events</td></tr>
<tr><td>Grade 3</td><td>Delay dose until resolved to ≤ Grade 1 <s>or baseline</s> and then reduce by 1 level, if determined by the investigator to be clinically significant.</td></tr>
<tr><td>Grade 4</td><td>Discontinue participant from study treatment.</td></tr>
</table></td></tr>
</table>

L 2 Country-specific Requirements for Canada

Table L21 Country-specific Requirements for Canada (Effective 13 December 2022)

Section # and Name	Description of Change with Reason
A7 – Data Quality Assurance	Prior text: Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years from the end of the study (as defined in the protocol) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. Modified text: Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years from the end of the study (as defined in the protocol) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. *Rationale: Health Canada reduced the retention period for clinical trial records for drugs and natural health products from 25 years to 15 years under the Food and Drug Regulations and Natural Health Products Regulations.*

L 3 Country-specific Requirements for France

Table L22 Country-specific Requirements for France (Effective 10 November 2022)

Section # and Name	Description of Change with Reason
Section 1.3, Schedule of Activities: Table 1	Change: Addition of Footnote 'cc' to clarify that Clinical Outcome Assessments are not applicable to date to participants in France. **Clinical Outcome Assessments** EORTC QLQ-C30, EORTC IL116, PGIS, EQ-5D-5L[cc] | | C1D1, Q3W from C1D1 for the first 48 weeks, and Q6W thereafter until EoT | At EoT visit, then Q6W (relative to C1D1) after EoT until 18 weeks after PD | | | | Section 8.1.5 PRO-CTCAE, EORTC IL117, PGI-TT[cc] | | C1D1, every week from C1D1 for the first 12 weeks, and Q3W thereafter until EoT | X | | | | Section 8.1.5 PGIC[cc] | | Q6W from C1D1 for the first 12 weeks (ie, 6 weeks and 12 weeks from C1D1) | | | | | Section 8.1.5 [bb] Only applicable to participants who are required to attend study visits on Day 8 of each cycle (ie, those randomized to receive Investigators Choice of Chemotherapy which are administered by IV infusion). [cc] **Not applicable to participants in France.** Note: All assessments on treatment days are to be performed prior to study intervention administration, unless otherwise indicated. Following the DCO for the primary analysis, PK assessments will be discontinued. Data collection following final study analysis until the end of the study is described in Section 8. Reason: Electronic Patient Reported Outcomes (ePROs) will not be collected from participants in France at this time until further notice. This is due to ePRO vendor (Medable) non-compliance to date with French CNIL regulations which require processing of directly identifying data and health data by the same vendor to remain excluded.
Section 8.1.5, Clinical Outcome Assessments (COA)	Change: Addition of note to clarify that PROs will not be collected to date from participants in France. The following PRO instruments will be administered in this study (see Appendix H): • EORTC QLQ-C30 (see Section 8.1.5.1) • EORTC IL116: selected breast and arm symptom scales from EORTC QLQ-BR45/IL (see Section 8.1.5.2) • Selected items from PRO-CTCAE (see Section 8.1.5.3) • EORTC IL117: selected symptomatic AE items from EORTC IL (see Section 8.1.5.4) • PGI-TT (see Section 8.1.5.5) • PGIS (see Section 8.1.5.6) • PGIC (see Section 8.1.5.7) • EQ-5D-5L (see Section 8.1.5.8) **Note : PROs will not be collected to date from participants in France**

	Reason: Electronic Patient Reported Outcomes (ePROs) will not be collected from participants in France at this time until further notice. This is due to ePRO vendor (Medable) non-compliance with French CNIL regulations which require processing of directly identifying data and health data by the same vendor to remain excluded.

Table L23 Country-specific Requirements for France (Effective 21 January 2022)

Section # and Name	Description of Change with Reason
Section 5.1, Inclusion Criteria: *Criterion #3*	Change: Progressed on or not suitable for endocrine therapy per investigator assessment, and treated with 1 to 2 lines of prior standard of care chemotherapy in the inoperable/metastatic setting. Participant must have documented progression on their most recent line of chemotherapy. Note: • If a chemotherapy drug is changed within 28 days of use to another drug in the same class (ie, antimetabolite to antimetabolite) for any reason, the first drug is not counted as a line (Flatiron 2019). Targeted agents (such as mTOR inhibitors, PD-1/PD-L1 inhibitors, PARP inhibitors), endocrine therapies, and CDK4/6 inhibitors on their own do not contribute to the count of prior lines of chemotherapy; however, regimens with such agents in combination with metastatic chemotherapy should be classified as one line of chemotherapy. • **Patients must have been treated with (neo)adjuvant anthracycline and/or taxane, if they received systemic treatment in the (neo)adjuvant setting, unless anthracycline and/or taxane was contraindicated or not considered the best treatment option for the subject in the opinion of the treating physician.** Reason: The French Regulatory Authority (ANSM) request to precise the standard of care chemotherapy that patients should have received prior to ennrolment. According to the ESMO guidelines, in the absence of medical contraindications or patient concerns, anthracycline- or taxane-based regimens, preferably as single agents, would usually be considered as first-line chemotherapy for HER2-negative advanced breast cancer in those patients who have not received these regimens as (neo)adjuvant treatment. Moreover, capecitabine, vinorelbine or eribulin (and gemcitabine as additional choice) are recommended for patients pre-treated with an anthracycline and a taxane. Thus, the sponsor should ensure that patients have had the opportunity to receive taxanes and anthracyclines (if not contraindicated) along the course of their disease. This request is in line with the EMA scientific advice EMA/SA/0000060979 (22/07/2021).
Section: 6.6.1, Dato-	Change:

