An Open-Label, Multinational, Multicenter, Phase 3b/4 Study of Trastuzumab Deruxtecan in Patients With or Without Baseline Brain Metastasis With Previously-Treated Advanced/Metastatic HER2-Positive Breast Cancer (DESTINY-Breast12)

ClinicalTrials.gov Identifier: **NCT04739761**

Clinical Study Protocol: Amendment 2, dated 07 June 2022

Clinical Study Protocol	
Study Intervention	Trastuzumab deruxtecan (T-DXd, AZD4552)
Study Code	D9673C00007
Version	Amendment 2
Date	07Jun2022

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Sponsor Name:

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Daiichi Sankyo Co., Ltd., 3-5-1, Nihonbashi-honcho, Chuo-ku, Tokyo, Japan
(Local sponsor for Japan)

Regulatory Agency Identifier Numbers:

US IND number: 146,111

EudraCT number: 2020-005048-46

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: D9673C00007

Amendment Number: Amendment 2

Study Intervention: Trastuzumab deruxtecan (T-DXd). The non-proprietary name of T-DXd is trastuzumab deruxtecan except in the US where it is fam-trastuzumab deruxtecan-nxki.

Study Phase: Phase 3b/4

Short Title: A Study of T-DXd in Patients With or Without Brain Metastasis Who Have Previously-Treated Advanced or Metastatic HER2 Positive Breast Cancer

Acronym: DESTINY-Breast12

Study Physician name and contact information will be provided separately.

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of issue**
Amendment 2	07-Jun-2022
Amendment 1	08-Apr-2021
Original protocol	06-Nov-2020

Amendment 2 07 Jun 2022

This amendment is considered 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 European Union.

Overall Rationale for the Amendment:

This amendment was prepared to allow for more patients in earlier lines in Cohort 1 versus later lines, as a result of published results from DESTINY-BREAST 03. The protocol was also updated to provide further emphasis on prophylaxis of nausea and vomiting as well as to correct minor inconsistencies.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.1 Synopsis; Section 4.1 Overall Design	Restriction of 25% added for the number of third-line patients enrolled in Cohort 1	To maximise the number of patients on 1L/2L within this cohort	Substantial
Section 1.3 Schedule of Activities	Requirement for HIV antibody test updated from "if required" to "if allowed by local regulations or IRB/EC)	For clarification	Non-substantial
	CCI [redacted]	For clarification	Non-substantial
Section 1.3 Schedule of Activities; Section 3 Objectives and Endpoints; Section 8.6.1 Collection of Mandatory Samples for CCI [redacted] Analysis	CCI [redacted] sampling updated to be subject to local laws and regulations	To allow for these samples not to be collected in countries where it is against local regulations	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.3 Synopsis; Section 3 Objectives and Endpoints; Section 8.5 Human Biological Samples Section 8.5.2 Immunogenicity Assessments; Section 9.4.4.3 Immunogenicity Assessments	ADA sampling and analysis removed from the protocol	ADA analysis is not a requirement for a Phase IIIb/IV study given the significant evidence already generated in the T-DXd study programme	Non-substantial
Section 1.3 Schedule of Activities Section 6.3 Measures to Minimize Bias: Randomization and Blinding	Central laboratory acceptance of HER2 tumor sample removed	For clarification	Non-substantial
Section 1.3 Schedule of Activities Section 6.3 Measures to Minimize Bias: Randomization and Blinding; Section 8.3.1 Time Period and Frequency for Collecting AE and SAE Information; Appendix A3 Informed Consent Process	Pre-screening updated to be mandatory for all participants	For clarification	Substantial
Section 1.3 Schedule of Activities; Section 6.6.1 Specific Toxicity Management and Dose Modification Information – T DXd	Clarification added for Troponin-T	Based on ESC advice	Non-substantial
Section 1.3 Schedule of Activities Section 8.2.5.2 Pulmonary Assessments Section 8.2.5.3 ILD/Pneumonitis Investigation	HRCT for screening and ILD/pneumonitis investigation updated to non-contrast	The injection of contrast has the potential for subtly (and unpredictably) increasing lung density, thereby increasing the difficulty in distinguishing between a reaction to the study treatment and the (temporary) impact of contrast on the lung	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 3 Objectives and Endpoints	New CCI endpoint added CCI	CCI	Substantial
Section 3 Objectives and Endpoints; Section 9.4.2.3.2 CCI	CCI	CCI	Substantial
Section 5.1 Inclusion Criteria	Inclusion criterion 1 updated to remove Japan-specific age of consent	Change in Japanese regulations; age of consent is now 18 years	Substantial
	Inclusion criterion 3b(ii) updated to clarify eligibility of participants with CNS lesions ≤ 2 cm	For clarification	Non-substantial
	Inclusion criterion 3c(i) updated to clarify completion of treatment		Non-substantial
	Inclusion criterion 4a updated to clarify dexamethasone treatment		Non-substantial
	Inclusion criterion 4b updated to clarify relation between anticonvulsants and start of T-DXd dosing		Non-substantial
	Inclusion criterion 8a updated to add evidence of disease progression on or within 6 months after HER2 targeted therapy	In order to include all approved SoC therapies in the study countries	Substantial
	Inclusion criterion 10 updated to clarify organ and bone marrow function parameters	For clarification	Non-substantial
Section 5.1 Inclusion Criteria; Section 5.2 Exclusion Criteria	Dexamethasone daily dose updated	For suitability of the steroid dose for participants with BMs	Substantial
Section 5.2 Exclusion Criteria	Exclusion criterion 6 removed	To remove duplicated information	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Exclusion criterion 20a updated to allow for denosumab treatment for bone lesions	For clarification	Non-substantial
	Exclusion criterion 20(c) removed	For clarification as TKIs approved for non-small cell lung cancer are not applicable in this study	Substantial
	Minor updates to exclusion criteria 8, 11, and 13 made; new exclusion criterion 20 added	For consistency with the clinical development programme	Non-substantial
Section 5.3.1 Caffeine, Alcohol and Tobacco	Abuse of caffeine and use of psychoactive drugs added; section name updated	For clarification	Non-substantial
Section 5.4 Screen Failures	Disposition wording updated for subjects that fail screening	Correction	Non-substantial
Section 6.2.1 Trastuzumab Deruxtecan Preparation, Administration, and Storage	Observation period added for first infusion of T-DXd	For clarification	Non-substantial
	Window added to infusion period added for subsequent cycles of T-DXd		
Section 6.5 Concomitant Therapy	Follow-up for ILD concomitant therapy updated	For clarification	Non-substantial
Section 6.6.1 Specific Toxicity Management and Dose Modification Information – T DXd	ILD Advisory Committee remit and ILD guidance references updated	For clarification	Non-substantial
Section 6.6.2 Dose Reductions, Interruptions, and Modifications; Appendix O Toxicity Management Guidelines	Dose delay time period from last infusion date updated	For consistency with the drug development programme	Non-substantial
Section 8.1.5.3 SRGQ-I	SRGQ-I updated to SRGQ in the first sentence	To correct an error	Non-substantial
Section 8.1.5.4 At-home Pulse Oximetry	Purpose of the walking assessment added	For clarification	Non-substantial
Section 8.1.5.5 Administration of ePRO Questionnaires	Clarification added in case of handheld device failure	For clarification	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 8.2.2 Vital Signs	Number of blood pressure measurements required reduced from 3 to 1	To reduce patient burden	Non-substantial
Section 8.2.4 Clinical Safety Laboratory Variables	Absolute neutrophil count and absolute lymphocyte count removed from Laboratory Safety Variables table	To remove duplication	Non-substantial
Section 8.2.5 Other Safety Assessments	Diffusion capacity of the lungs for carbon monoxide updated to be mandatory for participants with prior severe and/or clinically significant pulmonary disorders only and "if feasible" for all other participants	To reduce patient burden	Non-substantial
	For pulmonary assessments, it was clarified that non-contrast HRCT is to be performed at Screening, but CT is acceptable if HRCT is not feasible. It was also clarified that non-contrast HRCT is mandatory for suspected ILD/pneumonitis		
Section 8.3.11 Adverse Events of Special Interest	ILD Advisory Committee title updated	To correct typo	Non-substantial
Section 9.2 Sample Size Determination	Final analysis of Cohort 2 updated to clarify receipt of first dose by the last participant in the cohort and length of time in the study	For clarification	Non-substantial
Section 9.3 Populations for Analysis	Provision added to allow additional analysis sets to be included in the SAP	To allow for existing analysis sets to be constructed as needed	Non-substantial
Section 9.4.2.1.4 Subgroup Analyses	"(White vs non-White)" removed from race subgroup analyses	In line with Australian Health Authority request	Substantial
Appendix I 1 Female Participants	Definition of menopause removed	For consistency with the clinical development programme	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Appendix O Toxicity Management Guidelines	Minor updates made to Toxicity management guidelines for T-DXd	For consistency with the clinical development programme	Non-substantial
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized	Non-substantial

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

An Open-Label, Multinational, Multicenter, Phase 3b/4 Study of Trastuzumab Deruxtecan in Patients With or Without Baseline Brain Metastasis with Previously-Treated Advanced/Metastatic HER2-Positive Breast Cancer (DESTINY-Breast12)

Short Title:

A Study of T-DXd in Patients With or Without Brain Metastasis Who Have Previously-Treated Advanced or Metastatic HER2-Positive Breast Cancer

Rationale:

Several agents have been studied in patients with HER2-positive breast cancer with BMs. However, due to the decreased QoL and poor prognosis in this patient population, there is still a significant unmet need, particularly for later lines of treatment.

In DESTINY-Breast01, 184 patients with heavily pretreated breast cancer were treated with T-DXd at the recommended dose of 5.4 mg/kg. This study population included 24 patients who had CNS metastases at baseline. Within this small cohort, the efficacy response for T-DXd was encouraging, supporting a more extensive evaluation of T-DXd in these patients.

The current study is designed to evaluate the efficacy and safety of T-DXd in a real-world setting. Overall, this study will look to provide a much more robust and detailed understanding of T-DXd that will complement studies that are ongoing or already completed. This study will be conducted in participants with advanced/metastatic breast cancer, including participants with previously-treated, stable BM and participants with active BM, either previously untreated or progressing (but not requiring immediate local therapy), to evaluate their response to T-DXd treatment. Therefore, this study may provide additional treatment options for patients.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To describe the overall treatment effect of T-DXd in HER2-positive MBC patients with or without baseline BM	Participants without BM at baseline (Cohort 1): • ORR by RECIST 1.1 per ICR Participants with BM at baseline (Cohort 2): • PFS by RECIST 1.1 per ICR

Objectives	Endpoints
Secondary	
To describe the treatment effect on the development and progression of BM in patients with or without baseline BM using additional efficacy measurements	Participants in both cohorts: • OS • DoR by RECIST per ICR • Time to progression by RECIST per ICR • DoT on subsequent lines of therapy • PFS2 Participants without BM at baseline (Cohort 1): • Incidence of new symptomatic CNS metastasis during treatment In patients who develop isolated CNS progression, receive local therapy, and continue on protocol therapy: • Time to next progression (CNS or extracranial) or death • Site (CNS vs extracranial vs both) of next progression
To describe efficacy in patients with stable or untreated BM	Participants with BM at baseline (Cohort 2): • ORR by RECIST 1.1 per ICR • CNS PFS by CNS RECIST 1.1 per ICR • Time to new CNS lesions • CNS ORR by CNS RECIST 1.1 per ICR • CNS DoR by CNS RECIST 1.1 per ICR
To describe the effect of T-DXd on symptoms, functioning, and HRQoL in HER2-positive MBC patients with or without baseline BM	Changes in symptoms, functioning, and HRQoL as measured by • All patients: EORTC QLQ-C30, NANO scale, cognitive tests • BM patients: MDASI brain tumor-specific items • ILD/pneumonitis patients: SGRQ-I

Objectives	Endpoints
Safety	
To describe the safety profile of T-DXd	Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory results, and ECGs. Assessments related to AEs will also include: • Rate of investigator-assessed ILD/pneumonitis – PTs will be matched with most commonly reported terms within ILD cluster terms – Rate of ILD clinical symptom resolution among ILD patients who have been treated with high-dose steroid (total daily dose > 2 mg dexamethasone or equivalent) • Rate of AEs among patients with baseline BM who are treated with concurrent high-dose steroid (total daily dose > 2 mg dexamethasone or equivalent)

AE = adverse event; BM = brain metastasis; CNS = central nervous system; DoR = duration of response; CR = complete response; DoT = duration of treatment; ECG = electrocardiogram; EORTC = European Organization for the Research and Treatment of Cancer; HER2 = human epidermal growth factor receptor 2; HRQoL = health-related quality of life; ICR = independent central review; ILD = interstitial lung disease; MDASI = MD Anderson Symptom Inventory; NANO = Neurologic Assessment in Neuro-oncology; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PFS2 = time to second progression or death; PT = preferred term; QLQ-C30 = 30 item core quality of life questionnaire; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SGRQ-I = St. George's Respiratory Questionnaire – idiopathic pulmonary fibrosis version; T-DXd = trastuzumab deruxtecan.

For exploratory objectives, see Section 3 of the protocol.

Overall Design

This is a Phase 3b/4, open-label, multicenter, international study assessing the efficacy and safety of T-DXd in participants with or without BM, with previously-treated advanced/metastatic HER2-positive breast cancer whose disease has progressed on prior anti-HER2-based regimens and who received no more than 2 lines/regimens of therapy in the metastatic setting (excluding tucatinib). Participants will be enrolled into 1 of 2 cohorts according to the presence or absence of BMs at baseline.

Approximately 500 eligible participants will be treated in this study with 5.4 mg/kg T-DXd q3w until RECIST 1.1-defined radiological progression outside CNS, unless there is unacceptable toxicity, withdrawal of consent, or another criterion for discontinuation is met. To ensure adequate representation of participants with BM at baseline, the maximum number of participants without BM at baseline will be limited to 250. Cohort 1 will additionally be limited to include no more than 25% third-line participants. The study will evaluate ORR by RECIST 1.1, PFS by RECIST 1.1, the incidence of new symptomatic CNS metastasis, and

other measures of efficacy, and further characterize the safety and tolerability profile of T-DXd.

This study will be conducted in Europe, the US, Australia, and Japan.

Disclosure Statement: This is a Phase 3b/4, parallel cohorts, open-label, single-arm, multicenter, international study assessing the efficacy and safety of T-DXd in participants with or without BM, with previously-treated advanced/metastatic HER2-positive breast cancer.

Participant Population:

The target population of interest in this study is adults with previously-treated advanced/metastatic HER2-positive breast cancer whose disease has progressed on prior anti-HER2-based regimens and who received no more than 2 lines/regimens of therapy in the metastatic setting (excluding tucatinib). This study will include participants with previously-treated stable BM and participants with active BM, either previously untreated or progressing (but not requiring immediate local therapy). At the time of enrollment, participants must have an ECOG score of 0-1 and must not have LMD.

Number of Participants:

Approximately 500 eligible participants will be treated in the study. Of these, approximately 250 eligible participants without BM at baseline (Cohort 1) and 250 eligible participants with BM at baseline (Cohort 2) will be treated.

Intervention Groups and Duration:

All participants will receive IV T-DXd, 5.4 mg/kg, every 3 weeks (21-day cycle) until RECIST 1.1-defined radiological progression outside CNS. Participants may continue to receive T-DXd beyond progression, as long as they are continuing to show clinical benefit, as judged by the investigator, and in the absence of other discontinuation criteria.

Temporary interruption is allowed for local therapy of CNS-only progression. Dose delays, dose reductions to 4.4 mg/kg and further dose reductions to 3.2 mg/kg are allowed for the management of toxicities.

Follow-up of Participants Post Discontinuation of Study Intervention:

After study intervention discontinuation, all participants will undergo an EOT visit (within 7 days of discontinuation) and will be followed up for safety assessments 40 (+ up to 7) days after their last dose of study intervention (ie, the safety follow-up visit).

Participants who have discontinued study intervention prior to RECIST 1.1-defined radiological progression will be followed up with tumor assessments according to the SoA until RECIST 1.1-defined PD or death regardless of whether or not the participant started a

subsequent anticancer therapy, unless they have withdrawn all consent to study-related assessments.

In addition, all participants will be followed up for survival status and DoT on subsequent therapies after intervention discontinuation every 3 months (± 14 days) from the date of the safety follow-up until death, withdrawal of consent, or the end of the study, as per the SoA.

No intervention is planned 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.

Independent Data Monitoring Committee:

An IDMC composed of independent experts will be convened to review safety data and make recommendations to continue, amend, or stop the study based on safety findings.

Full details of the IDMC procedures and processes can be found in the IDMC Charter.

Statistical Methods

The primary objective of this study is to describe the overall treatment effect of T-DXd in HER2-positive MBC patients with or without baseline BM:

- In participants without BM at baseline (Cohort 1), this objective will be evaluated upon completion of the study by the ORR. The ORR is defined as the proportion of participants who have a confirmed CR or confirmed PR, as determined by ICR per RECIST 1.1, and will be assessed for all dosed participants in Cohort 1. CCI [redacted] The ORR will be assessed as a secondary endpoint for participants in Cohort 2.
- In participants with BM at baseline (Cohort 2), the primary objective will be evaluated by PFS as assessed by RECIST 1.1. CCI [redacted] The PFS will be defined as the time from the date of the first dose of

study intervention until the date of objective PD per RECIST 1.1 as assessed by ICR or death and will be assessed for all dosed participants in Cohort 2. PFS will be analyzed by the Kaplan-Meier method. 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. The proportion of participants alive and progression-free at 12-monthly intervals from the first date of dosing will be summarized.

For each study visit, participants will be programmatically assessed for RECIST 1.1 response of CR, PR, SD, PD, or NE based on an ICR of imaging scans and depending on the status of their disease compared with baseline and previous assessments. The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and will be adjudicated, if required. The tumor response endpoints (ORR, PFS, time to progression, and DoR) will be derived from the scan dates and overall visit responses.

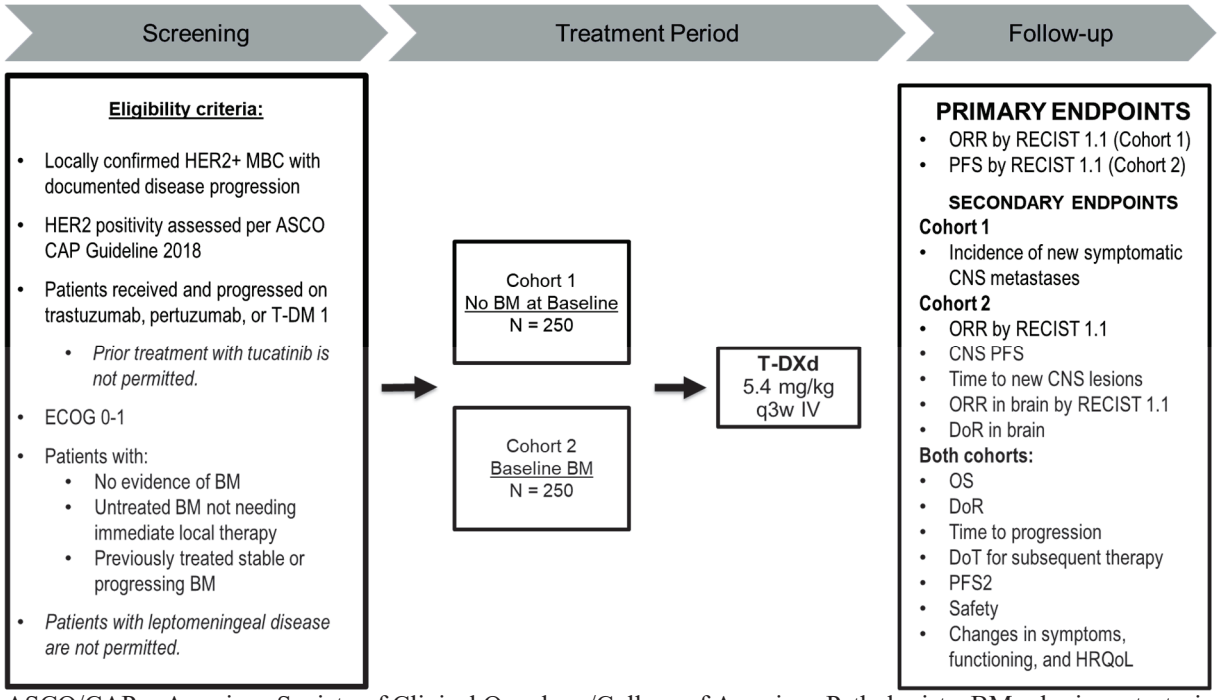
No formal hypothesis testing will be done for this single-arm, open-label study.

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

1.2 Schema

The study design is summarized in Figure 1.

Figure 1 Study Design



ASCO/CAP = American Society of Clinical Oncology/College of American Pathologists; BM = brain metastasis; CNS = central nervous system; DoR = duration of response; DoT = duration of treatment; ECOG = Eastern Cooperative Oncology Group; HER2 = human epidermal growth factor receptor 2; HRQoL = health-related quality of life; IV = intravenous; MBC = metastatic breast cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PFS2 = time to second progression or death; q3w = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; T-DM 1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

1.3 Schedule of Activities

The procedures for this study are presented in Table 1.

Unless all eligibility criteria have been met, participants must not be treated. When participants do not receive study intervention, participants should undergo a physical examination and vital signs assessment with additional assessments at the discretion of the investigator. All samples are collected before infusion unless otherwise indicated.

Participants will be enrolled into the study after signing the main ICF and will begin screening/baseline procedures. Screening will take place for up to 28 days from the date of enrollment. At the end of screening/baseline procedures, participants who pass the eligibility criteria will be assigned to treatment. Every effort should be made to minimize the time between treatment assignment and dosing. Dosing should occur no more than 3 days after treatment assignment. If it is anticipated that dosing cannot occur within 3 days, a discussion

with the AstraZeneca study physician is required. Participants who fail to meet the eligibility criteria will be termed “screen failures”.

A pre-screen ICF must be signed by patients to permit tumor tissue sample collection for HER2 status testing prior to the 28-day screening window. At the time of signing the pre-screen ICF, Investigators should ensure that there is a reasonable possibility that the patient would be a candidate for this study based on available information (e.g., medical history, availability of required number of slides for study).

Table 1 Schedule of Activities

Procedure	Screening -28 days	Cycle 1			Cycle 2	Cycle 3	Cycle 4 and subsequent cycles until PD	Post-intervention follow-up period			Details in CSP section or appendix
		Day 1	Day 8 (± 1 day)	Day 15 (± 1 day)	Day 1 (± 2 days)	Day 1 (± 2 days)	Day 1 (± 2 days)	EOT [a] or E/D	Safety F/U (40 + 7 days after last dose)	Progression/ survival F/U q3 months ± 14 days)	
Informed consent [b]	X										Section 5.1 and Appendix A 3
CCI [redacted]	X										Section 5.1 and Appendix A 3
Study Procedures and Assessments											
Inclusion and exclusion criteria	X										Sections 5.1, 5.2, and 5.3
Demography	X										Section 5.1
Full physical examination	X										Section 8.2.1
Targeted physical examination		X [c]			X [c]	X [c]	X [c]	X	X		Section 8.2.1
Height	X										Section 8.2.1
Weight	X	X [c]			X [c]	X [c]	X [c]	X	X		Section 8.2.1
Medical history (includes substance use and prior cancer treatment)	X	X [d]									Sections 5.1 and 5.2
Subsequent anticancer therapy (including surgery and radiation therapy)									X	X	Section 7.1.1

Table 1 Schedule of Activities

Procedure	Screening -28 days	Cycle 1			Cycle 2	Cycle 3	Cycle 4 and subsequent cycles until PD	Post-intervention follow-up period			Details in CSP section or appendix
		Day 1	Day 8 (± 1 day)	Day 15 (± 1 day)	Day 1 (± 2 days)	Day 1 (± 2 days)	Day 1 (± 2 days)	EOT [a] or E/D	Safety F/U (40 + 7 days after last dose)	Progression/ survival F/U q3 months ± 14 days)	
ECOG performance status	X	X [c]			X [c]	X [c]	X [c]	X	X		Section 8.2.5.4
12-lead ECG	X	X [c]					X (C4 and every 4 cycles) [c e]	X			Section 8.2.3
Vital signs [e]	X	X [c]	X	X	X [c]	X [c]	X [c]	X	X		Section 8.2.2
ECHO or MUGA (LVEF)	X						X (C5 and every 4 cycles [±7 days])	X			Section 8.2.5.1
Pulmonary function tests	X	If ILD/pneumonitis is suspected									Section 8.2.5.2
SpO_2	X	X [c]	X	X	X [c]	X [c]	X [c]	X	X		Section 8.2.5.2
Non-contrast HRCT	X	If ILD/pneumonitis is suspected									Section 8.2.5.2 and 8.2.5.3
Ophthalmologic assessments	X	As clinically indicated						X			Section 8.2.5.5
ILD/pneumonitis investigation		If ILD/pneumonitis is suspected									Section 8.2.5.3
AE [f]	At every visit and may be conducted by phone if not tied to a visit										Section 8.3

Table 1 Schedule of Activities

Procedure	Screening -28 days	Cycle 1			Cycle 2	Cycle 3	Cycle 4 and subsequent cycles until PD	Post-intervention follow-up period			Details in CSP section or appendix
		Day 1	Day 8 (± 1 day)	Day 15 (± 1 day)	Day 1 (± 2 days)	Day 1 (± 2 days)	Day 1 (± 2 days)	EOT [a] or E/D	Safety F/U (40 + 7 days after last dose)	Progression/ survival F/U q3 months ± 14 days)	
Concomitant therapy	At every visit and may be conducted by phone if not tied to a visit										Section 6.5
Laboratory Assessments											
Serum/urine pregnancy test (WOCBP only)	X	X [c]			X [c]	X [c]	X [c]	X	X		Sections 5.1, 5.2, and 8.2.4,
Hepatitis B/C serology	X										Sections 5.2 and 8.2.4
HIV antibody test (if allowed by local regulations or IRB/EC)	X										Sections 5.2 and 8.2.4
Clinical safety laboratory assessments (clinical chemistry, hematology)	X [g]	X [c]	X	X	X [c]	X [c]	X [c]	X	X		Section 8.2.4
Coagulation	X	As clinically indicated									Section 8.2.4
Urinalysis	X	As clinically indicated									Section 8.2.4
Troponin [h]	X	If at any time a participant reports signs or symptoms suggesting CHF, myocardial infarction, or other causes of myocyte necrosis						X			Sections 6.6.1, 8.2.4, and 8.2.5.1
Biomarker Assessments											

Table 1 Schedule of Activities

Procedure	Screening -28 days	Cycle 1			Cycle 2	Cycle 3	Cycle 4 and subsequent cycles until PD	Post-intervention follow-up period			Details in CSP section or appendix
		Day 1	Day 8 (± 1 day)	Day 15 (± 1 day)	Day 1 (± 2 days)	Day 1 (± 2 days)	Day 1 (± 2 days)	EOT [a] or E/D	Safety F/U (40 + 7 days after last dose)	Progression/ survival F/U q3 months ± 14 days)	
Mandatory (if available) archival FFPE (preferred) tumor tissue sample for confirmation of HER2 status and CCI CCI	X										Sections 6.3 and 8.6.1
Mandatory blood sample for CCI	X	X			X	X	X (C4 then aligned with RECIST assessments)[i]	X (progression only)			Section 8.6.1
Mandatory newly acquired biopsy (if archival tumor tissue not available) CCI CCI	X										Sections 6.3, 8.6.1, and 8.6.2
CCI					X (± 1 week)						Section 8.6.2
CCI								X (progression only)			Section 8.6.2

