Clinical Study Protocol

Investigational drug	Trastuzumab Deruxtecan (T-DXd; AZD4552; DS-8201a)
Study Code	D9670C00001
Version	5.0
Date	23 May 2023

A Phase 3, Randomized, Multi-center, Open-label Study of Trastuzumab Deruxtecan (T-DXd) Versus Investigator's Choice Chemotherapy in HER2-low, Hormone Receptor Positive Breast Cancer Patients whose Disease has Progressed on Endocrine Therapy in the Metastatic Setting (DESTINY-Breast06)

Sponsor Name:

AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifier Numbers:

US IND number: 146,111

EudraCT number: 2019-004493-26

EU CT number: 2023-505554-18-00

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol 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: D9670C00001

Amendment Number: 4

Study Treatments: Trastuzumab Deruxtecan (T-DXd; AZD4552; DS-8201a; fam-trastuzumab deruxtecan-nxki), capecitabine, paclitaxel and nab-paclitaxel

The non-proprietary name for the drug under investigation is trastuzumab deruxtecan except in the United States where it is fam-trastuzumab deruxtecan-nxki.

Study Phase:

Phase 3

Short Title:

Study of T-DXd vs Investigator's Choice Chemotherapy in HER2-low, Hormone Receptor Positive Breast Cancer Patients whose Disease has Progressed on Endocrine Therapy in the Metastatic Setting

Acronym: DESTINY-Breast06

Study Physician Name and Contact Information will be provided separately

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VERSION HISTORY

DOCUMENT HISTORY	
Document	**Date**
Amendment 4 (Version 5.0)	**23 May 2023**
Amendment 3 (Version 4.0)	27 April 2022
Amendment 2 (Version 3.0)	23 July 2021
Amendment 1 (Version 2.0)	22 May 2020
Original Protocol (Version 1.0)	20 March 2020

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 4 (23 May 2023)

The primary reasons for this amendment are to reduce informative censoring in PFS by BICR, including collection of additional tumor assessment scans following investigator-determined disease progression, based on RECIST 1.1, and to align with the EU CTR requirements. All available scans beyond disease progression (per investigator) will be collected.

Substantial and non-substantial changes to the CSP and rationale for each change are noted in the tables below.

Substantial Changes		
Section Number and Name	**Description of Change**	**Brief Rationale**
1.1 Synopsis 1.3.2 Treatment Period 1.3.3 Follow-up Period 4.1 Overall Design 7.1.2 Procedures for Discontinuation of Study Treatment 8.1.1 RECIST 1.1 Assessments Appendix G Guidelines for Evaluation of Objective Tumor Response using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)	Added clarification that it is mandatory to perform an additional imaging assessment following investigator-determined RECIST progression. Added requirement for submission of any available subsequent tumor assessment scans for central review until the primary PFS analysis DCO or until the Sponsor notifies the site to discontinue (whichever is earlier). Added that subsequent imaging assessments should include brain scans for patients enrolled with stable brain metastases or if clinically indicated.	To reduce informative censoring in PFS by BICR, when investigator has assessed progression but BICR does not agree.
2.3.1 Potential Risks of T-DXd 2.3.4 Overall Benefit/Risk Conclusion	Added text regarding higher incidence of ILD in patients with baseline moderate renal impairment and increased ILD education requirements for these patients.	To provide guidance to Investigators regarding ILD education expectations.

Non-substantial Changes		
Section Number and Name	**Description of Change**	**Brief Rationale**
Title page	Added EU CT number	To conform to the EU CTR transition
1.1 Synopsis 9.1.1 Multiple Testing Procedure	Revised text to clarify that the same significance levels will be used for the interim OS analyses in the HER2-low and ITT population.	To clarify how the significance levels for the interim OS analyses will be determined in the two populations
1.1 Synopsis 9.3 Populations for Analysis	Revised description for HER2-low and HER2-low SAF analysis sets to specify that IHC status will be obtained from IRT.	To clarify the data source for HER2 IHC status
1.3 Schedule of Assessments 1.3.3 Follow-up Period 8.6.2 Immunogenicity Assessments	Removed requirement for the collection of blood samples for ADA evaluation at EOT and follow up	To align with sponsor standards for the T-DXd program
1.3.2 Treatment Period	Removed requirement for collection of blood sample for plasma exploratory clinical benefit or safety analyses (mandatory)	To align with sponsor standards for the T-DXd program
1.3.2 Treatment Period	For clarification, added requirement to SoA for additional blood samples for plasma and serum exploratory clinical or safety analysis if ILD/ pneumonitis is suspected	For clarification and consistency
1.3.2 Treatment Period	Revised footnote p to refer to Section 8.2.10 for further instructions on PK sampling related to ILD	For clarification and consistency
1.3.2 Treatment Period 8.2.9 Ophthalmologic Assessments	Removed requirement for ophthalmologic assessment at EOT	To align with sponsor standards for the T-DXd program
1.3.2 Treatment Period 8.2.7 Echocardiograms/ Multi Gated Acquisition Scans	Removed requirement for troponin measurement at EOT	To align with sponsor standards for the T-DXd program
4.4 End of Study Definition	Revised definition to encompass both FDA and EU regulatory requirements.	Update required to comply with regulatory requirement (e.g., EU CTR)
1.3.2 Treatment Period 6.5 Concomitant Therapy 8.6.1 Pharmacokinetics	Removed instructions relating to the use of, and PK sampling for chloroquine/ hydroxychloroquine from text and updated corresponding SoA table footnote. These medications are simply prohibited.	To align with sponsor standards for the T-DXd program
5.2 Exclusion Criteria 6.5 Concomitant Therapy 6.5.2 Restrictions on	Replaced “prednisone” with “prednisone/prednisolone” throughout	Update required to comply with regulatory requirement (e.g., EU CTR)

Non-substantial Changes		
Section Number and Name	**Description of Change**	**Brief Rationale**
Concomitant Medications/ Therapies Appendix H Toxicity Management Guidelines for T-DXd		
1.3.2 Treatment Period 8.2.10 Other Safety Assessments Appendix H Toxicity Management Guidelines for T-DXd	Added clarifications to wording on identification, evaluation and management of ILD.	To align with sponsor standards for the T-DXd program
8.4 Medication Error, Drug Abuse, and Drug Misuse Appendix B4 Medication Error, Drug Abuse, and Drug Misuse	Added 4 subsections to (renamed) section: 8.4.1 Timelines 8.4.2 Medication Error 8.4.3 Drug Abuse 8.4.4 Drug Misuse Added sections on drug abuse and drug misuse to Appendix B4	Update required to comply with regulatory requirement (e.g., EU CTR)
8.5 Overdose	Added further detail on timing for reporting of overdose	Update required to comply with regulatory requirement (e.g., EU CTR)
8.6 Human Biological Samples	Updated retention times for PK and ADA samples	To comply with ICH GCP, China Human Genetic Resources (HGR) regulation and AZ HBS global standards and policies for sample storage and retention
9.4 Statistical Analyses	Additional analyses to be performed at the time of the PFS and OS analyses for the HER2 IHC >0<1+ population will be specified in the SAP.	To clarify timing of additional analyses in HER2 IHC >0<1+ population.
Appendix A1 Regulatory and Ethical Considerations	Added subsection for “Regulatory Reporting Requirements for Serious Breaches.” Added clarifications on investigator responsibility for oversight of study conduct at the site. Added clarifications on regulatory reporting requirements for SAEs.	Update required to comply with regulatory requirement (e.g., EU CTR)
Appendix A6 Dissemination of Clinical Study Data	Updated information regarding timelines for submission of trial results summaries to EU CTIS	Update required to comply with regulatory requirement (e.g., EU CTR)

Non-substantial Changes		
Section Number and Name	**Description of Change**	**Brief Rationale**
Appendix A7 Data Quality Assurance	Revised text to include quality tolerance limits, specify medical oversight, and increase the minimum time that Investigators are required to maintain records and documents.	Update required to comply with regulatory requirement (e.g., EU CTR)
Appendix H ILD/Pneumonitis Management Guidance Flowchart for T-DXd	Deleted appendix and renumbered subsequent appendices	To remove repetition of information
Appendix H Toxicity Management Guidelines for T-DXd	Renumbered appendix due to deletion of previous Appendix H. Added footnote 'a' to table for dose modification clarification Updated QTc to QTcF in ECG QTcF prolonged section	Alignment with sponsor standards for the T-DXd program
Appendix I1 Concomitant Medication and T-DXd Dose Modification Relevant to COVID-19	Renumbered appendix due to deletion of previous Appendix H. Added details on COVID-19 testing, updated definition of COVID-19 recovery and made some other minor clarifications	To align with sponsor standards for the T-DXd program
Appendix K Country-specific Protocol Information	Added appendix	Update required to comply with EU CTR (EU CTR submissions only allow one version of the protocol used by all EU/EEA countries).

Amendment 3 (27 April 2022)

The primary reasons for this amendment are as follows:

- Removing the enrollment pause for HER2 IHC > 0 <1+ patients while awaiting the futility analysis.
- Updating inclusion criterion #2c to remove the requirement for matched results between historical/local HER2 results and central test results.
- Updating the multiple testing procedure (MTP) for the study.

The Phase 2 DAISY study (see Section 4.2.2 for further details) has provided further data showing T-DXd activity in patients with IHC0+ expression (inclusive of the HER2 IHC > 0 <1+ population included in this study). In view of this information, the enrollment pause that was initially conservatively included in this protocol for the HER2 IHC > 0< 1+ population after the first 70 patients were randomized until the IDMC makes a

recommendation on whether or not to stop recruitment in this population (approximately 32 weeks after the 70th HER2 IHC > 0 <1+ patient had been randomized), is being removed. The new available DAISY data support the removal of this pause, while the futility analysis (performed on the first 70 randomized HER2 IHC > 0 <1+ patients) is itself maintained.

Inclusion criteria 2c has been modified to remove the requirement that the central HER2 test result must match the local HER2 test result (i.e., local status as HER2 Low or HER2 >0<1+ must match central status) in order for a patient to be eligible for study participation. This modification will ensure that the central HER2 test is the primary determinant for study eligibility and will streamline enrollment procedures and reduce screen failures.

Lastly, this amendment will include a revision to the MTP of the study to allow immediate allocation of alpha to PFS ITT after the primary endpoint is significant. Specifically, if PFS HER2-low is significant, the 5% alpha will be split between PFS ITT (1.5% alpha) and OS HER2-low (3.5% alpha). To achieve 80% power for OS HER2-low at 3.5% alpha, the final OS analysis will now be performed when approximately 521 OS events have been observed in the HER2-low population.

Substantial and non-substantial changes to the CSP and rationale for each change are noted in the tables below.

Substantial changes		
Section # and Name	**Description of Change**	**Brief Rationale**
1.1 Synopsis; 9.1.1 Multiple Testing Procedure and 9.2 Sample Size Determination	Change in the MTP such that if PFS HER2-low is significant, the 5% alpha will be split between PFS ITT (1.5% alpha) and OS HER2-low (3.5% alpha) Change in the target number of events at the final OS analysis from 489 to 521 OS events in the HER2-low population; Expected information fraction at the first and second interim OS analyses were changed to 41% and 75% respectively.	To allow immediate allocation of alpha to PFS ITT if the primary endpoint is significant. Number of OS events in the HER2-low population that will trigger the final OS analysis was increased to achieve 80% power at 3.5% alpha
1.1 Synopsis; 9.1.1 Multiple Testing Procedure; 9.5.1 Interim Futility Analysis	Removal of the enrolment pause in the HER2 IHC > 0< 1+ patient population during the futility analysis.	Clinical evidence from the DAISY study providing confidence for the efficacy of T-DXd in the HER2 IHC > 0< 1+ population.
5.1 Inclusion Criteria	Removal of the requirement for matched results between historical/local HER2 results and	To ensure that the central HER2 test is the primary determinant for study eligibility to streamline enrolment

Substantial changes		
Section # and Name	**Description of Change**	**Brief Rationale**
	central test results (IC#2[c] of CSP version 3.0)	procedures and reduce screen failures
5.1 Inclusion Criteria	Reduction in the minimum age for eligible patients in Japan from 20 years to 18 years (IC#1)	Revision of Japanese civil code
5.2 Exclusion Criteria	Addition of statement that pre-screening for this study while a patient is on treatment in another clinical study is acceptable (EC#18)	Clarification
5.3 Lifestyle Considerations	Removal of bilateral tubal ligation as a recognized method of surgical sterilisation	Correction
5.4 Screen Failures	Update allowing rescreening of patients who previously had the local HER2 test result not confirmed by central HER2 testing, provided they have not been previously rescreened and did not have a HER2 positive central test result	Changes to IC#2
6.5 Concomitant Therapy	Addition of the recommendation to administer a combination regimen of two or three anti-emetic agents prior to each dose of T-DXd	Alignment with sponsor standards for the T-DXd program
6.6.1.1 T-DXd; 8.3.14.1 Specific Toxicity Management and Dose Modification Information for T-DXd	Increase in the permitted delay in T-DXd dosing from 49 days to 126 days since the previous dose	Alignment with sponsor standards for the T-DXd program
8.2.10.1 Pneumonitis (ILD) Investigation; 8.3.11 Adverse Events of Special Interest; 8.3.14.1 Specific Toxicity Management and Dose Modification Information for T-DXd	Addition of the requirement for patients with suspected ILD/pneumonitis to undergo a SARS-CoV-2 (COVID-19) test	IDMC request
9.5.1 Interim Futility Analysis	Addition of treatment recommendations for patients with HER2 IHC >0 <1+ in the event that recruitment in that subgroup is stopped	Clarification
Appendix I	Increase in the time after which T-DXd should be discontinued in the case of Grade 1 ILD/ pneumonitis occurring beyond cycle	Alignment with sponsor standards for the T-DXd program

Substantial changes		
Section # and Name	**Description of Change**	**Brief Rationale**
	Day 22 from 49 days to 126 days since the previous dose	

Non-substantial changes		
Section # and Name	**Description of Change**	**Brief Rationale**
1.1 Synopsis; 2.1 Study Rationale; 2.3.2 Potential Benefits of T-DXd; 2.3.4 Overall Benefit/Risk Conclusion; 4.2.2 Rationale for T-DXd in HR+, HER2 IHC >0 <1+, Advanced or Metastatic Breast Cancer	Addition of confirmed ORR and PFS results indicating efficacy of T-DXd in HER2 expression below IHC 1+ in patients with advanced breast cancer	Read-out of results for the DAISY study
1.1 Synopsis; 3 Objectives and Endpoints; 8.6 Human Biological Sample Biomarkers	Addition of statement allowing blood and tissue samples collected for exploratory biomarker analysis and associated data to be used for diagnostic development	Clarification
1.1 Synopsis; 1.3.2 Treatment Period; 1.3.3 Follow-up Period; 4.1 Overall Design; 7.1.2 Procedures for Discontinuation of Study Treatment; 8.1.1 RECIST 1.1 Assessments; Appendix G Guideline for Evaluation of Objective Tumor Response using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)	Re-labeling of the additional tumor assessment following investigator determined RECIST 1.1 progression as an additional tumor evaluation scan	Clarification that only an additional scan is required in this case, and that tumor assessment by the investigator is not expected
1.1 Synopsis; 9.1.1 Multiple Testing Procedure; 9.5.1 Interim Futility Analysis	Removal of statement “have discontinued from study treatment” to clarify how interim futility data cut off will be triggered .	Correction to language for data cut off trigger for interim futility analysis.
1.2 Study Schema	Removal of the requirement for the tissue for central IHC assessment to be archival	Correction
1.3.1 Enrollment/Screening Period; 1.3.2 Treatment Period; 8.2.4 Electrocardiograms; 8.3.11 Adverse Events of Special Interest	Reduction in the time window for recording triplicate ECGs from 15 minutes to 5 minutes	Alignment with sponsor standards for the T-DXd program

Non-substantial changes		
Section # and Name	**Description of Change**	**Brief Rationale**
1.3.2 Treatment Period; 8.2.7 Echocardiograms/ Multiple Gated Acquisition Scans; 8.3.14.1 Specific Toxicity Management and Dose Modification Information for T-DXd	Removal of the requirement for a repeat troponin assessment in the event of a Grade 3 troponin result	Alignment with sponsor standards for the T-DXd program
1.3.2 Treatment Period	Replacement of the ± 3 day window for ctDNA samples with a recommendation to collect the samples as close as possible to the RECIST assessment	Alignment with sponsor standards for the T-DXd program
2.2.2 Background Information on T-DXd	Update to the number of patients exposed across the T-DXd program and the approval status of T-DXd	Alignment with updates to the T-DXd investigator's brochure
2.3.1 Potential Risks of T-DXd	Removal of asthenia as an identified risk for T-DXd	Alignment with sponsor standards for the T-DXd program
2.3.2 Potential Benefits of T-DXd; 4.2.1 Rationale for T-DXd in HR+, HER2-low, Advanced or Metastatic Breast Cancer	Addition of successful outcome for PFS and OS for T-DXd compared to physician's choice of chemotherapy in later line HER2 low, advanced or metastatic breast cancer patients for whom ET is no longer an option and who have received 1 to 2 lines of chemotherapy in the metastatic setting	Read-out of results for the DESTINY-Breast04 study
2.3.2 Potential Benefits of T-DXd.	Text revised for comparison of DAISY study to historical chemotherapy data	Text revised for better contextualisation of DAISY study data
4.1 Overall design; 8.6.1 Collection of Mandatory Samples for Biomarker Analysis	Re-labeling of the IHC 2+, IHC 1+ and IHC >0 <1+ algorithms as cut-offs	Clarification
4.1 Overall design	Clarification of stratification factors at time of randomization	Clarification; to ensure proper balance and correct stratification across treatment arms, all stratification factors must be known for each patient at the time of randomization
6.2.1 T-DXd (DS-8201a)	Addition of a statement allowing T-DXd dose modification if a patient's body weight has changed below the threshold of ± 10%	Flexibility for sites which have a more conservative policy regarding dose modification for weight changes

Non-substantial changes		
Section # and Name	**Description of Change**	**Brief Rationale**
6.2.2 Paclitaxel, Capecitabine and Nab-paclitaxel	Addition of statement that investigator's choice chemotherapies will be administered according to drug label for centrally sourced medications	Alignment with the practice followed in the study
8.3.14.1 Specific Toxicity Management and Dose Modification Information for T-DXd	Removal of statement defining SAEs with onset or worsening after the safety follow-up visit as TEAEs if considered related to study treatment	Alignment with sponsor standards for the T-DXd program
8.3.14.1 Specific Toxicity Management and Dose Modification Information for T-DXd	Removal of the requirement for consultation with Study Physician or designee for dose reductions or discontinuation of T-DXd for patients with a delay in T-DXd dosing	Correction of an oversight error
9.2 Sample Size Determination	Re-labeling of the estimated number of patients to be screened/enrolled as the number of patients to be screened	Correction in line with Section 1.1
Appendix A4	Addition of a statement that results from the optional biopsy at disease progression will be provided back to the patient	Correction
Appendix I	Removal of the requirement for prior agreement of the Study Physician for dose reductions	Correction

Amendment 2 (23 July 2021)

The primary modification in this amendment is to update the patient population of the study to include patients who have progressed within 6 months of first line ET + CDK4/6i in the metastatic setting. The rationale for including this population is discussed below.

In the past few years, ET + CDK4/6 inhibitor regimens have become established as the standard of care for HR+, HER2-negative metastatic breast cancer (Cardoso et al 2020). However, following progression on ET + CDK4/6 inhibitor regimens, the median time to treatment failure or duration of treatment on subsequent regimens is short, as evidenced from the PALOMA-3, MONARCH-2 and TRend trials, for both subsequent chemotherapy (4.4 to 5.6 months) and endocrine therapy (3.7 to 5.3 months) (Rossi et al 2019, Sledge et al 2020, Turner et al 2018).

Therefore, patients whose HR+, HER2-negative breast cancer is classified as primary endocrine resistant (i.e., progression within 6 months of starting first-line treatment with ET + CDK4/6 inhibitors) for whom chemotherapy is considered the next most appropriate treatment represent a population of high unmet medical need in which T-DXd may potentially provide benefit. The criteria for this additional study population is consistent with the definition of primary endocrine resistance in the European Society of Medical Oncology guidelines (Cardoso et al 2020).