<table>
<tr><td>DXd Dose Modification/Toxicity Management Guidelines: Table 5</td><td>
<table>
<tr><th colspan="2"><u>Anemia</u></th></tr>
<tr><td>Grade 3
(Hemoglobin < 8.0 g/dL; transfusion indicated)</td><td>Delay dose until resolved to ≤ Grade 2, then maintain dose.</td></tr>
<tr><td>Grade 4
Life-threatening consequences; urgent intervention indicated</td><td>Delay dose until resolved to ≤ Grade 2, then reduce dose by 1 level.
Permanently discontinue Dato-DXd, if recurrent grade 4/life-threatening anemia occurs after dose reduction by 1 level.</td></tr>
</table>
<u>Reason:</u>

The French Regulatory Authority (ANSM) request to modify the protocol so as to permanently discontinue Dato-DXd in case of recurrent life-threatening Grade 4 anemia after one level dose reduction.</td></tr>
<tr><td>Section 6.4, Concomitant Therapy</td><td><u>Change:</u>

Any concomitant treatment, procedure, vaccine, or other medication considered necessary by the investigator for the participant’s safety and wellbeing (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 28 (+7) day safety follow-up period following the last dose of study intervention must be recorded in the eCRF along with:

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

The Study Clinical Lead 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.</td></tr>
</table>

	Restricted, prohibited, and permitted concomitant medications/therapies are described in more detail in Appendix I2. For participants randomized to receive ICC, refer to the local Prescribing Information with regard to warnings, precautions, and contraindications. Guidance regarding potential interactions with concomitant medications is provided in Appendix I1. **For management of patients receiving capecitabine, gemcitabine, eribulin mesylate and vinorelbine, investigators must refer to local prescribing information and to the SmPC website (https://base-donnees-publique.medicaments.gouv.fr/), especially for information concerning contraindications, special warnings and precautions, posology adaptation in case of toxicity, monitoring, as well as medications that are contraindicated or that must be used with caution.** Reason: The French Regulatory Authority (ANSM) request to modify the protocol in order to inform the investigators that they must refer to the SmPC of capecitabine, gemcitabine, eribulin mesylate and vinorelbine for the management of patients, especially concerning contraindications, special warnings and precautions, posology adaptation in case of toxicity, monitoring, as well as medications that are contraindicated or that must be used with caution, and, enclose the SmPC or refer to the website: http://base-donnees-publique.medicaments.gouv.fr which presents the updated version of the SmPCs of medications.
Section 1.3, Schedule of Activities: *Table 1, Footnote 'P'*	Change: Within 72 hours before randomization for all female subjects of childbearing potential; a positive urine pregnancy test result must immediately be confirmed using a serum test. Perform repeat pregnancy tests (urine or serum test per institutional guideline) within 72 hours before each cycle of study intervention and at end of treatment. **Pregnancy testing is to be repeated monthly during 7 months after treatment discontinuation.** Reason: The French Regulatory Authority (ANSM) request to modify the Table 1 Schedule of Activities and correspondent sections so as to extend the duration for monthly pregnancy testing to 7 months after treatment

	discontinuation, in order to align with post-treatment contraception duration.
Section 8.2.4, Clinical Safety Laboratory Assessments	Change: A negative result from a serum pregnancy test (which must have a sensitivity of at least 25 mIU/mL) must be available at the screening visit. Pregnancy tests should be conducted within 72 hours prior to randomization for all female participants of childbearing potential. Repeat pregnancy tests (urine beta-human chorionic gonadotropin or serum test per institutional guideline) should be performed 72 hours before infusion of each cycle and at the EoT visit. **Pregnancy testing is to be repeated monthly during 7 months after treatment discontinuation.** If a positive urine pregnancy test result is confirmed using a serum test in a female participant of childbearing potential, then the participant should not be treated. Reason: The French Regulatory Authority (ANSM) request to modify the Table 1 Schedule of Activities and correspondent sections so as to extend the duration for monthly pregnancy testing to 7 months after treatment discontinuation, in order to align with post-treatment contraception duration.