Table 1 Schedule of Activities

Procedure	Screening -28 days	Cycle 1			Cycle 2	Cycle 3	Cycle 4 and subsequent cycles until PD	Post-intervention follow-up period			Details in CSP section or appendix
		Day 1	Day 8 (± 1 day)	Day 15 (± 1 day)	Day 1 (± 2 days)	Day 1 (± 2 days)	Day 1 (± 2 days)	EOT [a] or E/D	Safety F/U (40 + 7 days after last dose)	Progression/ survival F/U q3 months ± 14 days)	
Blood sample for CCI CCI	X	X			X		X (C4 then aligned with RECIST assessments)[i]	X (progression only)			Section 8.6.1
Blood sample for CCI CCI	X	X			X		X (C4 then aligned with RECIST assessments)[i]	X (progression only)			Section 8.6.1
Blood samples for PK and CCI		At the time of ILD onset, if ILD/pneumonitis is suspected									Sections 8.2.5.3 and 8.6.1

Table 1 Schedule of Activities

Procedure	Screening -28 days	Cycle 1			Cycle 2	Cycle 3	Cycle 4 and subsequent cycles until PD	Post-intervention follow-up period			Details in CSP section or appendix
		Day 1	Day 8 (± 1 day)	Day 15 (± 1 day)	Day 1 (± 2 days)	Day 1 (± 2 days)	Day 1 (± 2 days)	EOT [a] or E/D	Safety F/U (40 + 7 days after last dose)	Progression/ survival F/U q3 months ± 14 days)	
Whole blood sample for gene expression analysis (RNA)	X	X			X		X (C4 then aligned with RECIST assessments)[i] and on suspected/ diagnosis of ILD	X (progression only)			Section 8.6.1
CCI [redacted]		X									Section 8.7 and Appendix D
CCI [redacted]		If ILD/pneumonitis is suspected									Section 8.6.2
CCI [redacted]		If ILD/pneumonitis is suspected									Section 8.6.2
Study intervention administration											
T-DXd		T-DXd at 5.4 mg/kg will be administered via IV infusion on Day 1 of each 3-week cycle									Sections 6 and 7
Efficacy measurements											
Tumor imaging (RECIST 1.1)	X	Every 6 weeks (± 1 week) from Cycle 1 Day 1 for 48 weeks, and then every 9 weeks (± 1 week, starting at Week 57) until RECIST 1.1-defined radiological PD						X			Section 8.1.1, Appendix G

Table 1 Schedule of Activities

Procedure	Screening -28 days	Cycle 1			Cycle 2	Cycle 3	Cycle 4 and subsequent cycles until PD	Post-intervention follow-up period			Details in CSP section or appendix
		Day 1	Day 8 (± 1 day)	Day 15 (± 1 day)	Day 1 (± 2 days)	Day 1 (± 2 days)	Day 1 (± 2 days)	EOT [a] or E/D	Safety F/U (40 + 7 days after last dose)	Progression/ survival F/U q3 months ± 14 days)	
Brain MRI (preferred)/CT imaging (CNS RECIST 1.1 and CCI)	X [j]	Every 6 weeks (± 1 week) from Cycle 1 Day 1 for 48 weeks, and then every 9 weeks (± 1 week, starting at Week 57) [k] until RECIST 1.1-defined radiological PD						X [j]			Section 8.1.1, Appendix G, Appendix H
Isotopic bone scan (scintigraphy)	X	As clinically indicated until RECIST 1.1-defined radiological PD									Section 8.1.1, Appendix G
Survival status									X	X	Sections 7.1.4 and 8.1.3
PFS2									X	X	Sections 7.1.3 and 8.1.3
Other assessments and procedures											
ePRO device allocation (ePRO device allocated only if participant does not have own compatible device) and training	X										Section 8.1.5.5
EORTC QLQ-C30, MDASI brain tumor-specific items [l]		Every 3 weeks from Cycle 1 Day 1, (or coinciding with the next cycle if not exactly 3 weeks gap), at the EOT Visit, and for up to 24 weeks post EOT or second progression, whichever occurs earlier									Section 8.1.5.1
Cognitive tests [l]		Every 12 weeks from Cycle 1 Day 1						X			Section 8.1.5.4
NANO scale [l]		X			X	X	X	X			Section 8.1.5.4
SGRQ-I		After diagnosis of ILD/pneumonitis and q1w thereafter until EOT						X	X		Section 8.1.5.1

Table 1 Schedule of Activities

Procedure	Screening -28 days	Cycle 1			Cycle 2	Cycle 3	Cycle 4 and subsequent cycles until PD	Post-intervention follow-up period			Details in CSP section or appendix
		Day 1	Day 8 (± 1 day)	Day 15 (± 1 day)	Day 1 (± 2 days)	Day 1 (± 2 days)	Day 1 (± 2 days)	EOT [a] or E/D	Safety F/U (40 + 7 days after last dose)	Progression/ survival F/U q3 months ± 14 days)	
MDASI lung cancer (ILD symptom-specific items)		Cycle 1 Day 1 before dosing and, after diagnosis of ILD/pneumonitis, daily until safety F/U visit									Section 8.1.5.2
At-home pulse oximetry		Resting: Cycle 1 Day 1 before dosing and, after diagnosis of ILD/pneumonitis, daily until safety F/U visit Walking: Cycle 1 Day 1 before dosing and, after diagnosis of ILD/pneumonitis, q1w until safety F/U visit									Section 8.1.5.4
CCI [redacted]											
CCI [redacted]	At each scheduled visit, the site should review clinical notes for any non-study-related hospital admissions and visits that have occurred										Section 8.8

[a] EOT is the date the investigator decides to permanently discontinue a participant from study intervention; the visit should occur within 7 days of the decision.

[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. A pre-screen ICF must be signed for participants to permit for tumor tissue sample collection (HER2 status) and testing prior to the 28-day screening window.

[c] Within 3 days before administration.

[d] If screening assessments have been performed within 3 days prior to starting study intervention, they do not have to be repeated at Cycle 1 Day 1 if the participant's condition has not changed. Medical history should include substance use (drugs, alcohol, caffeine, type and frequency of tobacco use, e-cigarette use, vaping [including dates]).

[e] If ECG is abnormal, follow institutional guidelines.

[f] During the pre-screening period, only SAEs directly related to tissue screening procedure (ie, if a participant undergoes a tumor biopsy) will be reported.

[g] Laboratory tests must be performed within 14 days of randomization/enrollment, and include hematology (red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count, differential white blood cell count [neutrophils, lymphocytes, monocytes, eosinophils, basophils]) and chemistry (total protein, albumin, alkaline phosphatase, ALT, AST, TBL, blood urea nitrogen, calcium, chloride, serum creatinine, lactate dehydrogenase, potassium, sodium and magnesium).

[h] Troponin-T (preferably high-sensitivity troponin-T) will be measured at screening and at EOT, and as needed based on participant-reported cardiac signs or symptoms suggesting CHF, myocardial infarction, or other causes of cardiac myocyte necrosis. If ECG is abnormal, follow institutional guidelines. Qualitative testing for Troponin-T or Troponin-I instead of Troponin-T may be acceptable to perform, if in accordance with local practice and if quantitative method or Troponin-T is not available. Positive results must be followed up with a quantitative measurement along with other institutional guidance (refer to Appendix O for additional management guidelines)

[i] Samples to be collected on Day 1 of Cycle 4, then every 6 weeks (± 1 week) until Week 48 and every 9 weeks (± 1 week) after Week 57.

[j] CCI [redacted]

[k] Brain imaging by IV contrast-enhanced MRI (preferred, unless contraindicated) or IV contrast-enhanced CT is required for all patients at screening/baseline and EOT visit.

[l] CCI [redacted]

[m] CCI [redacted]

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

AE = adverse event; ALT = alanine aminotransferase ; AST = aspartate aminotransferase ; BM = brain metastasis; C = cycle; CHF = congestive heart failure; CNS = central nervous system; CSP = clinical study protocol; CT = computed tomography; CCI [redacted] EC = ethics committee; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; E/D = Early Study Intervention/Discontinuation; EORTC = European Organization for Research and Treatment of Cancer; EOT = end-of-treatment; ePRO = electronic patient-reported outcome; FFPE = formalin-fixed and paraffin-embedded; F/U = follow-up; HER2 = human epidermal growth factor receptor 2; HIV = human immunodeficiency virus; CCI [redacted] HRCT = high-resolution computed tomography; ICF = informed consent form; ILD = interstitial lung disease; IRB = institutional review board; IV = intravenous; LVEF = left ventricular ejection fraction; MDASI = MD Anderson Symptom Inventory; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NANO = Neurologic Assessment in Neuro-oncology; PD = progression of disease; PFS2 = time to second progression or death; q1w = every 1 week; q3 months = every 3 months; QLQ-C30 = 30 item core quality of life questionnaire; CCI [redacted] CCI [redacted]; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RNA = ribonucleic acid; SAE = serious adverse event; SGRQ-I = St. George's Respiratory Questionnaire – idiopathic pulmonary fibrosis-specific version; SpO_2 = peripheral capillary oxygen saturation ; TBL = total bilirubin; T-DXd = trastuzumab deruxtecan; WOCBP = women of childbearing potential.

2 INTRODUCTION

Trastuzumab deruxtecan is an ADC that targets HER2. The non-proprietary name for T-DXd is trastuzumab deruxtecan except in the US where it is fam-trastuzumab deruxtecan-nxki.

2.1 Study Rationale

Several agents have been studied in patients with HER2-positive breast cancer with BMs. Specifically, the HER2CLIMB study showed that tucatinib is effective in active/stable treated or asymptomatic untreated BMs (Murthy et al, 2020). However, due to the decreased QoL and poor prognosis in this patient population, there is still a significant unmet need particularly in later lines of treatment.

Within the clinical development program for T-DXd, there is some data supporting the use of T-DXd in patients with BMs. In DESTINY-Breast01, 184 patients with heavily pretreated breast cancer were treated with T-DXd at the recommended dose of 5.4 mg/kg. This study population included 24 patients who had CNS metastases at baseline (Jerusalem et al, 2020). Within this small cohort, the efficacy response for T-DXd was encouraging, supporting a more extensive evaluation of T-DXd in this patient population.

The current study is designed to evaluate the efficacy and safety of T-DXd in a real-world setting. Overall, this study will look to provide a much more robust and detailed understanding of T-DXd that will complement studies that are ongoing or already completed. This study will be conducted in participants with advanced/metastatic breast cancer, including participants with previously-treated stable BM and participants with active BM, either previously untreated or progressing (but not requiring immediate local therapy), to evaluate their response to T-DXd treatment. Therefore, this study may provide additional treatment options for patients.

2.2 Background

A detailed description of the chemistry and pharmacology of T-DXd and the nonclinical and clinical efficacy and safety results of T-DXd are provided in the IB.

2.2.1 Background Information on the Disease to Be Treated

Despite advances in diagnosis and treatment, 10 to 15% of women diagnosed with MBC have cancer that has metastasized to the brain; this number can be as high as approximately 50% in women with HER2-positive breast cancer (Pestalozzi et al, 2013). Previously, having cancer that metastasized to the brain was associated with low life expectancy (~6 months), decreased QoL and a poor prognosis. With new therapies (eg, radiation, systemic therapy), life expectancy has increased to a median of 3.03 years (95% CI, 1.94-NE) (Anders, 2016). Although treatable, MBC remains largely an incurable disease with an estimated 5-year OS of only 25% (Cardoso et al, 2020).

Breast cancer treatment paradigms in the metastatic setting are defined by the expression of the HER2 and the ER and PgR, which are collectively referred to as HR. In women with HER2-positive breast cancer, there is overexpression and/or overamplification of HER2. Several HER2 targeted therapies such as HERCEPTIN® (trastuzumab), PERJETA® (pertuzumab), KADCYLA® (T-DM1), and TYKERB® (lapatinib) are used in breast cancer patients who have HER2 overexpression/overamplification.

Guidelines such as those from ASCO, ESMO, and National Comprehensive Cancer Network recommend patients with symptomatic BMs receive local therapy and continue the same anti-HER2 therapy if the patients continue to derive clinical benefit systemically. Recent studies have specifically included patients with HER2-positive breast cancer with BMs with positive results.

HER2CLIMB was a Phase 2, global, randomized, double-blind, placebo-controlled study in adults with locally advanced unresectable or metastatic HER2-positive breast cancer who previously received trastuzumab, pertuzumab, and T-DM1 separately or in combination (Murthy et al, 2020). At the time of the study, it included the largest number of patients with BMs (48% of the study population) studied in a registrational trial for HER2-positive MBC. The HER2CLIMB study evaluated tucatinib versus placebo in combination with trastuzumab and capecitabine. It met all primary and secondary endpoints demonstrating a 46% reduction in the risk of disease progression or death and an improvement in OS by a median of 4.5 months. Specifically, in patients with BMs, a 52% lower risk of disease progression or death was observed (Lin et al, 2020).

DESTINY-Breast01 (NCT03248492) was a Phase 2, open-label, single-group, multicenter study conducted in 2 parts (Modi et al, 2020). In Part 1 of the study, 3 doses were evaluated, and in Part 2, the selected dose of 5.4 mg/kg was used to evaluate the efficacy and safety of T-DXd in adult patients with pathologically documented HER2-positive MBC who had received previous treatment with T-DM1. A total of 253 patients were treated with T-DXd in both parts of this study, including 184 patients who received T-DXd at the recommended dose of 5.4 mg/kg. This study population included 24 patients who had CNS metastases at baseline. The ORR in this subset of patients was 58%, similar to the ORR of 61% in patients without CNS metastases (Jerusalem et al, 2020; Modi et al, 2020). The subset of patients with baseline CNS metastases also had a similar estimated mPFS (18.1 months) compared with the mPFS for the overall study population (16.4 months). However, clinical experience of T-DXd in this patient population is limited due to the small sample size and the inclusion and exclusion criteria for the study.

Improving the quality of MBC clinical research through the adoption and incorporation of clinically meaningful trial endpoints that measure both QoL and survival is important. To that end, there is a need to assess the efficacy of T-DXd in delaying the development of

symptomatic BM.

2.2.2 Background Information on T-DXd

As of 28 March 2019, AstraZeneca and Daiichi Sankyo Company, Limited (Daiichi Sankyo) entered into a joint global development and collaboration agreement for T-DXd, a HER2-targeting ADC.

Trastuzumab deruxtecan consists of an anti-HER2 antibody, MAAL-9001, covalently linked to ~8 molecules of MAAA-1162a (GGFG tetrapeptide cleavable linker and a TOPO-1 inhibitor payload [MAAA-1181a]). The antibody MAAL-9001 has the same amino acid sequence as trastuzumab, and thus T-DXd is similarly targeted to HER2-expressing tumors. The drug MAAA-1181a (DXd), a derivative of exatecan, is released after internalization and leads to apoptosis of the target tumor cells via the inhibition of TOPO-1.

Due to incorporation of a novel linker, T-DXd achieves a higher DAR of approximately 8 with homogeneous conjugation of DXd, compared with other approved ADCs, which have a DAR of 3 to 4 (Ogitani et al, 2016). In addition, the cleavable linker in T-DXd is stable in plasma, conferring a favorable safety profile as observed in nonclinical toxicology rat and monkey studies.

Trastuzumab deruxtecan exhibits HER2-specific anti-tumor activity via a mechanism of action that combines the mAb specificity with the broad cytotoxicity of the released drug. After binding to HER2 and internalization, the T-DXd linker is selectively cleaved by lysosomal enzymes preferentially expressed in tumor cells and releases the drug DXd in the cytoplasm. The drug DXd is an exatecan derivative with greater potency than SN-38, the active metabolite of irinotecan (Ogitani et al, 2016). The TOPO-1 inhibitor payload of T-DXd is released into the cytoplasm of the target cell where it enters the nucleus, inhibits TOPO-1, and arrests DNA synthesis, leading to apoptosis of target cells.

There are completed and ongoing clinical trials with T-DXd, either alone or in combination, across multiple HER2-expressing tumor types including breast cancer, gastric cancer, non-small cell lung cancer, and colorectal cancer (please refer to the T-DXd IB for a list of completed and ongoing trials and most recent patient exposure data).

For details on the schematic structures, molecular formula, finished product of T-DXd and the overall safety and clinical efficacy data from different studies that involved T-DXd, refer to the most recent IB.

T-DXd is approved in the US and Japan for the treatment of adult patients who have received prior treatments for HER2-positive breast cancer that is unresectable or metastatic (US)/recurrent (Japan). In the European Union, T-DXd received a conditional marketing authorization for the treatment of adult patients with unresectable or metastatic HER2-positive

breast cancer, who have received 2 or more prior anti-HER2 based regimens.

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 T-DXd are found below and in the IB.

2.3.1 Risk Assessment

The risks of T-DXd, HER2-targeted agents, and TOPO-1 inhibitors are summarised below. Toxicity management guidelines for T-DXd are provided in Appendix O.

2.3.1.1 Risks of T-DXd

Based on data from clinical trials that involved T-DXd, toxicities considered to be associated with administration of T-DXd include the important identified risks of ILD/pneumonitis and neutropenia (including febrile neutropenia). Other identified risks for T-DXd are infusion-related reactions, hematological AEs (anemia, leukopenia, lymphopenia, thrombocytopenia), pulmonary/respiratory AEs (cough, dyspnea, upper respiratory tract infection, epistaxis), gastrointestinal AEs (abdominal pain, constipation, diarrhea, dyspepsia, nausea, stomatitis, vomiting), hepatic AEs (hepatic function abnormality, ALT, AST, and alkaline phosphatase increased), skin AEs (alopecia, rash, pruritis), blood bilirubin increased, pneumonia, dry eye, dehydration, hypokalemia, decreased appetite, dizziness, fatigue, peripheral edema, pyrexia, and headache.

Based on the available preclinical data, review of the cumulative literature, and reported toxicities for the same class of agents, the important potential risks for T-DXd are embryofetal toxicity and LVEF decrease (re-labelled as ‘LV dysfunction’ as the undesirable clinical outcome of LVEF reductions, in accordance with the Revision 2 of the European Medicines Agency guidelines on Good Pharmacovigilance Practice. This re-labelling of the risk does not affect the nature or monitoring methods of the LVEF decrease as a potential risk associated with T-DXd). Keratitis is considered a potential risk for T-DXd.

Interstitial lung disease/pneumonitis and LVEF decrease are considered AESIs.

Trastuzumab deruxtecan has not been studied in subjects with severe/moderate hepatic impairment or severe renal impairment.

2.3.1.2 Risks of HER2-targeted Agents

Several agents that target HER2 and prevent its activation or heterodimerization have been

developed and marketed for the treatment of HER2-positive cancers. These include the mAbs trastuzumab and pertuzumab, the ADC T-DM1, and HER1- and HER2-associated TKIs, lapatinib, and neratinib. The safety profile of these HER2-targeted agents has been well described. The main safety risks identified in patients receiving HER2-targeted products are described below; these could potentially be expected to occur in patients receiving T-DXd.

Cardiotoxicity: Patients treated with trastuzumab are at increased risk for developing CHF (NYHA class IIIV) or asymptomatic cardiac dysfunction, including LVEF decrease. Cardiac dysfunction, mainly asymptomatic LVEF decrease, has also been observed with pertuzumab in combination with trastuzumab. Similarly, cardiac dysfunction has been observed in patients receiving T-DM1, at a lower incidence than in trastuzumab treated patients. Majority of cases have been asymptomatic decreases in LVEF. Cardiac dysfunction with lapatinib has occurred mainly in patients receiving the combination of trastuzumab and lapatinib and has consisted of predominantly asymptomatic LVEF decrease.

Pulmonary Toxicity: Cases of pulmonary toxicity, including ILD and pneumonitis, have been observed in patients receiving trastuzumab, T-DM1, and lapatinib. Occasionally these cases have been severe in nature and have resulted in fatal outcomes. Risk factors associated with ILD/pneumonitis include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine, and radiation therapy.

Hypersensitivity/Infusion-Related Reactions: The administration of therapeutic proteins is associated with a risk of hypersensitivity and/or infusion reactions. Hypersensitivity/infusion-related reactions have been reported with trastuzumab, pertuzumab and T-DM1. These can range from mild reactions to severe anaphylactic shock with fatal outcome as has been the case for trastuzumab.

Hepatic Toxicity: Cases of hepatic toxicity have occurred with T-DM1, lapatinib, and trastuzumab. In patients receiving T-DM1, hepatic toxicity has manifested mainly as transient asymptomatic liver transaminase elevations, although serious cases of drug-induced liver failure and nodular regenerative hyperplasia have also been reported. Lapatinib has also been associated with serious cases of DILI.

Hematological Toxicity: Hematological toxicity has been observed with all HER2-targeted therapies. Neutropenia, febrile neutropenia, leukopenia, and anemia have occurred commonly with trastuzumab, pertuzumab, and T-DM1. Thrombocytopenia, including Grade 3 and 4, is a common occurrence in T-DM1-treated patients. Although rare, serious hemorrhagic events have been reported in the setting of thrombocytopenia. Lower rates of thrombocytopenia have also occurred with trastuzumab and pertuzumab when used in combination with chemotherapy.

2.3.1.3 Risks of Topoisomerase I Inhibitors

The drug DXd is a derivative of exatecan (DX-8951f), a TOPO-1 inhibitor. Other products of the same class include irinotecan and topotecan. Exatecan is a camptothecin derivative which has previously been developed by the former Daiichi Pharmaceuticals Co., Ltd. as an anticancer therapy.

The main risks associated with the use of TOPO-1 inhibitors include hematological toxicities and gastrointestinal toxicities. Hematological toxicities, manifesting as neutropenia, febrile neutropenia, anemia, thrombocytopenia, and pancytopenia are commonly observed. An increased risk of infections, including neutropenic colitis and neutropenic sepsis, has been reported with these agents.

Diarrhea and delayed onset diarrhea, which can be severe and lead to dehydration, have been associated with TOPO-1 inhibitors. Other significant risks include ILD/pneumonitis, liver impairment, immune system disorders, and alopecia. Acute cholinergic syndrome, manifesting as diarrhea and other cholinergic symptoms, has been reported with irinotecan.

The safety profile of exatecan is broadly similar to the safety profile of other TOPO-1 inhibitors, with hematological toxicities and gastrointestinal toxicities being the most significant groups of events.

2.3.2 Benefits of T-DXd

Trastuzumab deruxtecan is under development for the treatment of HER2-expressing cancers and HER2-mutant tumors. Based on preliminary clinical observations in a Phase 1 study (Study DS8201-AJ101 [Phase 1; NCT02564900]), Study DS8201-A-U201 (DESTINY-Breast01, Phase 2; NCT03248492), and the DESTINY-Gastric01 Phase 2 study (NCT03329690), T-DXd demonstrated anti-tumor activity in HER2-expressing cancers, including gastric cancer and breast cancer, and a generally acceptable safety profile in these populations. Data from the Phase 2 DS8201-A-U204 (DESTINY-Lung01; [NCT03505710]) study also provides encouraging preliminary evidence of anti-tumor activity of T-DXd in tumors with HER2 mutations.

Human epidermal growth factor receptor 2-positive breast cancer is associated with a relatively high incidence of BM (up to ~50%; Freedman et al, 2019; Lin and Winer, 2007) and therefore therapies are needed that can address this patient population. DESTINY-Breast01 was a Phase 2, open-label, single-group, multicenter study in 253 patients with heavily pretreated breast cancer, including 24 patients with CNS metastases at baseline (13%). The demographic characteristics were consistent for patients with HER2-positive breast cancer with and without BM, including having a median of 6 prior lines of therapy (range, 3 to 16).

For all efficacy measures, T-DXd demonstrated similar results in the CNS subgroup compared to the overall study population. Among the 184 patients who received T-DXd at the

recommended dose of 5.4 mg per kilogram, the confirmed ORR on ICR was 60.9% (95% CI, 53.4 to 68.0) and 58.3% (95% CI, 36.6% to 77.9%) in the CNS subgroup. Median PFS in the CNS subgroup was 18.1 months (95% CI 6.7 to 18.1 months) compared to the overall study population (16.4 months [95% CI 12.7 months to NE]). Disease progression in the CNS among patients with non-CNS disease at baseline was 8% (Jerusalem et al, 2020). The median DoR and median time until response was consistent among the overall study population and the CNS subgroup.

These results from the DESTINY-Breast01 study demonstrated a positive response rate for T-DXd treatment in patients with HER2-positive MBC who had been previously treated with multiple therapies. However, there remains a need to generate more clinical data with T-DXd to evaluate its effects on delaying the development of symptomatic BM.

DESTINY-Breast03 was a Phase 3, multicenter, randomized, open-label, 2-arm, active-controlled head-to-head study of T-DXd versus trastuzumab emtansine (T-DM1) in patients with HER2-positive MBC previously treated with trastuzumab and taxane (Cortés et al, 2022). Patients in the T-DXd and control arms had median follow-up of 16.2 and 15.3 months, respectively. At the time point of the DCO, the number of patients remaining on treatment were 132/261(50.6%) in the T-DXd arm and 47/263 (17.9%) in the T-DM1 arm. T-DXd demonstrated a 72% reduction in the risk of disease progression or death compared to T-DM1 (hazard ratio [HR] 0.28; 95% confidence interval [CI] 0.22-0.37; p = 7.8 × 10-22). The median PFS for patients treated with T-DXd was not reached (95% CI 18.5-NE) compared to 6.8 months for T-DM1 (95% CI 5.6 to 8.2) as assessed by blinded independent central review (BICR). In the key secondary endpoint of PFS assessed by investigators, patients treated with T-DXd experienced a three-fold improvement in median PFS of 25.1 months versus 7.2 months for T-DM1 (HR 0.26; 95% CI 0.20-0.35; p = 6.5×10-24). A consistent PFS benefit was observed in key subgroups of patients treated with T-DXd, including hormone receptor status positive vs. HR-negative), prior pertuzumab treatment (yes vs no), visceral disease (yes vs no), prior lines of metastatic therapy (0-1 vs ≥ 2), and history of stable brain metastases (yes vs. no). There was a trend towards improved overall survival (OS) with T-DXd (HR 0.56; 95% CI 0.36-0.86; nominal p = 0.007172), however this analysis is not yet mature and did not cross the pre-defined threshold for statistical significance based on the number of observed events. At 12 months, 94.1% of patients treated with T-DXd were alive compared to 85.9% of patients treated with T-DM1. The confirmed objective response rate (ORR) more than doubled in the T-DXd arm versus the T-DM1 arm (79.7% vs. 34.2%). Forty-two (16.1%) complete responses (CR), and 166 (63.6%) partial responses (PR) were observed in patients treated with T-DXd compared to 23 (8.7%) CRs and 67 (25.5%) PRs in patients treated with T-DM1. Additionally, in DESTINY-Breast03, T-DXd monotherapy treatment resulted in greater efficacy compared to T-DM1 in patients with brain metastasis with a mPFS of 15.0 months with T-DXd (N = 43) vs 3.0 months with T-DM1 (N = 39) (Hurvitz et al, 2021).