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.1 Synopsis; 1.2 Schema; 2.1 Study Rationale; 2.2.1 Background Information on the Disease to be Treated; 4.1 Overall Design; 5 Study Population; 5.1 Inclusion Criteria	The study population was updated to include patients who progress on first line endocrine therapy + CDK4/6i within 6 months of starting therapy	To expand study population who have progressed on endocrine therapy + CDK4/6i and deemed appropriate to receive chemotherapy as next treatment	Substantial
5.1 Inclusion Criteria	IC #12 updated to add non-antibody based immunotherapy washout period	Added immunotherapy washout period, which was previously omitted by oversight	Substantial
5.1 Inclusion Criteria; 5.3 Lifestyle Considerations	Updated text (IC#14 and 16) regarding females of childbearing potential	To align with sponsor standards for the T-DXd program, MHRA and PEI feedback and CTFG guidelines	Substantial
5.1 Inclusion Criteria; 8.3.13.1 Paternal Exposure; Appendix A3	IC #15 updated with text regarding male contraception, and added text regarding preservation of sperm	To align with sponsor standards for the T-DXd program, MHRA and PEI feedback and CTFG guidelines	Substantial
5.2 Exclusion Criteria	Updated EC #4 to exclude patients with history of (non-infectious) ILD/pneumonitis that required steroids	Updated to allow patients with prior ILD/pneumonitis that did not require management with steroids to no longer be excluded; this is now aligned with sponsor standards for the T-DXd program	Substantial
Title page	Addition of co-international coordinating investigator	To include Giuseppe Curigliano as co-ICI	Non-substantial
1.1 Synopsis; 1.3.2 Treatment Period; 1.3.3 Follow-up Period; 4.1	Addition of scan following investigator determined	To confirm radiological progressive disease	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Overall Design; 8.1.1 RECIST 1.1 Assessments; Appendix G	RECIST 1.1 progression, if feasible		
1.1 Synopsis; 9.6.2 ILD Adjudication Committee	Addition of imaging data	Clarified that imaging data is also included for evaluation by the ILD Adjudication Committee	Non-substantial
1.3 Schedule of Assessments	Updated text to state patients will begin screening/baseline procedures after signing the main ICF	Clarification	Non-substantial
	Footnotes in Table 3 updated for corrections and clarifications	Correction and clarification	Non-substantial
1.3.1 Enrollment/Screening Period; 1.3.2 Treatment Period; 1.3.3 Follow-up Period; 8.2.5 Clinical Safety Laboratory Assessments	Addition of 'where available' for bicarbonate test	No longer a mandatory test, only performed where required	Non-substantial
1.3.2 Treatment Period	PK timepoints included in table and removed from footnotes	For clarity	Non-substantial
	Updated footnote h	To include guidance for SpO2 evaluation	Non-substantial
	Addition of text to footnote g to clarify ECG does not need to be repeated at Day 1 if performed within 3 days prior in screening period	Clarification	Non-substantial
	Laboratory related text in footnote i moved to create separate footnote k	Correction	Non-substantial
1.3.2 Treatment Period; 1.3.3 Follow-up Period	Updated text to specify targeted physical examination	To allow targeted physical examinations after the screening period	Non-substantial
1.3.2 Treatment Period; 8.2.7 Echocardiograms/Multiple Gated Acquisition Scans; 8.3.14.1 Specific Toxicity	Removed text from footnote n stating repeat testing is not required if troponin levels at baseline are above the upper	To align with sponsor standards for the T-DXd program	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Management and Dose Modification Information for T-DXd	limit of normal and below the level of myocardial infarction		
1.3.2 Treatment Period; 8.6.1 Collection of Mandatory Samples for Biomarker Analysis	Update of blood sampling timing	To include blood sampling collection up to disease progression	Non-substantial
1.3.2 Treatment Period; 8.6.2 Collection of Optional Biomarker Samples	Clinical care tumor biopsy replaced with tumor sample at disease progression	To clarify language of only collecting tumor samples at time of disease progression if consented for and not at other timepoints	Non-substantial
	Updated text to clarify tumor biopsy collection timing	Clarification	Non-substantial
2.3.1 Potential Risks of T-DXd	Updated text with most recent potential risks of T-DXd	To align with sponsor standards for the T-DXd program	Non-substantial
4.1.2 Duration of Patient Participation	Addition of text to state pre-screening period is included if signing optional pre-screen ICF	Clarification of pre-screening period	Non-substantial
4.2.2 Rationale for T-DXd in HR+, HER2 IHC >0 <1+, Advanced or Metastatic Breast Cancer	Text updated with regards to membrane staining	Clarification	Non-substantial
5 Study Population	Addition of definition of enrolled and randomized patients Updated enrollment to randomization throughout section	To clarify terms used in inclusion/exclusion criteria	Non-substantial
5.1 Inclusion Criteria	Literature reference in IC #2 updated	To use most recent literature reference for HR test results	Non-substantial
	IC #6 updated to state disease recurrence within 24 months of starting ET will be considered a line of therapy and include PARP inhibitor therapy is not considered a line of ET	To clarify that patients must be on adjuvant endocrine therapy when they recur in this time period and include PARP inhibitor therapy in the guidance for previous ET requirements	Non-substantial
	IC #11 updated to specify that all laboratory parameters listed	To ensure all patients meet all elements of the inclusion	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	in #11 must be met by the most recent results available	criteria at the time of enrollment	
5.1 Inclusion Criteria	IC #13 updated to include definition of women of childbearing potential	To clarify definition of women of childbearing potential in alignment with project standards for the T-DXd program	Non-substantial
5.2 Exclusion Criteria	EC #1 updated to include reference to contraindications section of local prescribing information	To update in line with MHRA and PEI feedback and local protocol versions	Non-substantial
	EC #6 updated to specify patients with complete pneumonectomy at screening will be excluded from the study	To clarify that only patients with complete pneumonectomy should be excluded. This is to align with sponsor standards for T-DXd program.	Non-substantial
	EC# 10, 11, 12, and 13 updated	To align with sponsor standards for the T-DXd program EC#10 updated to clarify that mRNA and replication deficient adenoviral vaccines are not considered live vaccines EC#11 updated to provide definition of chronic, stable toxicities with included examples EC#12 updated to clarify that criteria also excludes patients intending to become pregnant	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
		in addition to pregnant or breastfeeding patients EC#13 wording updated from excluding patients with a history of severe hypersensitivity to patients with known hypersensitivity	
	Removal of (old) EC #12 regarding concurrent chemotherapy, biologic, or hormonal therapy for cancer treatment	To remove repetition as previous anticancer therapy washout included in inclusion criterion #12 and concurrent treatments are prohibited medications	Non-substantial
	EC #18 and 19 added	EC#18 added to exclude patients who participated in another clinical study with a study treatment administered in the last 30 days prior to first dose of study treatment or concurrent enrollment in another clinical study EC#19 added to exclude patients with history of substance abuse or psychological conditions that may interfere with patient's participation	Non-substantial
5.4 Screen Failures	Text added for screen fails due local HER2 test results not confirmed by central HER2 testing and clarifying the possibility that patients can rescreen with pre-screening	To provide instructions for rescreen of patients who have screen failed due to IC #2(c) and clarify the possibility of pre-screening for rescreened patients	Non-substantial
6.1.1 Study Treatments; 6.4 Study Treatment Compliance	Updated packaging and labelling requirements for capecitabine	Correction	Non-substantial
6.2.1 T-DXd (DS-8201a)	Updated instruction for dose recalculation if patients weight change by ≥ ± 10% during the study	To align with sponsor standards for the T-DXd program	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
6.3.1 Patient Enrollment at Randomization	Addition of text to clarify patients who sign pre-screening ICF will be considered enrolled.	Clarification	Non-substantial
6.5 Concomitant Therapy	Text deleted from Table 10 that restrictions on the use of immunosuppressive medications may vary based on specific studies	To align with sponsor standards for the T-DXd program	Non-substantial
8.1.3 PFS2	Removed text regarding patients who started on subsequent cancer therapy post progression	Correction	Non-substantial
8.1.4.9 Administration of Patient-Reported Outcome Measures	Addition of text to include considering an appropriate back-up option for completion of PRO measures	To include a back-up option for flexibility if required	Non-substantial
8.2.6 Pulmonary Assessments	Text added to state SpO2 should be evaluated at end of infusion where applicable	For consistency with schedule of assessments	Non-substantial
8.3.1 Time Period and Frequency for Collecting AE and SAE Information; 8.3.6 Hy's Law; 8.3.11 Adverse Events of Special Interest	Removal of text regarding targeted questionnaires	To align with sponsor standards for the T-DXd program. Questions already integrated as part of data collection through eCRFs.	Non-substantial
8.3.12 Reporting of Serious Adverse Events	Text added to include completion of a paper SAE form if EDC not available	To align with sponsor standards for the T-DXd program	Non-substantial
8.4 Overdose	Use of email address for reporting overdose replaced with RAVE, or if technical issues by fax	Correction	Non-substantial
8.6.1 Collection of Mandatory Samples for Biomarker Analysis	Text added to exploratory biomarker information regarding IHC analysis and referring to the China lab manual for China-specific sample requirements	Clarification of collection of samples and sample requirements specific to China	Non-substantial
8.7 Optional Genomics Initiative Sample	Removal of text regarding collection of replacement genetic blood samples	This process is not being performed	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
9.3 Populations for Analyses	ADA population/analysis set amended to include reference to all patients who receive at least 1 dose of T-DXd per the protocol	Clarification	Non-substantial
9.4.2.2 Secondary Endpoints	Disease control rate definition updated	Correction	Non-substantial
9.4.3 Safety	Additional detail and text amended on how AE, vital signs, and laboratory data will be summarized/provided in CSR	To align with project-level updates	Non-substantial
Appendix A6	Addition of posting to European Union clinical trial register	To include description of clinical study on the European Union clinical trial register	Non-substantial
Appendix F	ASCO/CAP guidelines on HER2 testing in breast cancer updated	Correction to most recent guidelines	Non-substantial
Appendix G	Updated guidelines for evaluation of objective tumor response using RECIST 1.1 criteria	To update in line with the guideline for evaluation of objective tumor response using RECIST 1.1 criteria	Non-substantial
Appendix I	Table 27 (Toxicity Management Guidelines for T-DXd) updated to include further guidance for hematologic toxicity, cardiac toxicity, and pulmonary toxicity	To align with sponsor standards for the T-DXd program	Non-substantial
Appendix J1; 1.3.2 Treatment Period; 6.5 Concomitant Therapy; 8.5.1 Pharmacokinetics	Removed all reference to hydroxychloroquine and chloroquine from appendix. Language to these medications kept in or moved to (PK assessments) body of protocol.	Updated due to changing patterns of management of COVID. However, these medications may be used for purposes other than COVID-19 so information still stored in body of protocol.	Non-substantial
Appendix J2	Clarified CTCAE v5.0 is to be used for evaluating and reporting COVID-19-related AEs	Clarification	Non-substantial
Appendix K	Updated EORTC QLQ-BR45	To use most recent version	Non-substantial

Amendment 1 (22 May 2020)

Overall Rationale for the Amendment:

The overall rationale for the amendment is to provide additional guidance for investigators on the management of T-DXd in respect to COVID-19 and associated treatments. In addition, provision was made to collect plasma and serum samples to help assess potential impact of COVID-19 on data obtained in this trial. Furthermore, the schedule of assessments, inclusion/exclusion criteria and toxicity management guidelines were updated. The rationale for each of these changes is provided in the table below.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Throughout	Updated post-treatment follow-up schedule at 40 days window from ±7 days to +7 days	Amended window for follow-up visit to allow for adequate safety follow-up, given the half-life of T-DXd	Substantial
1.3 Schedule of Assessments 2.3.4 Overall Benefit/Risk Conclusion 5.1 Inclusion criteria 6.6.1 Individual Patient Dose Modifications 8.3.14 Management of Study Treatment-related Toxicities 8.6.1 Collection of Mandatory Samples for Biomarker Analysis 8.6.3 Other Study Related Biomarker Research	Guidance added on the management of T-DXd in respect to COVID-19 and associated treatments along with provision for additional blood samples for exploratory analyses of clinical benefit or safety	COVID-19 presents a potential safety risk, including respiratory manifestations. Management guidelines and benefit/risk considerations for COVID-19 have been included in Appendix J, and additional reporting and sampling procedures have been added to help assess potential impact of COVID-19 on data obtained in this trial	Substantial
1.3 Schedule of Assessments 5.1 Inclusion Criteria 6.5 Concomitant Therapy Appendix J	Specification of washout period prior to randomization for chloroquine/hydroxychloroquine and provided instructions related to restrictions and additional sample collection should T-DXd patients receive concomitant treatment with chloroquine or hydroxychloroquine.	A washout period and instructions related to restrictions and additional sample collections specified due to a possible interaction between T-DXd and chloroquine/ hydroxychloroquine	Substantial
5.2 Exclusion Criteria	Added exclusion criterion for patients randomized in a previous T-DXd trial	Added to discourage early patient withdrawal from earlier line T-DXd studies where patients are assigned to control	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
5.2 Exclusion Criteria	Removal of exclusion criterion #5 (history of clinically significant corneal disease), 11 (infection relating to active tuberculosis [covered by separate criterion excluding ongoing or active infection], 21 (drainage and CART not allowed within 2 weeks of randomization)	Removal of exclusion criterion #5 based on cumulative review of clinical data Exclusion criterion #11 removed as already covered under exclusion criterion #2 (Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection…) Exclusion criterion #21 removed as not relevant for breast cancer indication	Substantial
5.2 Exclusion Criteria	Amendment of exclusion criteria #6 for prior ILD to remove phrase on requiring steroid treatment. Patient's prior ILD no longer requires treatment with corticosteroid for patient to be excluded.	Updated exclusion criteria to exclude all patients with prior ILD to further mitigate the incidence of pulmonary toxicities	Substantial
5.2 Exclusion Criteria	Updated exclusion criterion #3 to remove the phrase "unstable angina pectoris, clinically important cardiac arrhythmias, or a recent (< 6 months) CV event including, unstable angina pectoris, and stroke" and included the provision for a cardiologist consultation for patients with troponin levels above ULN at screening and without any myocardial related symptoms.	Updated to remove redundant text and include the need for cardiologist consultation in patients with elevated troponin levels, as defined by the manufacturer, to rule out any asymptomatic signs of myocardial infarction	Substantial
1.3 Schedule of Assessments 8.2.7 Echocardiograms/ Multi gated Acquisition Scans 8.3.11 Adverse Events of Special Interest	Updated ECG and troponin collection frequency	Updated ECG measurements in line with the observations from a clinical study that showed no clinically meaningful impact of T-DXd on QTc. Data to date have shown that troponin-T testing is not an	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
8.3.14.1 Specific Toxicity Management and Dose Modification Information for T-DXd		indicator of LVEF decrease and therefore troponin will be measured at screening and EOT and as clinically indicated.	
1.3 Schedule of Assessments 8.5.2 Immunogenicity Assessments	Addition of ADA sample collection after 40-day (+7 day) follow-up for select patients	Provision of additional collection of ADA samples to monitor ADA positive patients at follow-up	Substantial
Appendix H Guidance for Management of Patients with Drug-Induced ILD/Pneumonitis and Appendix I Toxicity Management Guidelines for T-DXd	Update to ILD/pneumonitis management guidelines	Further recommendations provided on management of ILD/pneumonitis, in particular, more detailed recommendations around duration of systemic steroid treatment.	Substantial
Appendix I Toxicity Management Guidelines for T-DXd	Updates to AST/ALT increased, cardiac toxicity, and QTc prolongation management guidelines and removal of troponin management guidelines	Management of AST/ALT increased amended to provide greater clarity in patients with elevated AST/ALT at baseline. ECG QTc prolonged toxicity management guidelines amended to advise ruling out serum electrolyte related ECG changes. Data to date has shown that troponin testing is not an indicator of LVEF decrease. Troponin will only be measured at screening, at EOT and as clinically indicated.	Substantial
1.3 Schedule of Assessments	Allowance of a non-contrast enhanced CT instead of non-contrast HRCT if not feasible	Allowance for another modality if not feasible to attain HRCT	Non-substantial
1.3 Schedule of Assessments 5.1 Inclusion Criteria 8.2.5 Clinical Laboratory Assessments	Amended inclusion criterion h from “International normalized ratio (INR)/Prothrombin time (PT) and activated partial thromboplastin time” to “INR/PT and either partial thromboplastin or activated	To clarify that results from either partial thromboplastin or aPTT tests are acceptable	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	partial thromboplastin time (aPTT)"		
5.2 Exclusion Criteria	Updated wording for exclusion criterion #8 (lung-specific intercurrent illness) and 10 (spinal cord compression or CNS metastases)	Clarification of exclusion criteria to make them more specific to patients under treatment	Non-substantial
5.2 Exclusion Criteria	Exclusion criterion #4 "History of active primary immunodeficiency" removed Exclusion criterion #12 updated to include patients with "active primary immunodeficiency"	To only exclude patients with active primary immunodeficiency and not history of such disease	Non-substantial
6.5 Concomitant Therapy	Guidance regarding anti-emetics included	Based on current safety data, use of anti-emetics is recommended prior to and following T-DXd infusions	Non-substantial
1.3 Schedule of assessments 6.5.2 Restrictions on Concomitant Medications/Therapies	Use of tobacco products, e-cigarettes and vaping is strongly discouraged but not prohibited. History and current usage to be recorded. Minimum requirements for pulmonary function tests defined.	To gather further information on current tobacco usage and pulmonary function that may be relevant following review of vaping/e-cigarette literature.	Non-substantial
Throughout	Minor changes to protocol wording, tables and figures	To align with project standard or to provide clarification	Non-substantial
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized	Non-substantial

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title

A Phase 3 Randomized, Multi-center, Open-label Study of Trastuzumab Deruxtecan (T-DXd; DS-8201a) vs Investigator's Choice Chemotherapy in Human Epidermal Growth Factor Receptor 2 (HER2)-low, Hormone Receptor (HR) Positive Breast Cancer Patients whose Disease has Progressed on Endocrine Therapy (ET) in the Metastatic Setting (DESTINY-Breast06).

Study Rationale

Within breast cancers traditionally classified as HER2-negative, there exists a spectrum of HER2 expression. In addition to tumors with no detectable HER2 staining (i.e., immunohistochemistry [IHC] null), the category encompasses IHC 2+/in situ hybridization (ISH) negative and IHC 1+ cancers (defined in this study collectively as HER2-low), as well as cancers that have lower, but detectable HER2 staining, i.e., faint or barely perceptible and incomplete membrane staining that is seen in 10% or fewer tumor cells. These latter cancers are included in the IHC 0 category according to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines, and in this study are referred to as HER2 IHC >0 <1+.

Currently, patients with HR+, HER2-low or HER2 IHC >0 <1+ advanced or metastatic breast cancer follow the same treatment paradigm as HR+, HER2-negative breast cancer patients. In general, ET is considered the preferred option for HR+, HER2-negative breast cancer. The optimal treatment sequence is considered to be the use of ET + CDK4/6 inhibitors first line, followed by subsequent ET with targeted therapies (e.g., mTOR or PI3-K inhibitors [for PI3-K mutant tumors]) (Cardoso et al 2020). In patients whose disease has progressed after multiple lines of ET with or without targeted therapies, or in patients whose disease has primary endocrine resistance (progressive disease within the first 6 months of first-line ET for advanced breast cancer), chemotherapy may be appropriate as currently available anti-HER2 therapy has not demonstrated clinical benefit in these patients. In addition, for patients who have primary endocrine resistance (i.e., progressive disease within the first 6 months of first-line ET for advanced breast cancer), chemotherapy may also be appropriate as continued treatment with endocrine therapies following progression on ET + CDK4/6 inhibitors has been shown to provide less benefit (Rossi et al 2019, Sledge et al 2020, Turner et al 2018).

In clinical trials, in a heterogeneous breast cancer population, treatment with standard of care with single agent chemotherapy leads to response rates of 10% to 30%, a median progression-free survival (PFS) of 4-6 months and a median overall survival (OS) of

15-25 months. Chemotherapy is also associated with significant adverse events (AEs), including hematologic toxicities, nausea, vomiting, alopecia, and skin reactions. Therefore, there is a need for treatments with a better benefit/risk profile in this patient population who receive chemotherapy after endocrine treatment.

In the Phase 1 DS8201-A-J101 clinical trial (NCT02564900), trastuzumab deruxtecan (T-DXd; previously known as DS-8201a) demonstrated promising antitumor activity with an objective response rate (ORR) of 37% in HER2-low patients, with a majority of patients experiencing tumor shrinkage with durable response (Modi et al 2020). In addition, there were 11 patients in this study whose HER2 expression was locally reported (results from a local HER2 assay) as IHC 1+, 2+ or 3+ but who were categorized by a central laboratory as HER2 IHC 0 as per ASCO/CAP guidelines 2018. Of these 11 patients, 5 (45.5%) had a tumor response. In the Phase 2 DAISY clinical trial (NCT04132960), patients with advanced breast cancer who had received at least one prior line of chemotherapy were treated with T-DXd. In 37 patients with HER2 IHC 0+, confirmed ORR was 29.7% and median PFS was 4.2 months (Diéras et al 2022). Data from both studies suggest that the antitumor activity of T-DXd may extend to the population of patients with HER2 IHC < 1+, warranting further evaluation.

Therefore, in this Phase 3 study, T-DXd will be compared against investigator's choice single agent chemotherapy to determine if T-DXd can improve outcomes in HER2-low (IHC 2+/ISH- and IHC 1+), HR+ breast cancer patients whose disease has progressed on at least 2 lines of prior ET or within 6 months of first line ET + CDK4/6i in the metastatic setting (N=700). In addition to the primary population of HER2-low patients being studied, the study will also randomize approximately 150 patients with HER2 IHC >0 <1+ expression.

Objectives and Endpoints

Table 1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of T-DXd compared with investigator's choice chemotherapy in terms of PFS by BICR in the HR+, HER2-low (IHC 2+/ISH- and IHC 1+) population	• PFS by BICR according to RECIST 1.1 in the HR+, HER2-low population
Secondary	
The **key** secondary objectives are: • To assess the efficacy of T-DXd compared with investigator's choice chemotherapy in terms of OS in the HR+, HER2-low population • To assess the efficacy of T-DXd compared with investigator's choice chemotherapy in terms of PFS by BICR and OS in the ITT population (HER2 IHC >0 <1+ and HER2-low)	The **key** secondary endpoints are: • OS in the HR+, HER2-low population • PFS by BICR according to RECIST 1.1 in the ITT population (HER2 IHC >0 <1+ and HER2-low) • OS in the ITT population

Table 1 Objectives and Endpoints

Objectives	Endpoints
The other secondary objectives are: • To further assess the efficacy of T-DXd compared with investigator's choice chemotherapy in terms of PFS by Investigator assessment, ORR and DoR by BICR and Investigator assessment in the HR+, HER2-low population • To further assess the efficacy of T-DXd compared with investigator's choice chemotherapy in terms of ORR and DoR by BICR and Investigator assessment in the ITT population	The other secondary endpoints are: • ORR and DoR by BICR and Investigator assessment according to RECIST 1.1 in the HR+, HER2-low population • PFS by Investigator assessment according to RECIST 1.1 in the HR+, HER2-low population • ORR and DoR by BICR and Investigator assessment according to RECIST 1.1 in the ITT population (HER2 IHC >0 <1+ and HER2-low)
• To compare the effect of T-DXd with investigator's choice chemotherapy in terms of PFS2 according to Investigator assessment, time to first subsequent treatment or death (TFST) and time to second subsequent treatment or death (TSST) in the HR+, HER2-low population and the ITT population	• PFS2, TFST, TSST in the HR+, HER2-low population and the ITT Population
• To assess the safety and tolerability profile of T-DXd compared with investigator's choice chemotherapy	• AEs, changes from baseline in laboratory findings, ECHO/MUGA scans, ECGs and vital signs
• To assess the PK of T-DXd	• T-DXd, total anti-HER2 antibody and MAAA-1181a concentrations in serum
• To assess symptoms, functioning and HRQoL in patients treated with T-DXd compared with investigator's choice single agent chemotherapy	The PROs include: • Change from baseline in EORTC QLQ-C30 and EORTC QLQ-BR45 scale scores • Time to deterioration in EORTC QLQ-C30 scores
• To investigate the immunogenicity of T-DXd	• Number and percentage of patients who develop ADA for T-DXd
Exploratory [a]	
• To collect blood and tissue samples pre-treatment, on-treatment and post-treatment for defining biological responses to T-DXd and to investigate predictive markers of response, acquired resistance and other markers that may correlate with likelihood of clinical benefit or tolerability; samples and generated data may be used to support diagnostic development	Biomarkers that include but are not limited to biomarkers of T-DXd sensitivity/resistance and immunological biomarkers are: • Protein expression (IHC and proteomic analysis including, but not limited to ERBB2, related family members and TOPO-1 expression) • Mutational profiling in tissue, blood and ctDNA • Plasma and blood analysis for ctDNA (exploration of genetic alterations in ctDNA and dynamic changes, including ctDNA clearance) • mRNA expression (exploration of gene expression, molecular subtype and gene

Table 1 Objectives and Endpoints

Objectives	Endpoints
	expression changes following treatment) in tissue and blood
• To explore the impact of treatment and disease state on health utility using the EQ-5D-5L • To assess patient-reported treatment tolerability • To assess the patient's overall impression of the severity of their cancer symptoms, change in condition since starting the study and benefit/risk assessment • To explore the impact of treatment and disease on health care resource use	• EQ-5D-5L health state utility index • Patient-reported treatment tolerability (PRO-CTCAE and PGI-TT) • Proportion of patients with overall PGIS, PGIC and PGI-BR • Health care resource use will be captured, including inpatient admissions, intensive care unit admissions, and length of stay in hospital.
• To explore & optimize technologies for detection of HER2 protein expression	• Exploration of IHC and non-IHC methods to determine tumoral HER2 expression

ADA = anti-drug antibody; AE = adverse events; BICR = Blinded independent central review; ctDNA = circulating tumor DNA; DoR = duration of response; ECG = electrocardiogram; ECHO/MUGA = echocardiogram/multigated acquisition; EORTC QLQ = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L = European Quality of Life 5-Domain 5-Level Scale; ERBB = erythroblastic oncogene B; HER2 = human epidermal growth factor 2; HR = hormone-receptor; HRQoL = health-related quality of life; IHC = immunohistochemistry; ISH = in situ hybridization; ITT = intent-to-treat population; mRNA = messenger RNA; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PFS2 = time from randomization to second progression or death; PGI-BR = Patient Global Impression – Benefit/Risk; PGIC = Patient Global Impression–Change; PGIS = Patient Global Impression–Severity; PGI-TT = Patient Global Impression–Treatment Tolerability; PK = pharmacokinetics; PRO = patient-reported outcome; PRO-CTCAE = patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; RECIST 1.1 = Response Evaluation Criteria In Solid Tumors 1.1; TFST = time to first subsequent treatment or death; TOPO = topoisomerase; TSST = time to second subsequent treatment or death.

[a] Patients randomized into the study in China will be excluded from exploratory objectives requiring the provision of additional tumor or blood samples, with the exception of samples for exploratory safety or clinical benefit analyses to identify candidate markers which may correlate with likelihood of clinical benefit/tolerability (Section 8.7.1).