L 4 Country-specific Requirements for Germany

Table L24 Country-specific Requirements for Germany (Effective 15 November 2022)

Section # and Name	Description of Change with Reason
N/A	Editorial change: adaption of the referenced CSP version
N/A	According to AstraZeneca's procedures the Clinical Study Protocol (CSP) version 4.0 from 10 October 2022 was signed by the sponsor electronically only. This Addendum to the CSP contains the signature of the National Coordinating Investigator as requested by local regulatory authority. The protocol version 4.0 has no further impact on the German addendum and therefore no additional changes were made.
N/A	According to AstraZeneca's procedures the Clinical Study Protocol (CSP) version 3.0 from 19 April 2022 was signed by the sponsor electronically only.
Overall study conduct, tumor sampling	No invasive sampling for fresh tumor specimen for the purpose of testing with companion diagnostics will be done for study participants. Therefore, no fresh biopsies will be taken during the study and only archived residual tumor material will be used at Screening. No optional paired tumor biopsy and no optional fresh tumor biopsy at progression will be conducted. Study participants will be informed in ICF accordingly.
2.3.2 Benefit assessment	"Additionally, at the time of disease progression, participants will be offered an optional tumor biopsy, which will provide real-time next-generation sequencing results from the FoundationOne®CDx, that may help guide next treatment options." Is deleted from section 2.3.2
8.6.2 Collection of Optional Biomarker Samples	"Optional tumor tissue samples for exploratory biomarker research • Paired tumor biopsy: A baseline biopsy will be taken (where the participant has provided informed consent) before initial dosing of study intervention (at screening or pre-dose on C1D1), and a paired (second) biopsy will be taken on-treatment. The paired on-treatment biopsy can be collected C2D1 and C2D7. On-treatment sample may also be collected outside of this specified timepoint with prior agreement from the Sponsor. Paired preclinical treatment and on-treatment tumor samples must be obtained from the same lesion where clinically feasible to maximize the utility for assessment of pharmacodynamic changes. These optional paired tumor samples will be mandatory at select sites. • Tumor biopsy on disease progression: An additional tumor biopsy sample should be obtained at termination of treatment/documented RECIST 1.1 disease progression in participants that have signed the additional optional

Section # and Name	Description of Change with Reason
Table 1	consent. These samples will be used to explore mechanisms of resistance. The on-study provision of tumor tissue is encouraged only if clinically appropriate and not considered detrimental to participant care. Biopsies at study entry, on treatment, and progression are optional for the majority of participants in this study, and participants will not be excluded from the study if these samples are not collected. These optional biopsy samples will be mandatory at select sites." Is deleted from Section 8.6.2 "Optional tumor biopsy (FFPE/FF) at Progression" and "Optional paired tumor biopsy (FFPE/FF)" is deleted from Table 1
Section 7.1 Discontinuation of Study Intervention	The wording in this section is changed from Participants may be discontinued from study intervention in the following situations: to Participants ***must*** be discontinued from study intervention in the following situations: • RECIST 1.1-defined radiological progression (refer to Section 8.1.1 and Appendix F). • An AE that, in the opinion of the investigator or AstraZeneca, contraindicates further dosing. • Any AE that meets criteria for discontinuation defined in the TMGs (see the Annex document to this CSP), or as defined in the local Prescribing Information for the ICC agents. • 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 (refer to Appendix G and Section 8.3.14). • Initiation of subsequent anticancer therapy, including another investigational agent. Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study. Crossover within the study is not permitted.
Appendix G Contraception Requirements	Women of childbearing potential who are not totally sexually abstinent (ie, refraining from heterosexual intercourse during the entire period of risk

Section # and Name	Description of Change with Reason
G1 Female participants	associated with study interventions) and intend to be sexually active with a non-sterilized male partner must use at least 1 highly effective method of contraception (Table 16). Is changed to: Women of childbearing 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-sterilized male partner must use at least 1 highly effective non-hormonal method of contraception (Table 16). Hormonal methods of contraception must not be used by female patients participating in this study.

L 5 Country-specific Requirements for India

Table L25 Country-specific Requirements for India (Effective 02 November 2021)

<table>
<tr><th>Section # and Name</th><th>Description of Change with Reason</th></tr>
<tr><td>Section 6.6.1, Table 5: Dose Modifications for Non-hematologic and Hematologic Toxicity Related to Dato-DXd</td><td>The following sections do not specify dose reduction by 1 level for Grade 3 toxicities:
<table>
<tr><th colspan="2">Other Laboratory Adverse Events</th></tr>
<tr><td>Grade 3</td><td>Delay dose until resolved to ≤ Grade 1 or baseline level, if determined by the investigator to be clinically significant.</td></tr>
<tr><td>Grade 4</td><td>Discontinue participant from study treatment.</td></tr>
<tr><th colspan="2">Other Non-laboratory Adverse Events</th></tr>
<tr><td>Grade 3</td><td>Delay dose until resolved to ≤ Grade 1 or baseline, if determined by the investigator to be clinically significant.</td></tr>
<tr><td>Grade 4</td><td>Discontinue participant from study treatment.</td></tr>
</table>
The text should read as follows:
<table>
<tr><th colspan="2">Other Laboratory Adverse Events</th></tr>
<tr><td>Grade 3</td><td>Delay dose until resolved to ≤ Grade 1 ~~or baseline level~~ and then reduce by 1 level, if determined by the investigator to be clinically significant.</td></tr>
<tr><td>Grade 4</td><td>Discontinue participant from study treatment.</td></tr>
<tr><th colspan="2">Other Non-laboratory Adverse Events</th></tr>
<tr><td>Grade 3</td><td>Delay dose until resolved to ≤ Grade 1 ~~or baseline~~ and then reduce by 1 level, if determined by the investigator to be clinically significant.</td></tr>
<tr><td>Grade 4</td><td>Discontinue participant from study treatment.</td></tr>
</table></td></tr>
</table>