In addition, several other studies report promising intracranial efficacy for T-DXd. TUXEDO-1 study, a Phase 1 study of previously treated HER2+ MBC patients with active brain metastases, T-DXd monotherapy demonstrated an intracranial response in 83.3% (5/6) patients enrolled in the first stage of the trial ungating full enrolment (N = 15) in the study (Bartsch et al, 2021); active brain metastases were defined as newly diagnosed brain metastases or brain metastases with radiological progression after prior local therapy. Similarly in DEBBRAH, a Phase 2 study of previously treated HER2+ or HER2-low patients MBC with a history of brain metastases and/or leptomeningeal carcinomatosis, T-DXd monotherapy demonstrated preliminary efficacy and a manageable toxicity profile in the 34 patients enrolled as of the 15 September 2021 data cut-off with the most frequent adverse events being fatigue (52.9% [18/34]), nausea (41.2% [14/34]), vomiting (32.4% [11/34]), neutropenia (26.5% [9/34]), diarrhoea (26.5% [9/34]), and anaemia (26.5% [9/34]); enrolment is completed in cohort 1 (N = 8) and cohort 3 (N = 9), and efficacy data were reported (Batista et al, 2021). In DEBBRAH cohort 1, HER2+ MBC patients with non-progressing brain metastases after radiotherapy and/or surgery were enrolled; 87.5% (7/8) patients were alive without disease progression at 16 weeks meeting the primary endpoint with a median follow-up time of 8.5 months. While in DEBBRAH cohort 3, HER2+ MBC with progressing brain metastases after local treatment were enrolled; CNS ORR was 44.4% (4/9) meeting the primary endpoint with a median follow-up time of 8.8 months.

Finally, in a retrospective multi-institutional cohort of patients with HER2+ breast cancer and brain metastases treated with T-DXd monotherapy, the CNS ORR in patients with measurable brain metastases at baseline was 73% (11/15), and in the subset of patients with untreated or progressive brain metastases the CNS ORR was 70% (7/10) as of the 1 June 2021 data cut-off (Kabraji et al, 2021).

2.3.3 Overall Benefit/Risk Conclusion

There is an unmet medical need for better therapies in treatment of HER2-positive MBC in order to improve clinical outcomes. There are multiple treatment options for HER2-positive breast cancer patients in the adjuvant and neoadjuvant settings; however, once resistance develops against HER2-targeting therapy, limited effective treatment options are available. Rechallenge with previously administered therapies can be attempted, but their efficacy may be compromised, usually depending on the disease-free interval between the last adjuvant therapy and metastatic disease (Metzger-Filho et al, 2016). New treatments may provide prolongation of survival and improvement of QoL.

Results from the DESTINY-Breast01 study demonstrated that T-DXd was beneficial in patients with HER2-positive MBC who had been previously treated with multiple therapies. Improved anti-tumor activity against BMs was seen in patients who had stable, treated CNS metastases at baseline and was similar to the efficacy results in the overall study population.

The safety profile of T-DXd in the CNS subgroup was consistent with the non-CNS subgroup and with that seen in the overall patient population. Treatment-emergent AEs in the CNS subgroup were generally consistent with the overall patient population and were predominantly gastrointestinal or hematologic in nature.

The recent read-out of the DESTINY-Breast03 trial demonstrated a highly statistically significant and clinically meaningful improvement in PFS over the T-DM1 in second-line HER2-positive MBC, and the totality of the data show compelling superiority of treatment benefit from T-DXd over T-DM1. These data provide strong confirmation of the single-arm, open label, Phase 2 DESTINY-Breast01 study data in patients with unresectable or metastatic late-line HER2-positive breast cancer. Overall, the available data suggest that T-DXd has the potential to offer a positive benefit risk profile in patients in earlier lines of HER2-positive breast cancer.

The important identified risks associated with administration of T-DXd are ILD/pneumonitis and neutropenia, including febrile neutropenia; LVEF decrease and embryofetal toxicity are considered important potential risks. To specifically mitigate the incidence of pulmonary toxicities, strict inclusion/exclusion criteria have been included in this CSP, prohibiting most participants with pre-existing pulmonary comorbidities from entering the study. In addition, baseline pulmonary function tests will be performed for all participants. For hematological toxicities, the use of growth factors is allowed at the discretion of the investigator. Participants will be monitored closely throughout the study and clinical and laboratory assessments will be performed before every cycle. The TMGs (Appendix O) are also provided to assist with the management of the most commonly seen AEs.

The emergence of COVID-19 presents a potential safety risk for participants; therefore, several risk mitigation factors are included in this study. Details regarding instructions related to COVID-19 and a more detailed description of benefit/risk considerations relevant to COVID-19 are provided in Appendix L. Note that no vaccine against COVID-19 has been tested when given alongside T-DXd. Therefore, it is not known what effect (if any) T-DXd has on the effectiveness and safety of COVID-19 vaccines.

Trastuzumab deruxtecan has the potential to provide meaningful clinical benefit. Considering the measures to minimize risks to participants, the benefit/risk assessment supports the proposed study.

3 OBJECTIVES AND ENDPOINTS

Table 2 Objectives and Endpoints

Objectives	Endpoints
Primary	
To describe the overall treatment effect of T-DXd in HER2-positive MBC patients with or without baseline BM	Participants without BM at baseline (Cohort 1): • ORR by RECIST 1.1 per ICR Participants with BM at baseline (Cohort 2): • PFS by RECIST 1.1 per ICR
Secondary	
To describe the treatment effect on the development and progression of BM in patients with or without baseline BM using additional efficacy measurements	Participants in both cohorts: • OS • DoR by RECIST 1.1 per ICR • Time to progression by RECIST 1.1 per ICR • DoT on subsequent lines of therapy • PFS2 Participants without BM at baseline (Cohort 1): • Incidence of new symptomatic CNS metastasis during treatment In patients who develop isolated CNS progression, receive local therapy, and continue on protocol therapy: • Time to next progression (CNS or extracranial) or death • Site (CNS vs extracranial vs both) of next progression
To describe efficacy in patients with stable or untreated BM	Participants with BM at baseline (Cohort 2): • ORR by RECIST 1.1 per ICR • CNS PFS by CNS RECIST 1.1 per ICR • Time to new CNS lesions • CNS ORR by CNS RECIST 1.1 per ICR • CNS DoR by CNS RECIST 1.1 per ICR

Table 2 Objectives and Endpoints

Objectives	Endpoints
To describe the effect of T-DXd on symptoms, functioning, and HRQoL in HER2-positive MBC patients with or without baseline BM	Changes in symptoms, functioning, and HRQoL as measured by: • All patients: EORTC QLQ-C30, NANO scale, cognitive tests • BM patients: MDASI brain tumor-specific items • ILD/pneumonitis patients: SGRQ-I
Safety	
To describe the safety profile of T-DXd	Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory results, and ECGs. Assessments related to AEs will also include: • Rate of investigator-assessed ILD/pneumonitis – PTs will be matched with most commonly reported terms within ILD cluster terms – Rate of ILD clinical symptom resolution among ILD patients who have been treated with high-dose steroid (total daily dose > 2 mg dexamethasone or equivalent) • Rate of AEs among patients with baseline BM who are treated with concurrent high-dose steroid (total daily dose > 2 mg dexamethasone or equivalent)
Exploratory	
CCI	CCI • CCI CCI • CCI
CCI	CCI • CCI • CCI • CCI • CCI
CCI	CCI
CCI	CCI

Table 2 Objectives and Endpoints

Objectives	Endpoints
CCI	CCI
CCI	CCI

AE = adverse event; BM = brain metastasis; CCI; CNS = central nervous system; CCI DoR = duration of response; DoT = duration of treatment; ECG = electrocardiogram; EORTC = European Organization for the Research and Treatment of Cancer; HER2 = human epidermal growth factor receptor 2; CCI HRQoL = health-related quality of life; ICR = independent central review; ILD = interstitial lung disease; MDASI = MD Anderson Symptom Inventory; NANO = Neurologic Assessment in Neuro-oncology; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PFS2 = time to second progression or death; PT = preferred term; QLQ-C30 = 30 item core quality of life questionnaire; CCI; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SGRQ-I = St. George's Respiratory Questionnaire – idiopathic pulmonary fibrosis version; T-DXd = trastuzumab deruxtecan; CCI.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3b/4, open-label, multicenter, international study assessing the efficacy and safety of T-DXd in participants with or without BM, with previously-treated advanced/metastatic HER2-positive breast cancer whose disease has progressed on prior anti-HER2-based regimens and who received no more than 2 lines/regimens of therapy in the metastatic setting (excluding tucatinib). (Figure 1). Participants will be enrolled into 1 of 2 cohorts according to the presence or absence of BMs at baseline.

Approximately 500 eligible participants will be treated in this study with 5.4 mg/kg T-DXd q3w until RECIST 1.1-defined radiological progression outside CNS, unless there is unacceptable toxicity, withdrawal of consent, or another criterion for discontinuation is met. To ensure adequate representation of participants with BM at baseline, the maximum number of participants without BM at baseline will be limited to 250. Cohort 1 (participants without BM at baseline) will additionally be limited to include no more than 25% third-line participants. In DESTINY-Breast 03, T-DXd demonstrated statistically significant progression free survival benefit over T-DM1, irrespective of number of prior lines on treatment, resulting in international guidelines establishing T-DXd as the standard of care for 2L HER2+ mBC, replacing T-DM1. Limiting recruitment in Cohort 1 to 25% third line participants reflects the change in clinical practice. The study will evaluate ORR by RECIST 1.1, PFS by RECIST 1.1, the incidence of new symptomatic CNS metastasis, and other measures of efficacy, and further characterize the safety and tolerability profile of T-DXd. For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints.

For an overview of the study design see Figure 1, Section 1.2. For details on treatments given during the study, see Section 6.1.

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. In case access to the study site is restricted for vendors, remote monitoring may be conducted by CRO-appointed staff, as permitted by local regulations, laws, and site capability.

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 for the mitigation procedures (note, in the case of verbal consent, the ICF should be signed at the participant's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated study physician.
- Home or remote visit: Performed by a site qualified HCP or HCP provided by a third-party vendor.
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home study intervention administration: Performed by a site qualified HCP, HCP provided by a third-party vendor, or by the participants or the participant's caregiver, if possible. Additional information related to the visit can be obtained via telemedicine.

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

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Design

The current study is designed to evaluate the efficacy and safety of T-DXd in a real-world setting. Overall, this study will look to provide real-world data and a detailed understanding of T-DXd that will complement studies that are ongoing or already completed. This study will include participants who have been previously treated for their breast cancer, including those who also have BMs to evaluate their response to T-DXd treatment. Therefore, this study may provide additional treatment options for patients.

4.2.2 Rationale for T-DXd in MBC

Several agents have been studied in patients with HER2-positive breast cancer with BMs. Specifically, the HER2CLIMB study showed that tucatinib is effective in active/stable treated or asymptomatic untreated BMs (Murthy et al, 2020). However, HER2-positive breast cancer with BMs remains an incurable disease. Due to the decreased QoL and poor prognosis in this patient population, there is still a significant unmet need particularly in later lines of treatment.

Within the clinical development program for T-DXd, there is some data supporting the use of

T-DXd in patients with BMs. In DESTINY-Breast01, 184 patients with heavily pretreated breast cancer were treated with T-DXd at the recommended dose of 5.4 mg/kg. This study population included 24 patients who also had BMs (Jerusalem et al, 2020). Within this small cohort, the efficacy response was encouraging, supporting a more extensive evaluation of T-DXd in this patient population.

4.2.3 Rationale for Study Endpoints

The primary objective for this study is to describe the overall treatment effect of T-DXd in HER2-positive MBC patients with or without baseline BM. The primary endpoint for Cohort 1 (participants with no BM at baseline) is ORR by ICR according to RECIST 1.1, and the primary endpoint for Cohort 2 (participants with BM at baseline) is PFS by ICR according to RECIST 1.1.

For patients without BMs, the ORR is an early indication of treatment effect. The use of ORR will allow an early assessment on whether T-DXd is providing benefit to patients in a real-world setting that is similar to other studies where this has been analyzed. The use of ORR in patients with BM is not found to provide a good indication of response, as it is often uninterpretable in a population with recent CNS-directed therapy such as radiation therapy. Additionally, interlesional variability of response to treatment can render the evaluation of response in multiple metastases problematic. As a result, PFS has been chosen as the primary endpoint in the BM cohort.

The secondary endpoints (Section 3) are in line with the recommendations outlined in the NCI Breast Cancer Steering Committee Working Group Report, where for HR-positive/ HER2-positive breast cancer in the first line setting it is appropriate to have the following secondary endpoints: OS, duration of disease control, time to treatment failure, and PROs (Seidman et al, 2018).

The secondary symptoms, functioning, and overall HRQoL endpoints will show the overall influence of the benefits and toxicity of the treatment from the patient's perspective and will aid in understanding the benefit/risk evaluation. These clinical outcomes assessments are well-established instruments that have been previously included in cancer clinical studies.

Biological samples will be used to CCI
CCI

4.3 Justification for T-DXd Dose

For this study, a T-DXd dose of 5.4 mg/kg given as an IV infusion once every 3 weeks (21-day cycle) will be used. This is the approved dose for adult patients with unresectable or metastatic HER2-positive breast cancer (ENHERTU, 2019). For information on dose

modifications for T-DXd, see Section 6.6.

For additional details on the nonclinical and clinical data on T-DXd, see the T-DXd IB.

4.4 End of Study Definition

A participant is considered to have completed the study when he/she has completed all phases of the study including the last visit (Section 1.3).

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

The end of the study is defined as completing the last expected visit/contact of the last participant undergoing the study. The DCO for final analysis is defined Section 9.2. 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 adults with previously-treated advanced/metastatic HER2-positive breast cancer whose disease has progressed on prior anti-HER2-based regimens and who received no more than 2 lines/regimens of therapy in the metastatic setting (excluding tucatinib). This study will include participants with previously-treated stable BM and participants with active BM, either previously untreated or progressing (but not requiring immediate local therapy). At the time of enrollment, participants must have an ECOG score of 0-1 and must not have LMD.

Prospective approval of protocol deviations to recruitment and enrollment 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.

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 Pathologically documented breast cancer that:
   (a) Is unresectable/advanced or metastatic, and
   (b) Has confirmed HER2-positive status as determined according to ASCO/CAP guidelines (Wolff et al, 2018) evaluated at a local laboratory

3 Participant must have either:
   (a) No evidence of BM, or
   (b) Untreated BM on screening contrast brain MRI / CT scan
      (i) not needing immediate local therapy, or
      (ii) For participants with untreated CNS lesions:

         If lesion ≤ 2 cm, no discussion with study physician is required prior to enrollment

         If lesion is > 2.0 cm, discussion with and approval from the study physician is required prior to enrollment, or
   (c) Previously-treated stable or progressing BM
      (i) Previously-treated BM with local therapy may either be radiographically stable for ≥ 4 weeks since completion of treatment or may have progressed since prior

local CNS therapy, provided that there is no clinical indication for immediate re-treatment with local therapy

(ii) Patients treated with CNS local therapy for newly identified lesions found on contrast brain MRI / CT scan performed during screening for this study who also have other sites of disease assessable by RECIST 1.1

4 Participants with BMs must be neurologically stable and:

(a) Be receiving the equivalent of dexamethasone ≤ 3 mg/day if treatment is required

(b) If receiving an anticonvulsant regimen, the regimen must have been stable for ≥ 14 days before first day of dosing

(c) Relevant records of any CNS treatment must be available to allow for classification of TLs and NTLs

5 For participants requiring radiotherapy due to BMs, there should be an adequate washout period before day of first dosing:

(a) ≥ 7 days since stereotactic radiosurgery or gamma knife

(b) ≥ 21 days since whole brain radiotherapy

6 ECOG performance status 0-1 with no deterioration over the previous 2 weeks prior to baseline or day of first dosing.

7 All participants must provide a FFPE tumor sample that meets the tissue requirements specified in Section 8.6.1 for tissue-based analysis (including but not restricted/limited to IHC staining to determine HER2 expression and CCI [redacted] CCI [redacted]. If an archival tumor tissue sample is not available, a newly acquired sample from a biopsiable tumor must be collected at study entry.

8 Previous breast cancer treatment:

(a) Radiologic or objective evidence of disease progression on or after HER2 targeted therapies.

Note: Disease progression within 6 months after adjuvant treatment with HER2 targeted therapies is also acceptable.

(b) No more than 2 lines/regimens of therapy in the metastatic setting.

Note: A line/regimen of treatment should be counted based on a progression event.

9 Participant with the following measurable or non-measurable disease:

(a) At least 1 lesion that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes, which must have short axis ≥ 15 mm) with CT or MRI and is suitable for accurate repeated measurements.

(b) Or the following non-measurable diseases:

(i) Non-measurable, bone-only disease that can be assessed by CT or MRI or X-Ray. Lytic or mixed lytic bone lesions that can be assessed by CT or MRI or X-ray in the absence of measurable disease as defined above is acceptable;

patients with sclerotic/osteoblastic bone lesions only in the absence of measurable disease are not eligible.

(ii) Non-measurable CNS disease (Cohort 2 only).

10 Adequate organ and bone marrow function within 14 days before the day of first dosing as described in Table 3 below. All parameters must meet the inclusion criteria on the same day and must be the most recent results available.:

Table 3 Parameters for Adequate Organ and Bone Marrow Function

Adequate bone marrow function	
Platelet count	≥ 100,000/mm^3. (Platelet transfusion is not allowed within 1 week prior to screening assessment)
Hemoglobin	≥ 9.0 g/dL NOTE: Participants requiring ongoing transfusions or growth factor support to maintain hemoglobin ≥ 9.0 g/dL are not eligible. (Red blood cell transfusion is not allowed within 1 week prior to screening assessment.)
Absolute neutrophil count	≥ 1500/mm^3 (granulocyte-colony stimulating factor administration is not allowed within 1 week prior to screening assessment)
Adequate hepatic function	
ALT and AST	≤ 3 × ULN (< 5 × ULN in participants with liver metastases)
TBL	≤ 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
Serum albumin	≥ 2.5 g/dL
Adequate renal function	
CrCL	≥ 30 mL/min as determined by Cockcroft Gault (using actual body weight) or modified Cockcroft Gault Males: CrCL (mL/min) = $\frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$ Females: CrCL (mL/min) = $\frac{\text{Weight (kg)} \times (140 - \text{Age}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$
Adequate blood clotting function	
International normalized ratio or Prothrombin time and either partial thromboplastin or activated partial thromboplastin time	≤ 1.5 × ULN

CrCL = calculated creatinine clearance; ULN = upper limit of normal.

11 LVEF ≥ 50% within 28 days before day of first dosing

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.

Reproduction

14 Negative pregnancy test (serum) for women of childbearing potential who are sexually active with a non-sterilized male partner

Female participants must be 1 year post-menopausal, 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). 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 for a minimum of 3 months before entering the study to 7 months after the last dose (see Appendix I for complete list of highly effective birth control methods). 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. Not engaging in sexual activity for the duration of the study and drug washout period (7 months after the last dose of study intervention) is an acceptable method provided it is the usual lifestyle of the participant (consideration must be made to the duration of the clinical trial); however, periodic or occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. 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 T-DXd administration. They should refrain from breastfeeding throughout this time. Preservation of ova may be considered prior to starting the study treatment.

15 Non-sterilized 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 I) from the time of screening throughout the total duration of the study and the drug washout period (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 (4 months after the last dose of study intervention) is an acceptable method provided it is the usual lifestyle of the participant (consideration must be made to the duration of the clinical trial); however, periodic, or occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male participants must not donate or bank sperm during this same time period. Preservation of sperm should be considered prior to starting the study treatment.

Informed Consent

16 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.

17 Provision of signed and dated written Optional CCI [redacted] CCI [redacted]

5.2 Exclusion Criteria

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

Medical Conditions

1 Known or suspected LMD. If LMD has been reported radiographically on baseline MRI but is not suspected clinically by the investigator, the participant must be free of neurological symptoms of LMD[1]

2 Prior exposure to tucatinib treatment

3 As judged by the investigator, any evidence of diseases (such as severe or uncontrolled systemic diseases, including ongoing or active infection, uncontrolled hypertension, renal transplant, active bleeding diseases, or serious chronic gastrointestinal conditions associated with diarrhea) substantially increase risk of incurring AEs, which, in the investigator's opinion, makes it undesirable for the participant to participate in the study or would jeopardize compliance with the protocol

4 Refractory nausea and vomiting, chronic gastrointestinal disease, or previous significant bowel resection that would preclude adequate absorption, distribution, metabolism, or excretion of T-DXd

5 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, other solid tumors curatively treated, or contralateral breast cancer.

[1] LMD is a clinical diagnosis, defined as positive CSF cytology and/or unequivocal radiologic or clinical evidence of leptomeningeal involvement. Patients with leptomeningeal symptoms in the setting of leptomeningeal enhancement would be considered to have LMD even in the absence of positive CSF cytology, unless a parenchymal lesion can adequately explain the neurologic deficit. In contrast, asymptomatic or minimally symptomatic patients with mild or nonspecific leptomeningeal enhancement would not be considered to have LMD. In such patients, CSF sampling is not required to formally exclude LMD but can be performed at the investigator's discretion on the basis of level of clinical suspicion.

6 Based on screening contrast brain MRI / CT scan, participants must not have any of the following:

   (a) Any untreated brain lesions > 2.0 cm in size, unless discussed with the study physician and approval is given

   (b) Ongoing use of systemic corticosteroids for control of symptoms of BMs at a total daily dose of > 3 mg of dexamethasone (or equivalent). However, participants on a chronic stable dose of ≤ 3 mg total daily of dexamethasone (or equivalent) may be eligible with discussion and approval by the study physician.

   (c) Any brain lesion thought to require immediate local therapy, including (but not limited to) a lesion in an anatomic site where increase in size or possible treatment-related edema may pose risk to participant (eg, brain stem lesions). Participants who undergo local treatment for such lesions identified by screening contrast brain MRI / CT scan may still be eligible for the study based on criteria described under CNS inclusion criteria 3 and 5.

   (d) Have poorly controlled (> 1/week) generalized or complex partial seizures, or manifest neurologic progression due to BMs notwithstanding CNS-directed therapy

7 Has spinal cord compression

8 Known active hepatitis B or C infection, such as those with serologic evidence of viral infection within 28 days of Cycle 1 Day 1. Participants with past or resolved HBV infection are eligible, if negative for HBsAg and positive for anti-HBc. Participants positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

9 Active primary immunodeficiency, known to have tested positive for HIV

10 Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals

11 Receipt of live, attenuated vaccine (mRNA and replication deficient adenoviral vaccines are not considered attenuated live vaccines) within 30 days prior to the first dose of T-DXd.

   Note: Patients, if enrolled, should not receive live vaccine during the study and up to 30 days after the last dose of T-DXd.

12 Has substance abuse or any other medical conditions such as clinically significant cardiac or psychological conditions, that may, in the opinion of the investigator, interfere with participation in the clinical study or evaluation of the clinical study results

13 Participants with a medical history of myocardial infarction (MI) within 6 months before screening, symptomatic CHF (NYHA Class II to IV), unstable angina pectoris, or a recent (< 6 months) cardiovascular event including stroke. Participants with troponin levels above ULN at screening (as defined by the manufacturer), and without any myocardial related symptoms, should have a cardiologic consultation to rule out MI.

14 Investigator judgment of 1 or more of the following:
   (a) Mean resting corrected QTcF interval > 470 ms (females) or > 450 msec (males), obtained from triplicate ECGs performed at screening
   (b) 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
   (c) Congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives
15 History of arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia), which is symptomatic or requires treatment (CTCAE Grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Participants with atrial fibrillation controlled by medication or arrhythmias controlled by pacemakers may be permitted upon discussion with the study physician.
16 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.
17 Lung criteria:
   (a) Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disorder (eg, pulmonary emboli within 3 months of study enrollment, severe asthma, severe COPD, restrictive lung disease, pleural effusion, etc)
   (b) Any autoimmune, connective tissue or inflammatory disorders (ie, rheumatoid arthritis, Sjogren's, sarcoidosis, etc.) where there is documented, or a suspicion of pulmonary involvement at the time of screening. Full details of the disorder should be recorded in the eCRF for participants who are included in the study.
   (c) Prior pneumonectomy

Prior/Concomitant Therapy

18 Prior exposure, without adequate treatment washout period before the day of first dosing, to chloroquine/hydroxychloroquine: < 14 days
19 Anticancer chemotherapy
   (a) Immunotherapy (non-antibody-based therapy), retinoid therapy, hormonal therapy: < 3 weeks (< 2 weeks or 5 half-lives, whichever is longer, for small-molecule targeted agents such as 5-fluorouracil-based agents, folinate agents, and weekly paclitaxel)
   (b) < 6 weeks for nitrosoureas or mitomycin C
   (c) Antibody-based anticancer therapy: < 4 weeks. Denosumab for the treatment of bone lesions will be permitted.

(d) Any concurrent anticancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is allowed.

20 Unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤ 1 or baseline. Note: Subjects may be enrolled with chronic, stable Grade 2 toxicities (defined as no worsening to > Grade 2 for at least 3 months prior to randomization/enrolment and managed with standard of care treatment) that the investigator deems related to previous anticancer therapy, such as:

(a) Chemotherapy-induced neuropathy

(b) Fatigue

(c) Residual toxicities from prior IO treatment: Grade 1 or Grade 2 endocrinopathies which may include:

- Hypothyroidism/hyperthyroidism
- Type 1 diabetes
- Hyperglycemia
- Adrenal insufficiency
- Adrenalitis
- Skin hypopigmentation (vitiligo)

21 Palliative radiotherapy with a limited field of radiation within 2 weeks (palliative stereotactic radiation therapy to other areas within 1 week) or with wide field of radiation, radiation to the chest, or to more than 30% of the bone marrow within 4 weeks before the first dose of study intervention.

22 Major surgical procedure (excluding placement of vascular access) or significant traumatic injury within 4 weeks of the first dose of study intervention or an anticipated need for major surgery during the study.

23 Participants with prior exposure to immunosuppressive medication within 14 days prior to first study dose, except for intranasal and inhaled corticosteroids or systemic corticosteroids at doses less than 3 mg/day of dexamethasone or equivalent are to be excluded. Steroids as premedication for hypersensitivity reactions due to radiographic contrast agents are allowed. Prophylactic or supportive treatment of study drug-induced AEs will be otherwise as per investigator's discretion and institutional guidelines. Any concurrent chemotherapy, anticancer investigational product or biologic, radiotherapy (except palliative radiotherapy to areas other than chest, after consultation with the study physician), or hormonal therapy for cancer treatment are considered exclusionary during the study. Note, local therapy is allowed for participants with BM while on study treatment.

Prior/Concurrent Clinical Study Experience

24 Previous treatment in the present study

25 Participation in another clinical study with a study intervention or investigational medicinal device administered in the last 30 days or 5 half-lives, whichever is longer, prior to first dose of study intervention, randomization into a prior T-DXd study regardless of treatment assignment, or concurrent enrollment in another clinical study, unless it is an observational (noninterventional) clinical study or during the follow-up period of an interventional study

26 Participants with a known hypersensitivity to study intervention or any of the excipients of the product or other monoclonal antibodies

Other Exclusions

27 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca / Daiichi Sankyo staff and/or staff at the study site)

28 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

29 Currently pregnant or breastfeeding

5.3 Lifestyle Considerations

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

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

2 Participants should not donate blood or blood components while participating in this study and up to and including the safety follow-up period.

Restrictions relating to concomitant therapies are described in Appendix K.

5.3.1 Tobacco, Alcohol, Psychoactive Drugs and Caffeine

1 Use of tobacco products, e-cigarettes and vaping is strongly discouraged but not prohibited. Any prior or current use of these products as well as prior or current use of alcohol and psychoactive drugs, should be recorded in the eCRF. Prior or current abuse of caffeine must be documented in the eCRF as well.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. 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 for screen failures including patients who are identified in the pre-screening phase as not eligible.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened a single time. Rescreened participants should be assigned the same participant number (ie, E-code) as for the initial screening. However, rescreening should be documented so that its effect on study results, if any, can be assessed.