Overall Design

The study is an open-label, multi-center, randomized study in HR+, HER2-low breast cancer patients whose disease has progressed on at least 2 lines of prior ET or within 6 months of first line ET + CDK4/6i in the metastatic setting. The primary purpose of the study is to determine the efficacy and safety of T-DXd compared with investigator's choice single agent chemotherapy in the target population. Approximately 850 patients (700 patients with HER2 IHC 2+/ISH- and IHC 1+ [HER2-low] expression and 150 patients with HER2 IHC >0 <1+ expression) will be randomized 1:1 across approximately 300 centers globally to receive either T-DXd or investigator's choice single agent chemotherapy (capecitabine, paclitaxel or nab-paclitaxel) until RECIST 1.1 defined disease progression (PD), unless there is unacceptable toxicity, withdrawal of consent, or another criterion for discontinuation is met.

The details of study treatment and their schedules are provided in Table 2. To ensure adequate representation of each subgroup of the HER2-low population, at least 240 patients in each HER2 IHC group (IHC 2+/ISH- and IHC 1+) across both treatment arms (120 patients per arm) will be randomized.

Table 2 Study Treatments and Duration

Compound	Dose	Route	Schedule
T-DXd	5.4 mg/kg	IV	Every 3 weeks
Capecitabine	1000 or 1250 mg/m^2	Oral	Twice daily orally for 2 weeks followed by a 1-week rest period in 3-week cycles
Paclitaxel	80 mg/m^2	IV	Every week (qw) in 3-week cycles
Nab-paclitaxel [a]	100 mg/m^2	IV	Every week (qw) for 3 weeks followed by a one-week rest period in 4-week cycles

IV = intravenous; qw = every week

[a] Although nab-paclitaxel is given in 4-week cycles, the schedule of assessments must be followed (see Table 5; e.g., tumor assessment scans every 6 weeks [q6w ± 1 week]).

RECIST 1.1 tumor assessments will be performed using CT or MRI scans of the chest, abdomen and pelvis at screening (as baseline) with follow-ups at q6w ± 1 week from the date of randomization for 48 weeks, and then q9w ± 1 week, starting at Week 48, until objective RECIST 1.1 disease progression by investigator assessment (see SoAs in Section 1.3). Patients who permanently discontinue study treatment for reasons other than objective RECIST 1.1 disease progression, withdrawal of consent, closure of study or death (regardless of whether subsequent anticancer therapy was started) should continue to have RECIST 1.1 scans performed as per schedule until RECIST 1.1 disease progression. Following investigator-determined RECIST 1.1 progression, it is mandatory to perform an additional imaging assessment (preferably within 4 to 6 weeks after investigator PD) for central review to support the primary endpoint of PFS by BICR. In addition, every attempt should be made to continue to collect and submit subsequent scans (completed per standard practice / as clinically indicated) for central review until the primary PFS analysis DCO, or until the Sponsor notifies the site to discontinue (whichever is earlier) regardless of whether the subject has started another anti-cancer therapy. Scans following investigator determined RECIST 1.1 progression should include brain scans for patients who are enrolled with baseline stable brain metastases or if clinically indicated.

The study will compare PFS, OS and other measures of efficacy between the study treatment groups and further characterize the safety and tolerability profile of T-DXd.

Duration of Treatment: Unless specific treatment discontinuation criteria are met or the patient withdraws consent, all patients will continue receiving treatment until RECIST 1.1 defined disease progression. For patients randomized to the investigator's choice single agent

chemotherapy arm, crossover to T-DXd will not be permitted.

Follow-up of Patients post Discontinuation of Study Treatment: After discontinuation of study treatment, all patients will have post-treatment follow-up scheduled at 40 days (+7 days) after their last dose of study treatment. Patients who have discontinued treatment for reasons other than progressive disease per RECIST 1.1 will also be followed up with tumor assessments until radiological progression (or death). All patients will be followed up for PFS2 and survival status, unless consent was withdrawn.

Survival: All patients randomized should be followed up for survival unless consent was withdrawn. Long-term/survival follow-up visits will be performed every 3 months (±14 days) from the date of the 40-day (+7 days) follow-up visit until death, withdrawal of consent, or study closure, whichever occurs first.

Number of Patients:

The study will screen approximately 1417 patients to randomize approximately 850 patients (700 HER2 IHC 2+/ISH- and IHC 1+ [HER2-low] patients and 150 HER2 IHC >0 <1+ patients). To ensure adequate representation of each subgroup of the HER2-low population, at least 240 patients in each HER2 IHC group (IHC 2+/ISH- and IHC 1+) across both treatment arms (120 patients per arm) will be randomized. The HER2-low (IHC 2+/ISH- and IHC 1+) strata will be closed once a total of 700 patients have been randomized in these strata. At this time, a decision will be made by AstraZeneca on whether recruitment into the HER2 IHC >0 <1+ population will be stopped if the 150-patient target has not been met.

Data Monitoring Committees:

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. An IDMC comprised of independent experts will be convened and will meet approximately 6 months after the study has started or after the first 60 patients have been randomized, whichever occurs first. The IDMC will review unblinded 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 and at each meeting make recommendations to continue, amend, or stop the study based on safety findings. In addition, the IDMC will be asked to review efficacy data at pre-specified timepoints (e.g., interim futility analysis for HER2 IHC >0 <1+ population).

An interstitial lung disease (ILD) Adjudication Committee will review all cases of potential ILD/pneumonitis. To ensure adequate evaluation, relevant additional data from within the

clinical database and other sources, including imaging data, may be provided to the adjudication committee to fully characterize medical history (e.g., smoking, radiation and pulmonary history), diagnostic evaluation, treatment and outcome of the event. Further details can be found in the ILD Adjudication Charter.

Statistical methods

Efficacy

The primary endpoint of the study is PFS by BICR according to RECIST 1.1 in the HER2-low population. PFS is defined as the time from the date of randomization until the date of disease progression, as defined by RECIST 1.1, or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomized therapy or receives another anticancer therapy prior to progression. The key secondary efficacy endpoints include OS in the HER2-low population, PFS by BICR according to RECIST 1.1 in the Intent-to-treat (ITT) population and OS in the ITT population. The null hypothesis for the primary and key secondary efficacy endpoints (PFS and OS) is that there is no difference in PFS/OS distribution between T-DXd and the investigator's choice chemotherapy. Other secondary efficacy endpoints include PFS by Investigator assessment according to RECIST 1.1 in the HER2-low population and objective response rate (ORR) and duration of response (DoR) by BICR and Investigator assessment according to RECIST 1.1, time to second progression or death (PFS2), time to first subsequent treatment or death (TFST) and time to second subsequent treatment or death (TSST) in the HER2-low and ITT populations.

The ITT population comprises all patients randomized (HER2 IHC >0 <1+/1+/2+ population). The HER2-low population comprises the subset of patients included in the ITT population with HER2 IHC 1+/2+ as determined per the IRT data for HER2 IHC expression. The ITT population and HER2-low population will be used for all efficacy endpoints and will be analyzed according to randomized treatment regardless of the treatment received (ITT principle).

PFS in the HER2-low population and ITT population will be tested once, when PFS reaches approximately 65% maturity (456 events) in the HER2-low population. This is estimated to occur 29 months after the first patient is randomized (4 months after randomization is completed) assuming a non-uniform accrual of patients with a duration of 25 months. At this time, it is expected that at least 553 events (65% maturity) will have been observed in the ITT population.

OS in the HER2-low population and ITT population will be tested at two interim and one final

analyses as described below:

- The first interim OS analysis will be performed at the time of the final PFS analysis. It is expected that 216 OS events (31% maturity or 41% information fraction) will have been observed in the HER2-low population and 263 OS events will have been observed in the ITT population.
- The second interim OS analysis will occur when approximately 392 OS events have been observed in the HER2-low population (56% maturity or 75% information fraction). This is anticipated to occur approximately 44 months after the first patient is randomized. It is expected that 477 OS events have been observed in the ITT population at this time.
- The final OS analysis will be performed when approximately 521 OS events have been observed in the HER2-low population (74% maturity), which is expected to occur approximately 63 months after the first patient is randomized. At this time, it is estimated that 632 OS events will have been observed in the ITT population.

To strongly control the family wise error rate at 5% in terms of the primary and key secondary endpoints, a multiple testing procedure (MTP) with the following gatekeeping strategy will be employed:

Step 1: Test PFS in the HER2-low population at a 5% alpha level. If significance is achieved, go to Step 2.

Step 2: Test PFS in the ITT population at a 1.5% alpha level and OS in the HER2-low population at the 3.5% alpha level. If PFS in the ITT population is significant, the 1.5% alpha will be recycled to OS in the HER2-low population. Similarly, if OS in the HER2-low population is significant at either the interim or final analysis, the 3.5% alpha will be recycled to PFS in the ITT population (i.e., PFS in the ITT population at the PFS analysis data cut off (DCO) will be tested at 5% alpha). If both PFS in the ITT population and OS in the HER2-low population are significant, go to Step 3.

Step 3: Test OS in the ITT population at a 5% alpha level.

The 3.5% initial alpha allocated to OS in the HER2-low population will be distributed between the two interim and final analyses using the Lan DeMets spending function that approximates the O'Brien Fleming alpha-spending approach (Lan and DeMets 1983). Under this procedure, the adjusted significance levels at the interim and final analyses are determined by the information fraction available at the time of analysis (i.e., exact number events observed), giving greater weight to analyses performed at the end of the study than those performed earlier.

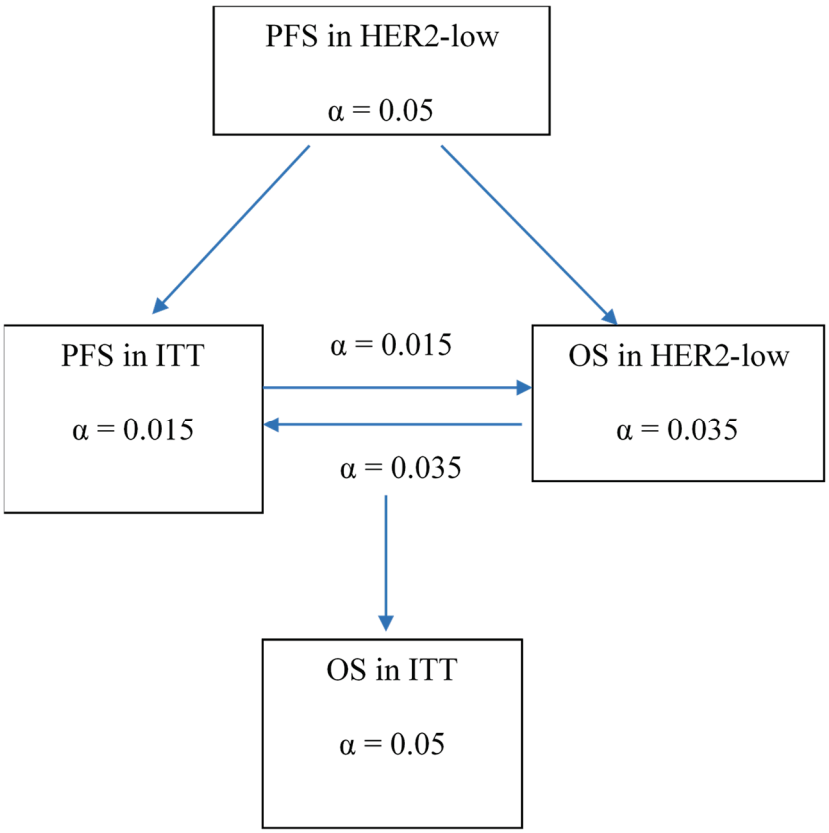
If PFS in the ITT population is significant at 1.5% alpha (Step 2 above) such that this alpha is

reallocated to OS in the HER2-low population, the adjusted significance levels at each of the analysis time points for OS in the HER2-low population will be updated per the Group sequential Holm variable procedure (Ye et al 2013). The Lan DeMets spending function that approximates the O'Brien-Fleming alpha-spending approach will be used to derive the updated significance levels. The same significance levels will be used for the interim OS analyses in the HER2-low population and ITT population. The significance level at the final OS analysis will be derived separately for each population and will be based on the actual number of events at the interim and final analysis, and the alpha already spent at the interim analyses for the HER2-low and ITT population, respectively.

The gatekeeping procedure is also shown in Figure 1.

An interim futility analysis will be performed after the first 70 patients in the HER2 IHC >0 <1+ population have been randomized and have had at least 24 weeks of follow-up from the point of randomization or withdrawn from the study. The IDMC will make a recommendation on whether or not to stop recruitment in the HER2 IHC >0 <1+ population based on the results of the futility analysis. If it is decided to limit further recruitment only to the HER2-low population, tests on the ITT population will not be performed.

Figure 1 Multiple Testing Procedure



HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ITT = intent-to-treat; OS = overall survival; PFS = progression-free survival
Note: Tests on the ITT population will not be performed if the interim futility analysis in the HER2 IHC>0 <1+ population results in the cessation of enrollment of HER2 IHC>0 <1+ patients in this study.

For the primary endpoint, PFS distribution in the HER2-low population will be compared between T-DXd and investigator's choice chemotherapy using a stratified log-rank test adjusting for prior CDK4/6 inhibitor use (yes vs no), HER2 IHC expression (IHC 1+ vs IHC 2+/ISH-), and prior taxane use in the non-metastatic setting (yes vs no). The stratification variables in the statistical modelling will be based on the values entered in interactive response technology (IRT). If there are insufficient events per stratum, the strata will be pooled following a pooling strategy that will be prespecified in the statistical analysis plan (SAP). The hazard ratio and its confidence interval (CI) will be estimated from a stratified Cox Proportional Hazards model with strata being the same as the stratification variables from IRT.

Sample Size Estimate

The study provides adequate power to show a statistically significant between-treatment difference in PFS in the HER2-low population. Based on a 2-sided significance level of 5%, a total of 456 PFS events (65% maturity) will provide at least 95% power to detect a hazard ratio of 0.55 (increase in median PFS from 5.5 to 10 months) in the HER2-low population, assuming an exponential distribution for both treatment groups.

If PFS in the HER2-low population is significant, the study also provides sufficient power to demonstrate a statistically significant difference in OS in the HER2-low population. Based on a 2-sided alpha of 3.5% and taking into account two interim OS analyses, a total of 521 OS events will be required to achieve 80% power to detect a hazard ratio of 0.77 (increase in median OS from 20.5 to 26.6 months) in the HER2-low population, assuming an exponential distribution for both treatment groups. Assuming 74% maturity at the time of the final OS analysis, approximately 700 patients will need to be randomized in the HER2-low population.

In addition to the 700 patients in the HER2-low population, approximately 150 patients with HER2 IHC >0 <1+ expression will be randomized, which will total up to approximately 850 patients randomized in the study.

Safety

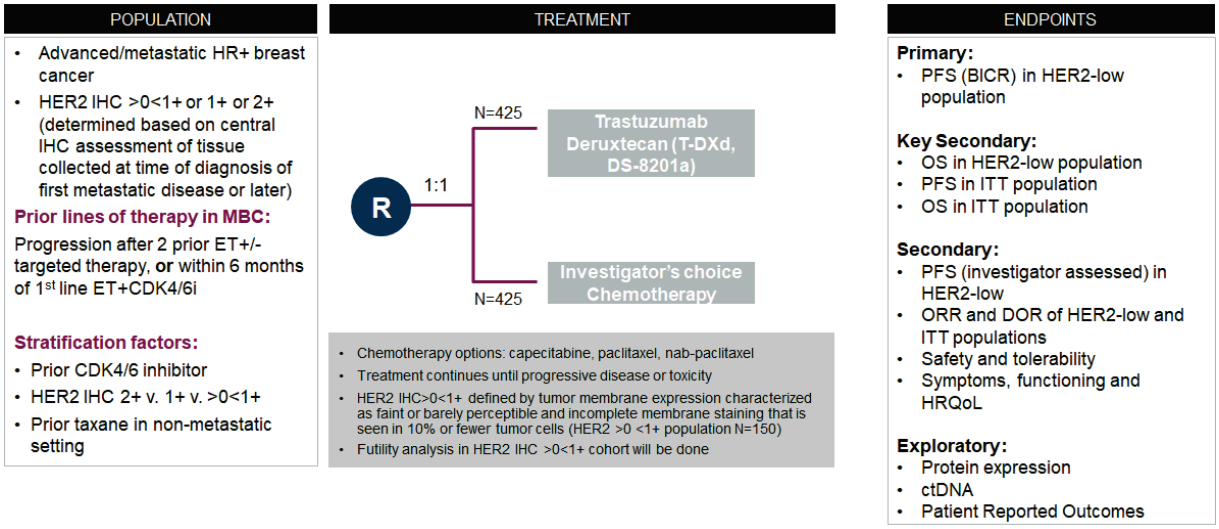
Safety summaries will be provided using the safety analysis set (SAF) and the HER2-low SAF. The SAF will include all patients who received at least 1 dose of study treatment while HER2-low SAF will include the subset of patients from SAF with HER2 IHC 1+/2+ as determined per the IRT data for the HER2 IHC expression. Safety data will be presented using

descriptive statistics unless otherwise specified. Safety data will be summarized according to the treatment received. Data from all cycles of treatment will be combined in the presentation of safety data. AEs including serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to dose reductions, and adverse events of special interest (AESIs) will be listed individually by patient using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. The number of patients experiencing each AE will be summarized by treatment arm and CTCAE Grade. Other safety summaries will be outlined in the SAP.

1.2 Study Schema

The study design is summarized in Figure 2.

Figure 2 Study Design



BICR = blinded independent central review; CDK = cyclin-dependent kinase; ctDNA = circulating tumor DNA; DoR = duration of response; ET = endocrine therapy; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; HRQoL = health-related quality of life; IHC = immunohistochemistry; ISH = in situ hybridization; ITT = intent-to-treat; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; T-DXd = trastuzumab deruxtecan

1.3 Schedule of Assessments

The procedures for the screening and treatment periods of this study are presented in Table 3 and Table 4, respectively. Whenever vital signs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs and then blood draws. Whenever electrocardiograms (ECGs), vital signs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (e.g., pharmacokinetic [PK] blood sample) to occur at the timepoints indicated in the schedule of assessments (SoAs).

After signing the main informed consent form (ICF), patients 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, the patients who pass the eligibility criteria check will be randomized into the study. Every effort should be made to minimize the time between randomization and dosing. Dosing should occur no more than 3 days after randomization. If it is anticipated that dosing cannot occur within 3 days, a discussion with the AstraZeneca Study Physician is required. Patients who fail to meet the eligibility criteria will be termed as “screen failures.”

An optional pre-screen ICF may 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, never previously HER2-positive). When a pre-screen ICF is signed, it is recommended that the main ICF and other study procedures not be started until the sample submitted for HER2 testing is accepted for central laboratory testing.

1.3.1 Enrollment/Screening Period

Table 3 shows all procedures to be conducted at the screening visit.

Table 3 Schedule of Assessments for Screening/Baseline

Procedures	Screening/Baseline		For details, see Section
	Days -28 to -1	Days -14 to -1 [a]	
Informed consent			
Written informed consent; consent for study procedures [b]	X		5.1 and 8.2.1
Informed consent: blood sample collection for optional genetic analysis	X		8.8
Tumor assessments			
Tumor assessment by RECIST 1.1 (CT or MRI ±X-ray) [c]; Submit baseline images for BICR	X		8.1.1
Brain MRI/CT imaging [d]	X		8.1.1
Whole body bone (scintigraphy) scan [e]	X		8.1.1
Study procedures and assessments			
Verify inclusion/exclusion criteria	X		5.1 and 5.2
History of prior cancer treatment	X		5.1
Demographics, including baseline characteristics		X	5.1
High Resolution CT of the chest [f]	X		8.2.6
Pulmonary function test [g]	X		8.2.6
SpO2		X	8.2.6
Medical history [h]		X	5.1
Physical examination (full)		X	8.2.2
ECOG performance status		X	8.2.8
ECHO/MUGA scan (for LVEF evaluation) [i]	X		8.2.7
12-lead ECG (triplicate) [j]		X	8.2.4
Vital signs [k]		X	8.2.3
Assessment of AEs/SAEs [l]	X		8.3
Concomitant medications	X		6.5
Ophthalmologic assessments [m]	X		8.2.9
Laboratory assessments			
Clinical chemistry [a, n]		X	Table 12
Hematology [a, n]		X	Table 13
Troponin [o]		X	8.2.7
Coagulation [a, p]		X	Table 13
Urinalysis [q]		X	Table 14
Pregnancy test [r]		X	8.2.5
Hepatitis B Surface Antigen / Hepatitis C serology	X		8.2.5
HIV Antibody test (as required by local regulations)	X		8.2.5

Table 3 Schedule of Assessments for Screening/Baseline

Procedures	Screening/Baseline		For details, see Section
	Days -28 to -1	Days -14 to -1 [a]	
Biomarker assessments			
FFPE tumor tissue sample for confirmation of HER2 status centrally (mandatory) [s, t]	X		8.7.1
Blood sample for plasma biomarker assessment (ctDNA) (mandatory) [u]	X		8.7.1
Blood sample for gene expression assessment (mandatory) [u]	X		8.7.1
Blood sample for PBMC isolation (mandatory) [u]	X		8.7.1
Paired biopsies (optional) [v]	X		8.7.2
Other Assessments			
Healthcare resource use (HOSPAD)	X		8.9

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine transaminase; aPTT = activated partial thromboplastin time; AST = aspartate transaminase; BICR = blinded independent central review; BUN = blood urea nitrogen; CT = computed tomography; ctDNA = circulating tumor DNA; DLCO = diffusing capacity of the lungs for carbon monoxide; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed and paraffin-embedded; FEV1 = forced expiratory volume; FVC = forced vital capacity; G-CSF = granulocyte-colony stimulating factor; HER2 = human epidermal growth factor receptor 2; HIV = human immunodeficiency virus; HRCT = high-resolution computed tomography; ICF = Informed Consent Form; ILD = interstitial lung disease; INR = international normalized ratio; IV = intravenous; LDH = lactate dehydrogenase; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition scans; PBMC = periphery blood mononuclear cell; PFT = pulmonary function test; PT = prothrombin time; PTT = partial thromboplastin time; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SpO2 = pulse oximetry; TBL = total bilirubin; ULN = upper limit of normal

Note: Dosing should occur no more than 3 days after randomization. If it is anticipated that dosing cannot occur within 3 days, a discussion with the AstraZeneca Study Physician is required.

[a] For enrollment into the study, adequate organ and bone marrow function (values mentioned below for different parameters) should be confirmed within **14** days before randomization: (see inclusion criterion #11; Section 5.1)

[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. All patients will be required to provide consent to supply a sample of their tumor for entry into this study. This consent is included in the main patient ICF. An optional pre-screen ICF may be signed for 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 a candidate for this study based on available information (e.g., medical history, availability of required number of slides for study). The collection of additional biopsies upon progression is strongly encouraged. 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 patient. However, all results from the screening assessments must have been obtained within 14 or 28 days of randomization depending on procedure

Table 3 Schedule of Assessments for Screening/Baseline

Procedures	Screening/Baseline		For details, see Section
	Days -28 to -1	Days -14 to -1 [a]	

[c] RECIST 1.1 assessments will be performed on images from IV contrast-enhanced CT (preferred) or MRI of the chest, abdomen, and pelvis for all patients. For patients with bone-only disease that is non-measurable, X-ray is also an acceptable imaging modality in addition to the required CT or MRI of the chest, abdomen and pelvis. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Digital copies of all scans should be maintained at the Investigative site as source documents.

[d] Brain imaging by IV contrast-enhanced MRI (preferred) or IV contrast-enhanced CT will be required for all patients at screening/baseline. If brain metastases are discovered at baseline, note that patient must not meet exclusion criterion #8 to be eligible for the study and those patients who are enrolled with baseline stable brain metastases will receive regularly scheduled follow-up brain scans (q6w ±1 week from the date of randomization for 48 weeks, and then q9w ±1 week, starting at Week 48 thereafter until RECIST 1.1 disease progression) while on study.

[e] Any suspicious abnormalities (i.e., hotspots) identified on the bone scans at baseline and on subsequent bone scans MUST be confirmed by X-ray, CT scan with bone windows or MRI. The same modality must be used throughout the trial for confirmation for a given lesion/patient. Bone lesions identified as target lesions or non-target lesions at baseline will be followed up according to the same assessment schedule as for all other lesions.