The global clinical study protocol and its amendments (as applicable) for the study is to be read as follows:

<table>
<tr><th>Section # and Name</th><th>Description of Change with Reason</th></tr>
<tr><td>8.3.5 Adverse Events Based on Examinations andTests</td><td>Previous Text:
The results from the CSP-mandated laboratory tests, vital signs, physical examinations, ECGs, and echocardiogram/MUGA scans will be summarized in the CSR.
Deterioration as compared with baseline in protocol-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 not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, e.g., dose adjustment or study intervention interruption).
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 (e.g., anemia versus low hemoglobin value). In the absence of clinical signs</td></tr>
</table>

Section # and Name	Description of Change with Reason
	or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s). Deterioration of a laboratory value, which 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. **Revised Text:** The results from the CSP-mandated laboratory tests, vital signs, physical examinations, ECGs, and echocardiogram/MUGA scans will be summarized in the CSR. Deterioration as compared with baseline in protocol-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 not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, e.g., dose adjustment or study intervention interruption). 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 (e.g., anemia versus low hemoglobin 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, which 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. However, all the events occurring at the Indian sites (the reason whatsoever) that meet the criteria for seriousness (SAEs) from the time of signing the ICF, throughout the treatment period, including the safety follow up period (28 [+7] days after the discontinuation of study intervention) and if an event that starts after the defined safety follow-up period noted above and is considered to be due to a late onset toxicity to the study intervention, should be reported as an SAE per local regulatory requirements to the Sponsor (appropriate AstraZeneca representatives), Indian regulatory authority and the concerned Ethics Committees in accordance with New Drugs and Clinical Trials Rules, 2019.

Section # and Name	Description of Change with Reason
	Reason for change: Per Indian regulatory requirements, all the events that meet criteria for seriousness have to be reported expeditiously to the Sponsor, Indian regulatory authority and the concerned Ethics Committees.
8.3.7 Disease Progression	**Previous Text:** 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 metastases or progression of existing metastasis to the primary cancer under study should be considered as PD and not an AE. Events, which are unequivocally due to PD, should not be reported as an AE during the study. Death due to disease progression should be recorded on the Death eCRF. **Revised Text:** 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 metastases or progression of existing metastasis to the primary cancer under study should be considered as PD and not an AE. Events, which are unequivocally due to PD, should not be reported as an AE during the study. Death due to disease progression should be recorded on the Death eCRF. However, all the events occurring at the Indian sites (the reason whatsoever) that meet the criteria for seriousness (SAEs) from the time of signing the ICF, throughout the treatment period, including the safety follow up period (28 [+7] days after the discontinuation of study intervention) and if an event that starts after the defined safety follow-up period noted above and is considered to be due to a late onset toxicity to the study intervention, should be reported as an SAE per local regulatory requirements to the Sponsor (appropriate AstraZeneca representatives), Indian regulatory authority and the concerned Ethics Committees in accordance with New Drugs and Clinical Trials Rules, 2019. **Reason for change:** Per Indian regulatory requirements, all the events that meet criteria for seriousness have to be reported expeditiously to the Sponsor, Indian regulatory authority and the concerned Ethics Committees.
8.3.10 Deaths	**Previous Texts:** All deaths that occur during the study intervention period, or within the protocol-defined 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.

Section # and Name	Description of Change with Reason
	• 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 protocol-defined 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 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. **Revised Text:** All deaths that occur during the study intervention period, or within the protocol-defined 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 protocol-defined 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 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. However, all the events occurring at the Indian sites (the reason whatsoever) that meet the criteria for seriousness (SAEs) from the time of signing the ICF, throughout the treatment period, including the safety follow up period (28 [+7] days after the discontinuation of study intervention) and if an event that starts

Section # and Name	Description of Change with Reason
	after the defined safety follow-up period noted above and is considered to be due to a late onset toxicity to the study intervention, should be reported as an SAE per local regulatory requirements to the Sponsor (appropriate AstraZeneca representatives), Indian regulatory authority and the concerned Ethics Committees in accordance with New Drugs and Clinical Trials Rules, 2019. **Reason for change:** Per Indian regulatory requirements, all the events that meet criteria for seriousness have to be reported expeditiously to the Sponsor, Indian regulatory authority and the concerned Ethics Committees.

Study sites affected by this addendum:

This Clinical Study Protocol - Addendum affects all the study sites in India and will prevail if in conflict with any other section in the Clinical Study Protocol (CSP) (including its appendices).