All assessments must be repeated for rescreening unless they are within 28 days of inclusion in the study or as applicable as some screening assessments could be valid for more than 28 days.

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

Participant enrollment 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. Study intervention in this study refers to T-DXd.

6.1 Study Intervention Administered

The study treatment to be administered in this study is shown in Table 4.

Table 4 Study Treatment

Study treatment name	Dosage presentation	Unit dose strength	Dosage level	Route of administration	Packaging and labeling	Use	Sourcing
T-DXd (DS-8201a) [a]	Vial	Powder for concentrate for solution for infusion 100 mg/vial	5.4 mg/kg	IV	T-DXd will be provided in a vial in a carton. Each vial and carton will be labeled in accordance with GMP Annex 13 and per country regulatory requirements [a]	Experimental	Provided centrally by AstraZeneca

[a] Label text for T-DXd (DS-8201a) will show "DS-8201a" depending on the agreed product name used in the respective approved study master label document. All naming conventions for these compounds are correct during this transitional period.
GMP = Good Manufacturing Practice; IV = intravenous; T-DXd = trastruzumab deruxtecan.

Duration of Treatment

All participants will receive T-DXd, 5.4 mg/kg, IV, every 3 weeks until RECIST 1.1-defined radiological progression outside CNS. Participants may continue to receive T-DXd beyond progression, as long as they are continuing to show clinical benefit, as judged by the investigator, and in the absence of other discontinuation criteria.

6.2 Preparation/Handling/Storage/Accountability of Interventions

1 The investigator or designee (eg, pharmacist) must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2 Only participants enrolled in the study and who meet eligibility requirements may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally

controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

3 The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

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

6.2.1 Trastuzumab Deruxtecan Preparation, Administration, and Storage

Trastuzumab deruxtecan will be supplied by AstraZeneca as a 100 mg/vial lyophilized powder for concentrate for solution for infusion. Following reconstitution with sterile water for injection the solution contains 20 mg/mL T-DXd in 25 mM histidine/histidine HCl, 90 mg/mL sucrose, 0.03% (w/v) polysorbate 80; it has a pH of 5.5. The post-reconstitution label-claim volume is 5 mL.

The reconstituted product is a clear to opalescent, colorless to yellow liquid, and practically free from visible particles.

Preparation of T-DXd

The dose of T-DXd for administration must be prepared by the investigator's or site's designated study intervention manager using aseptic technique. Total time from needle puncture of the T-DXd vial to the start of administration must not exceed:

- 24 hours at 2°C to 8°C (36° F to 46° F)
- 4 hours at room temperature

If the final product is stored at both refrigerated and ambient temperature, the total time must not exceed 24 hours.

After preparation and during administration, the prepared IV bag must be covered by light protection cover.

Administration of T-DXd

It is recommended that participants receive prophylactic anti-emetic agents prior to infusion of T-DXd and on subsequent days. Antiemetics such as 5-HT_3 antagonists or NK1 receptor antagonists and/or steroids (eg, dexamethasone) should be administered in accordance with the prescribing information or institutional guidelines.

Trastuzumab deruxtecan will be administered using an IV bag containing 5% (w/v) dextrose injection infusion solution and delivered through an IV administration set with a 0.2- or

0.22-µm filter. The standard infusion time for T-DXd 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 infusion time for subsequent cycles is 30 minutes ± 10 minutes. However, if there are interruptions during infusion, the total allowed time must not exceed 3 hours at room temperature.

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.

Refer to the Pharmacy Instructions for detailed information about preparation and administration of T-DXd.

Monitoring of T-DXd Administration

Participants will be monitored during and after infusion of T-DXd. Vital signs will be measured according to the SoA (Section 1.3).

Management of study intervention-related toxicities are described in Section 6.6.1. As with any biologic product, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

A 1-hour observation period is recommended after the first IV infusion of T-DXd. For subsequent infusions, the recommended observation period is 30 minutes.

Storage of T-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.

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

6.3 Measures to Minimize Bias: Randomization and Blinding

This is an open-label, single-arm, 2-cohort study. All eligible participants will receive T-DXd.

Participant Enrollment

Investigators should keep a record (ie, the participant screening log) of participants who entered screening and/or pre-screening.

At screening/baseline (Days -28 to -1), 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 the first dose of study intervention. A pre-screen ICF must be signed by patients to permit for tumor tissue sample collection (HER2 status) and testing prior to the 28-day screening window. At the time of signing pre-screen ICF, investigators should ensure that there is a reasonable possibility that the patient would be candidate for this study based on available information (eg, medical history, availability of required number of slides for study).
- Participants will be identified to the IRT per country regulations. Obtain a CCI [redacted] through the IRT in the following format: CCI [redacted] This number is the participant's unique identifier and is used to identify the participant on the eCRFs. If a participant withdraws from the study, his/her enrollment code cannot be reused. Withdrawn participants will not be replaced.
- Obtain sample and send for HER2 testing. A mandatory FFPE tumor sample from archival tumor tissue or fresh biopsy must be provided that meets the tissue requirements specified in Section 8.6.1 is required. Obtaining the sample should be given the highest priority and, as such, the sample may be obtained and sent for testing prior to the 28-day screening window (after obtaining signed pre-screen ICF) in order to permit analysis prior to the first dose of study intervention. Tumor lesions used for newly acquired biopsies should not be the same lesions used as RECIST 1.1 TLs, unless there are no other lesions suitable for biopsy; and in this instance only core needle (not excisional/incisional) biopsy is allowed.
- Determine participant eligibility (see Sections 5.1 and 5.2).
- Obtain signed informed consent for CCI [redacted] (optional). Participants who decide not to sign the CCI [redacted] ICF, but the general study ICF, are eligible for study enrollment and all other study procedures.

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

The day participants receive the first dose of study treatment is Cycle 1 Day 1. Every effort

should be made to minimize the time between screening/baseline and dosing. Dosing should occur no more than 3 days after treatment assignment. If it is anticipated that dosing cannot occur within 3 days, a discussion with the AstraZeneca study physician is required. Participants must not be treated unless all eligibility criteria have been met.

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

Where a participant does not meet all the eligibility criteria but is 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.

Methods for Assigning Treatment Groups

Not applicable; this is a single-treatment group study with 2 cohorts.

Study intervention will be centrally assigned using IRT. Before the study is initiated, directions for the IRT will be provided to each site. The site will contact the IRT to confirm cohort selection prior to the start of study intervention administration for each participant. Once a cohort is fully enrolled, the IRT will be closed for this cohort. When study intervention is provided centrally by the sponsor, the IRT will provide the kit identification number to be allocated to the participant at each dispensing visit.

6.4 Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

Participants are dosed at the site and will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of dose administered in the clinic 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 by a member of the study site staff other than the person administering the study intervention.

Deviation(s) from the prescribed dosage regimen should 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, or other medication considered necessary by the investigator for the participant's safety and wellbeing, or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the participant is receiving from the time of screening or receives during the study including the 40-day 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 physician should be contacted if there are any questions regarding concomitant or prior therapy. If any concomitant therapy is administered due to new or unresolved AE, it should be recorded.

In special cases, such as cases with ILD, documentation of concomitant therapy is required even after the safety follow-up period.

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 K.

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

Drug-drug Interactions

There is no information to date on drug-drug interactions with T-DXd, either pre-clinically or in participants. There may be a hypothetical interaction between T-DXd and hydroxychloroquine and/or chloroquine, therefore concomitant treatment with hydroxychloroquine or chloroquine is not allowed during the study treatment.

Results from Study DS8201-A-A104 suggested that strong cytochrome P450 3A4 inhibitors (eg, boceprevir, clarithromycin, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, telaprevir, telithromycin, and voriconazole) or organic anion transporting polypeptide 1B inhibitors (eg, lopinavir/ritonavir, cyclosporine, and rifampicin) can be administered without T-DXd dose adjustment.

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

6.5.1 Other Protocol Restrictions or Supportive Treatments

Other CSP restrictions or supportive treatments are listed below (refer also to Appendix K):

T-DXd is emetogenic, which includes delayed nausea and/or vomiting. Prior to each dose of T-DXd, patients should be premedicated with a combination regimen of 2 or 3 medicinal products (eg dexamethasone with either a 5-HT3 receptor antagonist and/or an NK1 receptor antagonist, as well as other medicinal products as indicated) for prevention of chemotherapy-induced nausea and vomiting.

Hematopoietic growth factors may be used for treatment based on the clinical judgment of the investigator.

Concomitant use of dietary supplements, medications not prescribed by the investigator, and alternative/complementary treatments is discouraged, but not prohibited.

Prophylactic or supportive treatment of study intervention-induced AEs will otherwise be as per investigator's discretion and institutional guidelines.

6.6 Dose Modification

Dose modification guidelines for T-DXd-related toxicities are shown in Appendix O. Appropriate and optimal treatment of the toxicity is assumed prior to considering dose modifications. Prior to discontinuation of study intervention due to toxicities, please consult with the study physician.

6.6.1 Specific Toxicity Management and Dose Modification Information – T-DXd

All dose modifications (interruption, re-initiation, reduction and/or discontinuation) should be based on the worst preceding toxicity (NCI CTCAE v5.0). Specific criteria for interruption, re-initiation, dose reduction and/or discontinuation of T-DXd are listed in Appendix O, which is applicable only to TEAEs that are assessed as related to use of T-DXd by the investigator(s).

For non-drug-related TEAEs, follow standard clinical practice. Appropriate clinical experts should be consulted as deemed necessary.

All confirmed or suspected COVID-19 infection events must be recorded in the eCRF. Please refer to Appendix L for additional information on dose modification for suspected or confirmed COVID-19 infection for participants treated with T-DXd.

ILD/Pneumonitis Management Guidance

Please refer to the ILD/pneumonitis management summary flow chart in Appendix N for the management of drug-induced ILD/pneumonitis. 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 defined in the current Site Manual List of MedDRA Preferred Terms).

ILD/pneumonitis should be ruled out if a participant develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough, or fever. If the AE is confirmed to have an etiology other than ILD/pneumonitis, follow the management guidance outlined in Appendix O.

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. As soon as ILD/pneumonitis is suspected, corticosteroid treatment should be started promptly as per clinical treatment guidelines (See Appendix N and Appendix O for further guidance).

If the AE is confirmed to be ILD/pneumonitis, follow the management guidance outlined in Appendix N and Appendix O. All events of ILD/pneumonitis regardless of severity or seriousness will be followed until resolution including after study intervention discontinuation.

All cases of potential ILD/pneumonitis will be reviewed internally by medical monitor and study safety physician. An ILD Advisory Committee will also be consulted unless the ILD Advisory Committee charter is out of scope. To ensure adequate and relevant evaluation, systematic additional data collection will be conducted for all cases that will be brought for evaluation. This additional data collection 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 for AEs reported using selected MedDRA Preferred Terms.

LVEF decrease Management Guidance

Refer to the management guidance outlined in Appendix O.

- Left ventricular ejection fraction will be measured by either ECHO or MUGA scan. All ECHOs/MUGAs will be evaluated by the investigator or delegated physician for monitoring cardiac function.
- Troponin-T (preferably high-sensitivity troponin-T) will be measured at screening and at EOT, and as needed based on participant-reported cardiac signs or symptoms suggesting CHF, MI, or other causes of cardiac myocyte necrosis. If ECG is abnormal, follow institutional guidelines. Qualitative testing for Troponin-T or Troponin-I instead of Troponin-T may be acceptable to perform, if in accordance with local practice and if quantitative method or Troponin-T is not available. Positive results must be followed up

with a quantitative measurement along with other institutional guidance (refer to Appendix O for additional management guidelines).

Electrocardiograms will be performed at screening, prior to administration of study intervention for every 4th cycle (once) and if an abnormality is detected or if there is a troponin increase. Triplicate ECGs will be performed at screening. Subsequent ECGs will be performed in triplicate only if abnormalities are noted. Twelve-lead ECGs will be performed, and standard ECG parameters will be measured, including RR, PR, QT intervals, and QRS duration. All ECGs must be evaluated by investigator or delegated physician for the presence of abnormalities prior to the injection of study intervention at every cycle. Whether or not measurement is performed, date performed, results, and findings for each parameter is to be recorded in the eCRF.

6.6.2 Dose Reductions, Interruptions, and Modifications

Once the dose of T-DXd has been reduced because of toxicity, all subsequent cycles should be administered at that lower dose level unless further dose reduction is required (Table 5). More than 2 dose reductions are not allowed, and the study intervention will be discontinued if further toxicity that meets the requirement for dose reduction occurs.

Table 5 Dose Reduction Levels of T-DXd

Starting dose	Dose level -1	Dose level -2
5.4 mg/kg	4.4 mg/kg	3.2 mg/kg

T-DXd = trastuzumab deruxtecan

Dose Interruption and Modification/TMGs

Every effort should be made to limit study drug delay. In circumstances of adverse event management or medical intervention, the study drug can be held up to 18 weeks (126 days) from the last T-DXd dose, however, two consecutive doses must be administrated at least 19 days apart. During this time scheduled CT/MRI scans should continue as per protocol, and participants should fulfil all of the following criteria:

- Study drug may be resumed with confirmation of continued benefit per RECIST 1.1. Scans should be performed at the frequency defined per protocol, while the drug is being held.
- At minimum 1 restaging scan must be done within 6 weeks prior to restarting the study drug.
- IP(s) is/are restarted within the guidance of the TMGs for T-DXd and any combination agents, if appropriate.
- No prohibited concomitant medications have been administered since the last dose of T-DXd.

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

In addition, investigators may consider dose reductions or discontinuations of T-DXd according to the participant's condition and after discussion with the study physician or designee. For management of dose delays due to T-DXd related events, the TMGs in Appendix O should be followed, as applicable.

In summary, if a participant experiences a clinically significant and/or unacceptable toxicity, dosing will be interrupted or permanently discontinued depending on the severity of the toxicity, and supportive therapy administered as required.

On improvement of an AE for which T-DXd was temporarily interrupted, T-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, T-DXd may be restarted at a one dose level reduction on improvement of the AE or discontinued if the participant is receiving the lowest protocol-specified dose level (Appendix O).

In case a dose reduction is necessary, the study intervention will be administered as described in Appendix O.

Appropriate and optimal treatment of the toxicity is assumed prior to considering dose modifications. Prior to discontinuation of study intervention due to toxicities, please consult with the study physician.

6.7 Intervention After the End of the Study

No intervention is planned 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.

After the final DCO for this study, AstraZeneca will continue to supply T-DXd to participants who received T-DXd until meeting any discontinuation criteria as defined in Section 7.1. Where possible, if commercial supply of T-DXd is available in the local market then this route should be used.

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 T-DXd may be transitioned to such a study, and the current study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visits and assessments per its protocol. Any participant who would be proposed to move to such a study would be asked to sign a new ICF.

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 survival, either through direct contacts or by collecting public records (eg, death certificates) as allowed by local laws. The investigator should instruct the participant to contact the site before or at the time if study intervention is stopped. A participant that decides to discontinue study intervention will always be asked about the reason(s) and the presence of any AEs. The reason for discontinuation should be documented in the source document and the appropriate section of the eCRF.

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

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

- RECIST 1.1-defined radiological progression outside CNS (refer to Section 8.1.1 and Appendix F).
- Those patients who receive local therapy (radiation) for isolated CNS progression, providing there is no other systemic progression may be allowed to continue study assigned treatment until a second progression (brain or body) is observed. Study treatment will be discontinued at the time of second progression (see Section 7.1.1).
- Investigator determination that the participant is no longer benefiting from study intervention.
- An AE that, in the opinion of the investigator or AstraZeneca, contraindicates further dosing.
- Any AE that meets criteria for discontinuation defined in the dose modification guidelines for management of study intervention-related toxicities (see Section 6.6).
- 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.
- Initiation of subsequent anticancer therapy, including another investigational agent.

- Subjective disease progression (global deterioration of health status) without objective evidence of PD according to RECIST 1.1.
- Study terminated by AstraZeneca.
- Participant lost to follow-up.
- Death.

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

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

7.1.1 Temporary Discontinuation

Temporary discontinuation of T-DXd may be required for the management of drug-induced ILD/pneumonitis (Appendix N).and other toxicities (Appendix O), CCI [redacted] CCI [redacted].

CCI [redacted]

CCI [redacted]

CCI [redacted]

- CCI [redacted]
- CCI [redacted]

- CCI
- CCI
- CCI
- CCI

CCI

CCI

7.1.2 Follow-up of Participants Post Discontinuation of Study Intervention

All participants who discontinue the study intervention will be followed up for safety assessments 40 (+ up to 7) days after their last dose of study intervention. Additional assessments to be performed at the time of the 40-day safety follow-up are detailed in the SoA (Section 1.3). 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 assessments as indicated in the SoA (Section 1.3) until RECIST 1.1-defined PD or death regardless of whether or not the participant started a subsequent anticancer therapy, unless they have withdrawn all consent to study-related assessments.

7.1.3 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.

7.1.4 Follow-up for Survival

Participants will be followed up for survival status as indicated in the SoA (Section 1.3) until death, withdrawal of consent, or the end of the study. Survival information may be obtained via telephone contact with the participant or the participant's family, or by contact with the participant's current physician. Additional assessments to be performed at the time of survival follow-up are detailed in the SoA.

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.

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 on any ongoing AEs and concomitant medications (eg, telephone contact at 40 [+ up to 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 early study intervention discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

The participant will discontinue the study intervention and be withdrawn from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried in line with what was stated in the ICF 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 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 lost to follow-up and withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant during survival follow-up within legal and ethical boundaries for all participants enrolled, 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, PFS2, and OS, the survival status of all participants in the full analysis and the safety analysis sets should be rechecked; 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 (Section 1.3). 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, 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.

8.1 Efficacy 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. When assessing whether a progression event has occurred, please ensure that COVID-19 and other infective lymphadenopathies have been excluded first.

For the brain, images from MRI (preferred, unless contraindicated) with and without IV contrast, or contrast-enhanced CT, will be collected for all participants at baseline, and for participants with BMs at regular (follow-up) intervals during study intervention.

Participants with active (untreated or progressive) and measurable BMs should have CNS lesions included as TL(s) for RECIST 1.1 assessments. The assessment of RECIST endpoints could include TLs within and outside the CNS (if possible), while assessment of CNS RECIST endpoints (eg, CNS ORR, CNS DoR) will only include TLs within the CNS. Both endpoints will be analyzed separately and may include overlapping or different TLs.

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 (Table 1). Screening/baseline imaging should be performed no more than 28 days before start of study intervention and ideally should be performed as close as possible to and prior to the start of study intervention. Scanning/tumor assessments continue throughout treatment until RECIST 1.1-defined radiological progression. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the participant has not progressed, every attempt should be made to perform the subsequent assessments at the next scheduled visit.

The RECIST 1.1 assessments of baseline images identify TLs (defined as measurable) and NTLs. On-study images are evaluated for TLs and NTLs chosen at baseline, and for NLs when they appear. This allows determination of follow-up TL response, NTL lesion response, the presence of unequivocal NLs, and overall time point responses (CR, PR, SD, PD, or NE). For the evaluation of tumor response, refer to Appendix G for RECIST 1.1 / CNS RECIST 1.1 and Appendix H for CCI [redacted] criteria.

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 ICR. Digital copies of all original scans should be stored at the investigator site as source documents. Electronic image transfer from the sites to the iCRO is strongly encouraged. An ICR of images will be performed at the discretion of AstraZeneca. Results of these independent reviews will not be communicated to investigators, and results of investigator tumor assessments will not be shared with the central reviewers.

Further details of the ICR 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 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. 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.

8.1.5 Clinical Outcome Assessments

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. Clinical outcome assessments can be reported by a participant (PRO), a clinician, an observer, 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, functioning, and HRQoL of the participant to aid understanding of the risk/benefit profile. In this study, COAs will be used to assess changes in disease and treatment-related symptoms, including those related to BM and ILD/pneumonitis, functioning including neurological and cognitive functioning for those with BM, and overall HRQoL.

A PRO is one type of COA and is a general term referring to all outcomes and symptoms that are directly reported by the participant. PROs have become important in evaluating the effectiveness 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: EORTC QLQ-C30 (all participants), MDASI brain tumor-specific items (participants with BM), and for participants who develop ILD/pneumonitis, the SGRQ-I and MDASI lung cancer (ILD symptom-specific items) (see Appendix J).

Additional COAs for all participants include the clinician-completed NANO scale and participant-completed cognitive function tests, and for participants who develop ILD/pneumonitis, at-home pulse oximetry.

Clinical outcome assessments will be administered according to the SoA (Section 1.3).

8.1.5.1 EORTC QLQ-C30

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group 1993. It consists of 30 items 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 and vomiting); a 2-item global QoL scale; 5 single items assessing additional symptoms commonly reported by cancer patients (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 patient population (see Appendix J).

8.1.5.2 MDASI Symptom Diary

The MDASI symptom diary is a validated, multi-item, cancer-specific PRO questionnaire capturing symptom severity and interference (Cleeland et al, 2000).

MDASI brain tumor-specific items

The MDASI brain tumor module includes 9 symptoms specific to brain tumors (weakness on one side of the body, difficulty understanding, difficulty speaking, seizures, difficulty concentrating, problems with vision, change in appearance, change in bowel pattern (diarrhea or constipation), and irritability). These 9 items will be used to capture symptoms associated with BMs for those diagnosed with BM. Each item is rated on an 11-point numeric rating scale, with higher scores indicating greater symptom severity.

MDASI lung cancer (ILD symptom-specific items)

Three items from the MDASI lung cancer module will be used to capture the core ILD/pneumonitis symptoms of cough, shortness of breath, and chest heaviness/tightness. Each item is rated on an 11-point numeric rating scale, with higher scores indicating greater symptom severity.

8.1.5.3 SGRQ-I

The original SGRQ is a commonly used, validated instrument capturing HRQoL for patients with chronic respiratory disease. The SGRQ-I is an idiopathic pulmonary fibrosis-specific version of the instrument developed and validated for use among patients with idiopathic pulmonary fibrosis, a type of ILD (Yorke et al, 2010). The SGRQ-I will be used to assess the HRQoL among participants who have been diagnosed with ILD/pneumonitis. It includes 34 of the original SGRQ items determined to be most reliable for assessing the HRQoL of participants with idiopathic pulmonary fibrosis. The instrument yields 3 domain scores (symptoms, activity, and impact) as well as a total score, with scores ranging from 0 to 100 (see Appendix J). Higher scores indicate greater impairment in HRQoL.

8.1.5.4 Other COAs

NANO Scale

The NANO scale is a clinician-reported assessment of neurologic functioning in neuro-oncology patients (Nayak et al, 2017). The instrument captures 9 domains (gait, strength, ataxia, sensation, visual fields, facial strength, language, level of consciousness, and behavior) and was developed to provide a simple, objective assessment of neurologic function that would be combined with radiographic assessment to provide an overall outcome assessment for neuro-oncology patients in clinical trials and in daily practice.

Cognitive Tests

Computerized, self-completed cognitive tests will be used to capture cognitive function, including attention, memory, and executive function. These gamified tests include Reaction

Time, Paired Assistance Learning, and Spatial Working Memory and are low-burden, highly sensitive, precise measures of cognitive function.

At-home Pulse Oximetry

An electronic, wireless pulse oximetry device will be provided to participants diagnosed with ILD/pneumonitis. The research nurse or appointed site staff will train participant on the use of the device. All participants will complete a resting and walking assessment at the baseline visit before dosing. After diagnosis of ILD/pneumonitis, at-home pulse oximetry testing will be performed by the participant once daily while resting (after at least 10 minutes of rest) at approximately the same time each day and once weekly while walking, in accordance with the SoA (Section 1.3).

For the walking assessment participants will walk in their homes for 3 minutes at their own pace on level ground and with any walking aid they would normally use. The walk should be discontinued if at any time the participant experiences severe shortness of breath, anterior chest pain, or if the participant feels that he or she is unable to continue walking. The measurement of pulse oximetry should be taken immediately after the participants have completed the 3 minutes of the walking assessment. The lower limit SpO2 value after the 3 minutes of walking is the value to be recorded.

The research nurse or appointed site staff will check the participant's adherence to the correct use of the pulse oximetry at each site visit.

8.1.5.5 Administration of ePRO Questionnaires

The PRO questionnaires will be self-administered electronically by the participants using a provisioned handheld device at the time points indicated in the SoA, if a linguistically validated version is available in the language of their country of residence.

Participants should complete the ePROs at home prior to the site visit or at the site visit, if the assessment time point coincides with a scheduled site visit.

Participants must be instructed to bring the 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.

In case of handheld device failure, the site should follow the ePRO device failure mitigation plan which has been agreed by AstraZeneca.

Approximately 2 to 20 minutes is required for participants to complete the questionnaires, depending on the visit.

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 patient that these questions are being asked to find out, directly from them, how they feel.
- It is vital that the ePRO reporting is initiated on Cycle 1 Day 1 as specified in the SoA to capture the effect of study intervention. The ePRO device must be charged and fully functional at the beginning of the baseline visit to ensure that the PROs can be completed at the start of the visit.
- The participant should bring the ePRO device to each site visit so the research nurse or appointed site staff can check if there are available PRO questionnaires to be completed and that the device is functioning properly.
- PRO questionnaires completed at sites must be completed prior to treatment administration performed at the site and ideally before any discussions of health status 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.
- PRO questionnaires should be completed by the participant in a quiet and private location.
- The participants 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 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 electronically. 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 participants 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 PRO 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 that requires PRO completion, the participant may be exempted from completing the PRO questionnaires at that site visit.
- Site staff must not read or complete the PRO questionnaires on behalf of the participant. If the participant is unable to read the questionnaire (eg, is blind, 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 patient cannot complete the PRO questionnaires due to reasons other than being blind, illiterate, or not fluent in the language, the AstraZeneca study team must be contacted to determine if they can be exempted. Participants exempted in this 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 the participant speaks.
- If PRO questionnaires are completed at home, 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 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 should 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). A solution to enhance/resolve compliance should be discussed with the participant. Discussions 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 (Section 1.3).

8.2.1 Physical Examinations

- A complete physical examination will include assessments of the following: head, eyes, ears, nose, and throat and the respiratory, cardiovascular, gastrointestinal, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems.
- Targeted physical examinations are to be used by the investigator on the basis of clinical observations and symptomatology. A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

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

8.2.2 Vital Signs

Vital signs will be performed as specified in the SoA (Section 1.3).

Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

Vital signs will consist of 1 pulse and 1 blood pressure measurement. The blood pressure readings will be recorded on the eCRF.

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 ECGs will be performed at screening. Subsequent ECGs will be performed in triplicate only if abnormalities are noted. ECGs will be taken after the participant has been resting semi-supine 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. Refer to Section 7 for QTcF withdrawal criteria and any additional QTcF readings that may be necessary.

All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal. Any clinically significant abnormalities detected require triplicate ECG results. At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should preferably be completed within 5 minutes.

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

Whenever vital signs and blood draws are scheduled for the same nominal time, the vital signs assessments should preferably occur first. Whenever ECGs, vital signs, and blood draws are scheduled for the same nominal time, ECG assessments should preferably occur first, then

vital signs assessments, and then blood draws; the timing of the first 2 assessments should be preferably such that it allows the blood draw to occur at the timepoints indicated in the SoA.

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 (Section 1.3).