[f] A non-contrast HRCT scan of the chest is preferred if feasible, otherwise a non-contrast CT is acceptable. The HRCT/CT chest scan will be performed for all patients, in addition to standard CT/MRI scans of chest/abdomen/pelvis for tumor assessments. If both an HRCT/CT of the chest for assessment of ILD/pneumonitis and a diagnostic IV contrast enhanced chest CT scan for tumor response assessment (as part of chest-abdomen-pelvis imaging) are to be acquired in the same imaging session, HRCT/CT should be performed first. HRCT scans are acquired on study as and when ILD/pneumonitis is suspected/as clinically indicated.

[g] PFT at a minimum should include spirometry (minimum requirement of: FVC [L], FVC % predicted, FEV1 [L], FEV1 % predicted, FEV1/FVC %). DLCO will be performed (when feasible), but for patients with prior severe and/or clinically significant pulmonary disorders, DLCO is a requirement.

[h] To include history, type and frequency of tobacco use, e-cigarette use, vaping (including dates)

[i] An ECHO/MUGA scan to assess LVEF will be conducted at screening. The modality of the cardiac function assessments must be consistent within patient (i.e., if ECHO is used for the screening assessment, then ECHO should also be used for subsequent scans if required). The patients should also be examined using the same machine and operator whenever possible.

[j] At screening, ECGs will be obtained in triplicate (3 individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should be completed within 5 minutes). ECGs will be taken in a supine/semi-recumbent position.

[k] Height will be measured at screening only

[l] For patients who sign the pre-screening ICF, only SAEs directly related to tissue screening procedure (i.e., if a patient undergoes a tumor biopsy) will be reported during the pre-screening period.

[m] Ophthalmologic assessments including visual acuity testing, slit lamp examination and fundoscopy will be performed at screening.

[n] Laboratory tests 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, ALP, ALT, AST, total bilirubin, BUN/urea, calcium, chloride, serum creatinine, LDH, sodium, potassium, bicarbonate (where available) and magnesium

[o] Collect blood samples for troponin (preferably high-sensitivity troponin-T) at screening

[p] Coagulation parameters: PT or INR and PTT or aPTT are to be assessed at baseline.

[q] Protein, blood, microscopy assessment (if indicated), and specific gravity

Table 3 Schedule of Assessments for Screening/Baseline

Procedures	Screening/Baseline		For details, see Section
	Days -28 to -1	Days -14 to -1 [a]	

[r] For women of childbearing potential, a negative result from a serum pregnancy test must be available at the screening visit (see inclusion criterion #13). A pregnancy test (urine or serum test per institutional guideline) 72 hours before randomization is required. Within 72 hours before randomization, if a positive urine pregnancy test result is confirmed using a serum test in a female patient of child bearing potential, then the patient should not be randomized into the study.

[s] A mandatory FFPE tumor sample obtained at the time of metastatic disease or later must be provided; the most recently collected pre-randomization tumor sample from the time of metastatic disease or later is required. If no archival specimens are available, a newly acquired biopsy specimen is acceptable. If applicable, a coagulation sample (not needed for needle biopsies but needed for surgical biopsies) should be taken 24 hours prior to tumor biopsy. 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.

[t] Not applicable if the patient went through pre-screening and tumor sample was collected and submitted to HER2 central laboratory before screening.

[u] This sample will not be collected in China.

[v] Paired biopsies (optional): Baseline sample: at screening or pre-dose on Cycle 1, Week 1, Day 1 (see Table 5 for more details on on-treatment schedules)

1.3.2 Treatment Period

Procedures to be conducted during the treatment period through end of treatment (EOT) are presented in Table 5. Patients must not be randomized and must not be treated unless all eligibility criteria have been met.

At study visits when patients do not receive study treatment, all of the assessments scheduled to be done before infusion will be performed.

The timing of ECGs and vital sign assessments should be such that it allows the blood draw (e.g., PK blood sample) to occur at the exact nominal time. All samples are collected before infusion unless otherwise indicated.

Table 4 Schedule of Assessments During the Treatment Period and at End of Treatment

Procedures	Cycle 1				Cycle 2 [a]		Cycle 3		Cycle 4 and subsequent cycles until PD Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine) [b]		EOT [c]	For details, see Section
	Day 1		Day 8	Day 15	Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine)[b]		Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine)[b]					
	BI	EOI	(±1 day)	(±1 day)	BI	EOI	BI	EOI	BI	EOI		
Study procedures and assessments												
Physical examination (targeted)	X [d]				X [d]		X [d]		X [d]		X	8.2.2
Vital signs	X	X	X	X	X	X	X	X	X		X	8.2.3
Body weight [e]	X				X		X		X		X	8.2.3
High resolution CT of the chest [f]	Only if ILD/pneumonitis is suspected											8.2.6
12-lead ECG [g]	X								X (C4 and every 4 cycles thereafter until EOT)		X	8.2.4
SpO2	X [h]	X	X	X	X [h]	X	X [h]	X	X [h]		X	8.2.6
ECOG performance status	X [d]				X [d]		X [d]		X [d]		X	8.2.8
Concomitant medications	X											6.5
AEs/ SAEs	X											8.3

Table 4 Schedule of Assessments During the Treatment Period and at End of Treatment

Procedures	Cycle 1				Cycle 2 [a]		Cycle 3		Cycle 4 and subsequent cycles until PD		EOT [c]	For details, see Section
	Day 1		Day 8	Day 15	Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine)[b]		Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine)[b]		Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine) [b]			
	BI	EOI	(±1 day)	(±1 day)	BI	EOI	BI	EOI	BI	EOI		
ECHO or MUGA (LVEF)									X [i] (Day 1 of Cycle 5 and every 4 cycles [± 7 days] thereafter until EOT)		X	8.2.7
Ophthalmologic assessments [j]	As clinically indicated											8.2.9
Laboratory assessments												
Clinical chemistry [l]	X [d, k]		X	X	X [d]		X [d]		X [d]		X	Table 12
Hematology [l]	X [d, k]		X	X	X [d]		X [d]		X [d]		X	Table 13
Coagulation [m]	As clinically indicated											Table 13
Troponin [n]	As clinically indicated											8.2.7
Pregnancy test	X [o]				X [o]		X [o]		X [o]		X	8.2.5
Urinalysis	As clinically indicated											Table 14
Pharmacokinetic and Immunogenicity assessments (only for patients who receive T-DXd) [p]												
Pre-dose blood sample for T-DXd PK analysis	X (Within 6 h BI)				X (Within 6 h BI)				X (Within 6 h BI at C4, C6, and C8)			8.6.1
Post-dose blood sample for T-DXd PK analysis		X (Within 15 min after EOI, and 5 hrs [± 2 hrs] post-infusion)				X (Within 15 min after EOI)				X (Within 15 min after EOI, C4 only)		8.6.1

Table 4 Schedule of Assessments During the Treatment Period and at End of Treatment

Procedures	Cycle 1				Cycle 2 [a]		Cycle 3		Cycle 4 and subsequent cycles until PD		EOT [c]	For details, see Section
	Day 1		Day 8	Day 15	Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine)[b]		Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine)[b]		Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine) [b]			
	BI	EOI	(±1 day)	(±1 day)	BI	EOI	BI	EOI	BI	EOI		
Blood sample for T-DXd ADA assessment in serum	X (Within 8 h BI)				X (Within 8 h BI)				X (Within 8 h BI at C4 and every 4 cycles thereafter until EOT)			8.6.2
Study treatment administration												
T-DXd	Administered intravenously on Day 1 of each 3-week cycle											Table 9
Capecitabine	Ingested twice daily orally for 2 weeks, followed by a 1-week rest period in 3-week cycles											Table 9
Paclitaxel	Administered intravenously every week in 3-week cycles											Table 9
Nab-paclitaxel [q]	Administered intravenously every week for 3 weeks, followed by a 1-week rest period in 4-week cycles											Table 9
Tumor assessments												
Tumor assessment by RECIST 1.1 (CT or MRI ± X-ray) [r]	RECIST 1.1 tumor assessments will be performed using CT or MRI scans of the chest, abdomen and pelvis at screening (as baseline) with follow-ups at q6w ± 1 week from the date of randomization for 48 weeks, and then q9w ± 1 week, starting at Week 48, until objective RECIST 1.1 disease progression by investigator assessment. Patients who permanently discontinue study treatment for reasons other than objective RECIST 1.1 disease progression, withdrawal of consent, closure of study or death (regardless of whether subsequent anticancer therapy was started) should continue to have RECIST 1.1 scans performed as per schedule until RECIST 1.1 disease progression. Following investigator-determined RECIST 1.1 progression, it is mandatory to perform an additional imaging assessment (preferably within 4 to 6 weeks after investigator PD) for central review to support the primary endpoint of PFS by BICR. In addition, every attempt should be made to continue to collect and submit subsequent scans (completed per standard practice / as clinically indicated) for central review until the primary PFS analysis DCO, or until the Sponsor notifies the site to discontinue (whichever is earlier) regardless of whether the subject has started another anti-cancer therapy.											8.1.1
Brain MRI/CT imaging	Regularly scheduled follow-up brain scans (q6w ±1 week from the date of randomization for 48 weeks, and then q9w ±1 week, starting at Week 48 thereafter until RECIST 1.1 disease progression per investigator assessment) are mandatory for all patients who are enrolled with baseline stable brain metastases, while patients without brain metastases do not need additional brain scans for subsequent tumor assessments, unless clinically indicated. Following investigator determined RECIST 1.1 progression, subsequent imaging assessments as described above should include brain scans for patients who are enrolled with baseline stable brain metastases or if clinically indicated.											8.1.1

Table 4 Schedule of Assessments During the Treatment Period and at End of Treatment

Procedures	Cycle 1				Cycle 2 [a]		Cycle 3		Cycle 4 and subsequent cycles until PD		EOT [c]	For details, see Section
	Day 1		Day 8	Day 15	Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine)[b]		Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine)[b]		Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine) [b]			
	BI	EOI	(±1 day)	(±1 day)	BI	EOI	BI	EOI	BI	EOI		
Whole body bone scan	As clinically indicated											8.1.1
Biomarker assessments												
Tumor sample at disease progression (optional) [s]	If consented for, this tumor sample should be obtained at time of disease progression.											8.7.2
Blood sample for plasma biomarker assessment (ctDNA) (mandatory) [t]	X				X		X		X [u] (C4-7 Day 1, then every 6 weeks [q6w ±1 week; in alignment with RECIST assessments])		X (At progression)	8.7.1
Blood sample for gene expression assessment (mandatory) [t]	X				X						X (At progression only)	8.7.1
Blood sample for PBMC isolation (mandatory) [t]	X				X		X					8.7.1

Table 4 Schedule of Assessments During the Treatment Period and at End of Treatment

Procedures	Cycle 1				Cycle 2 [a]		Cycle 3		Cycle 4 and subsequent cycles until PD		EOT [c]	For details, see Section
	Day 1		Day 8	Day 15	Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine)[b]		Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine)[b]		Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine) [b]			
	BI	EOI	(±1 day)	(±1 day)	BI	EOI	BI	EOI	BI	EOI		
Additional blood samples for plasma and serum exploratory clinical or safety analyses	If ILD/pneumonitis is suspected											8.2.10
Blood sample for serum exploratory clinical benefit or safety analyses (mandatory) [v]	X								X (C4 and every 4 cycles thereafter until EOT)		X	8.7.1
Blood sample for Genomics Initiative (optional)	X [t, w]											8.8
Paired biopsies (optional) [t, x]	X				X							8.7.2
Other assessments and procedures												
Healthcare resource use (HOSPAD) [y]	At each scheduled visit, the site should review clinical notes for any non-study related hospital admissions and visits that have occurred.											8.9
Allocate ePRO device [z]	X											8.1.4

Table 4 Schedule of Assessments During the Treatment Period and at End of Treatment

Procedures	Cycle 1				Cycle 2 [a]		Cycle 3		Cycle 4 and subsequent cycles until PD		EOT [c]	For details, see Section
	Day 1		Day 8	Day 15	Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine)[b]		Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine)[b]		Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine) [b]			
	BI	EOI	(±1 day)	(±1 day)	BI	EOI	BI	EOI	BI	EOI		
ePRO patient training [aa]	X											8.1.4
EORTC QLQ-C30, EORTC QLQ-BR45, EQ-5D-5L, PRO-CTCAE, PGIS, PGIC, PGI-TT, PGI-BR	EORTC QLQ-C30, EORTC QLQ-BR45, EQ-5D-5L, PGIS, PGIC: • Before infusion on Cycle 1 Day 1 (up to -3 days) • Q3W (±3 days) relative to Cycle 1 Day 1 dosing until PFS2 regardless of delays in dosing • Also at EOT visit unless already completed the same day; if discontinued treatment for reasons other than disease progression, also at disease progression visit unless already completed the same day • PGIC: As above except no assessment on Cycle 1 Day 1. PRO-CTCAE and PGI-TT: As above except assessments will stop at EOT rather than continue to PFS2 PGI-BR: Weeks 12, 15, 18, 21 (±3 days) relative to Cycle 1 Day 1 dosing unless EOT occurs first, at EOT visit unless completed the same day, and stops at EOT.											8.1.4

ADA = anti-drug antibody; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine transaminase; aPTT = activated partial thromboplastin time; AST = aspartate transaminase; BI = before infusion; BUN = blood urea nitrogen; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ctDNA = circulating tumor DNA; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; EORTC QLQ = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EOT = end of treatment; EQ-5D-5L = European Quality of Life 5-Domain 5-Level Scale; FDG-PET = fluorodeoxyglucose-positron emission tomography; HOSPAD = hospital admission; ILD = interstitial lung disease; INR = international normalized ratio; IV = intravenous; LDH = lactate dehydrogenase; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition scans; PBMC = periphery blood mononuclear cell; PD = disease progression; PFS2 = time from randomization to second progression or death; PGI-BR = Patient Global Impression – Benefit/Risk; PGIC = Patient Global Impression–Change; PGIS = Patient Global Impression–Severity; PGI-TT = Patient Global Impression–Treatment Tolerability; PK = pharmacokinetic; PRO = patient reported outcomes; PT = prothrombin time; PTT = partial thromboplastin time; q3w = every 3 weeks; q6w = every 6 weeks; q9w = every 9 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event; SpO2 = pulse oximetry

Note: Dosing should occur no more than 3 days after randomization. If it is anticipated that dosing cannot occur within 3 days, a discussion with the AstraZeneca Study Physician is required.

[a] Laboratory, SpO2, and vital sign assessments on D8 and D15 after Cycle 1, and D22 (D22 only applicable if on nab-paclitaxel) visits are performed per local standard practice and will need to be recorded only as clinically indicated.

[b] For paclitaxel and nab-paclitaxel, a window of ± 1 day is applied for all infusions.

[c] EOT is the date the Investigator decides to discontinue a patient from study treatment; the visit should occur within 7 days of the decision.

[d] Within 3 days before study treatment administration.

[e] Body weight is recorded at Day 1 of each cycle until EOT.

Table 4 Schedule of Assessments During the Treatment Period and at End of Treatment

Procedures	Cycle 1				Cycle 2 [a]		Cycle 3		Cycle 4 and subsequent cycles until PD		EOT [c]	For details, see Section
	Day 1		Day 8	Day 15	Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine)[b]		Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine)[b]		Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine) [b]			
	BI	EOI	(±1 day)	(±1 day)	BI	EOI	BI	EOI	BI	EOI		

[f] A non-contrast HRCT scan of the chest is preferred if feasible, otherwise a non-contrast CT is acceptable. The HRCT/CT chest scan will be performed for all patients, in addition to standard CT/MRI scans of chest/abdomen/pelvis for tumor assessments. If both an HRCT/CT of the chest for assessment of ILD/pneumonitis and a diagnostic IV contrast enhanced chest CT scan for tumor response assessment (as part of chest-abdomen-pelvis imaging) are to be acquired in the same imaging session, HRCT/CT should be performed first. HRCT scans are acquired on study as and when ILD/pneumonitis is suspected/as clinically indicated.

[g] ECGs are performed within 3 days prior to dosing. ECGs will be performed in triplicate only if an abnormality is noted. When performed in triplicate, 3 individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should be completed within 5 minutes, while in a supine/semi-recumbent position. If the screening ECG is performed within 3 days prior to Cycle 1 Day 1 (first infusion day), it does not have to be repeated at Day 1.

[h] Within 3 days prior to Day 1 of each cycle, SpO2 should be evaluated by the Investigator or the delegate physician. SpO2 should be evaluated by the Investigator or the delegate physician at the timepoints specified in the schedule of assessments.

[i] ECHO or MUGA scan assessments (note: the same test must be used for the patient throughout the study) will be performed before infusion on Cycle 5 and every 4 cycles (e.g., Cycles 5, 9, 13). The modality of the cardiac function assessments must be consistent within patient (i.e., if ECHO is used for the screening assessment, then ECHO should also be used for subsequent scans if required). The patients should also be examined using the same machine and operator whenever possible.

[j] Ophthalmologic assessments including visual acuity testing, slit lamp examination and fundoscopy will be performed at screening, and as clinically indicated.

[k] If screening laboratory assessments are performed within 3 days prior to Cycle 1 Day 1 (first infusion day), they do not need to be repeated at Day 1.

[l] Laboratory tests 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, ALP, ALT, AST, total bilirubin, BUN/urea, calcium, chloride, serum creatinine, LDH, potassium, sodium, bicarbonate (where available) and magnesium.

[m] Coagulation parameters: PT or INR and PTT or aPTT will be assessed as clinically indicated.

[n] Collect blood samples for troponin (preferably high-sensitivity troponin-T) at screening and if at any time a patient reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of myocyte necrosis. If ECG is abnormal, follow institutional guidelines.

[o] Perform repeat pregnancy tests (urine or serum test per institutional guideline) 72 hours BI of each cycle and at end of treatment.

[p] Please see Section 8.2.10 for further instruction on PK sampling related to ILD.

[q] Although nab-paclitaxel is given in 4-week cycles, the schedule of assessments must be followed (e.g., tumor assessment scans every 6 weeks ± 1 week)

[r] RECIST 1.1 assessments will be performed on images from IV contrast-enhanced CT (preferred) or MRI of the chest, abdomen, and pelvis, with or without X-Ray (for patients with bone-only, non-measurable disease where X-Ray was used as part of baseline assessment). Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. If an unscheduled assessment was performed (e.g. to investigate clinical signs/symptoms of progression) and the patient has not progressed, every attempt should be made to perform the subsequent imaging at the next regularly scheduled visit. New RECIST 1.1 lesions may be identified also by FDG-PET scans, X-ray, bone (scintigraphy) scans. Response assessment scans must be reviewed for evidence of disease progression and ILD/pneumonitis prior to administration of the next scheduled dose of study treatment. Digital copies of all scans should be maintained at the investigative site as source documents.

[s] Optional additional tumor biopsies collected upon disease progression can be submitted for further analysis.

Table 4 Schedule of Assessments During the Treatment Period and at End of Treatment

Procedures	Cycle 1				Cycle 2 [a]		Cycle 3		Cycle 4 and subsequent cycles until PD		EOT [c]	For details, see Section
	Day 1		Day 8	Day 15	Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine)[b]		Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine)[b]		Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine) [b]			
	BI	EOI	(±1 day)	(±1 day)	BI	EOI	BI	EOI	BI	EOI		

[t] This sample will not be collected in China

[u] ctDNA to be drawn at next RECIST scan after Cycle 7 Day 1. Following this draw, subsequent ctDNA collection will be q6w ± 1 week until Week 48, and q9w ± 1 week post Week 48 and at disease progression, in alignment with RECIST assessments. Samples should be drawn as close as possible to the RECIST assessment (preferably within a window of +/- 3 days).

[v] Blood samples for serum isolation will be analyzed for all patients. Blood samples will be collected from patients assigned to the investigator's choice chemotherapy arm. Samples for patients assigned to T-DXd will be obtained from already collected T-DXd samples (e.g., back-up ADA samples), thus an additional sample will not be required for serum isolation.

[w] The blood sample will be obtained from the patients on Cycle 1 Day 1 (first infusion day) prior to study treatment administration (at or after randomization). If for any reason the sample is not drawn on Cycle 1 Day 1, it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE.

[x] Paired biopsies (optional): Baseline sample: at screening or pre-dose on Cycle 1 Week 1 Day 1. On-treatment sample: at Cycle 2, Week 1, Day 1 (any day between Cycle 2, Week 1, Day 2 and Cycle 2, Week 3 is allowed) recommended >4 hours post-dose.

[y] If a patient discontinues study treatment for reasons other than RECIST 1.1 progression, the HOSPAD form should continue to be administered until progression has been confirmed.

[z] The electronic PRO device should be charged and fully functional prior to the patient's arrival at the site for Cycle 1 Day 1 (-3 days) to ensure that the PROs can be completed at the start of the visit.

[aa] The patient should be trained on the use of the device, including the importance of completing the PRO questionnaires throughout the study in accordance with the completion schedule.

Note: For suspected ILD/pneumonitis, treatment with study treatment should be interrupted pending evaluation.
Evaluations should include:

1 high resolution CT of the chest
2 pulmonologist consultation (infectious disease consultation if clinically indicated)
3 pulmonary function tests (including FVC and CO diffusing capacity) and pulse oximetry (SpO2)
4 arterial blood gases if clinically indicated
5 bronchoscopy and bronchoalveolar lavage as clinically indicated and feasible
6 COVID-19 test
7 CBC, blood culture, differential WBC, CRP
8 one blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible
9 additional blood samples for plasma and serum exploratory biomarker analysis as soon as ILD/pneumonitis is suspected, if feasible

Table 4 Schedule of Assessments During the Treatment Period and at End of Treatment

Procedures	Cycle 1				Cycle 2 [a]		Cycle 3		Cycle 4 and subsequent cycles until PD		EOT [c]	For details, see Section
	Day 1		Day 8	Day 15	Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine)[b]		Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine)[b]		Day 1 ± 1 day (paclitaxel, nab-paclitaxel)/± 2 days (T-DXd, capecitabine) [b]			
	BI	EOI	(±1 day)	(±1 day)	BI	EOI	BI	EOI	BI	EOI		
Other tests could be considered, as needed.												