L 6 Country-specific Requirements for United Kingdom

Table L26 Country-specific Requirements for United Kingdom (Effective 19 May 2022)

Section # and Name	Description of Change with Reason
Section 5.1 Inclusion Criteria #16	**Inclusion #16 states** - "Male participants who intend to be sexually active with a female partner of childbearing potential must be surgically sterile or using an acceptable method of contraception (see Appendix G) from the time of screening throughout the total duration of the study and the drug washout period (at least 4 months after the last dose of study intervention) to prevent pregnancy in a partner. Male participants must not donate or bank sperm during this same time period. Not engaging in heterosexual activity (sexual abstinence) for the duration of the study and drug washout period is an acceptable practice if this is the preferred usual lifestyle of the participant; however, periodic or occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception." **To clarify for the UK:** If administered with either Gemcitabine or Vinorelbine, non-sterilized male participants must use an acceptable method of contraception and refrain from donating or banking sperm from the time of screening throughout the total duration of the study and the drug washout period (i.e., at least 6 months after the last dose of study intervention).
Section 8.3.14.2 Paternal Exposure	To clarify specifically for non-sterilized male participants administered either Gemcitabine or Vinorelbine who intend to be sexually active with a female partner of childbearing potential, that they must use an acceptable method of contraception and refrain from donating or banking sperm from the time of screening throughout the duration of the study and the drug washout period (i.e., at least 6 months after the last dose of study intervention).
Appendix G, G2 Male Participants with a Female Partner of Childbearing Potential	To clarify specifically for non-sterilized male participants administered either Gemcitabine or Vinorelbine who intend to be sexually active with a female partner of childbearing potential, that they must use an acceptable method of contraception and refrain from donating or banking sperm from the time of screening throughout the duration of the study and the drug washout period (i.e., at least 6 months after the last dose of study intervention).

Appendix M Abbreviations

Abbreviation or Special Term	Explanation
5-HT3	5-hydroxytryptamine receptor
ADA	antidrug antibody
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
AxMP	auxiliary medicinal product
BCRP	breast cancer resistance protein
BICR	Blinded Independent Central Review
BID	twice daily
BoR	best objective response
CAP	College of American Pathologists
CD	cluster of differentiation
CHF	congestive heart failure
CI	confidence interval
ClinRO	clinician-reported outcome
C_{max}	maximum observed concentration
CNS	central nervous system
COA	clinical outcome assessment
COPD	chronic obstructive pulmonary disorder
COVID-19	coronavirus 2019-nCoV
CR	complete response
CRF	case report form
CrCl	calculated creatinine clearance
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation or Special Term	Explanation
ctDNA	circulating tumor DNA
CTIS	Clinical Trial Information System (EU)
CTR	Clinical Trial Regulation
CYP	cytochrome P450
Dato-DXd	Datopotamab deruxtecan (DS-1062a)
DCO	data cutoff
DCR	disease control rate
DILI	drug-induced liver injury
DLCO	diffusion capacity of the lungs for carbon monoxide
DNA	deoxyribonucleic acid
DoR	duration of response
DXd	MAAA-1181a
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
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EoT	end of treatment
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQoL 5-dimension, 5-level health state utility index
ER	estrogen receptor
EU	European Union
FDA	Food and Drug Administration
FEV1	forced expiratory volume – 1 second
FEV6	forced expiratory volume – 6 seconds
FF	fresh-frozen
FFPE	formalin fixed and paraffin embedded
FIH	first-in-human
FU	follow up
FVC	forced vital capacity
GCP	Good Clinical Practice

Abbreviation or Special Term	Explanation
GHS	global health status
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCP	health care professional
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HL	Hy's Law
HLT	High Level Term (MedDRA)
HOSPAD	Hospital Admission form
HR	hormone receptor
HRCT	high-resolution computed tomography
HRQoL	health-related quality of life
HRT	hormone replacement therapy
5-HT3	5-hydroxytryptamine 3
IA	interim analysis
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICC	Investigator's Choice Chemotherapy
ICF	informed consent form
ICH	International Council for Harmonisation
iCRO	imaging Contract Research Organization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	immunohistochemical
IL	item library
ILD	interstitial lung disease
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	Interactive Response Technology
ITT	intent-to-treat

Abbreviation or Special Term	Explanation
IV	intravenous
LVEF	left ventricular ejection fraction
MATE2-K	multidrug and toxin extrusion protein 2
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRP1	multidrug resistance-associated protein 1
mTOR	mammalian target of rapamycin
MTP	multiple testing procedure
MUGA	multigated acquisition
NCI	National Cancer Institute
NE	not evaluable
NIMP	non-investigational medicinal product
NK1	Neurokinin 1
NL	new lesion
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
NTL	non-target lesion
OAS	Ophthalmologic Analysis Set
OATP	organic anion transporting polypeptide
ObsRO	observer-reported outcome
ORR	objective response rate
OS	overall survival
PARP	poly (ADP-ribose) polymerase
PAS	pharmacokinetic analysis set
PD	progression of disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PEF	peak expiratory flow
PET	positron emission tomography
PFS	progression-free survival
PFS (Inv)	progression-free survival (as per investigator assessment)
PFS2	time to second progression or death
PGIC	Patients' Global Impression of Change
PGIS	Patients' Global Impression of Severity

Abbreviation or Special Term	Explanation
PGI-TT	Patient's Global Impression of Treatment Tolerability
P-gp	p-glycoprotein
PgR	progesterone receptor
PHL	potential Hy's Law
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
PS	Performance Status
PT	Preferred Term (MedDRA)
PTT	partial thromboplastin time
Q3W	every 3 weeks
Q6W	every 6 weeks
Q9W	every 9 weeks
QLQ-C30	30-item core quality of life questionnaire
QoL	quality of life
QTcF	QT interval corrected by Fridericia's formula
RANKL	receptor activator of nuclear factor-κB ligand
RECIST 1.1	Response Evaluation Criteria in Solid Tumours, Version 1.1
RNA	ribonucleic acid
RV	residual volume
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	safety analysis set
SD	stable disease
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SoC	standard of care
SpO_2	peripheral capillary oxygen saturation
TBL	total bilirubin
T-DXd	trastuzumab deruxtecan
TEAE	treatment emergent adverse event
TFST	time to first subsequent therapy
TL	target lesion
TLC	total lung capacity