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

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

Other safety laboratory tests include assessment for pregnancy (serum [at screening] or urine [other time points]), hepatitis B and C serology (optional), and HIV antibody test (as required by local regulations). Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Pregnancy tests will be conducted within 72 hours before the day of first dosing for all female participants 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) 72 hours before infusion of each cycle and at EOT. A negative result for serum pregnancy test (test must have a sensitivity of at least 25 mIU/mL) must be available at the screening visit and urine beta-human chorionic gonadotropin pregnancy test prior to each administration of study intervention.

The following laboratory variables will be measured (Table 6).

Table 6 Laboratory Safety Variables

Hematology/hemostasis (whole blood)	**Clinical chemistry (serum or plasma)**
Hemoglobin	Creatinine
Leukocyte count	Bilirubin, total
Leukocyte differential count (absolute count; neutrophils, lymphocytes, monocytes, eosinophils, basophils)	Alkaline phosphatase
Platelet count	AST
Total white blood cell count	ALT
Total red blood cell count	Albumin
Hematocrit	Potassium
	Calcium, total
Urinalysis	Sodium
Hemoglobin/erythrocytes/blood	Gamma-glutamyl transferase
Protein/albumin	Lactate dehydrogenase
Glucose	Protein, total
	Urea nitrogen/blood urea nitrogen
Coagulation	Troponin
Coagulation variables (aPTT, PTT, and INR)	Magnesium
	Chloride
	Serum creatinine

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

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.

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

8.2.5 Other Safety Assessments

8.2.5.1 Echocardiogram/Multigated Acquisition Scan

An ECHO or MUGA scan to assess LVEF will be performed at the visits as shown in SoA

(Section 1.3). The modality of the cardiac function assessments must be consistent for a given participant (ie, if ECHO is used for the screening assessment for a given participant, then ECHO should also be used for subsequent scans for that participant). The participants should also be examined using the same machine and operator whenever possible, and quantitative measurements should be taken (ie, accurate to 1% and not estimated to 5%). All ECHOs/MUGAs will be evaluated by the investigator or delegated physician for monitoring cardiac function.

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

8.2.5.2 Pulmonary Assessments

Pulse oximetry (SpO_2) should be evaluated by investigator or the delegate physician prior to the administration of study intervention at each visit after at least 10 minutes of rest.

Pulmonary function tests should include basic spirometry at a minimum with optional additional components as mentioned in Table 7.

Table 7 Spirometry Components

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

DLCO = diffusion capacity of the lungs for carbon monoxide; FEV = forced expiratory volume; FEV1 = FEV-1 second; FEV6 = FEV-6 seconds; FVC = forced vital capacity; L = liters; PEF = peak expiratory flow; RV = residual volume; TLC = total lung capacity.

The DLCO will be performed/encouraged if feasible, but for participants with prior severe and/or clinically significant pulmonary disorders, DLCO is a requirement.

A non-contrast HRCT scan of the chest will be performed at screening. If HRCT is not feasible, a non-contrast CT is acceptable. A non-contrast HRCT is mandatory if ILD/pneumonitis is suspected. Chest CT and/or chest HRCT scans will be reviewed separately for safety for the presence of ILD/pneumonitis prior to administration of the next scheduled dose of T-DXd. 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, non-contrast HRCT should be performed first.

8.2.5.3 ILD/Pneumonitis Investigation

If new or worsening pulmonary symptoms (eg, dyspnea, cough or fever) or radiological abnormality suggestive of ILD/pneumonitis is observed, study intervention should be interrupted and a full investigation is required based on the investigator's judgment as described in the T-DXd TMGs (Appendix O). Evaluations should include:

- HRCT (without contrast).
- Pulmonologist consultation (infectious disease consultation as clinically indicated).
- Blood culture and CBC. Other blood tests could be considered as needed.
- Bronchoscopy and CCI [redacted] as clinically indicated and feasible.
- Pulmonary function tests (Section 8.2.5.2) and SpO_2.
- Arterial blood gases if clinically indicated.
- One blood sample collection for PK as soon as ILD/pneumonitis is suspected, if feasible.
- Additional blood samples for CCI [redacted] as soon as ILD/pneumonitis is suspected, if feasible (see Section 8.6.1), as well as CCI [redacted] if available.
- Additional ECG, and/or MUGA and/or ECHO required for ILD investigation.
- Collect family history and exposure history for ILD (Appendix P), in addition to prior and current use of substance already collected at screening/Cycle 1 Day 1.
- Other tests could be considered, as needed.

The results of the full diagnostic workup (including HRCT [without contrast], blood and sputum culture, hematological parameters, etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory non-contrast 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. Troponin measurements will be done to rule out cardiac etiology.

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

- Other items
  - When ILD/pneumonitis is suspected during study treatment, the following markers should be measured where possible:
    - β-D-glucan

- Tumor markers: particular tumor markers that are related to disease progression
  - Additional clinical chemistry: C-reactive protein, lactate dehydrogenase

An ILD Advisory Committee will provide support for the assessment 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. The additional data collection 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 for AEs reported based on a set of predefined list of PTs.

8.2.5.4 ECOG Performance Status

ECOG performance status will be assessed times specified in the SoA (Section 1.3) 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 will be performed as specified in the SoA (Section 1.3) and will include visual acuity testing (according to local clinical practice), slit lamp examination, and fundoscopy.

8.3 Adverse Events and Serious Adverse Events

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

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

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

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

During the pre-screening period, only SAEs directly related to tissue screening procedures (ie, if a patient undergoes a tumor biopsy) will be reported. All other SAEs will be recorded from the time of signing of the main ICF.

AEs and SAEs (other than ILD/pneumonitis) will be collected from the time of signature of the main ICF, throughout the treatment period and including the safety follow-up (which is 40 + up to 7 days after the discontinuation of all study interventions). For ILD/pneumonitis, safety follow-up will be continued until resolution of ILD/pneumonitis. 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.

A TEAE is defined as an AE that occurs, having been absent before the first dose of study intervention, or has worsened in severity or seriousness after the initiating the study intervention until 47 days after last dose of the study intervention. SAEs with an onset or worsening 48 days or more after the last dose of study intervention, if considered related to the study intervention, are also TEAEs.

The following types of events should be reported by the investigator in eCRF AE page(s) in the clinical study database within 24 hours of becoming aware:

- SAEs.
- All potential ILD cases should be reported within 24 hours; including both serious and non-serious potential ILD cases (potential ILD/pneumonitis is described in the ILD Site Pocket Guide).
- Hepatic events (both serious and non-serious) that meet the PHL criteria defined as an elevated (ALT or AST) $\geq 3 \times$ ULN and an elevated TBL $\geq 2 \times$ ULN that may occur either at different time points or simultaneously during the study. A targeted questionnaire is built within the eCRF to collect relevant additional information for these potential cases.
- Overdose, defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. An “excessive and medically important” overdose includes any overdose in which either an SAE, a non-serious AE, or no AE occurs and is considered by the investigator as clinically relevant, i.e. poses an actual or potential risk to the subject.
  - Overdose is always serious. By definition an overdose is medically important, which meets the seriousness criterion of Important Medical Event. An overdose can occur

with or without an AE. AEs can either be serious or non-serious. Details of the overdose including T-DXd dosage, clinical course, associated AEs, and outcome must be captured in the Narrative form of the CRF within EDC.

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.

8.3.2 Follow-up of AEs and SAEs

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

Adverse Event Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Initial CTCAE grade, plus any changes in CTCAE grade
- Whether the AE is serious or not (Appendix B)
- Investigator causality rating against the study intervention (yes or no)
- Action taken with regard to study intervention
- 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 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 T-DXd 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, and ECHO/MUGA scans will be summarized in the CSR.

Deterioration as compared with baseline in protocol-mandated laboratory values, vital signs, and ECGs should therefore only be reported as AEs if they fulfill 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 be 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 vs low hemoglobin value). Any diagnosis of the undesirable clinical outcome of LV dysfunction, a valid or qualifying reduction of LVEF (as measured by MUGA or ECHO) should be confirmed and included in the AE report. In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AEs.

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. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of HL.

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 disease progression and not an AE. Events that 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

Events related to the disease under study commonly occur in studies of chronic diseases with a variable pattern, eg, respiratory conditions such as asthma, COPD, or rhinitis; neuropsychiatric conditions such as depression, seizure disorders, or multiple sclerosis; and cardiac disorders such as angina or heart failure. Symptoms of disease under study are those which might be expected to occur as a direct result of breast cancer. Events that are unequivocally due to breast cancer should not be reported as AEs 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. An autopsy 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 T-DXd safety profile and require close monitoring and rapid communication by the investigators to AstraZeneca. An AESI can be serious or non-serious.

All AESIs will be recorded in the eCRF using a recognized medical term or diagnosis that accurately reflects the event. Serious AESIs will be recorded and reported as per Section 8.3.13. Adverse events will be assessed by the investigator for severity, relationship to the study intervention, possible etiologies, and whether the event meets criteria for an SAE and therefore requires immediate notification to AstraZeneca. If an AE evolves into a condition that meets the regulatory definition of “serious,” it will be reported on the SAE Report Form.

Based on the available preclinical and clinical data, review of the cumulative literature,

reported toxicities for the same class of agents and biological plausibility, the following events are considered to be AESIs. Additional relevant information regarding the AESIs ILD/pneumonitis and LVEF decrease, for the T-DXd clinical program regardless of seriousness is to be collected through the targeted questionnaires within the clinical study database.

ILD/Pneumonitis

ILD is considered an important identified risk, based on a comprehensive cumulative review of potential ILD/pneumonitis cases reviewed by the independent ILD Advisory Committee, the available safety data from the clinical development program, available data from recent epidemiology/literature, biological plausibility, and safety information from drugs of similar class. Refer to the current T-DXd IB for a summary of preliminary clinical study data.

For broad surveillance of ILD/pneumonitis, a predefined list of PTs is utilized for enhanced data collection.

Refer to Appendix N for guidelines on management of study drug-induced ILD/pneumonitis.

LVEF Decrease

Left ventricular ejection fraction decrease in association with T-DXd is considered to be an important potential risk, based on the available preclinical data, literature, and available safety information for drugs of similar class. Refer to the current T-DXd IB for a summary of preliminary clinical trial data.

For broad surveillance of LVEF decrease, relevant PTs under the Standardized MedDRA Queries of Cardiac Failure is included for enhanced data collection; additional data for these PTs are collected via the targeted safety questionnaire of heart failure.

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

For participants continuing to receive T-DXd after the final DCO, AEs and SAEs will be collected, but only SAEs will be reported. In addition, it is recommended that investigators monitor the participant's safety laboratory results periodically during treatment with T-DXd in order to manage AEs, consistent with the dose modification guidelines for management of study intervention-related toxicities (see Section 6.6). 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 T-DXd (or within the 40 + up to 7 days following the last dose of T-DXd) 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.

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 an SAE to the appropriate AstraZeneca representative by telephone.

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

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

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

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.

8.3.14.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, T-DXd should be discontinued immediately.

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 abnormality) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 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

Male participants should refrain from fathering a child or donating sperm during the study and for 4 months after the last dose of study treatment. In addition, local prescribing information relating to contraception and the time limit for such precautions should be followed for marketed products used in this study.

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 abnormality) occurring from the date of the first dose of study intervention until 4 months after the last dose of study intervention should be followed up and documented in the medical record and provided to the AstraZeneca Patient Safety data entry site. Consent from the partner must be obtained before the information is collected and reported to AstraZeneca.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the investigator must obtain the consent of the participant's partner. The 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

If a medication error occurs in the course of the study, then the investigator or other site personnel informs 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 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.

The definition of a medication error can be found in Appendix B.

8.3.16 Medical Device Deficiencies

This section is not applicable for oncology studies.

8.4 Overdose

Use of T-DXd of 20% more than the intended w/v dose is considered to be an overdose.

There is currently no specific treatment in the event of overdose of T-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.

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

- 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 the protocol). Additional use includes but is not limited to confirmation and/or requalification of the assay as well as additional assay development work. 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

Pharmacokinetic parameters are not evaluated in this study.

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 (Section 1.3). For all tumor specimens, FFPE tissue blocks are preferred. If it is not possible to provide a tissue block, a minimum of 20 freshly-cut unstained serial tumor slides are to be provided.

The following mandatory samples will be collected from all participants, including screen failures where possible:

Archival Tumor Tissue / Fresh Biopsy

- A tumor sample is required from each participant from either primary or recurrent cancer. Where possible, the most recently acquired archival sample is required. From submitted archival tumor blocks, cores may be removed to construct tissue microarrays for CCI [redacted]. If the sample is from a biopsy of a metastatic site, a second biopsy from a different metastatic site is requested (if available).
- If an archival tumor tissue sample is not available, then a newly acquired sample from a biopsiable tumor must be collected prior to dosing with study treatment. Tumor lesions used for the biopsy should not be the same lesions used as RECIST 1.1 TLs, unless there

are no other lesions suitable for biopsy and, in this instance, only core needle (not excisional/incisional) biopsy is allowed.

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  - CCI
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- CCI
- CCI

- CCI [redacted]
- CCI [redacted]

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 CCI [redacted] Samples

Collection of optional samples for CCI [redacted] assessment is also part of this study as specified in the SoA (Section 1.3) and is subject to agreement to optional consent.

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CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

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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 CCI

CCI

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 CCI

CCI

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8.8 CCI

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- CCI
- CCI

9 STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by AstraZeneca or its representatives.

A comprehensive SAP will be prepared before enrollment of the first participant.

9.1 Statistical Hypotheses

No formal hypothesis testing is planned for this study.

9.2 Sample Size Determination

Approximately 500 eligible participants will be treated in the study. Of these, approximately 250 eligible participants without BM at baseline (Cohort 1) and approximately 250 eligible participants with BM at baseline (Cohort 2) will be treated.

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CCI [redacted]

CCI [redacted]

CCI [redacted]

Table 8 CCI [redacted]

CCI [redacted]

CCI [redacted]

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CCI [redacted]

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Table 9 CCI

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9.3 Populations for Analyses

The following populations are defined:

Table 10 Populations for Analysis

Population/Analysis Set	Description
Enrolled	All participants who sign the ICF.
FAS	All participants who are enrolled in the study and received at least 1 dose of treatment.
SAF	Participants who have received at least 1 dose of treatment.
CCI analysis set	The CCI analysis set includes participants CCI CCI

ICF = informed consent document; FAS = full analysis set; PRO = patient-reported outcomes; SAF = safety analysis set.

Additional analysis sets will be included in the SAP as required.

9.4 Statistical Analyses

The SAP will be finalized prior to enrollment of the first participant, and it will include a more

technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.4.1 General Considerations

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

Timing of the Primary Analysis

The primary analysis for each cohort will be performed independently. If the enrollment completion dates for both cohorts are at least 3 months apart, to avoid delay of primary analysis of the earlier completed cohort, separate database locks will be performed.

9.4.2 Efficacy

9.4.2.1 Primary Endpoints

9.4.2.1.1 Calculation or Derivation of Tumor Response Variables

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.

Participants will be assessed by ICR for RECIST 1.1 response of CR, PR, SD, PD, or NE depending on the status of their disease compared with baseline and previous assessments (Appendix G). Baseline will be assessed within the 28 days prior to the first dose of study intervention. The tumor response endpoints (PFS, ORR, CNS PFS, time to progression, time to CNS progression, DoR, and CNS DoR) will then be derived from the scan dates and overall visit responses.

CCI [redacted]**-based Assessments**

CCI [redacted]

CCI [redacted]

ICR

An ICR of radiological scans will be performed on all participants.

All images will be collected centrally. The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1, CNS RECIST 1.1, and CCI and will be adjudicated, if required. For each participant, the ICR will define the overall visit response data (CR, PR, SD, PD, or NE) and the relevant scan dates for each time point (ie, for visits where response or progression is/is not identified). If a participant has had a 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, time to progression, and DoR) will then be derived from the scan dates and overall visit responses.

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

9.4.2.1.2 Objective Response Rate

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

The analysis will include all dosed participants in Cohort 1 as a primary endpoint, and all dosed participants in Cohort 2 as a secondary endpoint.

Data obtained from first dose 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 stop 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 estimate of ORR. The estimate and its 95% CI using normal approximation will be provided. Additionally, ORR estimate and its 95% CI at selected intervals (eg, 6, 9, 12 months) from the first date of dosing will be summarized.

9.4.2.1.3 Progression-Free Survival

The PFS is the primary endpoint for Cohort 2.

The PFS will be defined as the time from the date of the first dose of study intervention until the date of objective PD per RECIST 1.1 as assessed by ICR or death (by any cause in the absence of progression), (ie, date of event or censoring – date of the first dose of study intervention + 1). The analysis will include all dosed participants, regardless of whether the participant withdraws from 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 Day 1, unless they die within 2 visits of baseline (6 weeks plus 1 week allowing for a late assessment within the visit window).

Analysis Methods

The primary PFS will be based on the ICR assessment of PD by RECIST 1.1 for all dosed participants in Cohort 2.

The PFS will be analyzed by Kaplan-Meier method. Median PFS and its 95% CI using Brookmeyer and Crowley method will be provided.

Kaplan-Meier plots of PFS will be presented. 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. The proportion of participants alive and progression-free at selected intervals (eg, 6, 9, 12 months) from the first date of dosing will be summarized.

9.4.2.1.4 Subgroup Analyses

Subgroup analyses will be conducted by cohort, and descriptive statistics of primary endpoints will be provided for T-DXd in the following subgroups of the FAS (but not limited to):

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- CCI

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

The subgroup analyses 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.

9.4.2.2 Secondary Endpoints

Overall survival, DoT on subsequent therapy, DoR, time to progression, CNS PFS, PFS2, and CCI will be analyzed using the same methodology specified for PFS. Detailed censoring rules will be specified in SAP.

9.4.2.2.1 Overall Survival

Overall survival is defined as the time from the date of the first dose of study intervention until death due to any cause. The analyses will include all dosed participants, regardless of whether the participant withdraws from therapy or receives another anticancer therapy. Any participant not known to have died at the time of analysis will be censored based on the last recorded date on which the participant was known to be alive.

Overall survival will be analyzed for participants in both cohorts and for the Cohort 2 subgroups of stable vs active (untreated or progressing) BM at baseline.

9.4.2.2.2 Duration of Treatment on Subsequent Therapy

Duration of treatment on subsequent therapy will be defined as the time from the date of first dose of a subsequent therapy until date of the last dose of that therapy.

The analysis will include all dosed participants who start a subsequent line of therapy.

9.4.2.2.3 Duration of Response

Duration of response will be defined as the time from the date of first documented confirmed response until date of documented progression per RECIST 1.1 as assessed by ICR or death due to any cause.

The analysis will include all dosed participants 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.

9.4.2.2.4 Time to Progression

Time to progression per RECIST 1.1 is defined as the time from the date of the first dose of study intervention to the date of documented disease progression and will be summarized descriptively in Cohort 1 and Cohort 2.

9.4.2.2.5 PFS2

The PFS2 is defined as time from the first dose of study intervention to second progression (the earliest of the progression event subsequent to first subsequent therapy) or death. Second progression will be defined according to local standard clinical practice. Following discontinuation of study treatment due to disease progression, as determined by the investigator according to RECIST 1.1 assessment, patients who started on subsequent cancer therapy post progression will continue to be followed at the 40 day (+ up to 7 days) follow-up

visit, and every 3 months (± 14 days) thereafter for documentation of progression on subsequent anticancer therapy.

The PFS2 will be analyzed for participants in both cohorts using the same methodology specified for PFS.

9.4.2.2.6 Incidence of New Symptomatic CNS Metastases

The incidence rate is defined as:

$$\frac{number\ of\ new\ symptomatic\ CNS\ metastases\ during\ treament\ period}{total\ number\ of\ subjects\ without\ symptomatic\ CNS\ at\ begining\ of\ study}$$

9.4.2.2.7 Time to Next Progression (CNS or Extracranial) or Death

The time to next progression is defined as the time from the date of the first documented isolated CNS progression to the date of the next documented disease progression (CNS or extracranial) per RECIST 1.1 or death and will be summarized descriptively in patients who develop isolated CNS progression, receive local therapy, and continue on protocol therapy.

9.4.2.2.8 Site of Next Progression

Site of next progression will be summarized descriptively in patients who develop isolated CNS progression, receive local therapy, continue on protocol therapy, and have a subsequent documented disease progression (CNS or extracranial) per RECIST 1.1.

9.4.2.2.9 CNS PFS

The endpoint of CNS PFS is defined as time from the first dose of study intervention to CNS progression per CNS RECIST 1.1 or death resulting from any cause, whichever occurs first.

The endpoint of CNS PFS will be analyzed for participants in Cohort 2 and for the Cohort 2 subgroups of stable vs active (untreated or progressing) BM at baseline using the same methodology specified for PFS.

9.4.2.2.10 Time to New CNS Lesions

The time to new CNS lesions is defined as the time from the date of the first dose of study intervention to the date of documented new CNS lesions, and will be summarized descriptively in Cohort 2.

9.4.2.2.11 CNS ORR by CNS RECIST

The CNS ORR is defined as the proportion of participants with measurable BM at baseline who have a confirmed CR or confirmed PR of brain lesions, as determined by ICR per CNS RECIST 1.1.

The analysis will include all dosed participants in Cohort 2 and for the Cohort 2 subgroups of stable vs active (untreated or progressing) BM at baseline.

Data obtained from first dose until brain progression, or the last evaluable assessment in the absence of brain progression, will be included in the assessment of ORR, regardless of whether the participant withdraws from therapy. Participants who stop 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 estimate of CNS ORR.

9.4.2.2.12 CNS Duration of Response

The CNS DoR will be defined as the time from the date of first documented confirmed CNS response until date of documented CNS progression per CNS RECIST 1.1 as assessed by ICR or death due to any cause.

The analysis will include all dosed participants in Cohort 2 who have a confirmed response, regardless of whether the participants withdraws from therapy, receives another anticancer therapy, or clinically progresses prior to RECIST 1.1 progression. This analysis will also be conducted for the Cohort 2 subgroups of stable vs active (untreated or progressing) BM at baseline.

9.4.2.2.13 Clinical Outcome Assessments

Change in symptoms, functioning, and HRQoL as measured by the EORTC QLQ-C30, NANO scale, and cognitive tests (for all participants), MDASI brain tumor-specific items (for participants with BM), and SGRQ-I, (for participants with ILD/pneumonitis) while on treatment will be analyzed. Full details of the COA analyses will be provided in the SAP.

9.4.2.3 Exploratory Endpoints

9.4.2.3.1 CCI

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9.4.2.3.2 CCI

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9.4.2.3.3 CCI

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9.4.2.3.4 CCI

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9.4.2.3.5 CCI

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9.4.2.3.6 CCI

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9.4.2.3.7 CCI

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9.4.2.3.8 CCI

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CCI

CCI [redacted]

Analysis Methods

CCI [redacted]

9.4.3 Safety

Safety summaries will be provided using the safety analysis set. 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.

Some safety parameters will also be analyzed in the subgroup of participants who entered the study within less than 2 weeks of stereotactic radiation. Subgroup analyses will be described in the SAP.

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.

Adverse Events

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

Adverse events, including SAEs, AEs leading to discontinuation, AEs leading to dose reductions, and AESIs, will be listed individually by patient and coded using MedDRA Preferred Terms from the most recent version of MedDRA that will have been released for execution at AstraZeneca.

Adverse events will be presented by system organ class and/or PT, covering number and percentage of patients reporting at least one event and number of events where appropriate.

Adverse events occurring prior to start of study treatment, TEAEs, and post-treatment AEs will be presented separately.

An overview of AEs will be presented for the number and percentage of patients with any AE,

AEs with outcome of death, SAEs, and AEs leading to discontinuation of study treatment, as well as AEs leading to study treatment dose interruptions, AEs leading to study treatment dose reduction and AEs leading to withdrawal from study as well as the number of individual occurrences in those categories.

Separate AE tables will be provided taking into consideration the relationship to study treatment as assessed by the Investigator, CTCAE grade, seriousness, death, and events leading to discontinuation of study treatment as well as other action taken related to study treatment, AESIs, other significant AEs, and timing of events.

An additional table will present the number and percentage of patients with the most common AEs. Most common AEs will be defined in the SAP.

In accordance with the requirements of the FDA, a separate table will present non-serious AEs occurring in more than 5% of patients in any treatment group.

Key patient information will be presented for patients with AEs with outcome of death, serious AEs, and AEs leading to discontinuation of study treatment.

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

The following events are considered treatment-emergent:

- AEs with an onset date on or after first dose of study treatment
- Worsening of pre-existing events on or after first dose of study treatment until 47 days after last dose of the study treatment

Serious AEs with an onset or worsening 48 days or more after the last dose of study treatment, if considered related to the study treatment, are also TEAEs.

Vital Signs

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

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

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 HL will be performed and reported as

appropriate.

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.

9.4.4 Other Analyses

9.4.4.1 CCI

CCI status will be assessed for participants in each treatment group according to prespecified criteria that may be detailed in the SAP. CCI analyses may be described in a separate analysis plan and may be reported outside the CSR in a separate report. The results of this CCI assessment will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

9.4.4.2 CCI

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

9.5 Interim Analyses

An interim analysis of the primary endpoint of PFS in Cohort 2 is planned for when approximately 125 (50%) eligible participants are enrolled in Cohort 2.

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

9.6 Data Monitoring Committees

For details on data monitoring committees, refer to Appendix A 5.

9.6.1 IDMC

An IDMC comprising independent experts will be convened and will meet approximately 6 months after the study has started or after the first 60 participants have been treated, whichever occurs first, to review safety data and make recommendations to continue, amend, or stop the study based on safety findings. The committee will meet approximately every 6 months thereafter.

Full details of the IDMC procedures and processes can be found in the IDMC Charter.

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety.

9.6.2 Steering Committee

A steering committee has been established to advise the sponsor on aspects of study development and implementation. A subgroup of the steering committee will be set up to provide a parallel assessment of ILD/pneumonitis risk. This subgroup will make available to the investigator their report and highlight any unidentified risk.

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 Organisations 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 CRO but the accountability remains with AstraZeneca.

Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward 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 an 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 or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

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

- A pre-screen ICF must be signed for patients to permit for tumor tissue sample collection for HER2 status testing prior to the 28-day screening window.
- 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.

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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.

A 6 Dissemination of Clinical Study Data

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

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on the eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory authority inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of 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, CROs).
- 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 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.

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 participant signing the pre-screen ICF is considered the first act of recruitment and will be the study start date.

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

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

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

- Failure of the investigator to comply with the 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 CROs 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 fulfills 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 abnormality 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 fulfill 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 an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). 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 NCI CTCAE v5 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).