1.3.3 Follow-up Period

Table 5 Schedule of Assessments for Post-treatment Follow-up and Long-term Follow-up

Procedures	Post-treatment follow-up [40 days (+7 days) after last dose] [a]	Long term/Survival follow-up (every 3 months after the post-treatment follow-up ± 14 days) [b]	For details, see Section
Vital signs	X		8.2.3
Body weight	X		8.2.3
Physical examination (targeted)	X		8.2.2
SpO2 [c]	X		8.2.6
ECOG performance status	X		8.2.8
Clinical chemistry [d]	X		Table 12
Hematology [d]	X		Table 13
Coagulation tests	As clinically indicated		Table 13
Pregnancy test	X		8.2.5
Concomitant medications	X		6.5
AEs/SAEs [e]	X		8.3
PFS2 assessment	X	X [f]	8.1.3
Healthcare resource use (HOSPAD)	X		8.9
EORTC QLQ-C30, EORTC QLQ-BR45, EQ-5D-5L, PGIS, PGIC	Q3W (±3 days) relative to Cycle 1 Day 1 dosing until PFS2. For PGIC, note that no assessment on Cycle 1 Day 1 is performed.		8.1.4
Survival status		X	8.1.2
Subsequent cancer therapy following discontinuation of study treatment	X	X	8.1.2

Table 5 Schedule of Assessments for Post-treatment Follow-up and Long-term Follow-up

Procedures	Post-treatment follow-up [40 days (+7 days) after last dose] [a]	Long term/Survival follow-up (every 3 months after the post-treatment follow-up ± 14 days) [b]	For details, see Section
Tumor assessment by RECIST 1.1 (CT or MRI ± X-ray) [g]	RECIST 1.1 tumor assessments will be performed using CT or MRI scans of the chest, abdomen and pelvis at screening (as baseline) with follow-ups at q6w ± 1 week from the date of randomization for 48 weeks, and then q9w ± 1 week, starting at Week 48, until objective RECIST 1.1 disease progression per investigator assessment. Patients who permanently discontinue study treatment for reasons other than objective RECIST 1.1 disease progression, withdrawal of consent, closure of study or death (regardless of whether subsequent anticancer therapy was started) should continue to have RECIST 1.1 scans performed as per schedule until RECIST 1.1 disease progression. Following investigator-determined RECIST 1.1 progression, it is mandatory to perform an additional imaging assessment (preferably within 4 to 6 weeks after investigator PD) for central review to support the primary endpoint of PFS by BICR. In addition, every attempt should be made to continue to collect and submit subsequent scans (completed per standard practice / as clinically indicated) for central review until the primary PFS analysis DCO, or until the Sponsor notifies the site to discontinue (whichever is earlier) regardless of whether the subject has started another anti-cancer therapy. Scans following investigator determined RECIST 1.1 progression should include brain scans for patients who are enrolled with baseline stable brain metastases or if clinically indicated.		8.1.1
Whole body bone scan	Patients who permanently discontinue study treatment for reasons other than objective RECIST 1.1 disease progression, withdrawal of consent, closure of study or death (regardless of whether subsequent anticancer therapy was started) should have bone scans as clinically indicated		8.1.1

ADA = anti-drug antibody; AEs = adverse events; ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urea nitrogen; CRO = Contract Research Organization; CT = computer tomography; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EOT = end of treatment; EQ-5D-5L = European Quality of Life 5-Domain 5-Level Scale; FDG-PET = fluorodeoxyglucose-positron emission tomography; IV = intravenous; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PFS2 = time from randomization to second progression or death; PGIC = Patient Global Impression–Change;

Table 5 Schedule of Assessments for Post-treatment Follow-up and Long-term Follow-up

Procedures	Post-treatment follow-up [40 days (+7 days) after last dose] [a]	Long term/Survival follow-up (every 3 months after the post-treatment follow-up ± 14 days) [b]	For details, see Section

PGIS = Patient Global Impression–Severity; q3w = every 3 weeks; q6w = every 6 weeks; q9w = every 9 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SAEs = serious adverse events; SpO2 = pulse oximetry

[a] If EOT is >40 days (+7 days) after last treatment, then the EOT assessments can also function as the 40-Day (+7 days) follow-up visit.

[b] Long-term/Survival follow-up visits will be performed every 3 months (±14 days) from the date of 40-Day (+7 days) follow-up visit until death, withdrawal of consent, or study closure, whichever occurs first.

[c] SpO2 should be evaluated by the Investigator or the delegate physician.

[d] Laboratory tests 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, ALP, ALT, AST, total bilirubin, BUN/urea, calcium, chloride, serum creatinine, LDH, potassium, sodium, bicarbonate (where available) and magnesium.

[e] If any event that starts post the defined safety follow-up period noted above is considered to be due to a late onset toxicity to study treatment, then it should be reported as an AE or SAE as applicable.

[f] PFS2 is time from randomization to second progression (the earliest of the progression event subsequent to first subsequent anticancer 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 Investigator according to RECIST 1.1 assessment, patients who started on subsequent anticancer therapy post progression will continue to be followed at the 40-day (+7 days) follow-up visit, and every 3 months (±14 days) thereafter for documentation of progression on subsequent anticancer therapy.

[g] RECIST 1.1 assessments will be performed on images from IV contrast-enhanced CT (preferred) or MRI of the chest, abdomen, and pelvis, with or without X-ray (for patients with bone-only, non-measurable disease where X-ray was used as part of baseline assessment). Regularly scheduled follow-up brain scans (q6w±1 week from the date of randomization for 48 weeks, and then q9w ± 1 week, starting at Week 48 thereafter until RECIST 1.1 disease progression per investigator assessment) are mandatory for all patients who are enrolled with baseline stable brain metastases, while patients without brain metastases do not need additional brain scans for subsequent tumor assessments, unless clinically indicated. New lesions may be identified also by FDG-PET scans, X-ray, bone (scintigraphy) scans. If an unscheduled assessment was performed (e.g., to investigate clinical signs/symptoms of progression) and the patient has not progressed, every attempt should be made to perform the subsequent imaging at the next regularly scheduled visit. Digital copies of all scans should be maintained at the site as source documents. Digital images are sent to the Imaging CRO by electronic transfer.

2 INTRODUCTION

2.1 Study Rationale

Within breast cancers traditionally classified as HER2-negative, there exists a spectrum of HER2 expression. In addition to tumors with no detectable HER2 staining (i.e., immunohistochemistry [IHC] null), the category encompasses IHC 2+/ ISH negative and IHC 1+ cancers (defined in this study collectively as HER2-low), as well as cancers that have lower, but detectable HER2 staining, i.e., faint or barely perceptible and incomplete membrane staining that is seen in 10% or fewer tumor cells. These latter cancers are included in the category IHC 0 according to the ASCO/CAP guidelines, and in this study are referred to as HER2 IHC >0 <1+.

Currently, patients with HR+, HER2-low or HER2 IHC >0 <1+ advanced or metastatic breast cancer follow the same treatment paradigm as HR+, HER2-negative breast cancer patients. In general, ET is considered the preferred option for HR+, HER2-negative breast cancer. The optimal treatment sequence is considered to be the use of ET + CDK4/6 inhibitors first line, followed by subsequent ET with targeted therapies (e.g., mTOR or PI3-K inhibitors [for PI3-K mutant tumors]) (Cardoso et al 2020). In patients whose disease has progressed after multiple lines of ET with or without targeted therapies, chemotherapy may be appropriate (Cardoso et al 2018) as currently available anti-HER2 therapy has not demonstrated clinical benefit in these patients. In addition, for patients who have primary endocrine resistance (i.e., progressive disease within the first 6 months of first-line ET for advanced breast cancer), chemotherapy may also be appropriate as continued treatment with endocrine therapies following progression on ET + CDK4/6 inhibitors has been shown to provide less benefit (Rossi et al 2019, Sledge et al 2020, Turner et al 2018).

In clinical trials in a heterogeneous breast cancer population, the standard of care with single agent chemotherapy leads to response rates of 10% to 30%, median PFS of 4-6 months and median OS of 15-25 months. Chemotherapy is also associated with significant AEs, including hematologic toxicities, nausea, vomiting, alopecia, and skin reactions; thus, there is a need for treatments with a better benefit/risk profile in this patient population who receive chemotherapy after endocrine treatment.

In the Phase 1 DS8201-A-J101 clinical trial (NCT02564900), trastuzumab deruxtecan (T-DXd; previously known as DS-8201a) demonstrated promising antitumor activity with an ORR of 37% in HER2-low tumors, with a majority of patients experiencing tumor shrinkage with durable responses (Modi et al 2020). In addition, there were 11 patients in this study whose HER2 expression was locally reported as IHC 1+, 2+ or 3+ but were categorized by a central laboratory as HER2 IHC 0 as per ASCO/CAP guidelines 2018 (Table 6). Of these 11 patients, 5 (45.5%) had a tumor response. In the Phase 2 DAISY clinical trial (NCT04132960), patients with advanced breast cancer who had received at least one prior line

of chemotherapy were treated with T-DXd. In 37 patients with HER2 IHC 0+, confirmed ORR was 29.7% and median PFS was 4.2 months (Diéras et al 2022). Data from both studies suggest that the antitumor activity of T-DXd may extend to the population of patients with HER2 IHC < 1+, warranting further evaluation.

Therefore, in this Phase 3 study, T-DXd will be compared against investigator's choice single agent chemotherapy to determine if T-DXd can improve outcomes in HER2-low (IHC 2+/ISH- and IHC 1+), HR+ breast cancer patients whose disease has progressed on at least 2 lines of prior ET or within 6 months of first line ET + CDK4/6i in the metastatic setting (N=700). In addition to the primary population of HER2-low patients being studied, the study will also randomize approximately 150 patients with HER2 IHC >0 <1+ expression.

2.2 Background

A detailed description of the chemistry and pharmacology of T-DXd, the non-clinical and clinical efficacy and safety results of T-DXd are provided in the Investigator's Brochure (IB).

2.2.1 Background Information on the Disease to be Treated

Breast cancer is the second most common cancer in the world and the most frequent cancer in women with an estimated 2 million new cases in 2018 globally (11.6% of all new cancers). Breast cancer is also the fifth most common cause of death from cancer with an estimated 626,000 deaths. In Europe, an estimated 522,000 women were diagnosed with breast cancer in 2018 and 137,000 died from the disease (GLOBOCAN 2018). According to 2019 estimates, over 268,000 women in the United States (US) were diagnosed with breast cancer and 41,000 died from the disease (National Cancer Institute 2019). Despite advances in diagnosis and treatment, about 6% of women diagnosed with breast cancer in the US have metastatic disease at the time of first presentation and up to 30% of women with early stage non-metastatic breast cancer will develop distant metastatic disease (O'Shaughnessy 2005). Although treatable, metastatic breast cancer remains largely an incurable disease with an estimated 5-year OS of only 25% (Cardoso et al 2018). Breast cancer treatment paradigms in the metastatic setting are defined by the expression of the HER2 and the estrogen receptor (ER) and progesterone receptor (PgR), which are collectively referred to as hormone receptors (HR).

In approximately 20% of breast cancer cases, there is overexpression and/or overamplification of HER2. According to ASCO/CAP guidelines (see Appendix F), HER2 positivity is defined as tumors that have an IHC 3+ score or that show HER2 gene amplification by ISH; ISH testing is recommended in cases of IHC 2+ scoring. Several anti-HER2 targeted therapies such as HERCEPTIN® (trastuzumab), PERJETA® (pertuzumab), KADCYLA® (ado-trastuzumab emtansine [T-DM1]), and TYKERB® (lapatinib) have improved outcomes in breast cancer patients who have HER2 overexpression/overamplification, classified as HER2-positive tumors. Any tumor not meeting these criteria for HER2-positivity has

traditionally been referred to as “HER2-negative.”

The ASCO/CAP testing guidelines and nomenclature used in this study are outlined in Table 6. Refer to Figure 3 for HR+ breast cancer segmented by HER2 receptor status.

Table 6 ASCO/CAP HER2 2018 Testing Guidelines and Nomenclature Used in this Study

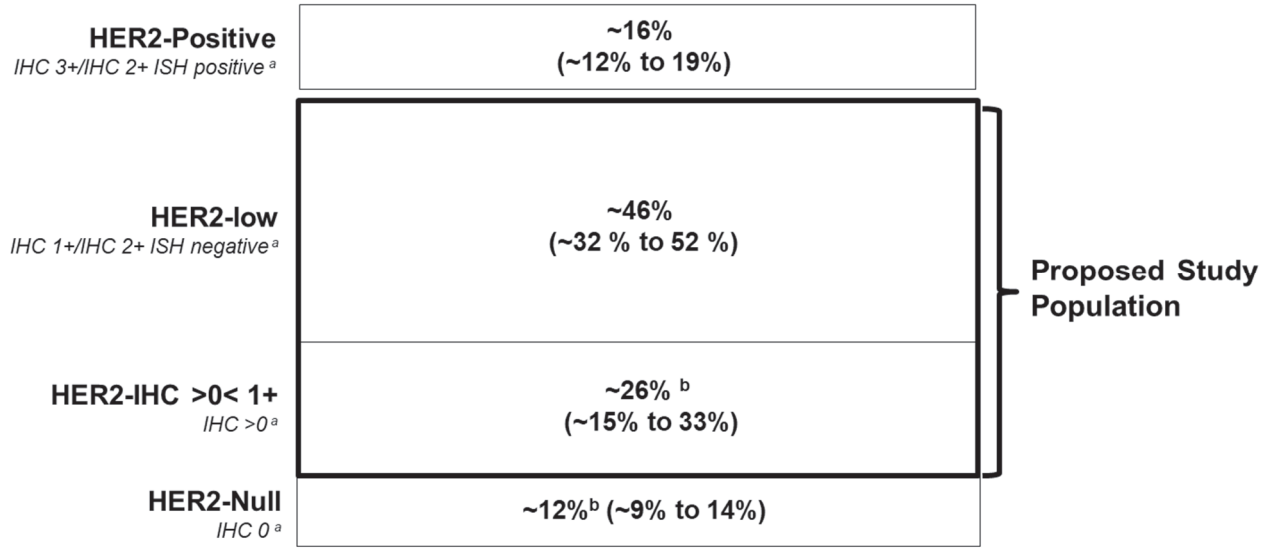
HER2 IHC testing result	IHC staining pattern			HER2 status per ASCO/CAP guidelines	Nomenclature used in this protocol
	Staining intensity	Membrane staining	Frequency		
IHC 3+	Intense	Complete, circumferential	>10% of tumor cells	HER2-positive (IHC2+ must be ISH+)	HER2-positive (IHC 2+ must be ISH+) [a]
IHC 2+[b]	Weak to moderate	Complete	>10% of tumor cells	HER2-negative (IHC 2+ must be ISH-; IHC 1+ and IHC 0 must be ISH- or untested)	HER2-low (IHC 2+ must be ISH-; IHC 1+ must be ISH- or untested)
IHC 1+	Faint/ barely perceptible	Incomplete	>10% of tumor cells		
IHC 0	Faint/ barely perceptible	Incomplete	>0 and ≤10% of tumor cells		HER2 IHC >0 <1+ (must be ISH- or untested)
	No staining observed				HER2 null

ASCO/CAP = American Society of Clinical Oncology/College of American Pathologists; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ISH = in situ hybridization.

[a] HER2-positive patients will not be included in this study.

[b] Unusual staining patterns of HER2 by IHC can be encountered that are not covered by these definitions. In practice, these patterns are rare and if encountered should be considered IHC 2+ equivocal. As one example, some specific subtypes of breast cancers can show IHC staining that is moderate to intense but incomplete (basolateral or lateral) and can be found to be HER2-amplified. Another example is circumferential membrane IHC staining that is intense but in ≤10% of tumor cells (heterogeneous but limited in extent). Such cases can be considered 2+ equivocal, but additional samples may reveal different percentages of HER2-positive staining.

Figure 3 Hormone Receptor-positive Breast Cancer Segmented by HER2 Receptor Status



HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ISH = in situ hybridization.
[a] HER2 standard-of-care IHC assay, ISH per guidelines. Prevalence estimates from (Owens et al 2004), (Lambein et al 2013) and data on file (available upon request).
[b] Lower confidence due to limited data

Currently, HR+ breast cancer patients whose tumors are HER2-low or HER2 IHC >0 <1+ follow the treatment paradigm for HR+, HER2-negative breast cancer patients and receive single agent chemotherapy after disease progression on ET and/or targeted therapy (e.g., CDK4/6 inhibitor) regimens as no anti-HER2 therapy has been approved for this population. Endocrine therapy, including aromatase inhibitors (AIs), selective ER modulators, and selective ER down-regulators, as well as targeted therapies such as CDK4/6 inhibitors, PI3-K inhibitors, and mTOR inhibitors have been shown to improve outcomes for patients with HR+, HER2-negative metastatic breast cancer and are considered standard of care for most patients in the metastatic setting (Andre et al 2019, Matutino et al 2018). Several studies have demonstrated a PFS benefit of AIs and fulvestrant, both of which have recently been used in combination with CDK4/6 inhibitors (Finn et al 2016, Goetze et al 2017, Hortobagyi et al 2018, Slamon et al 2018). The combination of ET and ribociclib has demonstrated an OS benefit among premenopausal women as first line therapy (Im et al 2019). In addition, combinations of abemaciclib (Sledge et al 2020) and ribociclib (Slamon et al 2019) with fulvestrant have demonstrated OS benefit.

The optimal treatment sequence for patients with HR+, HER2-negative metastatic breast cancer is considered to be the use of ET + CDK4/6 inhibitors first line, followed by subsequent ET with targeted therapies (e.g., mTOR or PI3-K inhibitors [for PI3-K mutant tumors]) (Cardoso et al 2020). In patients whose disease has progressed after multiple lines of

ET with or without targeted therapies, or patients whose disease has primary endocrine resistance (progressive disease within the first 6 months of first-line ET for advanced breast cancer), chemotherapy may be appropriate as currently available anti-HER2 therapy has not demonstrated clinical benefit in these patients.

When chemotherapy is recommended, the choice between single agent and combination therapy is decided based on several factors to individualize therapy. Generally, sequential single agent therapy is preferred over combination therapy (Cardoso et al 2009, NCCN 2019). Chemotherapy combinations may be used in select patients with rapidly progressing disease and visceral crisis. Single agent therapy options include anthracyclines, taxanes (e.g., paclitaxel and nab-paclitaxel), and anti-metabolites (e.g., capecitabine). Because of the availability of many agents and the lack of clear superiority of one agent over others, there is no ideal sequence of treatments that can be applied to all patients. Most studies have demonstrated responses of approximately 10% to 30%, a median PFS between 4 and 6 months and a median OS between 15 and 25 months in a heterogeneous metastatic breast cancer setting, with chemotherapy being associated with many adverse effects including hematologic toxicities, alopecia, skin reactions, nausea, diarrhea and vomiting (Baselga et al 2017, Gradishar et al 2005, Kaufman et al 2015, Miller et al 2007, Piccart-Gebhart et al 2008). Hence, a high unmet medical need exists and new treatment options are needed to further improve outcomes.

2.2.2 Background Information on T-DXd

Trastuzumab deruxtecan (T-DXd; DS-8201a) is a HER2-targeting antibody-drug conjugate (ADC) that is being developed as a therapeutic candidate for breast cancer and other HER2-expressing tumors. 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.

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

Due to incorporation of a novel linker, T-DXd achieves a higher drug-to-antibody ratio (DAR) of approximately 8 with homogeneous conjugation of MAAA-1181a, compared with all other currently 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.

T-DXd exhibits HER2-specific antitumor activity via a mechanism of action that combines the monoclonal antibody (mAb) specificity with the broad cytotoxicity of the released drug. After binding to HER2 and internalization, T-DXd is cleaved by lysosomal enzymes preferentially expressed in tumor cells and releases the drug MAAA-1181a in the cytoplasm. MAAA-1181a is an exatecan derivative with greater potency than SN-38, the active metabolite of irinotecan (Ogitani et al 2016). T-DXd is expected to exhibit antitumor activity through MAAA-1181a-induced apoptosis and, potentially, the antibody-dependent cellular cytotoxicity (ADCC) activity of MAAL-9001, which leads to the inhibition of Akt phosphorylation.

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.

As of 08 June 2021, an estimated total of 3462 patients have been treated with T-DXd (alone or in combination with nivolumab or pembrolizumab) or a comparator in 27 completed or ongoing clinical studies across multiple HER2-expressing tumor types including breast cancer, gastric cancer, non-small cell lung cancer (NSCLC), and colorectal cancer.

T-DXd is approved as a treatment in 40 countries including the US, European Union, and Japan for patients with unresectable or metastatic HER2-positive breast cancer who have received prior anti-cancer therapies. It is also approved in the US, Israel, Singapore, and Japan for the treatment of patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen.

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 International Council for Harmonisation (ICH)/Good Clinical Practice (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 Potential Risks of T-DXd

Based on data from clinical trials, toxicities considered to be associated with administration of T-DXd include the important identified risks of ILD/pneumonitis and neutropenia (including febrile neutropenia). A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment at baseline. Participants with moderate renal impairment should be monitored carefully. Other identified risks for T-DXd are infusion-related reactions, hematological adverse events (anemia, leukopenia, lymphopenia, thrombocytopenia), pulmonary/respiratory adverse events (cough, dyspnea, upper respiratory

tract infection, epistaxis), gastrointestinal AEs (abdominal pain, constipation, diarrhea, dyspepsia, nausea, stomatitis, vomiting), hepatic adverse events (hepatic function abnormality, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, and alkaline phosphatase increased), skin adverse events (alopecia, rash, pruritus), blood bilirubin increased, pneumonia, dry eye, dehydration, hypokalemia, decreased appetite, dizziness, fatigue, peripheral edema, pyrexia, and headache.

Based on the available pre-clinical data, review of the cumulative literature, and reported toxicities for the same class of agents, the important potential risks for T-DXd are left ventricular ejection fraction (LVEF) decrease (re-labelled as 'Left ventricular dysfunction' as the undesirable outcome of LVEF reductions, in accordance with the Revision 2 of the European Medicines Agency guidelines on Good Pharmacovigilance Practice. The 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) and embryo-fetal toxicity. Keratitis is considered a potential risk for T-DXd.

ILD/pneumonitis and LVEF decrease are considered adverse events of special interest (AESI).

T-DXd has not been studied in patients with severe/moderate hepatic impairment or severe renal impairment.

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 (HERCEPTIN®) and pertuzumab (PERJETA®), the ADC T-DM1 (KADCYLA®), and EGFR- and HER1- and 2-associated TKIs, lapatinib (TYKERB®) and neratinib (NERLYNX®). 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 congestive heart failure (CHF; New York Heart Association [NYHA] class II-IV) 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 drug-induced liver injury.

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.

Refer to Appendix H for toxicity management guidelines (TMGs) for T-DXd.

Topoisomerase I Inhibitors

MAAA-1181a is a derivative of exatecan (DX-8951f), a topoisomerase I 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 anti-cancer therapy.

The main risks associated with the use of topoisomerase I 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, which can be severe and lead to dehydration, have been associated with

topoisomerase I 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 topoisomerase I inhibitors, with hematological toxicities and gastrointestinal toxicities being the most significant groups of events.

2.3.2 Potential Benefits of T-DXd

T-DXd is under development for the treatment of HER2-expressing cancers and HER2-mutant tumors. Based on the clinical observations to date, T-DXd demonstrates antitumor activity in HER2-expressing cancers.

Initial evaluation of T-DXd in patients with HER2-positive (defined by ASCO/CAP guidelines as HER2 IHC 3+ or IHC 2+/ISH+), unresectable and/or metastatic breast cancer (studies DS8201-A-J101 [Phase 1] and DS8201-A-U201 [Phase 2; NCT03248492], both single-arm) demonstrated that T-DXd 5.4 mg/kg was associated with an ORR of 51.0% (95% confidence interval [CI]: 36.6, 65.2; n=51 patients) and 60.3% (95% CI: 52.9, 67.4; n=184 patients), respectively, in patients with multiple prior lines of therapy. In study DS8201-A-J101, in which the data are more mature (median follow-up of 15.5 months), the median duration of response as of 01 February 2019, was 12.7 months (95% CI: 6.7, not estimable) for the 5.4 mg/kg dose. At the DCO date of 01 August 2019 (median follow-up of 11.1 months), study DS8201-A-U201 showed a median duration of response of 14.8 months (95% CI: 13.8, 16.9). These data represent a substantial improvement over ORRs observed in similar settings, such as in the recent SOPHIA (NCT02492711) and NALA (NCT01808573) studies in which ORRs of approximately 30% were observed (Rugo et al 2019, Saura et al 2019).

In addition, evaluation of T-DXd in patients with HER2-low (defined as HER2 IHC 2+/ISH- or HER2 IHC 1+) advanced breast cancer refractory to or intolerant of standard treatment in the first-in-human Phase 1 Study DS8201-A-J101, demonstrated that the majority of patients experienced tumor shrinkage; durable responses were observed. Among the 54 patients with HER2-low breast cancer treated with either 5.4 mg/kg (n=21) or 6.4 mg/kg q3w (n=33), confirmed ORR by independent central review (ICR) was 37.0% (95% CI: 24.3, 51.3). Median confirmed duration of response (DoR) by independent central review (ICR) was 10.4 months (95% CI: 8.8, not estimable). Median PFS by ICR was 11.1 months (95% CI: 7.6, not estimable) and median OS was 29.4 months (95% CI: 12.9, 29.4). In addition, data from 11 patients in study DS8201-A-J101 whose HER2 expression was locally reported as IHC 1+, 2+ or 3+ were categorized by a central laboratory as HER2 IHC 0 as per ASCO/CAP guidelines 2018. Of these 11 patients, 5 had a tumor response (45.5%). In the Phase 2 DAISY study, patients with advanced breast cancer who had received at least one prior line of chemotherapy were treated with T-DXd. In 37 patients with HER2

IHC 0+, confirmed ORR was 29.7% and median PFS was 4.2 months (Diéras et al 2022). This compares favorably with historical data for chemotherapy that demonstrated ORR of 11.5% to 15.5% (Baselga et al 2017, Kaufman et al 2015). Data from both study DS8201-A-J101 and the DAISY study suggest that the antitumor activity of T-DXd may extend to the population of patients with HER2 IHC < 1+.