Abbreviation or Special Term	Explanation
TMG	toxicity management guideline
TNBC	triple-negative breast cancer
TPV	third-party vendor
TROP2	trophoblast cell surface antigen 2
TSST	time to second subsequent therapy
TTD	time from the date of randomization to the date of deterioration
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
WBC	white blood cell
WOCBP	women of childbearing potential
w/v	weight per volume

11 REFERENCES

Aaronson et al 1993
Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.

Alberti et al 1992
Alberti S, Miotti S, Stella M, Klein CE, Fornaro M, Menard S, et al. Biochemical characterization of Trop-2, a cell surface molecule expressed by human carcinomas: formal proof that the monoclonal antibodies T16 and MOv-16 recognize Trop-2. Hybridoma 1992; 11(5): 539-45.

Allison et al 2020
Allison KH, Hammond MEH, Dowsett M, McKernin SE, Carey LA, Fitzgibbons PL, et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Guideline Update. Arch Pathol Lab Med;144(5):545-563. doi: 10.5858/arpa.2019-0904-SA. Epub 2020 Jan 13. PMID: 31928354.

André et al 2019
André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, et al; SOLAR-1 Study Group. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med 2019; 380(20): 1929-1940.

Bardia et al 2020
Bardia A, Tolaney SM, Loirat D, Punie K, Oliveira M, Rugo HS, et al. LBA17 ASCENT: A randomized Phase III study of Sacituzumab Govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC). Annals of Oncology 2020; 31(Suppl. 4): S1142-S1215.

Bardia et al 2021
Bardia A, Juric D, Shimizu T, et al. Datopotamab deruxtecan (Dato-DXd), a TROP2-directed antibody-drug conjugate (ADC), for triple-negative breast cancer (TNBC): Preliminary results from an ongoing phase 1 trial. Presented at: ESMO Breast Cancer Virtual Congress 2021; May 5-8, 2021; Virtual. Abstract LBA4. Accessed at: https://www.annalsofoncology.org/action/showPdf?pii=S0923-7534%2821%2901141-8. Last accessed 19 May 2021.

Barrios 2010
Barrios, C.H, Liu, MC, Lee, S.C, et al. Phase III randomized trial of sunitinib versus capecitabine in patients with previously treated HER2-negative advanced breast cancer. Breast Cancer Res Treat 2010; 121, 121–131.

Basch et al 2014
Basch E, Reeve BB, Mitchell SA, Clauser SB, Minasian LM, Dueck AC, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst. 2014 Sep 29;106(9):dju244. doi: 10.1093/jnci/dju244. PMID: 25265940; PMCID: PMC4200059.

Bjelic-Radisic et al 2020
Bjelic-Radisic V, Cardoso F, Cameron D, Brain E, Kuljanic K, da Costa RA, et al. An international update of the EORTC questionnaire for assessing quality of life in breast cancer patients: EORTC QLQ-BR45. Ann Oncol. 2020 Feb;31(2):283-288. doi: 10.1016/j.annonc.2019.10.027. Epub 2019 Dec 18. Erratum in: Ann Oncol. 2020 Apr;31(4):552. PMID: 31959345.

Blum et al 1999
Blum JL, Jones SE, Buzdar AU, LoRusso PM, Kuter I, Vogel C, et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. J Clin Oncol 1999; 17(2): 485-93.

Brufsky 2011
Brufsky AM, Mayer M, Rugo HS, Kaufman PA, Tan-Chiu E, Tripathy D, et al. Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence, treatment, and survival in patients from registHER. Clin Cancer Res 2011; 17(14):4834-43.

Burman et al 2009
Burman CF, Sonesson C, Guilbaud O. A recycling framework for the construction of Bonferroni based multiple tests. Stat Med 2009;28:739-61.

Capecitabine USPI 2015
Capecitabine USPI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020896s037lbl.pdf. Last accessed 27 April 2021.

Cardoso et al 2018
Cardoso F, Spence D, Mertz S, Corneliussen-James D, Sabelko K, Gralow J, et al. Global analysis of advanced/metastatic breast cancer: Decade report (2005-2015). Breast 2018; 39: 131-138.

Cardoso et al 2020
Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020 Dec;31(12):1623-1649.

Cortes et al 2011
Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet 2011; 377(9769): 914-23.

Domenech and Vogel 2001
Domenech GH, Vogel CL. A review of vinorelbine in the treatment of breast cancer. Clin Breast Cancer 2001; 2(2): 113-28.

Dueck et al 2015
Dueck AC, Mendoza TR, Mitchell SA, Reeve BB, Castro KM, Rogak LJ, et al. Validity and Reliability of the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). JAMA Oncol. 2015 Nov;1(8):1051-9. doi: 10.1001/jamaoncol.2015.2639. Erratum in: JAMA Oncol. 2016 Jan;2(1):146. PMID: 26270597; PMCID: PMC4857599.