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 an 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 an 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.
- Rechallenge 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

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

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

Medication error includes situations where an error:

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were 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, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT 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
- Errors related to background and rescue medication, or SoC medication in open-label studies, even if an AstraZeneca product

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

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 while 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 6.2 Guidance Document

LABELING 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/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf)
- Biological samples transported in dry-ice require additional dangerous goods specification for the dry-ice content

Appendix D CCI

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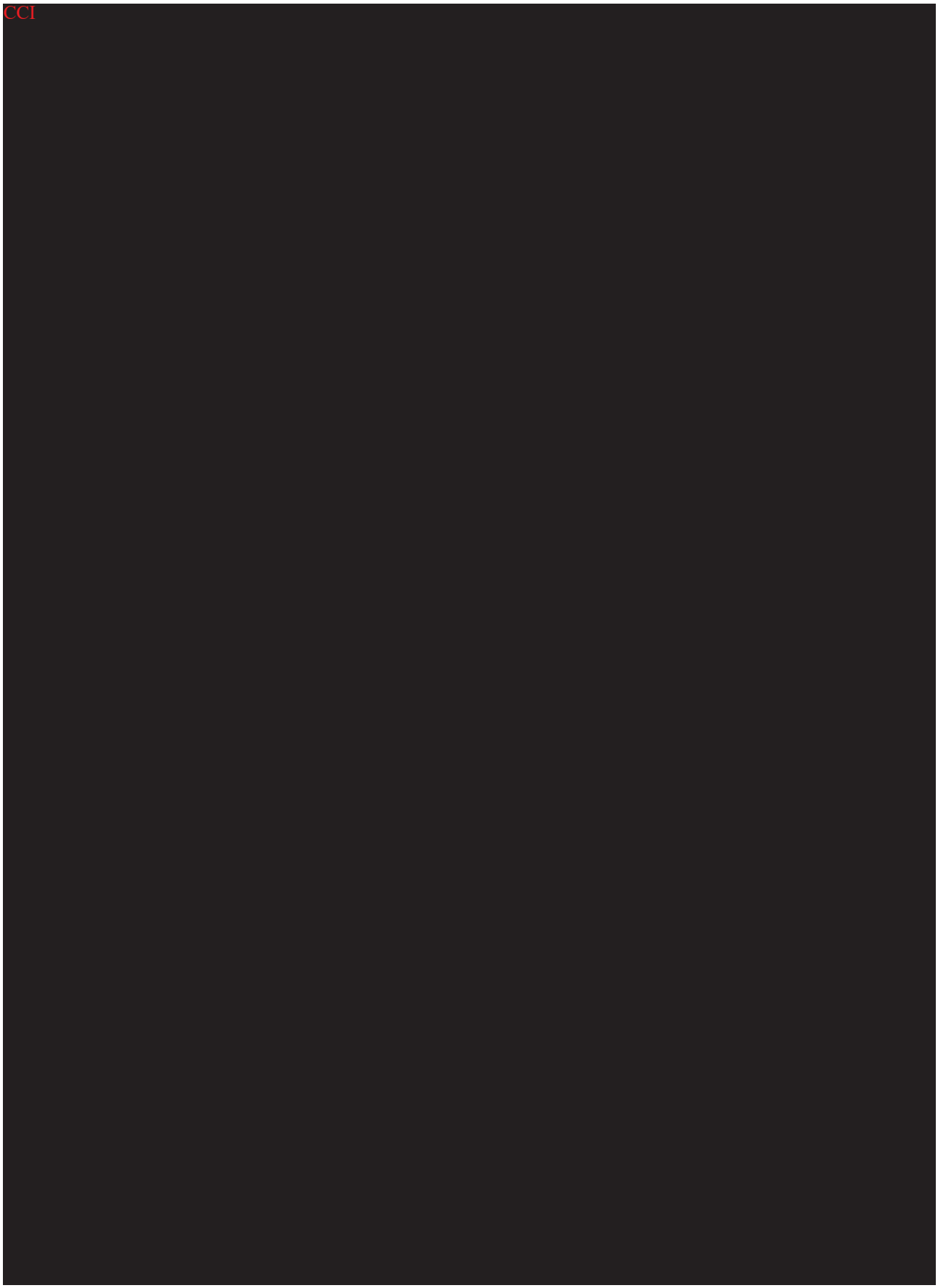
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Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

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.

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 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

PHL

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

HL

AST or ALT ≥ 3 × ULN **together with** TBL≥ 2 × ULN, where no other reason, other than the study intervention, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, 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 was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

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

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.

- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

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

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

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

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

E 6 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests that are recommended but not mandatory when using a central laboratory. When local laboratories are used, this list may be modified according to clinical judgment. Any test result must be recorded.

Hy's Law lab kit for central laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc
	HBsAg HCV 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

[a] HCV RNA; HCV DNA are only tested when IgG anti-HCV is positive or inconclusive.
[b] Carbohydrate-deficient transferrin and transferrin are not available in China. Study teams should amend this list accordingly.

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.

E 7 References

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 ASCO/CAP Guidelines on HER2 Testing in Breast Cancer

This protocol will determine HER2 status using guidelines from ASCO (per ASCO/CAP 2018 guidelines [Wolff et al, 2018]). Per the guidelines, patients are HER2-negative if they have IHC 0/1+ or have a FISH ratio of <1.8 or have <4 copies per tumor cell (Table 11).

Table 11 Summary of Guideline Recommendations

Procedure	Recommendation
Optimal algorithm for HER2 testing	Positive for HER2 is either IHC HER2 3+ (defined as uniform intense membrane staining of > 10% of invasive tumor cells) or FISH amplified (ratio of *HER2* to CEP17 of > 2.2 or average *HER2* gene copy number > 6 signals/nucleus for those test systems without an internal control probe) Equivocal for HER2 is defined as either IHC 2+ or FISH ratio of 1.8 to 2.2 or average *HER2* gene copy number 4 to 6 signals/nucleus for test systems without an internal control probe Negative for HER2 is defined as either IHC 0-1+ or FISH ratio of < 1.8 or average *HER2* gene copy number of < 4 signals/nucleus for test systems without an internal control probe These definitions depend on laboratory documentation of the following: 1 Proof of initial testing validation in which positive and negative HER2 categories are 95% concordant with alternative validated method or same validated method for HER2 2 Ongoing internal QA procedures 3 Participation in external proficiency testing 4 Current accreditation by valid accrediting agency
Optimal FISH testing requirements	Fixation for fewer than 6 hours or longer than 48 hours is not recommended Test is rejected and repeated if • Controls are not as expected • Observer cannot find and count at least 2 areas of invasive tumor • > 25% of signals are unscorable due to weak signals • > 10% of signals occur over cytoplasm • Nuclear resolution is poor • Autofluorescence is strong Interpretation done by counting at least 20 cells; a pathologist must confirm that counting involved invasive tumor Sample is subjected to increased counting and/or repeated if equivocal; report must include guideline-detailed elements
Optimal IHC testing requirements	Fixation for fewer than 6 hours or longer than 48 hours is not recommended Test is rejected and repeated or tested by FISH if

Table 11 Summary of Guideline Recommendations

Procedure	Recommendation
	• Controls are not as expected • Artifacts involve most of sample • Sample has strong membrane staining of normal breast ducts (internal controls) • Interpretation follows guideline recommendation • Positive HER2 result requires homogeneous, dark circumferential (chicken wire) pattern in > 30% of invasive tumor • Interpreters have method to maintain consistency and competency Sample is subjected to confirmatory FISH testing if equivocal based on initial results Report must include guideline-detailed elements
Optimal tissue handling requirements	Time from tissue acquisition to fixation should be as short as possible; samples for HER2 testing are fixed in neutral buffered formalin for 6 to 48 hours; samples should be sliced at 5 to 10 mm intervals after appropriate gross inspection and margins designation and placed in sufficient volume of neutral buffered formalin Sections should ideally not be used for HER2 testing if cut > 6 weeks earlier; this may vary with primary fixation or storage conditions Time to fixation and duration of fixation if available should be recorded for each sample
Optimal internal validation procedure	Validation of test must be done before test is offered Initial test validation requires 25 to 100 samples tested by alternative validated method in the same laboratory or by validated method in another laboratory Proof of initial testing validation in which positive and negative HER2 categories are 95% concordant with alternative validated method or same validated method for HER2 Ongoing validation should be done biannually
Optimal internal QA procedures	Initial test validation Ongoing quality control and equipment maintenance Initial and ongoing laboratory personnel training and competency assessment Use of standardized operating procedures including routine use of control materials Revalidation of procedure if changed Ongoing competency assessment and education of pathologists
Optimal external proficiency assessment	Participation in external proficiency testing program with at least 2 testing events (mailings)/year Satisfactory performance requires at least 90% correct responses on graded challenges for either test • Unsatisfactory performance will require laboratory to respond according to accreditation agency program requirements

Table 11 Summary of Guideline Recommendations

Procedure	Recommendation
Optimal laboratory accreditation	On-site inspection every other year with annual requirement for self-inspection • Reviews laboratory validation, procedures, QA results and processes, results, and reports • Unsatisfactory performance results in suspension of laboratory testing for HER2 for that method

CEP17 = chromosome 17 centromere; FISH = fluorescent in situ hybridization; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; QA = quality assurance
Excerpt from Wolff et al, 2007.

The following tables provide additional information from the ASCO/CAP Guidelines for what needs to be reported for IHC and FISH (Table 12 and Table 13).

Table 12 Reporting Elements for IHC (Local HER2 Test)

Patient identification information
Physician identification
Date of service
Specimen identification (case and block number)
Specimen site and type
Specimen fixative type
Time to fixation (if available)
Duration of fixation (if available)
Antibody clone/vendor
Method used (test/vendor and if FDA-approved)
Image analysis method (if used)
Controls (high protein expression, low-level protein expression, negative protein expression, internal)
Adequacy of sample for evaluation
Results
Percentage of invasive tumor cells exhibiting complete membrane staining
Uniformity of staining: present/absent
Homogeneous, dark circumferential pattern: present/absent
Interpretation
Positive (for HER2 protein expression); equivocal (FISH will be done and reported); negative (for HER2 protein expression); not interpretable
Comment
If an FDA-approved method is used, it should be stated; if the FDA-approved method has been modified, a statement in the report should be included indicating what modifications were made and that the changes have been validated; if the test is not FDA-approved or an FDA-approved test has been modified, a clear statement must be made that the laboratory reporting results takes responsibility for test performance

IHC = immunohistochemistry; FDA = US Food and Drug Administration; FISH = fluorescent in situ hybridization; HER2 = human epidermal growth factor receptor 2.

Table 13 Reporting Elements for FISH (Local HER2 Test)

Patient identification information
Physician identification
Date of service
Specimen identification (case and block number)
Specimen site and type
Specimen fixative type
Time to fixation (if available)
Duration of fixation (if available)
Probe(s) identification
Method used (specifics of test/vendor and if FDA-approved)
Image analysis method
Controls (amplified, equivocal, and nonamplified, internal)
Adequacy of sample for evaluation (adequate number of invasive tumor cells present)
Results
Number of invasive tumor cells counted
Number of observers
Average number of HER2 signals/nucleus or tile
Average number of CEP17 chromosome probes/nucleus or tile
Ratio of average HER2 signals/CEP17 probe signals
Note: Tile is unit used for image system counting
Interpretation
Positive (amplified); equivocal; negative (not amplified); not interpretable; if IHC is being done because of problems with assay or results, this should also be indicated
Comment
If an FDA-approved method is used, it should be noted; if the FDA-approved method has been modified, a statement in the report should be included indicating what modifications were made and that the changes have been validated; if the test is not FDA-approved or an FDA-approved test has been modified, a clear statement must be made that the laboratory reporting results takes responsibility for test performance

CEP17 = chromosome 17 centromere; FISH = fluorescent in situ hybridization; FDA = US Food and Drug Administration; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry.
Excerpt from: Wolff et al, 2007

Appendix G Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria

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.

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 14.

Table 14 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 Isotopic bone scan (Scintigraphy) ^{18}F-fluoro-deoxyglucose PET/CT

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), 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 artifacts (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. 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:

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

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

b. 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.

Brain scan

For the brain, images from MRI (preferred, unless contraindicated) with and without IV contrast, or contrast-enhanced CT, will be collected for all participants at baseline, and for participants with BMs at regular (follow-up) intervals during study intervention.

Regularly scheduled follow-up brain scans are mandatory for all patients who were enrolled with baseline stable or active BMs. A confirmatory scan for PD is required, no earlier than 4 weeks and no later than the next regularly scheduled imaging assessment. Patients who receive local therapy for isolated CNS progression should maintain their assessment schedule (including scans). Patients without BMs require a brain MRI / CT scan at EOT. Additional brain scans for subsequent tumor assessments are not required, unless clinically indicated.

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 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 (scintigraphy)

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. New lesions 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 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[2] 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

2 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.

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 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

All participants in this study will receive a baseline MRI (preferred) or CT scan and will be followed up with repeat scans every 6 weeks until Week 48 and every 9 weeks thereafter starting at Week 57. For participants suspected or diagnosed with BMs: All participants in this study will receive an IV contrast-enhanced MRI (preferred) or IV contrast-enhanced CT of the brain at screening/baseline. Regularly scheduled follow-up brain scans are mandatory for all participants with baseline stable BMs, while participants without BMs do not need additional brain scans for subsequent tumor assessments unless clinically indicated.

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[3] 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

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

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
- 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) [4]
- Previously irradiated lesions [5]

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

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

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

addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

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

The site and location of each TL should be documented, as well as the longest axis diameter for non-nodal lesions (or short axis diameter for lymph nodes). All measurements should be recorded in 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 MRI/CT 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 15 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 16 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 17.

Table 17 RECIST 1.1 Overall Visit Response

Target lesions	Non-target lesions	New lesions	Overall visit response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	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
NA	Non-CR/non-PD	No	SD (non-CR/non-PD)
NE	Non-PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Non-CR/Non-PD for overall response if only NTL (no TLs) are present at baseline.
Note: An overall assessment of CR (all other disease disappears/reverts to normal) would be changed to PR if ascites remains present radiologically.
CR = complete response; NA = not applicable (only relevant if there were no TLs at baseline or NTLs at baseline), NE = not evaluable; NTL = non-target lesion; PD = progression of disease; PR = partial response; SD = stable disease; TL = target lesion.

The following overall visit responses are possible depending on the extent of tumor disease at baseline:

- For participants with TLs (at baseline): CR, PR, SD, PD, or NE
- For participants with NTLs only (at baseline): CR, non-CR/non-PD, PD, or NE

Central imaging

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 ICR. Digital copies of all original scans should be stored at the investigator site as source documents. Electronic image transfer from the sites to the iCRO is strongly encouraged. An ICR of images will be performed at the discretion of AstraZeneca. Results of these independent reviews will not be communicated to investigators, and results of investigator 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 ICR will be documented in an Independent Review Charter.

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 tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Appendix H CCI

Introduction

CCI

CCI

Summary of the Response Criteria for CNS Metastases

Response criteria for CCI [redacted] are summarized in Table 18.

Table 18 Response Criteria for CNS Metastases per CCI [redacted]

	CR	PR	SD	PD
TL	CCI [redacted]			
NTL				
NL[b]				
CCI [redacted]				
CCI [redacted]				
CCI [redacted]				

CR = complete response; NL = new lesion; NTL = non-target lesion; PD = progression of disease; PR = partial response; SD = stable disease; TL = target lesion.

[a] Progression occurs when this criterion is met.

[b] CCI [redacted]

[c] CCI [redacted]

Central imaging

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 ICR. Digital copies of all original scans should be stored at the investigator site as source documents. Electronic image transfer from the sites to the iCRO is strongly encouraged. An ICR of images will be performed at the discretion of AstraZeneca. Results of these independent reviews will not be communicated to investigators, and results of investigator 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 ICR will be documented in an Independent Review Charter.

Appendix I Contraception Requirements

Contraception requirements for this study are as follows.

I 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.

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 19). They should have been stable on their chosen method of birth control for a minimum of 3 months before entering the study 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. 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 T-DXd administration. Preservation of ova may be considered prior to starting the study treatment.

I 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 (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 method of contraception provided that it is the 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 this period. Preservation of sperm should be considered prior to starting the study treatment.

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 19).

I 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 19. 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).

Hormonal methods of contraception are not advised in a breast cancer population and should only be used by the female partners of male participants.

Table 19 Highly Effective Methods of Contraception (<1% Failure Rate)

Non-Hormonal Methods	Hormonal Methods (Female Partners of Male Participants Only)
• 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®) • Levonorgestrel-releasing intrauterine system (eg, Mirena®) • 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

Appendix J Patient-reported Outcomes

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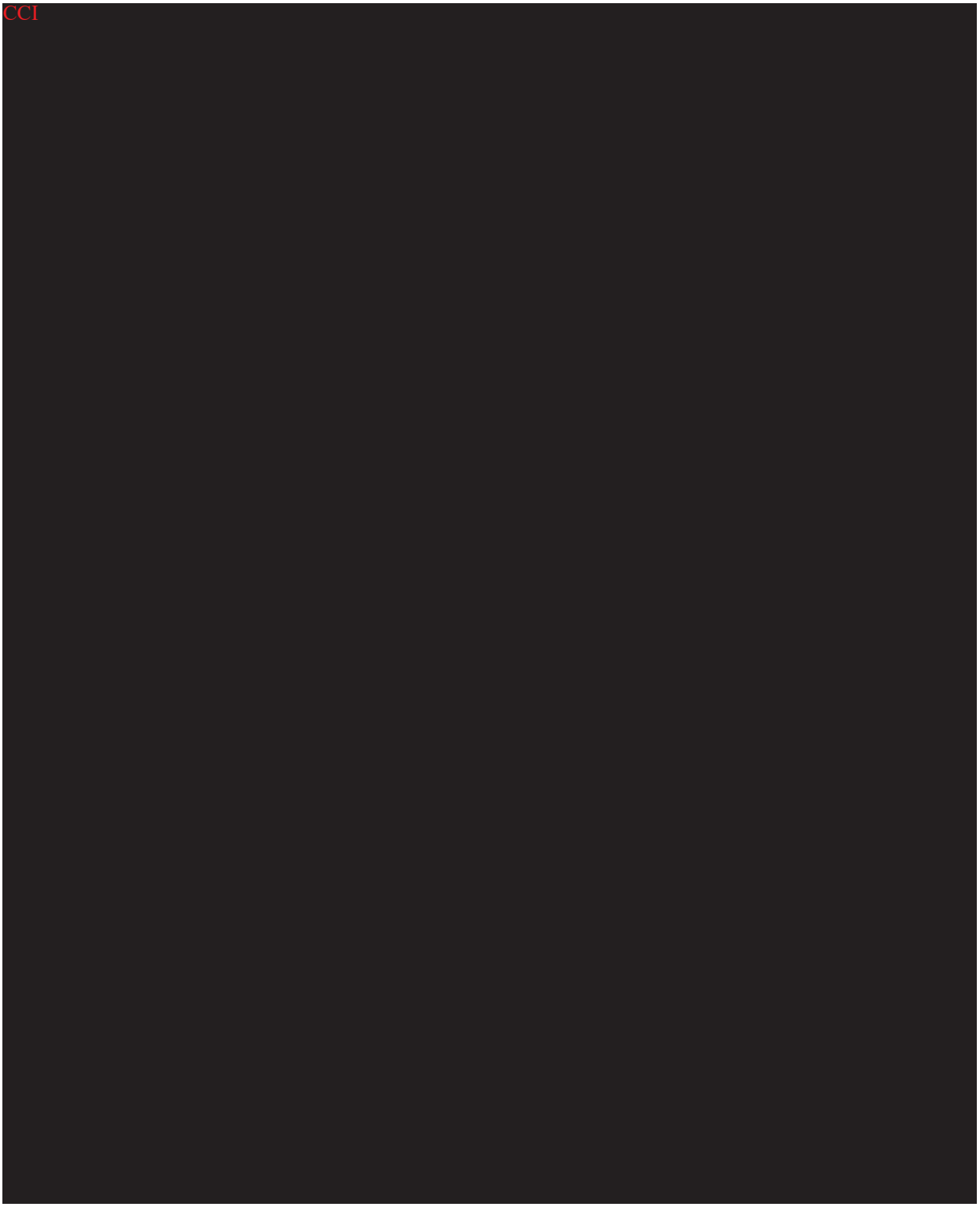


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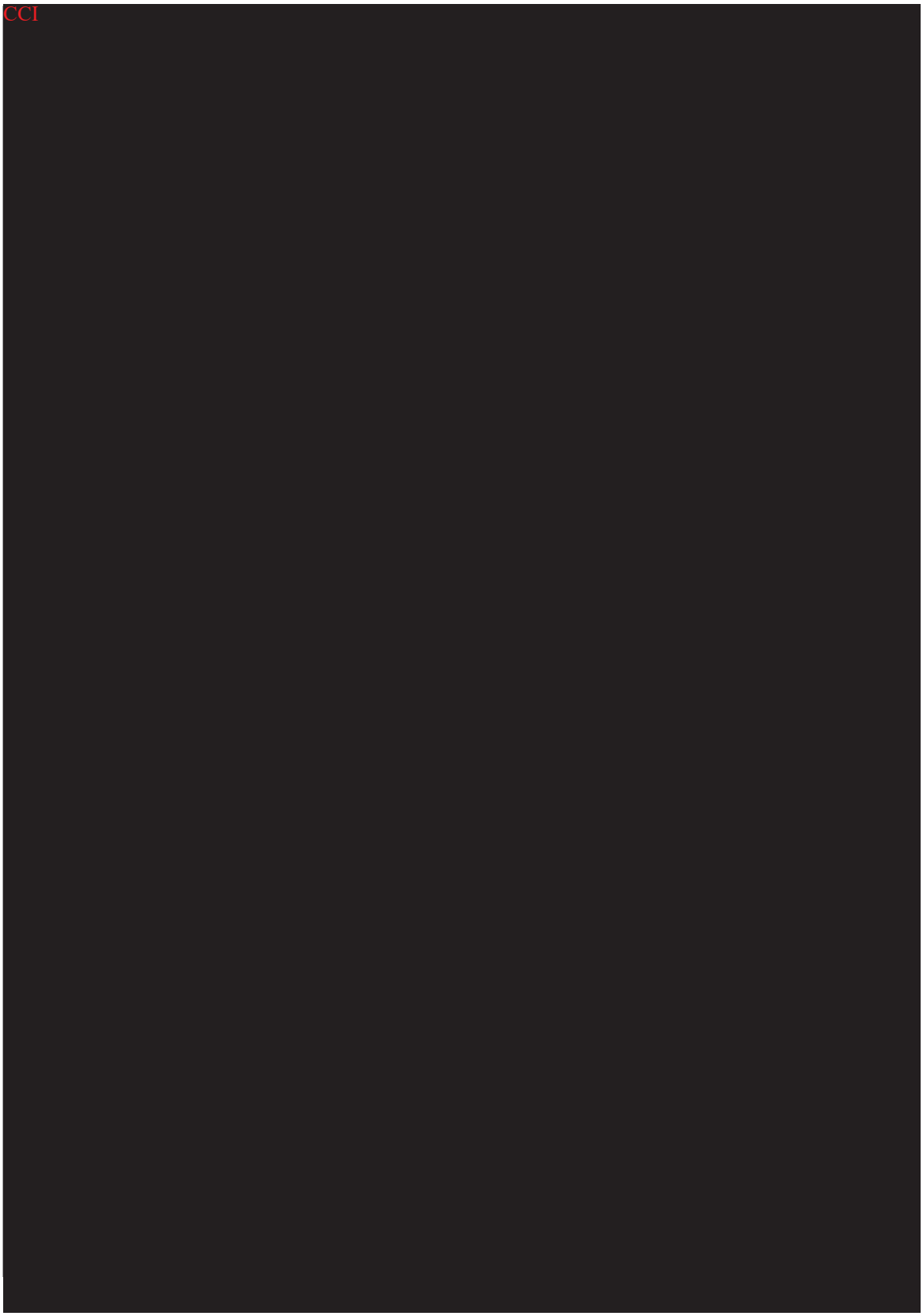
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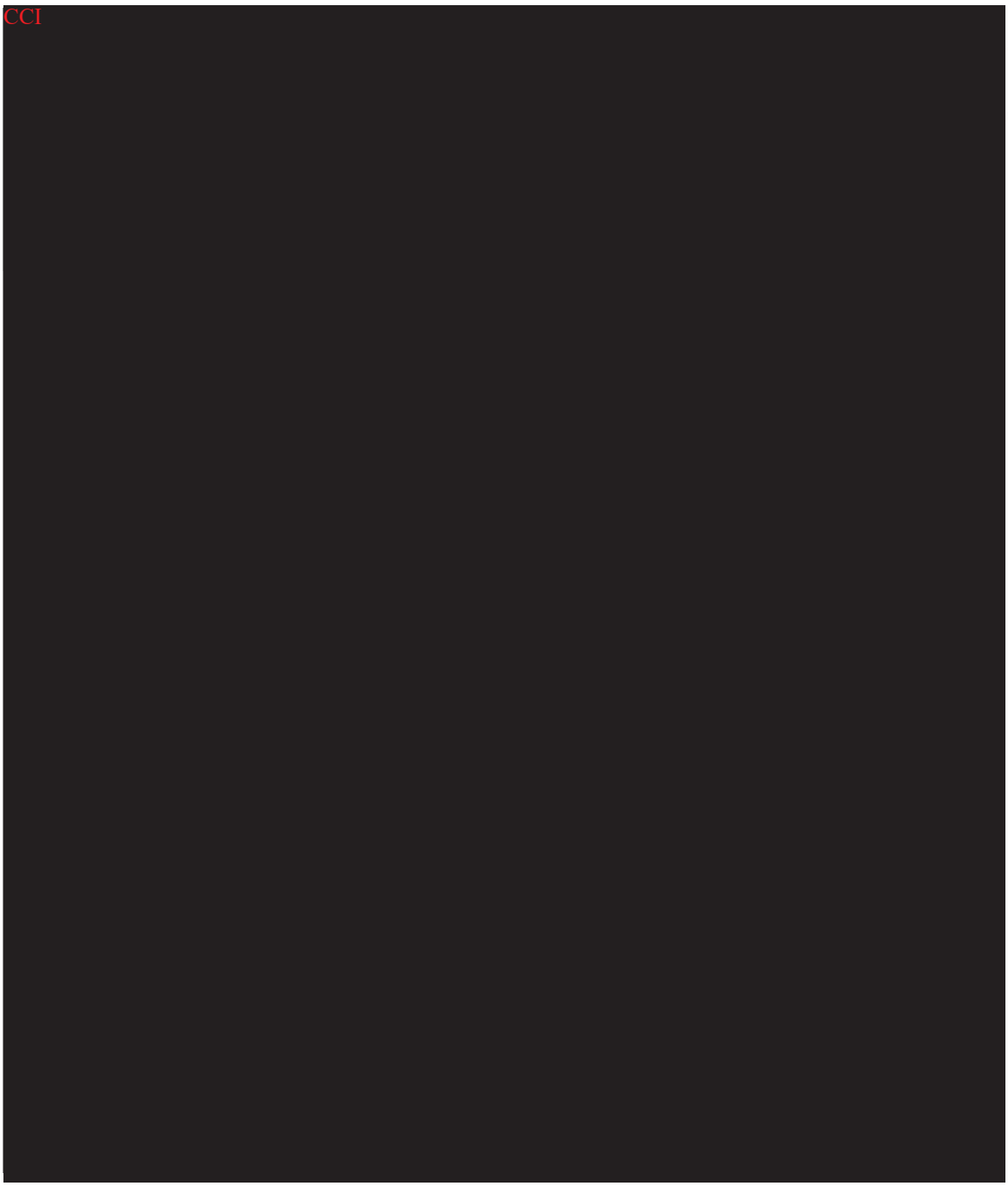
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Appendix K Guidance Regarding Restricted, Prohibited, and Permitted Concomitant Medications

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.

Restricted, prohibited, and permitted concomitant medications/therapies are described in Table 20, Table 21, and Table 22. Refer also to the dose modification guidelines for management of study intervention-related toxicities in Section 6.6. Participants must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

Table 20 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.
Hematopoietic growth factors	May be used for prophylaxis or treatment based on the clinical judgment of the investigator.
Dietary supplements, medications not prescribed by the investigator, and alternative/complementary treatments	Concomitant use is discouraged, but not prohibited.
Prophylactic or supportive treatment of study drug-induced AEs	As per investigator's discretion and institutional guidelines.

AE = adverse event; eCRF = electronic case report form.