The results from study DS8201-A-J101 (NCT02564900) comprise the primary data set to support initiation for this study and the DESTINY-Breast04 Phase 3 study (NCT03734029; DS8201-A-U303) (AstraZeneca 2022). The DESTINY-Breast04 study, compared to DESTINY-Breast06, has been initiated in later-line HER2-low, advanced or metastatic breast cancer patients for whom ET is no longer an option and who have received 1 to 2 lines of chemotherapy in the metastatic setting. Recently, this study has demonstrated that T-DXd significantly improved PFS and OS compared to physician's choice of chemotherapy.

2.3.3 Standard of Care (Investigator's Choice Chemotherapy)

The risks associated with capecitabine, paclitaxel and nab-paclitaxel are described in the local prescribing information.

2.3.4 Overall Benefit/Risk Conclusion

The standard of care with single agent chemotherapy in a heterogenous metastatic breast cancer population leads to response rates of 10% to 30%, median PFS of 4-6 months and median OS of 15-25 months. Chemotherapy is also associated with significant AEs, including hematologic toxicities, nausea, vomiting, alopecia, and skin reactions; thus, additional effective treatment options are needed for this patient population.

In the Phase 1 DS8201-A-J101 clinical trial, T-DXd demonstrated promising antitumor activity in HER2-low tumors with a majority of patients experiencing tumor shrinkage. Among the 54 patients with HER2-low breast cancer treated with either 5.4 mg/kg (n=21) or 6.4 mg/kg q3w (n=33), confirmed ORR by ICR was 37.0% (95% CI: 24.3, 51.3). Median confirmed DoR by ICR was 10.4 months (95% CI: 8.8, not estimable). Median PFS by ICR was 11.1 months (95% CI: 7.6, not estimable). Median OS was 29.4 months (95% CI: 12.9, 29.4). In the Phase 2 DAISY study, T-DXd showed promising antitumor activity in 37 patients with HER2 IHC 0+ advanced breast cancer who had received at least one prior line of chemotherapy. Confirmed ORR was 29.7% and median PFS was 4.2 months. In the Phase 3 DESTINY-Breast04 study in later line HER2-low, advanced or metastatic breast cancer patients for whom ET is no longer an option and who have received 1 to 2 lines of chemotherapy in the metastatic setting, treatment with T-DXd has led to significantly improved PFS and OS compared to physician's choice of chemotherapy.

The safety profile of T-DXd in patients with HER2-low breast cancer was consistent with that

observed in HER2-positive breast cancer. In the 54 patients with HER2-low breast cancer in the DS8201-A-J101 clinical study, ≥ Grade 3 treatment-emergent adverse events occurred in 34 patients (63.0%) with neutrophil count decrease, white blood cell (WBC) count decrease, anemia, hypokalemia, platelet count decrease, AST increase, decreased appetite, febrile neutropenia, cellulitis and diarrhea occurring in ≥ 5% of patients. Three patients with HER2-low breast cancer receiving the 6.4 mg/kg dose died due to treatment-related AEs, which included 2 TEAEs of pneumonitis and 1 TEAE of ILD (Modi et al 2020).

Several measures have been put in place to mitigate the incidence of pulmonary toxicities, including inclusion of eligibility criteria that prohibit patients with pre-existing pulmonary comorbidities from entering the study. In addition, baseline pulmonary function tests will be performed for all patients. For hematological toxicities, the use of growth factors is allowed, as per the Investigator's discretion. Patients will be monitored closely throughout the study and clinical and laboratory assessments will be performed before every cycle. TMGs (Appendix H) are also provided to assist with the management of the most commonly seen AEs.

ILD education is to be reemphasized in patients with moderate renal impairment. Physicians should consider more frequent patient contact in between visits (at least once in between cycles) in order to reinforce ILD education and the importance of prompt reporting of symptoms, until the investigator is confident the patient is familiar with the requirements.

The emergence of coronavirus 2019-nCoV (COVID-19) presents a potential safety risk for patients, therefore, several risk mitigation factors have been implemented 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 I.

This study will also randomize approximately 150 HER2 IHC >0 <1+ patients. Given the available data for T-DXd in the HER2 IHC >0 <1+ patients, a futility analysis specific to the HER2 IHC >0 <1+ population is planned after the first 70 HER2 IHC >0 <1+ patients are randomized (i.e., approximately 35 HER2 IHC >0 <1+ patients per treatment arm; see Section 9.5 for further details).

Based on these considerations, T-DXd has the potential to provide meaningful clinical benefit and given the measures put in place for mitigation, the benefit/risk assessment supports the proposed study.

3 OBJECTIVES AND ENDPOINTS

Table 7 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of T-DXd compared with investigator's choice chemotherapy in terms of PFS by BICR in the HR+, HER2-low (IHC 2+/ISH- and IHC 1+) population.	• PFS in the HR+, HER2-low population: Time from date of randomization until the date of objective radiological disease progression by BICR according to RECIST 1.1 or death (by any cause in the absence of progression)
Secondary	
The **key** secondary objectives are: • To assess the efficacy of T-DXd compared with investigator's choice chemotherapy in terms of OS in the HR+, HER2-low population • To assess the efficacy of T-DXd compared with investigator's choice chemotherapy in terms of PFS by BICR and OS in the ITT population (HER2 IHC >0 <1+ and HER2-low) The other secondary objectives: • To further assess the efficacy of T-DXd compared with investigator's choice chemotherapy in terms of PFS by Investigator assessment, ORR, and DoR by BICR and Investigator assessment in the HR+, HER2-low population • To further assess the efficacy of T-DXd compared with investigator's choice chemotherapy in terms of ORR and DoR by BICR and Investigator assessment in the ITT population	The **key** secondary endpoints are: • OS in the HR+, HER2-low population: Time from date of randomization until the date of death by any cause • PFS by BICR according to RECIST 1.1 in the ITT population (HER2 IHC >0 <1+ and HER2-low) • OS in the ITT Population The other secondary endpoints are: • ORR in the HR+, HER2-low population: The percentage of patients with at least 1 visit response of CR or PR by BICR and Investigator assessment according to RECIST 1.1 • DoR in the HR+, HER2-low population: Time from date of first detection of objective response until the date of objective radiological disease progression by BICR and Investigator assessment according to RECIST 1.1 or death in the absence of progression • PFS by Investigator assessment according to RECIST 1.1 in the HR+, HER2-low population • ORR and DoR by BICR and by Investigator assessment according to RECIST 1.1 in the ITT population (HER2 IHC >0 <1+ and HER2-low)

Table 7 Objectives and Endpoints

Objectives	Endpoints
• To compare the effect of T-DXd with investigator's choice chemotherapy in terms of PFS2 according to Investigator assessment, time to first subsequent treatment or death (TFST) and time to second subsequent treatment or death (TSST) in the HR+, HER2-low population and the ITT population	• PFS2 in the HR+, HER2-low population and the ITT population: time from randomization until second progression on next-line of treatment, as assessed by Investigator at the local site or death due to any cause • TFST in the HR+, HER2-low population and the ITT population: time from randomization to the start date of subsequent therapy after discontinuation of randomized treatment or death due to any cause • TSST in the HR+, HER2-low population and the ITT population: time from randomization to the start date of second subsequent therapy after discontinuation of randomized treatment or death due to any cause
• To assess the safety and tolerability profile of T-DXd compared with investigator's choice chemotherapy	• AEs, changes from baseline in laboratory findings, ECHO/MUGA scans, ECGs and vital signs
• To assess the PK of T-DXd	• T-DXd total anti-HER2 antibody and MAAA-1181a concentrations in serum
• To assess symptoms, functioning and HRQoL in patients treated with T-DXd compared with investigator's choice single agent chemotherapy	The PROs include: • Change from baseline in EORTC QLQ-C30 and EORTC QLQ-BR45 scale scores • Time to deterioration in EORTC QLQ-C30 scale scores
• To investigate the immunogenicity of T-DXd	• Number and percentage of patients who develop ADA for T-DXd
Exploratory [a]	
• To collect blood and tissue samples at pre-treatment, on-treatment and post-treatment for defining biological responses to T-DXd and to investigate predictive markers of response, acquired resistance and other markers that may correlate with likelihood of clinical benefit or tolerability; samples and generated data may be used to support diagnostic development	Biomarkers that include but are not limited to biomarkers of T-DXd sensitivity/resistance and immunological biomarkers are: • Protein expression (IHC and proteomic analysis including, but not limited to ERBB2, related family members and TOPO-1 expression) • Mutational profiling in tissue, blood and ctDNA • Plasma and blood analysis for ctDNA (exploration of genetic alterations in ctDNA and dynamic changes, including ctDNA clearance) • mRNA expression (exploration of gene expression, molecular subtype and gene expression changes following treatment) in tissue and blood

Table 7 Objectives and Endpoints

Objectives	Endpoints
• To explore the impact of treatment and disease state on health utility using the EQ-5D-5L • To assess patient-reported treatment tolerability • To assess the patient's overall impression of the severity of their cancer symptoms, change in condition since starting the study and benefit/risk assessment • To explore the impact of treatment and disease on health care resource use	• The EQ-5D-5L health state utility index will be used to derive health state utility based on patient-reported data • Proportion of patients experiencing treatment-related symptoms as measured by the PRO-CTCAE; patient perceived overall tolerability as measured by the PGI-TT • Proportion of patients reporting different levels of symptom severity as measured by the PGIS, change in condition as measured by the PGIC, and benefit/risk as measured by the PGI-BR. • Health care resource use will be captured, including inpatient admissions, intensive care unit admissions, and length of stay in hospital
• To explore & optimize technologies for detection of HER2 protein expression	• Exploration of IHC and non-IHC methods to determine tumoral HER2 expression

ADA = anti-drug antibody; AE = adverse events; BICR = blinded independent central review; CR = complete response; cfDNA = circulating free DNA; ctDNA = circulating tumor DNA; DoR = duration of response; ECG = electrocardiogram; ECHO/MUGA = echocardiogram/multigated acquisition; EORTC QLQ = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L = European Quality of Life 5-Domain 5-Level Scale; ERBB =erythroblastic oncogene B; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; HRQoL = health-related quality of life; IHC = immunohistochemistry; ISH = in situ hybridization; ITT = intent-to-treat; mRNA = messenger RNA; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PFS2 = time from randomization to second progression or death; PGI-BR = Patient Global Impression – Benefit/Risk; PGIC = Patient Global Impression–Change; PGIS = Patient Global Impression–Severity; PGI-TT = Patient Global Impression–Treatment Tolerability; PK = pharmacokinetics; PR = partial response; PRO = patient-reported outcome; PRO-CTCAE = Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; RECIST 1.1 = Response Evaluation Criteria In Solid Tumors, version 1.1; TFST = time to first subsequent treatment or death; TOPO = topoisomerase; TSST = time to second subsequent treatment or death

[a] Patients randomized into the study in China will be excluded from exploratory objectives requiring the provision of additional tumor or blood samples, with the exception of samples for exploratory safety or clinical benefit analyses to identify candidate markers which may correlate with likelihood of clinical benefit/tolerability (see Section 8.7.1).

4 STUDY DESIGN

4.1 Overall Design

The study is an open-label, multi-center, randomized study in HER2-low, HR+ breast cancer patients with disease progression on at least 2 lines of prior ET or within 6 months of first line ET + CDK4/6i in the metastatic setting. The primary purpose of the study is to determine the efficacy and safety of T-DXd compared with investigator's choice single agent chemotherapy in the target population. Approximately 850 patients (700 patients with HER2 IHC 1+/2+ expression and 150 patients with HER2 IHC>0 <1+ expression) will be randomized 1:1 across approximately 300 centers globally to receive either 5.4 mg/kg T-DXd q3w or investigator's choice single agent chemotherapy (paclitaxel, nab-paclitaxel or capecitabine) until RECIST 1.1 defined progressive disease (PD), unless there is unacceptable toxicity, withdrawal of consent, or another criterion for discontinuation is met. See Figure 2 for details on study schema. To ensure adequate representation of each subgroup of the HER2-low population, at least 240 patients in each HER2 IHC group (IHC 1+ and IHC 2+/ISH-) across both treatment arms (approximately 120 patients per arm) will be randomized. The study will compare PFS, OS and other measures of efficacy between the study treatment groups and further characterize the safety and tolerability profile of T-DXd.

The randomization will be stratified by:

- prior CDK4/6 inhibitor use (Yes vs No)
- HER2 IHC expression (IHC 2+/ISH- vs IHC 1+ vs IHC >0 <1+)
- prior taxane use in the non-metastatic setting (Yes vs No)

Stratification factor status must be known at the time of patient's randomization to the study.

CDK4/6 inhibitors are being increasingly utilized as part of standard of care for patients with HR+ breast cancer. To ensure that majority of patients have received prior CDK4/6 inhibitor therapy in the HER2-low population, no more than 343 patients (49% of 700 patients) who have not received prior therapy with CDK 4/6 inhibitors (e.g., palbociclib, abemaciclib, or ribociclib) will be randomized; a similar proportion of patients who have not received prior CDK4/6 therapy will be randomized in the HER2 IHC >0 <1+ population as well.

RECIST 1.1 tumor assessments will be performed using CT or MRI scans of the chest, abdomen and pelvis at screening (as baseline) with follow-ups at q6w ± 1 week from the date of randomization for 48 weeks, and then q9w ± 1 week, starting at Week 48, until objective RECIST 1.1 disease progression by investigator assessment (see SoAs in Section 1.3). Patients who permanently discontinue study treatment for reasons other than objective RECIST 1.1 disease progression, withdrawal of consent, closure of study or death (regardless of whether subsequent anticancer therapy was started) should continue to have RECIST 1.1

scans performed as per schedule until RECIST 1.1 disease progression. Following investigator-determined RECIST 1.1 progression, it is mandatory to perform an additional imaging assessment (preferably within 4 to 6 weeks after investigator PD) for central review to support the primary endpoint of PFS by BICR. In addition, every attempt should be made to continue to collect and submit subsequent scans (completed per standard practice / as clinically indicated) for central review until the primary PFS analysis DCO, or until the Sponsor notifies the site to discontinue (whichever is earlier) regardless of whether the subject has started another anti-cancer therapy.

An intravenous (IV) contrast-enhanced brain MRI (preferred) or IV contrast-enhanced CT of the brain is to be acquired for all patients at baseline. Regularly scheduled follow-up brain scans (q6w ±1 week from the date of randomization for 48 weeks, and then q9w ±1 week, starting at Week 48 thereafter until RECIST 1.1 disease progression per investigator assessment) are mandatory for all patients who are enrolled with baseline stable brain metastases, while patients without brain metastases do not need additional brain scans for subsequent tumor assessments, unless clinically indicated. Following investigator determined RECIST 1.1 progression, subsequent imaging assessments as described above should include brain scans for patients who are enrolled with baseline stable brain metastases or if clinically indicated.

For patients with bone-only disease that is non-measurable, X-ray may also be used in addition to the required CT or MRI of the chest, abdomen and pelvis. Any other areas of disease involvement or any other sites at which new metastatic disease is clinically suspected should be additionally imaged based on the signs and symptoms of individual patients.

Digital copies of all scans performed during the conduct of this study must be retained at site as source data. Sites shall submit the digital copies electronically to the imaging contract research organization (iCRO) for centralized review by blinded independent central review (BICR). Submission via alternative method such as compact disc (CD)/digital versatile disc (DVD) may be accepted on discussion with the study team if electronic submission is not possible. Patients will be followed for OS, regardless of whether study treatment is discontinued or delayed, unless the patient withdraws consent or study closure, whichever occurs first.

A mandatory formalin-fixed paraffin-embedded (FFPE) tumor sample obtained at the time of metastatic disease or later must be provided; the most recently collected pre-randomization tumor sample from the time of metastatic disease or later that meets the tissue requirements specified in Section 8.7.1 is required. If no archival specimens are available, a newly acquired biopsy specimen is acceptable. The tumor sample submitted should be of sufficient quantity to allow for assessment of HER2 status and for other exploratory biomarker analyses (for details of tumor tissue requirements see Section 8.7.1). Assessment of HER2 status will be performed

via a central laboratory.

Central testing of HER2 status will be conducted using a HER2 IHC assay, investigational for the IHC 2+, IHC 1+ and IHC >0 <1+ cut-offs. Tumor samples centrally confirmed to be HER2 IHC 2+ will be confirmed to be HER2 ISH negative using an approved HER2 ISH assay per manufacturers requirements. Testing will be carried out in a laboratory operating to GCP and with pathology staff fully trained by the diagnostic manufacturer to score reproducibly at all relevant HER2 IHC cut-offs (IHC >0 <1+ and IHC1+ and IHC 2+). In addition, an on-market assay will be used to centrally confirm ISH status according to the manufacturer's guidelines.

4.1.1 Duration of the Study

Enrollment is planned to occur over approximately 18-25 months. For each patient there will be a 40-day (+7 days) follow-up visit after the last study treatment administration, followed by long-term/survival follow-up visits every 3 months (±14 days) until death, withdrawal of consent, or study closure, whichever occurs first.

4.1.2 Duration of Patient Participation

The screening period is up to 28 days. Prior to the 28-day screening period, an optional pre-screen ICF may be signed by patients to permit a pre-screening period for tumor tissue sample collection for central HER2 status testing. For T-DXd, each cycle of treatment will be 21 days. For capecitabine and paclitaxel, each cycle of treatment will be 21 days. For nab-paclitaxel, each cycle of treatment will be 28 days (see Table 2 for further details). The number of treatment cycles with T-DXd and the investigator's choice chemotherapy (capecitabine, paclitaxel and nab-paclitaxel) is not fixed. Upon commencing study treatment, patients may continue receiving study treatment until RECIST 1.1 disease progression, withdrawal of consent or any of the discontinuation criteria as defined in Section 7.1.1 are met. Patients cannot switch between the investigator's choice single agent chemotherapy control agents while on-treatment during the study.

After study treatment discontinuation, patients will be contacted for the 40-day (+7 days) follow-up visit, followed by long-term/survival follow-up visits every 3 months (±14 days) to obtain information about subsequent treatment(s) and survival status.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for T-DXd in HR+, HER2-low, Advanced or Metastatic Breast Cancer

Preclinical data have demonstrated that T-DXd inhibits tumor growth in a patient-derived HER2-low tumor xenograft model that is insensitive to T-DM1. Results from the first-in-human Phase 1 DS8201-A-J101 study in patients with HER2-low (defined by

ASCO/CAP guidelines as HER2 IHC 2+/ISH- or HER2 IHC 1+) advanced breast cancer, refractory to or intolerant of standard treatment, demonstrated that the majority of patients experienced tumor shrinkage; durable responses were observed.

Among the 54 patients with HER2-low breast cancer treated with either 5.4 mg/kg (n=21) or 6.4 mg/kg q3w (n=33), confirmed ORR by ICR was 37.0% (95% CI: 24.3, 51.3). Median confirmed DoR by ICR was 10.4 months (95% CI: 8.8, not estimable). Median PFS by ICR was 11.1 months (95% CI: 7.6, not estimable) and median OS was 29.4 months (95% CI: 12.9, 29.4; (Modi et al 2020).

Furthermore, DESTINY-Breast04, a Phase 3 study in later line HER2-low, advanced or metastatic breast cancer patients, for whom ET is no longer an option and who have received 1 to 2 lines of chemotherapy in the metastatic setting, demonstrated that T-DXd significantly improved both PFS and OS (AstraZeneca 2022).

4.2.2 Rationale for T-DXd in HR+, HER2 IHC >0 <1+, Advanced or Metastatic Breast Cancer

In the DS8201-A-J101 study, patients were enrolled based on historical HER2 status. HER2 IHC was later assessed retrospectively by central laboratory testing of submitted archival samples via HercepTest™ at Mosaic Laboratories for IHC analysis, and by PathVysion HER-2 DNA Probe Kit at Mosaic Laboratories for the ISH analysis. Central confirmatory testing involved new HER2 IHC staining on the submitted archival samples. Based on central testing, there were 11 breast cancer patients treated at either 5.4 or 6.4 mg/kg whose HER2 expression was considered IHC 0 per ASCO/CAP guidelines. Among these 11 patients, 5 had objective responses, suggesting that the antitumor activity of T-DXd may also extend to the population of patients with HER2 IHC 0.

The on-market HER2 IHC assays are optimized to detect HER2 expression on tumor cell membrane above the basal level of HER2 expressed on epithelial cells. Current ASCO/CAP scoring guidelines for HER2 IHC 0 classification includes both patients whose tumors have no detectable HER2 expression (HER2 null) and those whose tumors have membrane staining that is incomplete and is faint/bare perceptible in greater than 0% and less than or equal to 10% of tumor cells. Given the mechanism of action of T-DXd as a HER2-targeting agent, it is hypothesized that some detectable expression of HER2 above normal is necessary to allow T-DXd to induce death in tumor cells. Therefore, this study will focus on further evaluating the subset of the ASCO/CAP defined HER2 IHC 0 population that has some detectable HER2 expression above normal; i.e., the HER2 IHC >0 <1+ population.

In addition to the J101 study, the DAISY study has provided additional evidence for the activity of T-DXd in the IHC >0 <1+ population. The DAISY study (Diéras et al 2022) treated 38 advanced breast cancer patients with HER2 IHC 0+ (defined as staining of ≤ 10% HER2

cells according to American Society of Clinical Oncology 2018 and GEFPICS recommendations) expression. Of these 38 patients, 12 patients were HR-, 26 were HR+ and a great majority (86.8%) of patients received ≥ 2 prior lines of metastatic treatment before receiving T-DXd. All patients were required to have a biopsy prior to entering the study. In 37 of these heavily pre-treated patients, T-DXd demonstrated a confirmed ORR of 29.7% and a median PFS of 4.2 months, providing further efficacy of T-DXd in HER2 expression below IHC 1+ in patients with advanced breast cancer.

Given the available data for T-DXd in the HER2 IHC >0 <1+ patients, a futility analysis specific to the HER2 IHC >0 <1+ population is planned after the first 70 HER2 IHC >0 <1+ patients are randomized (i.e., approximately 35 HER2 IHC >0 <1+ patients per treatment arm; see Section 9.5 for further details).

4.2.3 Rationale for Efficacy Endpoints

The primary endpoint is

- PFS by BICR according to RECIST 1.1 in the HR+, HER2-low population.

PFS has been selected as the primary endpoint based on the following considerations:

- PFS is not confounded by subsequent therapies.
- Several meta-analyses demonstrate a statistically significant correlation between hazard ratios of PFS and OS in metastatic breast cancer patients (Adunlin et al 2015, Lux et al 2019).
- PFS has been used as the primary endpoint in studies leading to the registration of recently approved treatments for breast cancer where the magnitude of effect was sufficient to establish clinical benefit.
- PFS provides the evidence of drug activity and the improvement in PFS is of clinical benefit to patients.
- PFS is an acceptable primary endpoint as described in, for example, the EMA Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95 Rev.5) and the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (December 2018).

This is in line with the guidelines outlined by the National Cancer Institute Breast Cancer Steering Committee Working Group Report, which recommends that it is appropriate to have PFS as the primary endpoint (Seidman et al 2018) in HR+, HER2-negative disease in the first line setting of metastatic breast cancer. This recommendation was based on the expectation that post-progression survival is long and that subsequent therapies will have great influence on OS.