EMA 2017
EMA. Guideline on the evaluation of anticancer medicinal products in man, September 2017. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-anticancer-medicinal-products-man-revision-5_en.pdf. Last accessed 28 April 2021.

EuroQol 2019
EuroQol Group. EQ-5D-5L User Guide: Basic information on how to use the EQ-5D-5L instrument, Version 3.0, September 2019. Available from: URL: https://euroqol.org/wp-content/uploads/2019/09/EQ-5D-5L-English-User-Guide_version-3.0-Sept-2019-secured.pdf. Accessed 18 December 2019.

FDA 2018
FDA. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. Guidance for Industry, December 2018. Available at: https://www.fda.gov/media/71195/download. Last accessed 28 April 2021.

FDA-NIH BEST Resource
FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016. Glossary. 2016 Jan 28 [Updated 2018 May 2]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK338448. Co-published by National Institutes of Health (US), Bethesda (MD).

Fornaro et al 1995
Fornaro M, Dell'Arciprete R, Stella M, Bucci C, Nutini M, Capri MG, et al. Cloning of the gene encoding Trop-2, a cell-surface glycoprotein expressed by human carcinomas. Int J Cancer 1995; 62(5): 610-8.

Gradishar et al 2005
Gradishar WJ, Tjulandin S, Davidson N, Shaw H, Desai N, Bhar P, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol 2005; 23(31): 7794-803.

Gridelli et al 1999
Gridelli C, Perrone F, Gallo C, et al. Single-agent gemcitabine as second-line treatment in patients with advanced non small cell lung cancer (NSCLC): a phase II trial. Anticancer Res 1999; 19:4535.

Harbeck et al 2019
Harbeck N, Penault-Llorca F, Cortes J, et al. Breast cancer. Nat Rev Dis Primers 2019; 5: 66.

Hay et al 2014
Hay JL, Atkinson TM, Reeve BB, Mitchell SA, Mendoza TR, Willis G, et al. Cognitive interviewing of the US National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Qual Life Res. 2014 Feb;23(1):257-69. doi: 10.1007/s11136-013-0470-1. Epub 2013 Jul 20. PMID: 23868457; PMCID: PMC3896507.

Howlader et al 2014
Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LA, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status, JNCI J Natl Cancer Inst 2014; 106(5): dju055.

Jerusalem et al 2018
Jerusalem G, de Boer RH, Hurvitz S, et al. Everolimus Plus Exemestane vs Everolimus or Capecitabine Monotherapy for Estrogen Receptor–Positive, HER2-Negative Advanced Breast Cancer: The BOLERO-6 Randomized Clinical Trial. JAMA Oncol 2018; 4(10): 1367–1374.

Kalinsky et al 2020
Kalinsky K, Diamond JR, Vahdat LT, Tolaney SM, Juric D, O'Shaughnessy J, et al. Sacituzumab govitecan in previously treated hormone receptor-positive/HER2-negative metastatic breast cancer: final results from a phase I/II, single-arm, basket trial. Ann Oncol 2020; 31(12): 1709-1718.

Kaufman et al 2015
Kaufman PA, Awada A, Twelves C, Yelle L, Perez EA, Velikova G, et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally

advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol 2015; 33(6): 594-601.

Kluetz et al 2018
Kluetz PG, O'Connor DJ, Soltys K. Incorporating the patient experience into regulatory decision making in the USA, Europe, and Canada. Lancet Oncol 2018;19(5):e267-74.

Lan and DeMets 1983
Lan KKG and DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983; 70659–663.

Lipinski et al 1981
Lipinski M, Parks DR, Rouse RV, Herzenberg LA. Human trophoblast cell-surface antigens defined by monoclonal antibodies. Proc Natl Acad Sci USA 1981; 78(8): 5147-50.

Martín et al 2007
Martín M, Ruiz A, Munoz M, et al. Gemcitabine plus vinorelbine versus vinorelbine monotherapy in participants with metastatic breast cancer previously treated with anthracyclines and taxanes: final results of the phase III Spanish Breast Cancer Research Group (GEICAM) trial. Lancet Oncol. 2007;8: 219–25.

Matutino et al 2018
Matutino A, Joy AA, Brezden-Masley C, Chia S, Verma S. Hormone receptor-positive, HER2-negative metastatic breast cancer: redrawing the lines. Curr Oncol 2018; 25(Suppl. 1): S131-S141.

Midgley and Kerr 2008
Midgley R, and Kerr DJ. Capecitabine: have we got the dose right? Nat Clin Pract Oncol 2008; 6: 17–24.

Miller et al 2005
Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbacher L, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol 2005; 23(4): 792-9.

Miller et al 2007
Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007; 357(26): 2666-76.

Modi et al 2020
Modi S, Saura C, Yamashita T, Park YH, Kim S-B, Kenji Tamura K, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. N Engl J Med 2020; 382: 610-621.

NCCN Guidelines 2020
NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. Version 3 2020. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx. Last accessed 28 April 2021.

O'Shaughnessy 2005
O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. Oncologist 2005; 10(Suppl. 3): 20-9.