With the exception of medications that are under investigation in the study (eg, SoC, comparators, or combination therapies), the medications in Table 21 are considered exclusionary during the study. The sponsor must be notified if a participant receives any of these during the study.

Table 21 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 for COVID-19, 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 L for further details).
Any concurrent chemotherapy, anticancer study intervention or biologic, radiotherapy (except palliative radiotherapy to areas other than chest, after consultation with the 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 hormone replacement therapy) is acceptable.
Live vaccine during the study and up to 30 days after the last dose of study treatment	Patients who have received live, attenuated vaccine within 30 days prior to the first dose of T-DXd will be excluded.

Table 21 Prohibited Medications/Therapies

Prohibited medication/class of drug/therapy	Usage
Immunosuppressive medications, including corticosteroids	T-DXd cannot be administered when the participant is taking immunosuppressive medications, including corticosteroids with the exception of: • short-term courses (< 2 weeks) • low to moderate dose • long-term, alternate-day treatment with short-acting preparations • maintenance physiological doses (replacement therapy) • administered topically (skin or eyes), by aerosol, or by intra-articular, bursal, or tendon injection Treatment with corticosteroids to prevent or treat hypersensitivity reactions to radiographic contrast agents is allowed. A temporary period of steroid treatment will be allowed for different indications after discussion with the study physician (eg, chronic obstructive pulmonary disease, radiation, nausea, etc). Participants with bronchopulmonary disorders may use bronchodilators if only administered intermittently. Use of immunosuppressive medications for the prevention and management of study treatment-related AEs or in patients with contrast allergies is acceptable. Immunosuppressive medications also include drugs like methotrexate, azathioprine, and tumor necrosis factor-alpha blockers. Treatment with corticosteroids to manage neurological symptoms in patients with BMs is permitted. The lowest effective dose should be used.

AE = adverse event; COVID-19 = coronavirus 2019-nCoV; T-DXd = trastuzumab deruxtecan.

Table 22 Supportive Medications/Therapies

Supportive medication/class of drug/therapy	Usage
Hormones for noncancer-related conditions (eg, insulin for diabetes and hormone replacement therapy)	Concurrent use is acceptable.
Prophylactic anti-emetic agents	See Table 23
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate AE event management, except for those medications identified as “prohibited,” as listed above	To be administered as prescribed by the investigator except for those medications identified as “prohibited,” as listed in Table 21

Table 22 Supportive Medications/Therapies

Supportive medication/class of drug/therapy	Usage
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 21
Corticosteroids and/or bisphosphonates for the treatment of bone and CNS metastases and for the treatment of specific adverse drug reactions (refer to Toxicity Management Guidelines in Appendix O.	Permitted
Inactivated viruses, such as those in the influenza vaccine	Permitted
Required for management of other medical conditions	As required except for those identified as "prohibited," as listed in Table 21

AE = adverse event; CNS = central nervous system; NK1 = neurokinin 1; T-DXd = trastuzumab deruxtecan; 5-HT_3 = 5-hydroxytryptamine 3.

Table 23 NCCN Guidelines for the prevention of acute and delayed emesis by moderate emetic risk parenteral anticancer agents

DAY 1: Select treatment option D, E, or F. **All treatment options are category 1 and should be started before anticancer therapy**[a]	**DAYS 2, 3:**
Treatment option D, use the following combination: • 5-HT3 RA (choose one): – Dolasetron 100mg PO once – Granisetron 10mg SQ once[b] (preferred), or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24h transdermal patch applied 24-48 h prior to first dose of anticancer therapy. – Ondansetron 16-24 mg PO once or 8-16mg IV once – Palonosetron 0.25 mg IV once (preferred) • Dexamethasone 12 mg PO/IV once[c,d]	Treatment option D: • Dexamethasone 8 mg[c,d] PO/IV daily on days 2, 3 OR • 5-HT3 RA monotherapy[e]: – Granisetron 1-2 mg (total dose) PO daily or 0.01 mg/kg (max 1 mg) IV daily on days 2 and 3 – Ondansetron 8 mg PO twice daily or 16 mg PO daily or 8-16 mg IV daily on days 2, 3 – Dolasetron 100 mg PO daily on days 2, 3
Treatment option E, use the following combination:[f] • Olanzapine 5-10 mg PO once[g] • Palonosetron 0.25 mg IV once	Treatment option E: • Olanzapine 5-10 mg PO daily on days 2, 3[g]

Table 23 NCCN Guidelines for the prevention of acute and delayed emesis by moderate emetic risk parenteral anticancer agents

DAY 1: Select treatment option D, E, or F. **All treatment options are category 1 and should be started before anticancer therapy**[a]	**DAYS 2, 3:**
• Dexamethasone 12 mg PO/IV once[c,d]	
Treatment option F, use the following combination:[f] • NK1 RA (choose one): – Aprepitant 125 mg PO once – Aprepitant injectable emulsion 130 mg IV once[h] – Fosaprepitant 150 mg IV once[i] – Netupitant300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once[i] – Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once[i] – Rolapitant 180 mg PO once[j] • 5-HT3 RA (choose one):[k,l] – Dolasetron 100mg PO once – Granisetron 10mg SQ once[b], or 2 mg PO once, or 0.01 mg/kg (max 1mg) IV once, or 3.1 mg/24h transdermal patch applied 24-48 h prior to first dose of anticancer therapy. – Ondansetron 16-24 mg PO once or 8-16 mg IV once – Palonosetron 0.25 mg IV once • Dexamethasone 12 mg PO/IV once[c,d]	Treatment option F: • Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO used on day 1) • ± Dexamethasone 8 mg[c,d] PO/IV daily on days 2, 3

[a] See NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) for Antiemesis, Principles of Managing Multiday Emetogenic Chemotherapy (AE-A)

[b] Granisetron extended-release injection is a unique formulation of granisetron using a polymer-based drug delivery system. This formulation is specifically intended for subcutaneous administration and is NOT interchangeable with the intravenous formulation. Granisetron extended-release injection has an extended half-life and should not be administered at less than 1-week intervals.

[c] Emerging data and clinical practice suggest dexamethasone doses may be individualized. Higher doses may be considered, especially when an NK1 RA is not given concomitantly. Lower doses, given for shorter durations, or even elimination of dexamethasone on subsequent days (for delayed nausea and emesis prevention) may be acceptable for non-cisplatin regimens based on patient characteristics. If dexamethasone eliminated on subsequent days for delayed nausea and emesis prevention, consider other alternative antiemetics (eg. Olanzapine). See NCCN Guidelines®, Antiemesis, Discussion.

[d] Use of corticosteroids premedications should be avoided with cellular therapies. See NCCN Guidelines®, Antiemesis, Pharmacologic Considerations for Antiemetic Prescribing (AE-B).

[e] No further 5-HT3 therapy required if palonosetron or granisetron extended-release injection administered, or if granisetron transdermal patch applied, on day 1

[f] A 3-drug prophylactic regimen (E or F) is recommended for select patients with additional patient-related risk factors (See AE-1) or previous treatment failure with a corticosteroid + 5-HT3 RA alone.

[g] Data suggests that a 5 mg dose of olanzapine is efficacious. Consider this dose especially for elderly or oversedated patients. Hashimoto H, et al. Lancet Oncol 2020;21:242-49. See NCCN Guidelines®, Antiemesis, Pharmacologic Considerations for Antiemetic Prescribing (AE-B).

[h] Aprepitant injectable emulsion is a unique formulation of aprepitant and is NOT interchangeable with the intravenous formulation of fosaprepitant.

[i] Available as a fixed combination product only.

[j] Rolapitant has an extended half-life and should not be administered at less than 2-week intervals.

[k] If netupitant/palonosetron or fosanetupitant/palonosetron fixed combination product used, no further 5-HT3 RA is required.

[l] When used in combination with an NK1 RA, there is no preferred 5-HT3 RA. See NCCN Guidelines®, Principles of Managing Multiday Emetogenic Chemotherapy (AE-A).

Appendix L Instructions Related to COVID-19

L 1 Eligibility, Concomitant Medication, and T-DXd Dose Modification Relevant to COVID 19

Exclusion Criteria

The following exclusion criterion has been added (see Section5.2):

- Prior exposure, without adequate treatment washout period before enrollment, to chloroquine/hydroxychloroquine: < 14 days

Prior and Concomitant Medications

In addition to Section 6.5, the following text is relevant for participants with COVID-19:

Concomitant treatment with chloroquine or hydroxychloroquine is not allowed during the study treatment. If treatment with chloroquine or hydroxychloroquine treatment is absolutely required for COVID-19, 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.

Dose Modification Criteria

All confirmed or suspected COVID-19 infection events must be recorded in the eCRF. Dose modifications will be based on the worst CTCAE grade. All interruptions or modifications must be recorded on the AE and drug administration eCRFs. Please use CTCAE v5.0 general grading criteria to evaluate COVID-19. All dose modifications (discontinuation, interruptions, or reductions) must be recorded on the AE and drug administration eCRFs.

Dose Modification Criteria for Suspected or Confirmed COVID-19

In addition to Section 6.6, the following text is relevant for participants with COVID-19:

Dose modification criteria for suspected or confirmed COVID-19
If COVID-19 infection is suspected, delay T-DXd and rule out COVID-19 per local guidance.

- If COVID-19 is ruled out, follow dose modification and management guidelines as outlined in the study protocol.
- If COVID-19 is confirmed or diagnosis is suspected after evaluation, follow dose modification as outlined below and manage COVID-19 per local guidance until recovery of COVID-19. Recovery is defined as no signs/symptoms, at least 1 negative reverse

transcriptase-PCR test result[6], and nearly or completely resolved chest CT findings). Then follow below dose modifications:

Table 24 COVID-19 Dose Modification Criteria

COVID-19 Worst Toxicity NCI CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for T-DXd
Grade 1	Resume T-DXd at the same dose.
Grade 2	Resume T-DXd at the same dose if chest CT findings are completely resolved. Reduce by 1 dose level if chest CT findings are nearly resolved.
Grade 3	Reduce by 1 dose level if chest CT findings are completely resolved. Discontinue study intervention. if chest CT findings are **not** completely resolved.
Grade 4	Discontinue study intervention.

[a] Closely monitor signs/symptoms after resuming T-DXd, initially with a phone call every 3 days for the first week, and then with a weekly phone call thereafter, for a total of 6 weeks.

COVID-19 = coronavirus 2019-nCoV; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; T-DXd = trastuzumab deruxtecan.

- In addition to the recommendations outlined in the table above, Investigators may consider dose modifications of the study drug according to the participant's condition and after discussion with the study Medical Monitor or designee.
- If an event is suspected to be drug-related ILD/pneumonitis, manage per protocol ILD/pneumonitis management guideline.

L 2 Benefit Risk Considerations for COVID-19

The emergence of COVID-19 presents a potential safety risk for participants. Several risk mitigation factors have been implemented in this study.

Moreover, with the outbreak of COVID-19, there is the potential for increased use of chloroquine and hydroxychloroquine to treat severely symptomatic participants, or even for prophylactic use. Chloroquine and hydroxychloroquine have shown in vitro to substantially affect the pH of the lysosome, a key intracellular compartment involved in the trafficking and payload release of T-DXd. As it is unknown whether chloroquine/hydroxychloroquine may

[6] If PCR testing is not available, the participant must not have any sign/symptoms for at least 2 weeks, in addition to meeting the requirement for chest CT imaging

affect the safety and efficacy of T-DXd, to be eligible for this clinical trial, use of chloroquine and hydroxychloroquine treatment must be completed at least 14 days prior to the first dose of T-DXd (see CSP Section 5.2). During study treatment, chloroquine and hydroxychloroquine are considered prohibited concomitant medications. However, in case treatment with chloroquine or hydroxychloroquine treatment is absolutely required for COVID-19, study intervention must be interrupted. After chloroquine or hydroxychloroquine is administered for COVID-19, then a washout period of at least 14 days is required before restarting study intervention.

Lastly, due to the potential overlapping impact of T-DXd and COVID-19 on the lung, the sponsor has also provided in this appendix, a dose modification and management plan for participants with confirmed or suspected COVID-19 who are being treated with T-DXd.

With these measures in place, it is considered the anticipated potential benefits for the participants enrolled in this study outweigh the potential risks.

Appendix M Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with 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 agreement from the sponsor.

Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections 8.1 to 8.8. 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.

Rescreening of Participants to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The investigator should confirm this with the designated study physician.

In addition, during study disruption there may be a delay between confirming eligibility of a participant and commencing of dosing with study intervention. If this delay is outside the screening window specified in Table 1, the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to rescreen a participant in addition to that detailed in Section 5.4. The procedures detailed in Section 1.3 must be undertaken to confirm eligibility using the same identification number as for the participant.

Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified HCP from the study site or TPV service may visit the participant's home or other remote location as per local SOPs, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix and the associated study instruction manual for mitigation due to civil crisis, natural disaster or public health crisis, 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 AEs, concomitant medication, to be reported and documented.

At-home or Remote Location Study Intervention Administration Instructions

If a site visit is not possible, at-home or remote location administration of study intervention may be performed by a qualified HCP, provided this is acceptable within local regulation/guidance. The option of at home or remote location study intervention administration ensures participants safety in cases of a pandemic where participants may be at increased risk by traveling to the site/clinic. This will also minimize interruption of study intervention administration during other study disruptions, eg, site closures due to natural disaster.

At-home or Remote Location Study Intervention Administration by a Qualified HCP or TPV Service

A qualified HCP from the study site or TPV service may administer the study intervention at the participant's home or other remote location according to the CSP and the study instruction manual for mitigation due to civil crisis, natural disaster, or public health crisis, and if allowed by local SOPs, as applicable. All necessary supplies and instructions for administration and documentation of study intervention administration will be provided. Additional information related to the visit can be obtained via a telemedicine or home visit.

At-home or Remote Location Study Intervention Administration by the Participant or His/Her Caregiver

Prior to at-home or remote location study intervention administration the investigator must assess the participant or his/her caregiver to determine whether they are appropriate for at home or remote location administration of study intervention. Once the participant or his/her caregiver is deemed appropriate for at-home or remote location administration, he/she must receive appropriate training. All necessary supplies and instructions for administration and documentation of study intervention administration will be provided. More information related to the visit can be obtained via a telemedicine or home/remote visit.

Data Capture During Telemedicine or Home/Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or TPV service in the source documents, or by the participant themselves.

Appendix N Guidance for Management of Participants with Drug-Induced ILD/Pneumonitis

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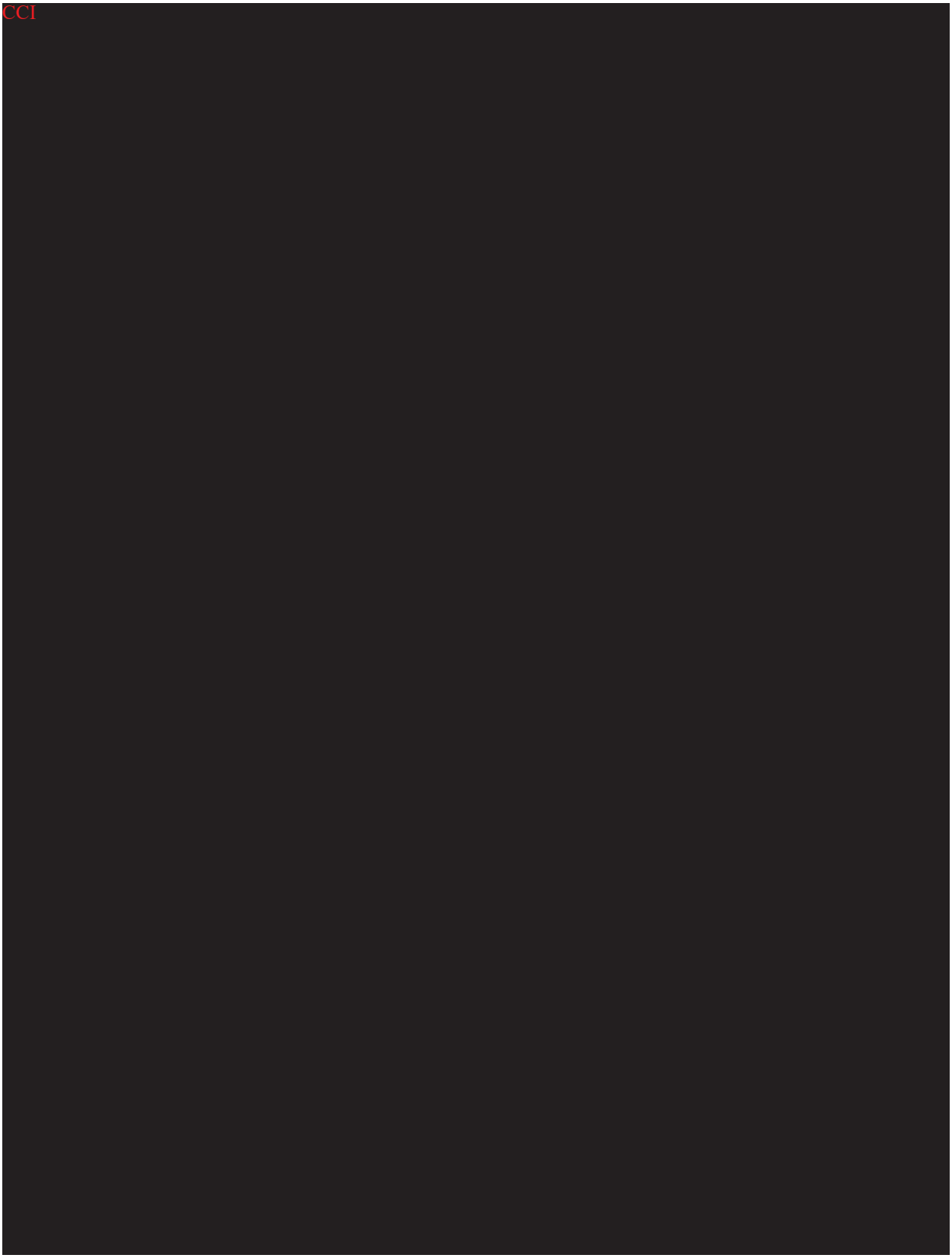

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Appendix O Toxicity Management Guidelines

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Table 25 Toxicity Management Guidelines for T-DXd

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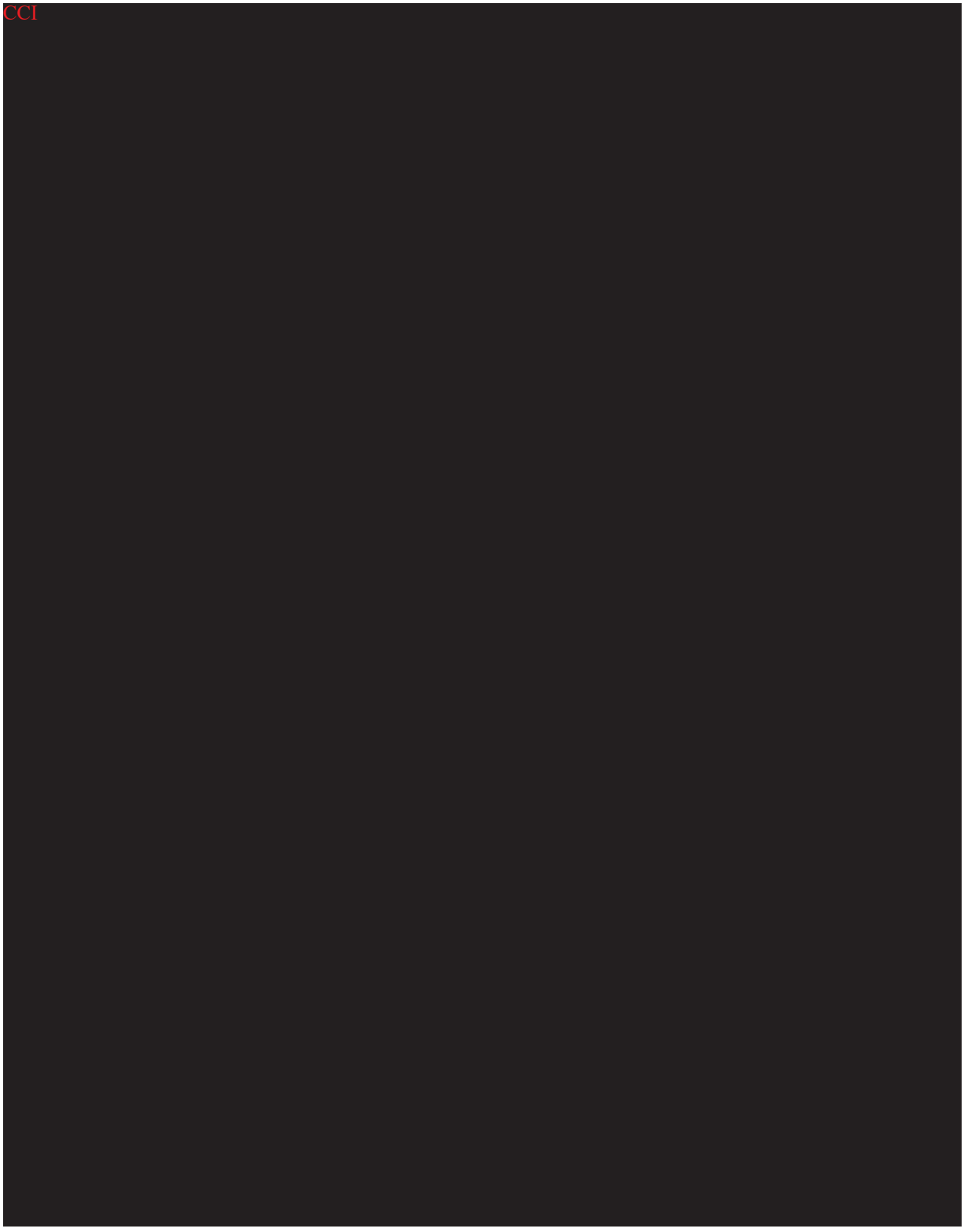

Table 25 Toxicity Management Guidelines for T-DXd

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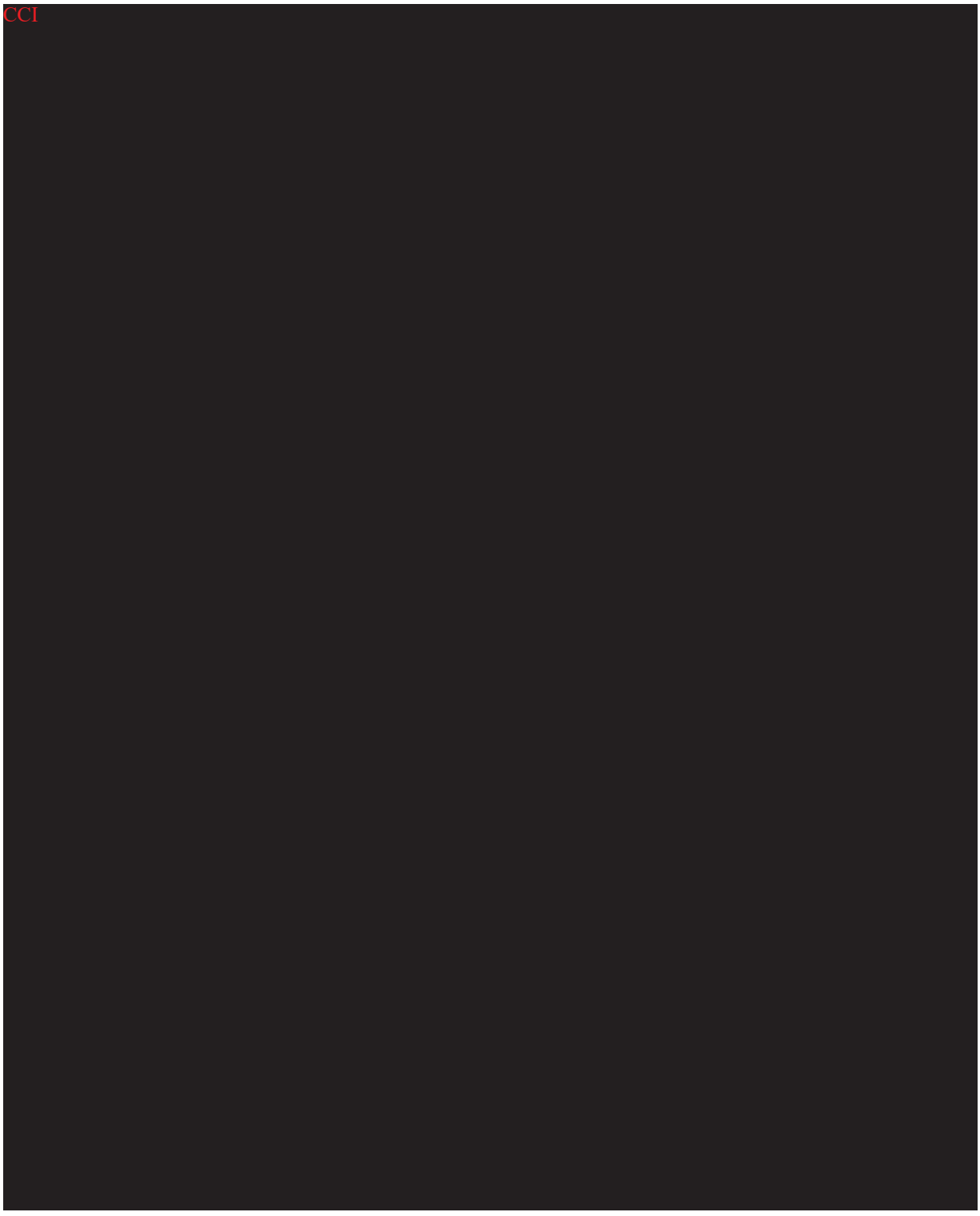