The **Key** secondary endpoints are:

- OS in the HR+, HER2-low population
- PFS by BICR according to RECIST 1.1 in the ITT population (HER2 IHC >0 <1+ and HER2-low)
- OS in the ITT population (HER2 IHC >0 <1+ and HER2-low)

The additional secondary endpoints are:

- ORR and DoR by BICR and Investigator assessment according to RECIST 1.1 in the HR+, HER2-low population
- ORR and DoR by BICR and Investigator assessment according to RECIST 1.1 in the ITT population (HER2 IHC >0 <1+ and HER2-low)
- PFS by Investigator assessment according to RECIST 1.1 in the HR+, HER2-low population
- Time from randomization to second progression or death (PFS2), time to first subsequent treatment or death (TFST) and time to second subsequent treatment or death (TSST) in the HR+, HER2-low and ITT population

The secondary endpoints are in line with the recommendations outlined in the National Cancer Institute Breast Cancer Steering Committee Working Group Report, where for HR+/HER2-negative breast cancer in the first line setting it is appropriate to have the following secondary endpoints: OS, response rate and patient-reported outcomes (PROs) (Seidman et al 2018).

Furthermore, PFS2, TFST and TSST will be examined to further evaluate the antitumor effect of T-DXd vs investigator's choice chemotherapy as exploratory endpoints to complement the antitumor effect noted from other, conventional endpoints (e.g., PFS, ORR, DoR and OS).

4.2.4 Rationale for Other Study Endpoints

As part of the secondary endpoint assessment, blood samples will be taken to allow for research into the PK and immunogenicity of T-DXd.

The secondary patient-reported symptoms, functioning and overall health-related quality of life (HRQoL) endpoints, assessed using the European Organisation for Research and Treatment of Cancer (EORTC) 30 Core Quality of Life Questionnaire and Breast Cancer-Specific Module, (QLQ-C30 and QLQ-BR45) 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. The EQ-5D-5L, developed by the EuroQol Group, is a generic questionnaire that provides a simple descriptive profile of health and a single

index value for health status for economic appraisal by payers. These PRO questionnaires are well-established instruments that have been previously included in cancer clinical studies.

Biological samples will be used to explore potential biomarkers in tumor, plasma, and/or serum, which may predict the progression of cancer (and associated clinical characteristics) and/or tumor response.

4.3 Justification for Dose

T-DXd, and 3 investigator's choice of single agent chemotherapy are used in the study. The justification for dose for each of these interventions are provided below.

4.3.1 T-DXd Dose Rationale

Based on all available information, a T-DXd dose of 5.4 mg/kg q3w has been chosen for this study. Doses including 5.4 mg/kg and 6.4 mg/kg T-DXd monotherapy have been tested in clinical studies and the maximum tolerated dose (MTD) was not reached in the dose escalation phase of the DS8201-A-J101 study. Both doses showed efficacy in different tumor types; efficacy was only marginally better at 6.4 mg/kg over 5.4 mg/kg. A numerically higher incidence of AEs ≥ Grade 3 (overall and causally related), serious adverse events (SAEs; including causally related), AEs leading to drug withdrawal (overall and causally related), AEs leading to dose reduction (overall and causally related) and ILD/pneumonitis was observed with 6.4 mg/kg compared to 5.4 mg/kg. Therefore, 5.4 mg/kg dose of T-DXd was chosen instead of the 6.4 mg/kg dose because of its superior benefit/risk profile.

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

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

4.3.2 Chemotherapy Dose Rationale

Three chemotherapy options were chosen for the proposed study based on the strength of the efficacy data in the first line setting, previously approved indications, and the responses obtained in feasibility questionnaires (completed by AstraZeneca Clinical representatives in 34 countries [including the US] following outreach to sites in their respective region). The chosen options are capecitabine, paclitaxel, and nab-paclitaxel.

In addition, the decision to limit the investigator's choice comparator treatment to 3 options was taken to also limit the heterogeneity of the comparator arm without limiting effective treatment choices.

The rationale for the dose of each chemotherapy agent is provided below. All regimens proposed are based on standard practice and the National Comprehensive Cancer Network (NCCN) guidelines for HER2-negative recurrent or Stage IV breast cancer.

- **Paclitaxel:** Paclitaxel will be administered at a standard of care dose of 80 mg/m^2 every week as opposed to the United States Prescribing Information (USPI) labelled paclitaxel dose of 175 mg/m^2 q3w. In a meta-analysis of randomized, controlled studies in advanced breast cancer (5 studies, 1471 patients), which compared weekly administration of paclitaxel with q3w administration, the analysis concluded that there was an improvement in OS with weekly paclitaxel (pooled hazard ratio, 0.78; 95% CI: 0.67 to 0.89; p=0.001). Additionally, the incidence of neutropenia, neutropenic fever, peripheral neuropathy, and other SAEs was significantly lower with weekly paclitaxel compared with paclitaxel q3w (Mauri et al 2010). Based on this meta-analysis and to be aligned to standard practice among breast cancer clinicians, the weekly regimen of 80 mg/m^2 is proposed for this study.
- **Nab-paclitaxel:** The q3w labelled dose of nab-paclitaxel (260 mg/m^2), established from the Phase 3 study comparing paclitaxel with nab-paclitaxel (Gradishar et al 2005) is not generally used in current clinical practice. Instead, weekly administration of nab-paclitaxel at a dose of 100 mg/m^2 is the most commonly utilized schedule given the better tolerability and suggestions of increased efficacy of weekly dosing compared with q3w dosing. The superiority of the weekly regimen of nab-paclitaxel was first demonstrated in a randomized, Phase 2 study conducted in patients with previously untreated metastatic breast cancer (Gradishar et al 2009). In this study, the ORR and PFS by independent radiologist assessment were higher for the weekly regimens of nab-paclitaxel vs q3w administration. The differences in PFS and ORR between the 100 and 150 mg/m^2 weekly dose levels of nab-paclitaxel were not statistically significant, but patients receiving the higher dose experienced a greater incidence of Grade 3 or 4 neutropenia (44% vs 25%) and Grade 3 sensory neuropathy (14% vs 8%). Subsequent clinical studies have not clearly demonstrated that weekly doses of nab-paclitaxel greater than 100 mg/m^2 are more efficacious. Therefore, for this study AstraZeneca proposes that patients receive 100 mg/m^2 nab-paclitaxel on Days 1, 8, and 15 of each 28-day cycle.
- **Capecitabine:** The approved labelled dose of 1250 mg/m^2 twice daily on Days 1 to 14 followed by a 7-day rest period has demonstrated efficacy in ORR and PFS. However, 26% to 65% of patients had their dose reduced by at least 20% in these trials (Miller et al 2005, Pallis et al 2012). The main treatment-limiting toxicities at the labelled dosage were hand and foot syndrome (HFS) and diarrhea. Based on this experience, a number of Investigators have evaluated capecitabine at a lower starting dose (1000 mg/m^2 twice daily) and demonstrated similar efficacy to the approved dose and a more favorable safety profile with an incidence of dose reduction, ranging from 16% to 34% in Phase 2 studies (Baselga et al 2012, El-Helw and Coleman 2005). These results are further supported by a meta-analysis of data from 34 studies comprising of 4833 patients. The results showed a significantly lower incidence of dose reduction (15.9% vs 39.0%; p=0.007), high-grade HFS (12.0% vs 19.0%; p=0.01), diarrhea (5.3% vs 9.1%; p=0.01), and neutropenia (1.8% vs 7.3%; p<0.01) and all-grade neutropenia (5.8% vs 25.4%; p=0.01) for capecitabine

1000 mg/m^2 compared with 1250 mg/m^2 (Nishijima et al 2016). Therefore, for this study, AstraZeneca proposes that patients have the option, based on Investigator's choice, to receive either the 1250 mg/m^2 dose as indicated in the label or the 1000 mg/m^2 dose.

For information on dose modifications for paclitaxel, nab-paclitaxel and capecitabine, see Section 6.6.1 and the respective local prescribing information.

4.4 End of Study Definition

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

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

A patient is considered to have completed the study if they have completed all phases of the study, including the last scheduled procedure shown in the SoA.

Patients must be withdrawn from the study if the study itself is stopped. The study may be stopped if, in the judgement of AstraZeneca, study patients are placed at undue risk because of clinically significant findings. The study may be terminated at individual centers if the study procedures are not being performed according to ICH GCP or if recruitment rate does not allow to complete study in the planned timeframe.

5 STUDY POPULATION

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

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this

study in order to be randomized to a study treatment. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures; refer to Section 5.4.

In this protocol, enrolled patients are defined as those who sign informed consent including the pre-screening ICF. Randomized patients are defined as those who undergo randomization and receive a randomization number. For procedures for withdrawal of incorrectly randomized patients see Section 6.3.2.

The study population for this study will include pathologically documented advanced or metastatic HR+, HER2-low breast cancer patients whose disease has progressed on at least 2 lines of prior ET or within 6 months of first line ET + CDK4/6i in the metastatic setting. Patients must be ≥18 years of age, RECIST 1.1 evaluable, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and have not received chemotherapy for metastatic disease.

5.1 Inclusion Criteria

Patients must meet the following criteria at screening:

1 Male or female patients ≥ 18 years of age.

2 Pathologically documented breast cancer that:
   (a) Is advanced or metastatic
   (b) Has a history of HER2-low or negative expression, defined as IHC 2+/ISH- or IHC 1+ (ISH- or untested) or IHC 0 (ISH- or untested) with a validated assay
   (c) Has HER2-low expression or HER2 IHC >0 <1+ expression as determined by the central laboratory result from a metastatic setting (see inclusion criterion #3).
   (d) Was never previously reported as HER2-positive (IHC 3+ or ISH+) as per ASCO/CAP guidelines.
   (e) Is documented as HR+ (either ER and/or PgR positive [ER or PgR ≥1%]) per ASCO/CAP guidelines (Allison et al 2020) in the metastatic setting. If a patient has had multiple ER/PgR results after metastatic disease, the most recent test result will be used to confirm eligibility.

3 Must have an adequate tumor tissue sample available for assessment of HER2 by central laboratory and other exploratory biomarker analyses and is preferred in FFPE blocks based on a mandatory FFPE tumor sample obtained at the time of metastatic disease or later; the most recently collected pre-randomization tumor sample from the time of metastatic disease or later that meets the tissue requirements specified in Section 8.7.1 is required. If no archival specimens are available, a newly acquired biopsy specimen is acceptable. (see Section 8.7.1 and the laboratory manual for additional details).

4 ECOG performance status of 0 or 1

5 Radiologic or objective evidence of disease progression on or after the last systemic therapy prior to starting study treatment

6 Must have had either:

(a) Disease progression on endocrine therapy + CDK4/6 inhibitor within 6 months of starting first line treatment for metastatic disease and considered appropriate for chemotherapy as the next treatment by the investigator, OR

(b) Disease progression on at least 2 previous lines of ET with or without a targeted therapy (such as CDK4/6, mTOR or PI3-K inhibitors) administered for the treatment of metastatic disease.

Of note with regards to the ≥2 lines of previous ET requirement:

- Single agent anti-CDK4/6 therapy for the treatment of metastatic disease is considered a line of therapy
- Disease recurrence while on the first 24 months of adjuvant ET, will be considered a line of therapy; these patients will only require 1 line of ET in the metastatic setting
- Any progression after discontinuing or completing a course of adjuvant ET will not be considered a line of therapy
- Single agent PARP inhibitor therapy is not considered a line of ET
- Changes in dosing schedules, or discontinuations/re-starting of the same drugs or the addition of a targeted therapy to an ET without progression (e.g., adding a CDK4/6 to a current aromatase inhibitor regimen) will not be considered separate lines of therapy.

7 No prior chemotherapy for advanced or metastatic breast cancer. Patients who have received chemotherapy in the neo-adjuvant or adjuvant setting are eligible, as long as they have had a disease-free interval (defined as completion of systemic chemotherapy to diagnosis of advanced or metastatic disease) of >12 months.

8 Life expectancy ≥12 weeks at screening

9 At least 1 lesion, not previously irradiated, that can be measured accurately at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with CT or MRI which is suitable for accurate repeated measurements, or

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.

10 LVEF ≥ 50% within 28 days before randomization.

11 Adequate organ and bone marrow function within 14 days before randomization. For all parameters listed below, the most recent results available must be used to meet the inclusion criteria:

(a) Hemoglobin ≥ 9 g/dL **Note**: Patients requiring ongoing transfusions or growth factor support to maintain hemoglobin ≥ 9 g/dL are not eligible. (Red blood cell transfusion is not allowed within 1 week prior to screening assessment)

(b) Absolute neutrophil count ≥ 1500/mm^3. (granulocyte-colony stimulating factor [G-CSF] administration is not allowed within 1 week prior to screening assessment)

(c) Platelet count ≥ 100000/mm^3. (Platelet transfusion is not allowed within 1 week prior to screening assessment)

(d) Total bilirubin (TBL) ≤ 1.5 × upper limit of normal (ULN) if no liver metastases or < 3 × ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastasis at baseline.

(e) ALT and AST ≤ 3 ×ULN, < 5 ×ULN in patients with liver metastasis.

(f) Serum albumin ≥ 2.5 g/dL

(g) Creatinine clearance ≥ 30 mL/min (as calculated using the Cockcroft and Gault equation)

Cockcroft-Gault equation:

$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg/dL)}$$ *{× 0.85 for females}*

(h) International normalized ratio (INR) or prothrombin time (PT) and either partial thromboplastin or activated partial thromboplastin time (aPTT) ≤ 1.5 ×ULN

12 Adequate treatment washout period before randomization, defined as:

(a) Major surgery: ≥ 4 weeks

(b) Radiation therapy including palliative stereotactic radiation therapy to chest: ≥ 4 weeks (palliative stereotactic radiation therapy to other areas ≥ 2 weeks).

(c) Hormonal therapy: ≥ 3 weeks

(d) Immunotherapy (non-antibody based therapy): ≥ 3 weeks

(e) Small molecule targeted agents: ≥ 2 weeks or 5 half-lives, whichever is longer

(f) Antibody-based anti-cancer therapy: ≥ 4 weeks with the exception of receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors (e.g., denosumab for the treatment of complications resulting from bone metastases)

(g) Chloroquine/Hydroxychloroquine: ≥ 14 days

13 Evidence of post-menopausal status (Section 5.3) or negative serum pregnancy test for females of childbearing potential who are sexually active with a non-sterilized male partner. For women of childbearing potential, 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 (β-HCG) pregnancy test prior to each administration of study treatment.

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

14 Female patients of childbearing potential who are sexually active with a non-sterilized male partner must use at least one highly effective method of contraception (Table 8) from the time of screening and must agree to continue using such precautions for 7 months after the last dose of study treatment. Not all methods of contraception are highly effective. Female patients must refrain from egg cell donation and breastfeeding while on study treatment and for at least 7 months after the last dose of study treatment. Abstinence is acceptable only as true abstinence when this is in line with the preferred and usual lifestyle of the patient for the duration of the study treatment and the drug washout period (7 months). Periodic abstinence (e.g., calendar ovulation, symptothermal, post-ovulation methods), the rhythm method, and the withdrawal method are not acceptable methods of contraception.

15 Non-sterilized male patients who are sexually active with a female partner of childbearing potential must use a condom with spermicide from screening and throughout the duration of the study treatment and the washout period (4 months after the last dose of T-DXd, 6 months after the last dose of paclitaxel or nab-paclitaxel, and 3 months after the last dose of capecitabine). Abstinence is acceptable only as true abstinence when this is in line with the preferred and usual lifestyle of the patient for the duration of the study treatment and the drug washout period. Periodic abstinence (e.g., calendar ovulation, symptothermal, post-ovulation methods), the rhythm method, and the withdrawal method are not acceptable methods of contraception. It is strongly recommended for the female partners of a male patient also use at least one highly effective method of contraception throughout this period, as described Table 8. In addition, male patients should refrain from fathering a child or donating sperm throughout the duration of the study and the washout period (4 months after the last dose of T-DXd, 6 months after the last dose of paclitaxel or nab-paclitaxel, and 3 months after the last dose of capecitabine). Preservation of sperm should be considered prior to randomization in this study.

16 Female patients 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 last dose of study treatment. They should refrain from breastfeeding throughout this time. Preservation of ova may be considered prior to randomization in this study.

5.2 Exclusion Criteria

Patients must NOT meet the following criteria at screening:

1 Ineligible for all options in the investigator's choice chemotherapy arm. Patients with contraindications to capecitabine, paclitaxel, and nab-paclitaxel treatment, per local prescribing information, cannot be enrolled to the study.

2 Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, uncontrolled or significant cardiovascular disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.

3 Uncontrolled or significant cardiovascular disease includes any of the following:

   (a) Patients with a medical history of myocardial infarction within 6 months before randomization or symptomatic CHF (NYHA Class II to IV). Patients with troponin levels above ULN at screening (as defined by the manufacturer), and without any myocardial infarction related symptoms, should have a cardiologic consultation before randomization to rule out myocardial infarction.

   (b) Uncontrolled hypertension

   (c) Uncontrolled and/or clinically important cardiac arrhythmias

   (d) Corrected QT interval by Fredericia's method (QTcF) prolongation to >470 ms (females) or >450 ms (male) based on average of screening triplicate 12-lead electrocardiogram (ECG)

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

5 Patients with prior use of immunosuppressive medication within 14 days prior to first study dose, except for intranasal and inhaled corticosteroids or systemic corticosteroids at doses less than 10 mg/day of prednisone/prednisolone or equivalent.

6 Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disorder (i.e., pulmonary emboli within three months prior to study randomization, severe asthma, severe chronic obstructive pulmonary disorder [COPD], restrictive lung disease, significant pleural effusion etc.), and any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (i.e., rheumatoid arthritis, Sjogren's syndrome, sarcoidosis etc.), and/or prior pneumonectomy (complete).

7 Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals

8 Has spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids or

anticonvulsants to control associated symptoms. Subjects with clinically inactive brain metastases may be included in the study. Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and study randomization.

9 Active primary immunodeficiency, known human immunodeficiency virus (HIV) infection, or active hepatitis B or C infection. Patients positive for hepatitis C antibody are eligible only if polymerase chain reaction is negative for HCV RNA. Participants should be tested for HIV prior to randomization if required by local regulations or by the IRB/IEC.

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

11 Has 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 enrollment and managed with standard of care treatment) that the investigator deems related to previous anticancer therapy, such as:

- Chemotherapy-induced neuropathy
- Fatigue
- Residual toxicities from prior IO treatment: Grade 1 or Grade 2 endocrinopathies which may include:

(a) Hypothyroidism/hyperthyroidism

(b) Type 1 diabetes

(c) Hyperglycaemia

(d) Adrenal insufficiency

(e) Adrenalitis

(f) Skin hypopigmentation (vitiligo)

12 Pregnant or breastfeeding female patients, or patients who are planning to become pregnant.

13 Patients with a known hypersensitivity to either the drug substances, inactive ingredients in the drug product or to other monoclonal antibodies

14 History of another primary malignancy within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in situ disease, other solid tumors curatively treated, or contralateral breast cancer.

15 Previous treatment with anti-HER2 therapy

16 Prior treatment with antibody drug conjugate that comprised an exatecan derivative that is a topoisomerase I inhibitor

17 Prior randomization or treatment in a previous T-DXd study regardless of treatment assignment.

18 Participation in another clinical study with a study treatment administered in the last 30 days prior to first dose of study treatment or concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study. Of note, pre-screening for this study while a patient is on treatment in another clinical study is acceptable.

19 Has substance abuse or any other medical conditions such as psychological conditions, that may, in the opinion of the Investigator, interfere with the patient's participation in the clinical study or evaluation of the clinical study results.

5.3 Lifestyle Considerations

The safety-specific restrictions of T-DXd are listed below and also in Section 6.5.

- Patients must be instructed not to take any medications, including over-the-counter products, during the treatment period and 40 days (+7 days) after the last study treatment, without first consulting with the Investigator.
- Patients, if enrolled, should not receive 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 study treatment will be excluded.
- Females of childbearing potential (defined as those who are not surgically sterile [i.e., bilateral oophorectomy, or complete hysterectomy] or post-menopausal) who are sexually active with a non-sterilized male partner must use at least one highly effective method of contraception (Table 8) from the time of screening and must agree to continue using such precautions for 7 months after the last dose of study treatment; cessation of birth control after this point should be discussed with a responsible physician. Female patients must not donate, or retrieve for their own use, ova from the time of screening and throughout the study treatment period, and for at least 7 months after the final study drug administration. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause (treatment with anti-hormonal therapies is considered an alternative medical cause). The following age-specific requirements apply:
- Women <50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all hormonal replacement therapy and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.

- Women ≥50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all hormonal replacement therapy, or had radiation-induced menopause with last menses >1 year ago, or had chemotherapy-induced menopause with last menses >1 year ago

A highly effective method of contraception is defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly and are described in Table 8. Note that some contraception methods are not considered highly effective (e.g., male or female condom with or without spermicide; female cap, diaphragm or sponge with or without spermicide; non-copper containing intrauterine device; progesterone-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).

All patients should also follow the local prescribing information relating to contraception, the time limits for such precautions, and any additional restrictions for paclitaxel, capecitabine and nab-paclitaxel.

Table 8 Highly Effective Methods of Contraception(< 1% failure rate)

Barrier/intrauterine methods	Hormonal methods (female partners [of childbearing potential] 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) • Copper T intrauterine device • Progesterone T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena®) [a]	Injection: Medroxyprogesterone injection (e.g., Depo-Provera®) [b] Levonorgestrel-releasing intrauterine system (e.g., Mirena®) [b] Implants: Etonogestrel-releasing implants (e.g., Implanon® or Norplant®) Intravaginal Devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (e.g., NuvaRing®) Combined pill: Normal and low dose combined oral contraceptive pill Minipill: Progesterone-based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based pill Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (e.g., Ortho Evra®)

[a] Also considered a hormonal method
[b] Hormonal contraception associated with inhibition of ovulation.

- Male patients with a female partner of childbearing potential
  - Non-sterilized male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus

spermicide from the time of screening throughout the total duration of the study treatment and the washout period (4 months after the last dose of T-DXd, 6 months after the last dose of paclitaxel or nab-paclitaxel, and 3 months after the last dose of capecitabine). Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from fathering a child or donating sperm during the study treatment and during the washout period (4 months after the last dose of T-DXd, 6 months after the last dose of paclitaxel or nab-paclitaxel, and 3 months after the last dose of capecitabine) after the last dose of study treatment.

  - Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 8).

- Due to the possibility of paclitaxel, nab-paclitaxel, and capecitabine chemotherapy causing irreversible infertility/testicular damage, men are advised to seek counselling on sperm storage before starting treatment, and preservation of sperm should be considered prior to randomization in this study.

Restrictions relating to concomitant medications are described in Section 6.5.

5.4 Screen Failures

Screen failures are patients who do not fulfill the eligibility criteria for the study, and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as “eligibility criteria not fulfilled” (i.e., patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (i.e., not randomized patients). Patients may be rescreened a single time, but they may not be re-randomized to treatment. In addition, patients who are pre-screened may also be rescreened one single time, and may enter pre-screening on rescreen. Rescreened patients should be assigned the enrollment number as for the initial screening. Rescreening should be documented so that its effect on study results, if any, can be assessed.

Of note, patients who previously screen failed due to having the local HER2 test result not confirmed by central HER2 testing (inclusion criterion #2[c] of CSP version 3.0) can be rescreened once, as long as they have not been previously rescreened and they were not HER2 positive by central HER2 test. Patients who screen failed because of having a central HER2 test of HER2 IHC 0 cannot be rescreened unless a strong rationale can be provided to allow for HER2 retesting (e.g., patient received a subsequent line of therapy). In the event Investigators would like to rescreen patients who have screen failed due to having a central HER2 test result of HER2 IHC 0, the rationale must be documented and a discussion with the AstraZeneca Study Physician is required.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT)

publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, local HER2 testing results, details about sample sent for central HER2 testing and any SAE for screen failures including patients who are identified in the pre-screening phase as not eligible.