Pau Ni et al 2010
Pau Ni IB, Zakaria Z, Muhammad R, Abdullah N, Ibrahim N, Aina Emran N, et al. Gene expression patterns distinguish breast carcinomas from normal breast tissues: the Malaysian context. Pathol Res Pract. 2010; 206(4): 223-8.

Piccart-Gebhart et al 2008
Piccart-Gebhart MJ, Burzykowski T, Buyse M, Sledge G, Carmichael J, Lück HJ, et al. Taxanes alone or in combination with anthracyclines as first-line therapy of patients with metastatic breast cancer. J Clin Oncol 2008; 26(12): 1980-6.

Possinger et al 1999
Possinger K, Kaufman M, Coleman R et al. Phase II study of gemcitabine as firstline chemotherapy in patients with advanced or metastatic breast cancer. Anticancer Drugs 1999; 10: 155–162.

Schott 2021
Schott AF. Chemotherapy in patients with hormone receptor-positive, HER2-negative advanced breast cancer. Available at: https://www.uptodate.com/contents/chemotherapy-in-patients-with-hormone-receptor-positive-her2-negative-advanced-breast-cancer/print. Last accessed 27 April 2021.

Seidman et al 2018
Seidman A, Bordeleau L, Fehrenbache Lr, Barlow W, Perlmutter J, Rubinstein L, et al. National Cancer Institute Breast Cancer Steering Committee Working Group Report on Meaningful and Appropriate End Points for Clinical Trials in Metastatic Breast Cancer. Journal of Clinical Oncology 2018; 36(32): 3259-3268.

Sprangers et al 1996
Sprangers MA, Groenvold M, Arraras JI, Franklin J, te Velde A, Muller M, Franzini L, Williams A, de Haes HC, Hopwood P, Cull A, Aaronson NK. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol. 1996 Oct;14(10):2756-68. doi: 10.1200/JCO.1996.14.10.2756. PMID: 8874337.

Sparano et al 2010
Sparano JA, Vrdoljak E, Rixe O, Xu B, Manikhas A, Medina C, et al. Randomized phase III trial of ixabepilone plus capecitabine versus capecitabine in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2010; 28(20): 3256-63.

Sung et al 2021
Sung H, Ferlay J, Siegel SL, Laversanne L, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Ca Cancer J Clin 2021; 0: 1–41.

Thomas et al 2007
Thomas ES, Gomez HL, Li RK, Chung HC, Fein LE, Chan VF, et al. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. J Clin Oncol. 2007 Nov 20;25(33):5210-7.

Twelves et al 2016
Twelves C, Awada A, Cortes J, Yelle L, Velikova G, Olivo MS, et al. Subgroup Analyses from a Phase 3, Open-Label, Randomized Study of Eribulin Mesylate Versus Capecitabine in Pre-treated Patients with Advanced or Metastatic Breast Cancer. Breast Cancer (Auckl). 2016;10: 77-84.

Von Minckwitz et al 2019
von Minckwitz G, Huang C-S, Mano MS, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med 2019; 380:617-628.

Wolff et al 2018
Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. Arch Pathol Lab Med 2018;142(11):1364-1382. doi: 10.5858/arpa.2018-0902-SA. Epub 2018 May 30. PMID: 29846104.

Yang et al 2021
Yang F, Rizvi Y, Yuca E, Zhao M, Evans K, Zheng X, et al. Abstract PS18-37: Loss of Trop2 protein in metaplastic carcinoma of breast by IHC. Cancer Res 2021; 81(Suppl. 4): PS18-37.

Yardley et al 2013
Yardley DA, Ismail-Khan RR, Melichar B, Lichinitser M, Munster PN, Klein PM, et al. Randomized phase II, double-blind, placebo-controlled study of exemestane with or without entinostat in postmenopausal women with locally recurrent or metastatic estrogen receptor-positive breast cancer progressing on treatment with a nonsteroidal aromatase inhibitor. J Clin Oncol. 2013; 31(17): 2128-35.

Youlden et al 2012
Youlden D.R, Cramb S.M, Dunn N.A, Muller J.M, Pyke C.M, Baade P.D. The descriptive epidemiology of female breast cancer: An international comparison of screening, incidence, survival and mortality. Cancer Epidemiol. 2012; 36: 237–248.

Yuan et al 2019
Yuan P, Hu X, Sun T, Li W, Zhang Q, Cui S, et al. Eribulin mesilate versus vinorelbine in women with locally recurrent or metastatic breast cancer: A randomised clinical trial. Eur J Cancer. 2019; 112: 57-65.

Zhao et al 2018
Zhao W, Kuai X, Zhou X, Jia L, Wang J, Yang X, et al. Trop2 is a potential biomarker for the promotion of EMT in human breast cancer. Oncology Reports 2018; 40: 759-766.

Signature Page for VV-RIM-05794073 v2.0

Approve: Document Level Task Verdict: Approved	PPD Content Approval 24-Apr-2024 14:14:08 GMT+0000

Approve: Document Level Task Verdict: Approved	PPD Content Approval 29-Apr-2024 11:34:17 GMT+0000

Approve: Document Level Task Verdict: Approved	PPD Content Approval 29-Apr-2024 12:27:00 GMT+0000

Signature Page for VV-RIM-05794073 v2.0