Table 25 Toxicity Management Guidelines for T-DXd

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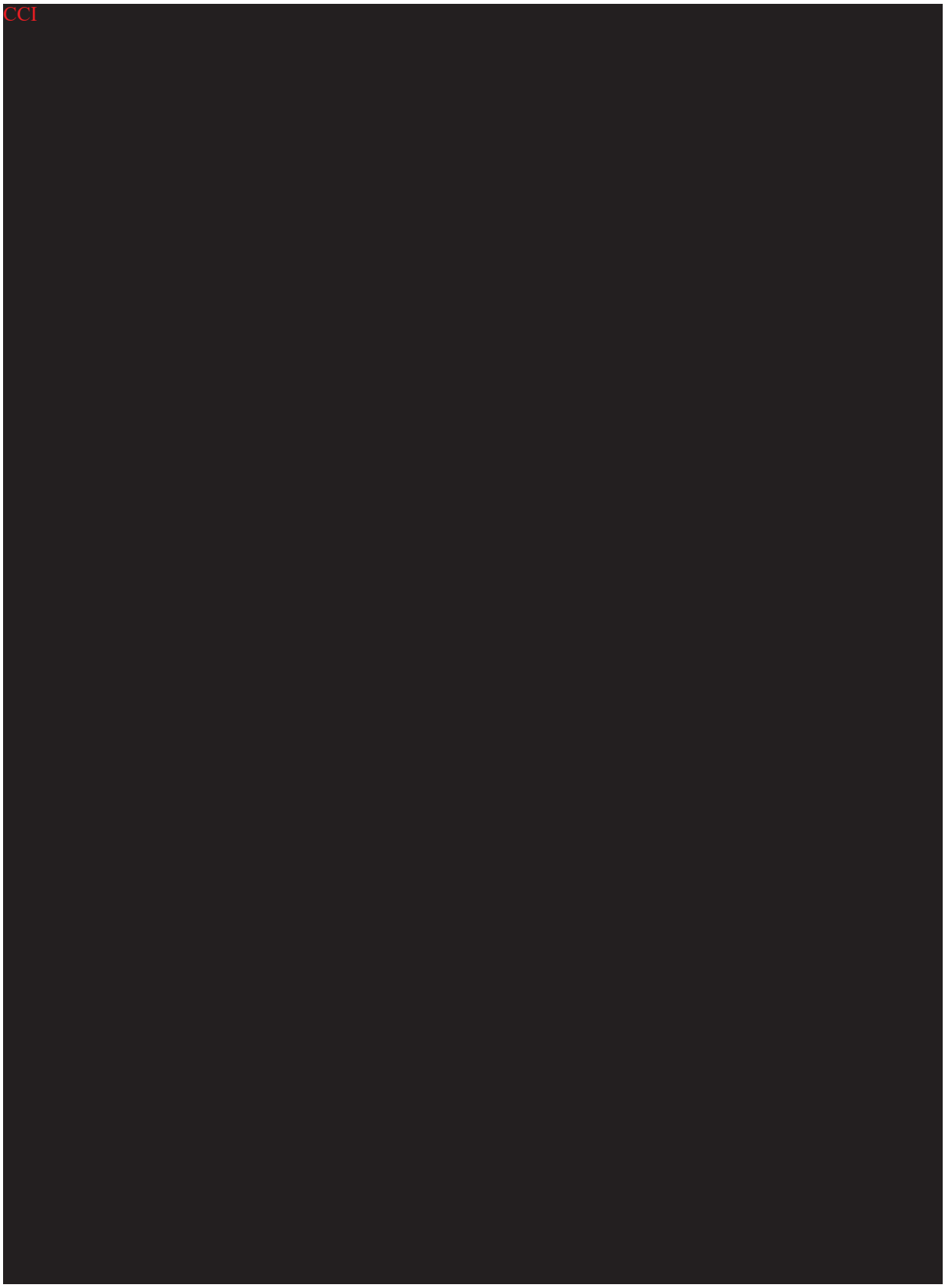

Table 25 Toxicity Management Guidelines for T-DXd

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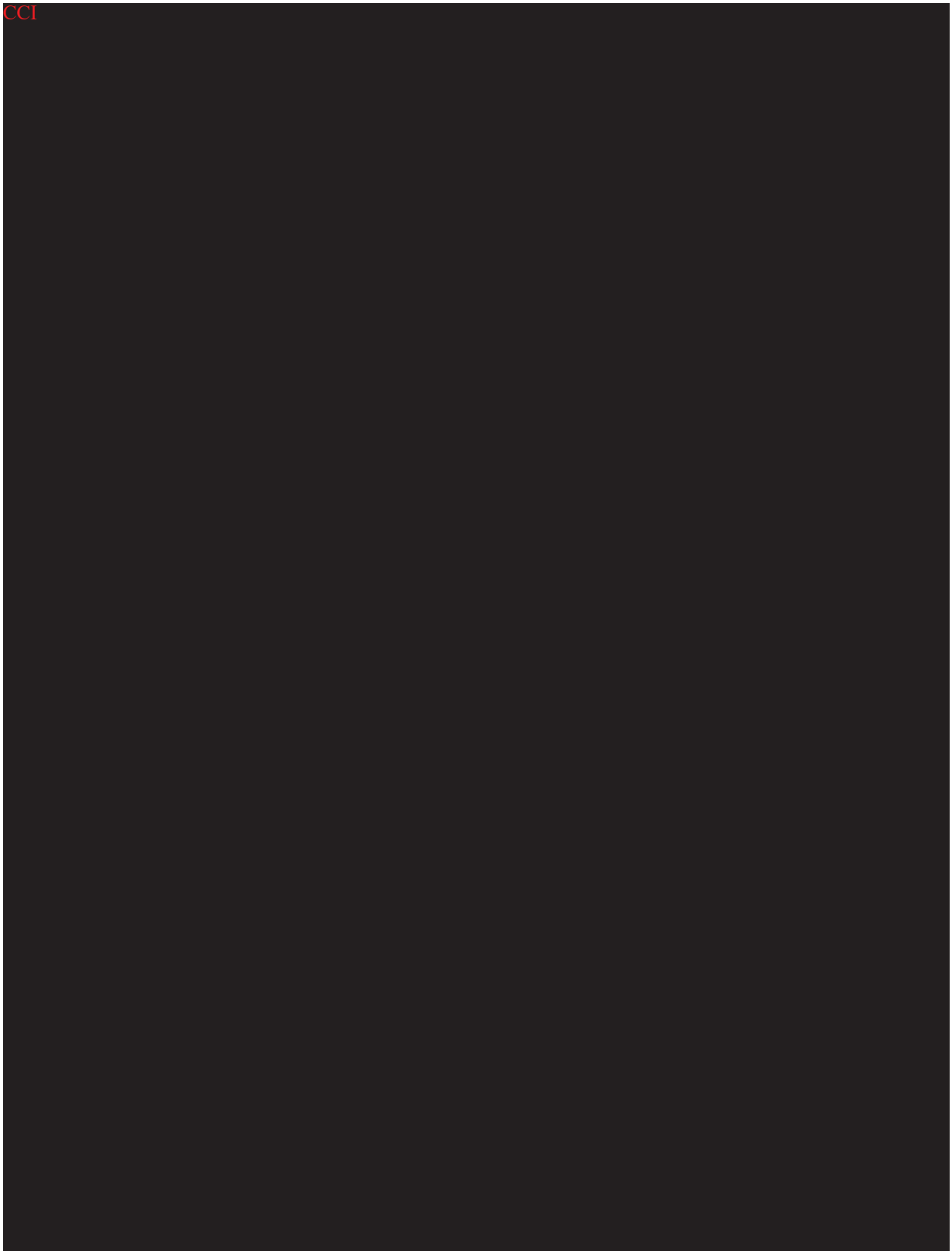

Table 25 Toxicity Management Guidelines for T-DXd

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Appendix P Family History and Exposure History for Interstitial Lung Disease

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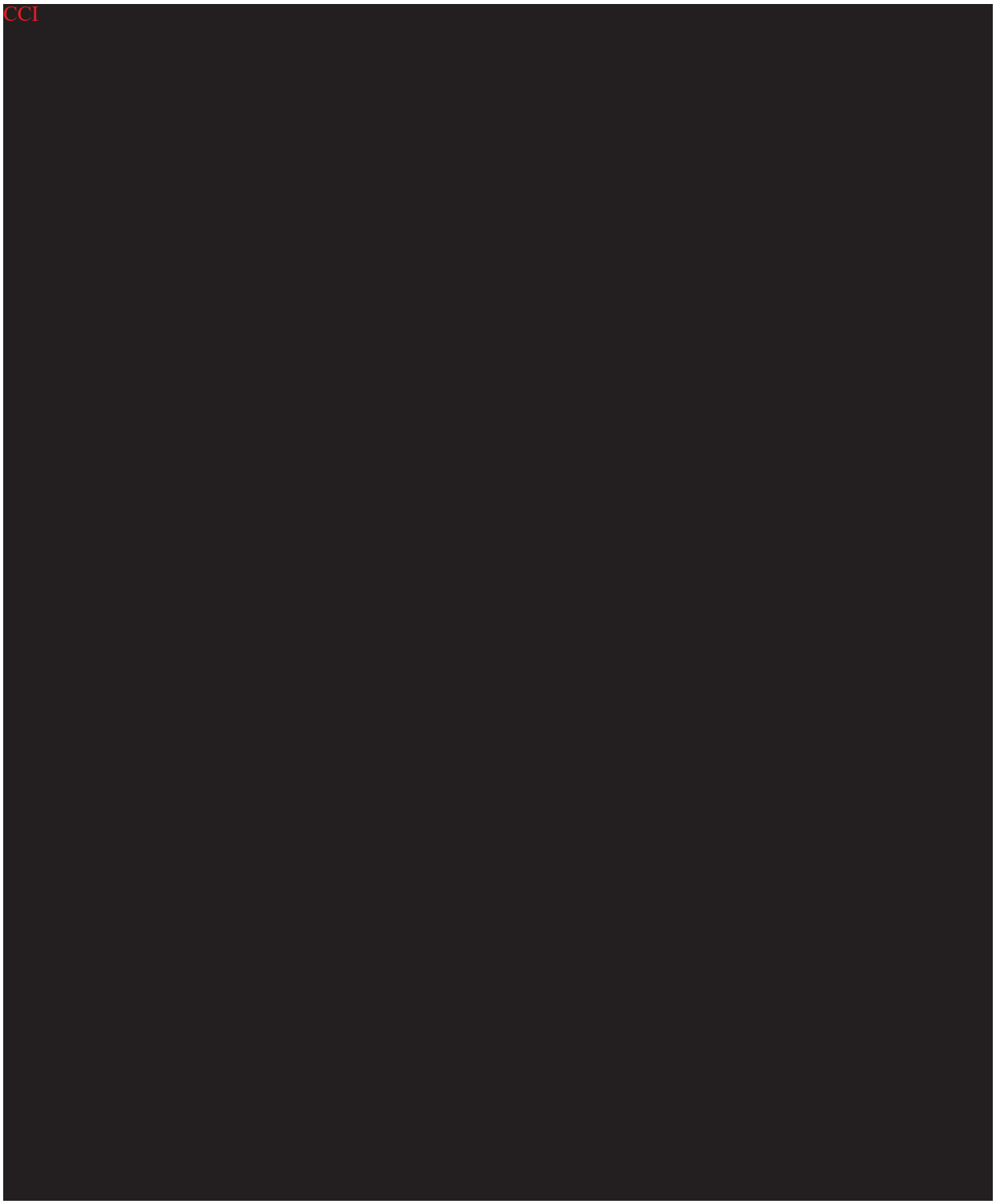
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Appendix Q Abbreviations

Abbreviation or Special Term	Explanation
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BM	brain metastasis
CCI	CCI
CAP	College of American Pathologists
CBC	complete blood count
CEP17	chromosome 17 centromere
CHF	congestive heart failure
CCI	CCI
CI	confidence interval
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
CRO	contract research organization
CSF	cerebrospinal fluid
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI	CCI
DAR	drug-antibody ratio
DCO	data cut-off
DILI	drug-induced liver injury
DLCO	diffusion capacity of the lungs for carbon monoxide
DNA	deoxyribonucleic acid

Abbreviation or Special Term	Explanation
DoR	duration of response
DoT	duration of treatment
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
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	electronic patient-reported outcome
EOT	end-of-treatment
ER	estrogen receptor
CCI	CCI
ESMO	European Society for Medical Oncology
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	formalin-fixed and paraffin-embedded
FISH	fluorescent in situ hybridization
GCP	Good Clinical Practice
GGFG	Gly-Gly-Phe-Gly
HBc	hepatitis B core antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCP	health care professional
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HL	Hy's Law
HR	hormone receptor
HRCT	high-resolution computed tomography
HRQoL	health-related quality of life
5-HT_3	5-hydroxytryptamine 3
IATA	International Airline Transportation Association

Abbreviation or Special Term	Explanation
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICR	Independent Central Review
iCRO	imaging Contract Research Organization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	immunohistochemistry
International coordinating investigator	If a study is conducted in several countries the international coordinating investigator is the investigator coordinating the investigators and/or activities internationally
ILD	interstitial lung disease
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
LMD	leptomeningeal disease
LV	left ventricle
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MBC	metastatic breast cancer
MDASI	MD Anderson Symptom Inventory
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	myocardial infarction
mPFS	median progression-free survival
MRI	magnetic resonance imaging
MUGA	multigated acquisition
NANO	Neurologic Assessment in Neuro-oncology
NCI	National Cancer Institute
NE	not evaluable
NK1	Neurokinin 1
NL	new lesion
NTL	non-target lesion
NYHA	New York Heart Association
ORR	objective response rate

Abbreviation or Special Term	Explanation
OS	overall survival
PCR	polymerase chain reaction
PD	progression of disease
CCI	CCI
PET	positron emission tomography
PFS	progression-free survival
PFS2	time to second progression or death
PgR	progesterone receptor
PHL	Potential Hy's Law
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PT	preferred term
q3w	every 3 weeks
QLQ-C30	30 item core quality of life questionnaire
QoL	quality of life
QTc	corrected QT interval
QTcF	QT interval corrected by Fridericia's formula
CCI	CCI
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SGRQ-I	St. George's Respiratory Questionnaire – idiopathic pulmonary fibrosis version
SoA	Schedule of Activities
SoC	Standard of care
SOP	standard operating procedure
SpO_2	peripheral capillary oxygen saturation
TBL	total bilirubin
T-DM1	trastuzumab emtansine
T-DXd	trastuzumab deruxtecan
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor

Abbreviation or Special Term	Explanation
TL	target lesion
TMG	toxicity management guideline
TOPO-1	topoisomerase I
TPV	telephone visit
ULN	upper limit of normal
US	United States
w/v	weight per volume

Appendix R Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 1 08-April-2021

This amendment is considered 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 European Union.

Overall Rationale for the Amendment:

This amendment was prepared to provide further explanation regarding the possibility to continue treatment after isolated CNS progression and CCI [redacted] CCI [redacted], to update safety monitoring requirements in line with requirements of the T-DXd program, to provide clarifications and complete information, and to correct minor inconsistencies.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.1 Synopsis	Revisions were made to study secondary objectives, description of overall design, participant population, study intervention and statistical methods.	The synopsis was revised to align with Sections 3, 4.1, 5, 6.1, 7.1, and 9.2.	Substantial
1.3 Schedule of activity	Never previously HER2 positive patients were removed from examples of study candidates.	This example was unlikely to happen and could be confusing.	Non-substantial
	Instruction in case of abnormal ECG was added as footnote e.	This clarification is in line with Section 6.6.1.	Non-substantial
	Incorrect instruction (previously footnote e) to conduct SpO_2 assessments at end of infusion on Day 1 of each cycle was removed.	This correction is in line with Section 8.2.5.2.	Substantial
	Instruction clarifying the time window for clinical laboratory tests at screening was added as footnote g.	This clarification is in line with inclusion criterion 10 and Section 8.2.4.	Non-substantial
	The description of mandatory tumor samples was revised, as only 1 tumor sample is mandatory (from archival tissue or fresh biopsy).	This revision was made in line with revisions in Section 8.6.1.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	CCI [redacted]	CCI [redacted]	Non-substantial
	It was clarified that tumor imaging is performed until RECIST 1.1-defined radiological PD.	This clarification was added in line with Section 8.1.1 and Appendix G.	Non-substantial
	The timing of brain scans was aligned to other tumor scans and footnote k (previously footnote j) was revised accordingly.	This correction was made to allow consistent assessment of tumor response in participants with and without BMs.	Substantial
	Isotopic bone scans were listed under a separate row from tumor imaging.	This revision was made to improve clarity and in line with Section 8.1.1 and Appendix G	Non-substantial
	The starting point of the 12-weekly cognitive tests was added.	This revision was made to improve clarity.	Substantial
	NANO scale assessments on Day 8 and Day 15 of Cycle 1 were removed.	This was a correction. Day 8 and Day 15 assessment were previously included in error.	Substantial
	MDASI ILD symptom-specific items were renamed MDASI lung cancer (ILD symptom-specific items)	This revision was in line with revisions in Section 8.1.5.2.	Non-substantial
2.2 Background	Treatments evaluated in the HER2CLIMB study were added in the summary of the study.	This was added for clarity.	Non-substantial
	Conditional marketing authorization in the European Union was added.	This was added for completeness as the information is pertinent for European sites.	Non-substantial
2.3.1 Risk assessment	The description of potential and identified risks was updated.	These updates were made in alignment with the latest available safety information for the T-DXd program.	Substantial
2.3.3 Overall Benefit/Risk Conclusion	The description of potential and identified risks was updated.	These updates were made in alignment with the latest available safety information for the T-DXd program and in line with revisions in section 2.3.1.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Information that vaccines against COVID-19 were not tested when given with T-DXd was added.	This information was added to clarify that effect of T-DXd on the effectiveness and safety of COVID-19 vaccines is unknown.	Substantial
3 Objectives and endpoints	It was specified that RECIST and CNS RECIST primary/secondary endpoints are assessed per ICR.	This revision was a clarification in line with Section 9.4.2.	Non-substantial
	The PFS, ORR, and DoR endpoints (CNS RECIST and CCI) related to brain/CNS lesions were renamed.	This revision was made to improve consistency in wording.	Substantial
	Local therapy for patients with BMs is no longer mentioned under the second secondary objective.	This information is not pertinent for the study objective.	Non-substantial
	Safety endpoints were revised to include standard safety parameters in addition to study-specific AE analysis.	The revisions were made to provide a more general description of safety analysis in line with Sponsor standards.	Substantial
	The objective to investigate immunogenicity of T-DXd was revised and CCI CCI	Collected samples will be CCI CCI	Substantial
	CCI	This revision was made to improve consistency.	Substantial
	MDASI ILD symptom-specific items were renamed MDASI lung cancer (ILD symptom-specific items)	This revision was in line with revisions in Section 8.1.5.2.	Non-substantial
4.1 Overall design	The description of the study population was revised and simplified.	Text was deleted to avoid redundancy with Section 5 and revisions were in line with revisions to inclusion criterion 8.	Non-substantial
4.4 End of study definition	Statement regarding patient withdrawal if the study is stopped was deleted.	This information is not pertinent for the end of study definition.	Non-substantial
	Reference to Section 9.2 was added for the definition of final DCO.	This was added for clarity.	Non-substantial
5 Study population	The overall description of the study population was revised.	Revisions were in line with revisions to inclusion criterion 8.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
5.1 Inclusion criteria	The description of screening brain scans in inclusion criterion 3 was reworded.	This revision was made for clarity and consistency with brain imaging methods in Section 8.1.1.	Substantial
	Inclusion criterion 5 was reworded to clarify that the criterion is related to the washout period required between radiotherapy and start of study treatment.	This revision was made to improve clarity.	Substantial.
	Inclusion criterion 7 to provide mandatory tumor sample was modified.	This revision was in line with revisions in Section 8.6.1.	Substantial
	Inclusion criterion 8 was reworded and split into 8(a) for evidence of disease progression after anti-HER2 treatments and 8(b) for maximum number of lines of therapy in the metastatic setting.	This revision was made to improve clarity and does not change the requirements.	Non-substantial
	Inclusion criterion 9 was reworded and split into 9(a) for measurable disease and 9(b) for non-measurable disease.	This revision was made to improve clarity and does not change the requirements.	Non-substantial
	Under inclusion criterion 10, calculation of CrCL is no longer optional.	This revision was made for alignment with other studies in the T-DXd program.	Substantial
	Under inclusion criterion 15 for female contraception requirement, duration of abstinence was changed to 7 months, in line with duration of contraception and further guidance was added as to when abstinence is an acceptable method of contraception.	This was a correction of an error with the duration of abstinence and further clarifications are in line with Appendix I..	Non-substantial
	Under inclusion criterion 15 for female contraception requirement, restrictions and recommendations regarding donation, use and preservation of ova was added.	These revisions are in line with Appendix I and safety recommendations for studies in the T-DXd program.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Under inclusion criterion 16 for male contraception requirement, further guidance was added as to when abstinence is an acceptable method of contraception.	The added guidance is in line with Appendix I.	Non-substantial
	Under inclusion criterion 16 for male contraception requirement, preservation of sperm prior to starting study treatment was added.	This revision is in line with safety recommendations for studies in the T-DXd program and added in response to MHRA.	Substantial
5.2 Exclusion criteria	Exclusion criterion 4 (related to the presence of pleural effusion, ascites, or pericardial effusion) was deleted.	This criterion was not necessary because it is already addressed under broader lung criteria listed under exclusion criterion 18(a), previously numbered as 19 (a).	Substantial
	Exclusion criterion 6 (previously criterion 7) was revised to exclude participants with persistent toxicities (CTCAE Grade >1) as Grade 2 toxicities can be significant.	This revision is in line with safety recommendations for studies in the T-DXd program and included in response to MHRA.	Substantial
	The description of screening brain scans in exclusion criterion 7 (previously criterion 8) was reworded.	This revision was made for consistency with brain imaging methods in Section 8.1.1.	Substantial
	Inclusion criterion 9 (previously criterion 10) regarding hepatitis B or C infection was revised.	This revision is in line with safety recommendations for studies in the T-DXd program, for clarification of which patients would be considered eligible.	Substantial
6.1 Study intervention administered	Duration of treatment was updated in alignment with discontinuation criteria.	This revision was made for consistency.	Non-substantial
6.3 Measures to minimize bias: randomization and blinding	Description of prescreening and collection of the mandatory tumor sample was revised.	This revision was in line with revisions to Section 8.6.1.	Substantial
6.6 Dose modification	Review of potential ILD/pneumonitis by the medical monitor and safety physician was described further.	This revision was added for clarity and for consistency with Section 8.2.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
7.1 Discontinuation of study intervention	Description that all study intervention should be returned by the participant was deleted.	This revision is a correction. The deleted statement is not applicable to the study, as all treatments are administered at the site.	Non-substantial
	CCI [redacted]	CCI [redacted]	Substantial
8.1 Efficacy assessments	Instruction to rule out COVID-19 and other infective lymphadenopathies when assessing whether a progression event occurred was added.	COVID-19 and other infective lymphadenopathies have a potential to bias the assessment of disease progression.	Substantial
	Clarification was added regarding the inclusion of CNS TLs for the assessment of tumor response endpoints per RECIST and CNS RECIST in patients with baseline BMs.	This revision was added to improve clarity.	Substantial
	For MDASI, the 3 ILD symptom-specific items were not modified, but it was clarified that they are taken from the lung cancer module instead of the MDASI symptom library.	This description is more specific.	Non-substantial
	For other COAs, an at-home pulse oximetry device is to be provided to participants diagnosed with ILD/pneumonitis and not all participants. Clarification was added that pulse oximetry while resting should be evaluated after at least 10 minutes of rest.	At-home pulse oximetry is only performed after diagnosis of ILD/pneumonitis. The clarification was added to ensure SpO_2 is measured consistently under the same resting conditions.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	For the administration of ePRO questionnaires, clarification was added that these should only be completed by participants if a linguistically validated version is available in the language of their country of residence. Possibility that participants will complete questionnaires using their own device was deleted.	Completing the questionnaire will not be possible if a linguistically validated version is not available. All participants will be provided a handheld device to complete questionnaires.	Substantial
8.2 Safety assessments	For pulmonary assessment at the site, it was clarified that pulse oximetry should be evaluated after at least 10 minutes of rest.	This clarification was added to ensure SpO_2 is measured consistently under the same resting conditions.	Substantial
	For pulmonary assessments, DLCO and HRCT at screening were changed to mandatory rather than strongly encouraged if feasible.	This is in line with necessary assessments for studies in the T-DXd program.	Substantial
	Collection of additional samples, safety evaluations, family history and exposure history for ILD was added in case of potential ILD/pneumonitis.	The additional data is necessary for the medical evaluation of potential ILD /pneumonitis.	Substantial
	Review of potential ILD/pneumonitis cases by an ILD Advisory Committee was added.	This review supports the assessment of potential ILD/pneumonitis cases.	Substantial
8.3 Adverse events and serious adverse events	Clarification was added that diagnosis of the undesirable clinical outcome of 'LV dysfunction', a valid or qualifying reduction of LVEF (as measured by MUGA or ECHO) should be confirmed and included in the AE report.	This is in line with the reporting of LV dysfunction for studies in the T-DXd program.	Substantial
	A description of predefined PTs for surveillance of ILD/pneumonitis was added.	This is in line with the surveillance of ILD/pneumonitis for studies in the T-DXd program.	Substantial
	A description of predefined PTs for surveillance of LVEF decrease was added.	This revision is in line with the surveillance of LVEF decrease for studies in the T-DXd program.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
8.6 Human biological sample biomarkers	The mandatory tumor sample was changed to include an archival tumor sample or a fresh biopsy (if archival tumor tissue is not available). CCI [redacted]	Only 1 mandatory sample is required for retrospective central confirmation of HER2 status. CCI [redacted]	Substantial
9.2 Sample size determination	The description of sample size was reworded from 500 eligible participants enrolled to 500 eligible participants treated in the study. The note defining "enrolled" participants was deleted because the text describes the number of eligible participants rather than all "enrolled" participants.	These revisions were made to improve clarity and do not change the number of study participants.	Non-substantial
	The determination of sample size was revised, without changing the sample size.	The revision is a correction in line with information provided in Table 9.	Non-substantial
	The DCO for final analysis for Cohort 1 and Cohort 2 was defined.	Definition was not provided previously.	Substantial
9.4 Statistical analyses	The description of PFS, ORR, and DoR endpoints (CNS RECIST and CCI [redacted]) related to brain/CNS lesions was revised.	These revisions were made in alignment with revisions to Section 3.	Substantial
	The assessment of PFS2 was removed from ICR.	This was previously included in error, as PFS2 is assessed locally.	Non-substantial
	Description of COA secondary endpoints was revised.	The correction was made for consistency with the SoA and Section 3.	Non-substantial
	A subgroup analysis of CCI [redacted] was added.	This subgroup analysis was added to analyze CCI [redacted]	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	The description of the AE statistical analysis was reworded, but does not modify the planned analyses.	The revisions were made to provide a more general description of AE analysis in line with Sponsor standards.	Non-substantial
9.6 Data monitoring committees	Review of efficacy data and interim analysis were removed from this section.	The IDMC will review safety data periodically and this is different from the interim efficacy analysis.	Substantial
Appendix A	Consent for CCI was added in Appendix A3.	This revision was in line with revisions in Section 7.1.	Substantial
Appendix G Guidelines for evaluation of objective tumor response using RECIST 1.1 criteria	Recommendations for brain scans were added.	Brain scans are needed for the evaluation of tumor response in patients with BMs.	Substantial
Appendix I Contraception requirements	Appendix I1 was revised to add text for preservation of ova prior to starting study treatment.	This revision is in line with safety recommendations for studies in the T-DXd program.	Substantial
	Appendix I2 was revised to add text for sexual abstinence.	This revision is in line with Appendix I3 and revisions made to inclusion criterion 16.	Substantial
	Appendix I2 was revised to add text for preservation of sperm prior to starting study treatment.	This revision is in line with safety recommendations for studies in the T-DXd program and added in response to MHRA.	Substantial
	Appendix I3 and Table 19 were revised to clarify that hormonal methods of contraception are not advised in a breast cancer population and should only be used by the female partners of male participants.	Hormonal methods of contraception are not recommended for breast cancer patient due to the hormone-sensitive nature of the tumor.	Substantial
Appendix L Instructions related to COVID-19	PK sampling was deleted from the title of Appendix L1.	This was a correction, as Appendix L1 does not describe PK sampling.	Non-substantial
	The description of the COVID-19 eligibility criteria was aligned to description in Section 5.	This revision was made to improve consistency.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	COVID-19 dose modification criteria were added.	T-DXd treatment recommendations in case of COVID-19 were provided due to the potential overlapping impact of T-DXd and COVID-19 on the lungs.	Substantial
Appendix O Toxicity management guidelines	Additional recommendations for Grade 4 hematological toxicity were provided.	These revisions are in line with recommendations for studies in the T-DXd program.	Substantial
	Additional clarification for Grade 1 pulmonary toxicity was provided.	These revisions are in line with recommendations for studies in the T-DXd program.	Substantial
Appendix P Family history and exposure history for interstitial lung disease	This appendix was created to describe the collection of additional family history and exposure history for ILD in case of potential ILD/pneumonitis.	This revision was included in alignment with revisions made in Section 8.2.	Substantial
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized	Non-substantial

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