6 STUDY INTERVENTIONS (TREATMENTS)

Study intervention or study treatment is defined as any investigational intervention/treatment (including marketed product comparator and placebo) or medical device(s) intended to be administered to a patient according to the study protocol. Study treatment in this study refers to T-DXd and investigator's choice chemotherapy (paclitaxel, nab-paclitaxel and capecitabine).

6.1 Study Interventions (Treatments) Administered

6.1.1 Study Treatments

The study treatments to be administered in this study are shown in Table 9.

Table 9 Study Treatments

Study treatment name	Dosage Presentation	Unit Dose Strength	Dosage level	Route of administration	Packaging and labeling	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 100 mg vials. Each vial will be labelled in accordance with GMP Annex 13 and per country regulatory requirement [a]	Provided centrally by AstraZeneca
Paclitaxel	Vial	Variable	80 mg/m^2	IV	If centrally sourced [b], product will be provided in vials. Each vial will be labelled in accordance with GMP Annex 13 and per regulatory country requirements.	Sourced locally by site [b]
Capecitabine	Tablet	Capecitabine 500 mg film-coated tablets and Capecitabine 150 mg film-coated tablets	1000 or 1250 mg/m^2	Oral	If centrally sourced [b], product will be provided either in blister packs in carton, bottles or in a wallet. If applicable, the blister pack and carton, or bottle, will be labeled. If provided in a wallet, only the wallet will be labelled. All labels will be labelled in accordance with GMP Annex 13 and per country requirements.	Sourced locally by site [b]

Table 9 Study Treatments

Study treatment name	Dosage Presentation	Unit Dose Strength	Dosage level	Route of administration	Packaging and labeling	Sourcing
Nab-paclitaxel	Vial	Variable	100 mg/m^2	IV	If centrally sourced [b], product will be provided in vials. Each vial will be labelled in accordance with GMP Annex 13 and per regulatory country requirements.	Sourced locally by site [b]

GMP = good manufacturing practice; IV = intravenous

[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.

[b] Under certain circumstances when local sourcing is not feasible, paclitaxel/nab-paclitaxel/capecitabine may be supplied centrally through AstraZeneca

6.1.2 T-DXd

T-DXd will be supplied by AstraZeneca as a 100 mg lyophilized powder for infusion after reconstitution and dilution. The reconstituted 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 5.0 mL.

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

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

6.2 Preparation/Handling/Storage/Accountability of Study Treatments

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use of the study treatments.
- Only patients randomized in the study will receive study treatment and only authorized site staff will supply or administer study treatment. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study treatments are provided in the Pharmacy Manual.

The study treatments provided for this study will be used only as directed in this protocol and the Pharmacy Manual. The study site staff will account for all study treatments dispensed to and returned from the patient. The study site staff will account for all study treatments received at the site, unused study treatments and for appropriate destruction of all unused study treatments. Certificates of delivery and destruction should be signed and filed in the study documentation.

6.2.1 T-DXd (DS-8201a)

T-DXd will be administered at room temperature by controlled infusion into a peripheral or central vein. 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 minimum infusion time for subsequent cycles is 30 minutes. However, if there are interruptions during the infusion, the total time should not exceed 3 hours at room temperature.

Patients will receive a dose of 5.4 mg/kg q3w. The number of treatment cycles with T-DXd is not fixed. Upon commencing study treatment, patients will continue receiving T-DXd until RECIST 1.1 disease progression, withdrawal of consent or any of the discontinuation criteria are met.

The patient's weight at screening will be used to calculate the initial dose. If, during the course of treatment, the patient's weight has changed by ≥ ± 10%, the patient's dose will be recalculated based on the patient's updated weight. However, sites can modify the dosage if the weight changes after screening and if the site's local practice is more conservative than the 10% threshold for dose adjustment (e.g., dose adjustment if 5% variance in the patient's weight).

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

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. If either preparation time or infusion time exceeds the time limit a new dose must be prepared from new vials. T-DXd does not contain preservatives, and any unused portion must be discarded.

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

6.2.2 Paclitaxel, Capecitabine and Nab-paclitaxel

Patients will receive the investigator's choice chemotherapy in doses specified in Table 9. Refer to the local label for details on handling. The investigator's choice of chemotherapy should be predefined, prior to randomization. The investigator's choice chemotherapies, paclitaxel, capecitabine and nab-paclitaxel, will either be locally sourced or centrally supplied by AstraZeneca and will be administered according to local prescribing information or treatment guidance in general use by the investigation site or drug label for centrally sourced medications. The number of treatment cycles for the investigator's choice chemotherapy is not fixed.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Patient Enrollment and Randomization

All patients will be randomly assigned to an arm using IRT. Before the study is initiated, the login information and directions for the IRT will be provided to each site.

If a patient withdraws from the study, then his/her randomization code cannot be reused. Withdrawn patients will not be replaced.

Investigators should keep a record of patients (i.e., the patient screening log) who entered screening and/or pre-screening.

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

- Obtain signed informed consent before any study-specific procedures are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of randomization. For patients with a single target lesion (TL), if screening biopsy is collected prior to screening imaging for baseline tumor assessment, allow approximately 2 weeks before imaging scans are acquired. An optional pre-screen ICF may 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 (e.g., medical history, availability of required number of slides for study). Patients who signed the pre-screening ICF will be considered enrolled.
- Obtain a unique 7-digit enrollment number (E-code) at pre-screening or screening, through IRT in the following format: ECCNNXXX (CC being the country code, NN being the center number, and XXX being the patient enrollment code at the center). This number is the patient's unique identifier and is used to identify the patient on the electronic case report forms (eCRFs).
- Obtain tumor sample and send for centralized HER2 testing. A mandatory FFPE tumor sample obtained at the time of metastatic disease or later must be provided; the most recently collected pre-randomization tumor sample from the time of metastatic disease or later that meets the tissue requirements specified in Section 8.7.1 is required. If no archival specimens are available, a newly acquired biopsy specimen is acceptable. Obtaining the tumor sample should be given very high priority and as such, an optional pre-screen ICF may be signed for patients to permit for sample collection and testing prior to the 28-day screening window in order to permit for analysis in a timely manner.

Screening procedures may be carried out while HER2 status is being tested, however it is recommended that the main ICF and other study procedures not be started until the sample submitted for HER2 testing is accepted for central laboratory testing. 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 patient eligibility (see Sections 5.1 and 5.2).
- Obtain signed informed consent for genetic research study (optional).

If the patient is ineligible and not randomized, such a patient should be recorded by site personnel in the IRT system as "screen-failure" and the IRT should be contacted to terminate the patient in the system.

The day patients receive the first dose of study treatment is Cycle 1 Day 1. Every effort should be made to minimize the time between randomization and dosing. Dosing should occur no more than 3 days after randomization. If it is anticipated that dosing cannot occur within 3 days, a discussion with the AstraZeneca Study Physician is required. Patients must not be randomized and must not receive study treatment unless all eligibility criteria have been met.

6.3.2 Procedures for Handling Incorrectly Randomized Patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be randomized or receive study medication. There can be no exceptions to this rule. Patients who are enrolled but subsequently found not to meet all the eligibility criteria must not be randomized to treatment, and they must be withdrawn from the study.

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

6.3.3 Methods for Assigning Treatment Groups (Randomization)

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

Randomization codes will be assigned strictly sequentially, within each stratum (refer to the 3

stratification factors in Section 4.1), as patients become eligible for randomization. When medication is provided centrally by AstraZeneca, the IRT will allocate kit identification numbers at each treatment visit. If medication is provided locally, IRT will not provide kit numbers.

6.3.4 Methods for Ensuring Blinding

This is an open-label study for the personnel at study sites; however, the trial will be conducted as "sponsor-blind" and the specific treatment to be taken by a patient will be assigned using an IRT (see Section 6.3.3 for details). To maintain the integrity of the study, AstraZeneca personnel directly involved in the study conduct will not undertake or have access to efficacy data aggregated by treatment arm prior to final data readout for the primary endpoint. Before the first patient is randomized, a Trial Integrity Document will be generated in which data access levels for relevant AstraZeneca personnel will be pre-specified.

6.4 Study Treatment Compliance

When patients are dosed at the site, they will receive study treatment directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study treatment and study patient identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study treatment start and stop dates, including any changes from the dosing schedule, dose interruptions, dose reductions, and dose discontinuations should be recorded in the eCRF. The reason should also be documented. The Investigator or pharmacist must retain records of all study treatments administered at the site. The Study Monitor will check these records to confirm compliance with the protocol administration schedule.

Capecitabine is the only oral intervention in this study and will be self-administered by the patients at home. Patients will be instructed to bring capecitabine dosing diaries and all blister packs, bottles, or wallets of capecitabine (empty, partially empty, or full) to the clinic for each study visit. For each cycle, participants should return all unused tablets during the dispensation visit of the subsequent cycle, at which point a new set of tablets will be dispensed to the participants. In this case, the compliance will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned tablets during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF. Accountability records should be maintained by the site staff and should be current and up to date. In case of low compliance, participants should be retrained by the site staff, and the retraining should be documented.

6.5 Concomitant Therapy

The Investigator must be informed as soon as possible about any medication taken from the

time of screening (signing main ICF) until the end of the clinical treatment phase of the study including the 40-day (+7 days) follow-up period following the last dose of study treatment.

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrollment or receives during the study must be recorded along with the following:

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

Patients must be instructed not to take any medications, including over-the-counter products, without first consulting with the Investigator. Concomitant use of dietary supplements, medications not prescribed by the Investigator, and alternative/complementary treatments is discouraged, but not prohibited.

Restricted, prohibited, and permitted concomitant medications are described in the following tables (Table 10 and Table 11) and apply to all treatment arms. Refer also to the dosing modification (Section 6.6) and TMGs (see Appendix H). Refer to the local prescribing information for capecitabine, paclitaxel and nab-paclitaxel, with regards to warnings, precautions, contraindications and prohibited medications during treatment.

Table 10 Prohibited Concomitant Medications

Prohibited medication/class of drug	Usage
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAbs against HER2 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment

Table 10 Prohibited Concomitant Medications

Prohibited medication/class of drug	Usage
Any concurrent chemotherapy, targeted therapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	• Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable). • For T-DXd treatment, palliative radiotherapy to the chest area is prohibited. • For both treatment arms, palliative radiotherapy (outside of palliative radiotherapy to the chest area) is permitted after consultation with the Study Physician. The lesions must be known to be present at the time of study entry and the Investigator clearly documents that the need for palliative radiotherapy is not indicative of disease progression. For patients with bone involvement, it is suggested to institute palliative radiotherapy before study initiation if possible and clinically appropriate (e.g., lesions at risk for spontaneous micro-fractures or painful lesions).
Live attenuated vaccines	Should not be given during the study and up to 30 days after the last dose of study treatment.
Immunosuppressive medications	T-DXd cannot be administered when the patient is taking immunosuppressive medications, including corticosteroids with the exception of: • Short-term courses (< 2 weeks) • Low to moderate dose (less than 10 mg/day of prednisone/prednisolone or equivalent) • Long-term, alternate-day treatment with short-acting preparations; maintenance physiologic doses (replacement therapy) • Administered topically (skin or eyes), by aerosol, or by intra-articular, bursal, or tendon injection. Treatment with corticosteroids to prevent or treat hypersensitivity reactions to radiographic contrast agents is allowed. Corticosteroids used as premedication for the prevention of nausea and vomiting is allowed. A temporary period of steroid treatment will be allowed for different indications after discussion with the Study Physician (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.). Patients with bronchopulmonary disorders who require intermittent use of bronchodilators (such as albuterol) will not be excluded from this study. Use of immunosuppressive medications for the management of treatment-related AEs or in patients with contrast allergies is acceptable.

Table 10 Prohibited Concomitant Medications

Prohibited medication/class of drug	Usage
	Immunosuppressive medications also include drugs like methotrexate, azathioprine, and tumor necrosis factor-alpha blockers.
Chloroquine/hydroxychloroquine	Concomitant treatment with chloroquine or hydroxychloroquine is not allowed during the study treatment.

AE = adverse event; HER2 = human epidermal growth factor receptor 2; mAb = monoclonal antibody

Table 11 Supportive Medications

Supportive medication/class of drug	Usage
Anti-emetic agents including 5-hydroxytryptamine receptor (5-HT3) antagonists, Neurokinin-1 (NK1) receptor antagonists and steroids (e.g., dexamethasone)	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 two or three medicinal products (e.g., 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.
Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc.])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted
Coumadin anticoagulants	Permitted
Hematopoietic growth factors	Hematopoietic growth factors may be used for prophylaxis or treatment based on the clinical judgment of the Investigator

6.5.1 Other Concomitant Medications

Other medications other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

6.5.2 Restrictions on Concomitant Medications/Therapies

Patients with prior use of immunosuppressive medication within 14 days prior to first study dose, except for intranasal and inhaled corticosteroids or systemic corticosteroids at doses less than 10 mg/day of prednisone/prednisolone 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, anti-cancer IP 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. Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. 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.

6.6 Dose Modification

6.6.1 Individual Patient Dose Modifications

6.6.1.1 T-DXd

The following dose modifications apply to toxicities that are attributable to T-DXd:

- Dose delays are permitted for T-DXd therapy. In instances for delays in dosing, the dosing interval for the next T-DXd cycle may be shortened as clinically feasible to gradually align with the schedule of tumor efficacy assessment. Two consecutive doses must be administered at least 19 days apart.
- Every effort should be made to limit T-DXd delay, however in circumstances of AE management or medical intervention, T-DXd can be held up to 18 weeks (126 days) from the last T-DXd dose. During this time scheduled CT/MRI scans should continue as per protocol, and patients should fulfil all of the following criteria:
  - T-DXd 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 scan must be done within 6 weeks prior to restarting the study drug.
  - T-DXd is restarted within the guidance of the TMGs for T-DXd.
  - No prohibited concomitant medications have been administered since the last dose of T-DXd.
- For management of dose delays due to T-DXd-related events, the TMGs (Appendix H) should be followed, as applicable.

In summary, if a patient experiences a clinically significant and/or unacceptable toxicity, dosing will be interrupted (or discontinued) or supportive therapy administered as required.

Dose Modification for ILD/Pneumonitis Cases

- ILD/pneumonitis Grade 1: If ILD/pneumonitis resolves before 28 days from day of event onset, T-DXd may be resumed at the same dose. If ILD/pneumonitis resolves after 28 days, T-DXd will be resumed at a lower dose as instructed in Table 16.
- ILD/pneumonitis Grade 2 and higher: Permanently discontinue T-DXd. Follow-up assessments should be completed as described in the SoA (Section 1.3).

See Section 8.2.10.1 for tests required if ILD/pneumonitis is suspected.

Any Grade 4 hematological toxicity with significant clinical symptoms that do not resolve with treatment within 4 weeks: resuming T-DXd will be possible if the toxicity resolves, and in consultation with the AstraZeneca Study Physician.

Dose Modification Criteria for Suspected or Confirmed COVID-19

Please see Appendix I for dose modification and management plan for patients with confirmed or suspected COVID-19 who are being treated with T-DXd.

6.6.1.2 Investigator's Choice Chemotherapy

Investigators should follow the local prescribing information and standard clinical practice regarding management of paclitaxel, nab-paclitaxel and capecitabine-related toxicities. The investigator's choice chemotherapy treatment can be interrupted for up to 28 days from the planned date of administration. If a patient requires a dose delay longer than 28 days, resumption of treatment should be discussed with the AstraZeneca Study Physician. The investigator's choice of chemotherapy should be predefined, prior to randomization.

Prophylactic therapy, supportive care prior to and after chemotherapy treatment should be given as needed on a prophylactic and treatment basis in compliance with institutional standards. Hematopoietic growth factors may be used for prophylaxis or treatment based on the clinical judgment of the Investigator in compliance with the standards of the center (see also Table 11).

6.7 Intervention after the End of the Study

No intervention is planned after the end of the study. After the final analysis, AstraZeneca will continue to supply open-label drug to patients receiving T-DXd and to patients receiving centrally supplied capecitabine, paclitaxel, and nab-paclitaxel up to the time that they discontinue the treatment for whatever reason.

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, patients currently receiving 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 patient who would be proposed to move to such a study would be asked to sign a new ICF.

7 DISCONTINUATION OF STUDY TREATMENT AND PATIENT DISCONTINUATION/WITHDRAWAL

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

7.1.1 Permanent Discontinuation of Study Treatment

Patients may be discontinued from study treatment in the following situations. Note that discontinuation from study treatment is NOT the same as a complete withdrawal from the study. Patients who permanently discontinue study treatment will continue to have follow-up assessments per the protocol. Patients will be permanently discontinued from the treatment if the following criteria are met:

- Withdrawal of consent by patient. The patient is, at any time, free to discontinue treatment, without prejudice to further treatment. A patient who discontinues study treatment is normally expected to continue to participate in the study (e.g., for safety and survival follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 1.3).
- Occurrence of any AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing
- Occurrence of any AE that meets the criteria for permanent discontinuation as defined in TMGs for T-DXd (Appendix H) or as defined in the local prescribing information for paclitaxel, nab-paclitaxel and capecitabine
- Pregnancy or intent to become pregnant
- Severe non-compliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from study treatment (e.g., refusal to adhere to scheduled visits)
- When a patient does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca Study Physician immediately, and a discussion should occur between the AstraZeneca Study Physician and the Investigator regarding whether to continue or discontinue the patient from treatment. (Section 6.3.2). The AstraZeneca Study Physician must ensure all decisions are appropriately documented. The Investigator should make documentation in the medical record as appropriate.
- Initiation of alternative anticancer therapy including another investigational agent
- Objective progressive disease, as determined by the investigator per criteria set forth in RECIST 1.1 (refer to Appendix G)

- Death
- Study terminated by AstraZeneca
- Lost to follow-up

All patients who are discontinued from study treatment should complete protocol-specified procedures for discontinuation of study treatment (details in Section 7.1.2) and follow-up procedures (details in Section 1.3). Discontinued patients will be followed for survival, either through direct contacts or by collecting public records (e.g., death certificates) as allowed by local laws.

The EOT visit should be performed as soon as the patient is permanently discontinued from study treatment (Table 4). The reason for discontinuation should be documented in the source document and the appropriate section of the eCRF.

7.1.2 Procedures for Discontinuation of Study Treatment

Discontinuation of study treatment does not impact the patient's participation in the study. A patient who decides to discontinue the study treatment will always be asked about the reason(s) for discontinuation and the presence of any AE. The patient should continue attending subsequent study visits, and data collection should continue according to the study protocol. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This follow-up could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Patients who are permanently discontinued from further receipt of study treatment, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued will enter follow-up (for details, see Section 1.3). Patients who have permanently discontinued from further receipt of study treatment will need to be recorded in the IRT.

Patients who permanently discontinue study treatment for reasons other than objective RECIST 1.1 disease progression, withdrawal of consent, closure of study or death (regardless of whether subsequent anticancer therapy was started) should continue to have RECIST 1.1 scans performed q6w ±1week for the first 48 weeks from randomization, and then q9w ±1week (starting at Week 48) thereafter until RECIST 1.1 disease progression by investigator assessment. Following investigator-determined RECIST 1.1 progression, it ismandatory to perform an additional imaging assessment (preferably within 4 to 6 weeks after investigator PD) for central review to support the primary endpoint of PFS by BICR. In addition, every attempt should be made to continue to collect and submit subsequent scans

(completed per standard practice / as clinically indicated) for central review until the primary PFS analysis DCO, or until the Sponsor notifies the site to discontinue (whichever is earlier) regardless of whether the subject has started another anti-cancer therapy. Scans following investigator determined RECIST 1.1 progression should include brain scans for patients who are enrolled with baseline stable brain metastases or if clinically indicated.

All patients will be followed for survival until the end of the study. Survival information may be obtained via telephone contact with the patient, patient's family, or by contact with the patient's current physician. Patients who decline to return to the site for evaluations should be contacted by telephone, following the timing and procedures indicated in the SoAs (see Section 1.3), as an alternative.

7.2 Patient Withdrawal from the Study

- A patient 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.
- A patient who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (e.g., telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an EOT visit should be conducted, as shown in the SoA (Table 5) and for data to be collected at the time of study withdrawal and follow-up (Table 5) and for any further evaluations that need to be completed.
  - The patient will discontinue the study treatment and be withdrawn from the study at that time.
- If the patient withdraws consent for disclosure of future information, AstraZeneca may retain and continue to use any data collected before such a withdrawal of consent.
- If a patient withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow up

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed (see Section 4.4) and there is insufficient information to determine the patient's vital status at that time. The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Efforts to reach the patient should continue until the end of the study. Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study. Site personnel, or an independent third party, will attempt to collect the vital status of the patient within legal and ethical boundaries for all patients randomized, including those who did not get study treatment. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the patient will not be considered lost to follow-up. AstraZeneca 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.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoAs (see Section 1.3)
- The Investigator will ensure that data are recorded on the eCRFs. The RAVE Web Based Data Capture system will be used for data collection and query handling.
- The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.
- Immediate safety concerns should be discussed with AstraZeneca immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoAs (see Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (e.g., blood count and imaging assessments) 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.

- Data management will be performed by AstraZeneca or a delegate according to the Data Management Plan.
- Aes and medical/surgical history will be classified according to the terminology of the latest version of MedDRA. Medications will be classified according to the World Health Organization (WHO) Drug. Classification coding will be performed by AstraZeneca or a delegate. The data collected through third party sources will be obtained and reconciled against study data.
- Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail. The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.
- When all data have been coded, validated, signed, and locked, a clean file will be declared.
- SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

8.1 Efficacy Assessments

8.1.1 RECIST 1.1 Assessments

RECIST 1.1 tumor assessments will be performed using CT or MRI scans of the chest, abdomen and pelvis at screening (as baseline) with follow-ups at q6w ± 1 week from the date of randomization for 48 weeks, and then q9w ± 1 week, starting at Week 48, until objective RECIST 1.1 disease progression by investigator assessment (see SoAs in Section 1.3). Patients who permanently discontinue study treatment for reasons other than objective RECIST 1.1 disease progression, withdrawal of consent, closure of study or death (regardless of whether subsequent anticancer therapy was started) should continue to have RECIST 1.1 scans performed as per schedule until RECIST 1.1 disease progression. Following investigator-determined RECIST 1.1 progression, it is mandatory to perform an additional imaging assessment (preferably within 4 to 6 weeks after investigator PD) for central review to support the primary endpoint of PFS by BICR. In addition, every attempt should be made to continue to collect and submit subsequent scans (completed per standard practice / as clinically indicated) for central review until the primary PFS analysis DCO, or until the Sponsor notifies the site to discontinue (whichever is earlier) regardless of whether the subject has started another anti-cancer therapy.

For patients with bone-only disease that is non-measurable, RECIST 1.1 tumor assessments

may be performed using X-ray in addition to the required CT or MRI scans of the chest, abdomen and pelvis.

In addition, an IV contrast-enhanced MRI (preferred) or IV contrast-enhanced CT of the brain is to be included for all patients at screening/baseline. Regularly scheduled follow-up brain scans (q6w ±1 week from the date of randomization for 48 weeks, and then q9w ±1 week, starting at Week 48 and continuing until RECIST 1.1 disease progression per investigator assessment) are mandatory for all patients who were enrolled with baseline stable brain metastases, while patients without brain metastases do not need additional brain scans for subsequent tumor assessments, unless clinically indicated. Following investigator determined RECIST 1.1 progression, subsequent imaging assessments as described above should include brain scans for patients who are enrolled with baseline stable brain metastases or if clinically indicated.

The on-study imaging schedule MUST be followed regardless of any delays in dosing. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. If an unscheduled assessment was performed (e.g., to investigate clinical signs/symptoms of progression) and the patient has not progressed, every attempt should be made to perform the subsequent imaging at their next regularly scheduled visit. A bone scan (scintigraphy) will be performed for all patients at baseline and subsequent scans will be performed as clinically indicated. During study treatment, response assessment scans must be reviewed for evidence of disease progression and ILD/pneumonitis prior to administration of the next scheduled dose of study treatment.

Guidelines on valid imaging modalities, image acquisition, and tumor evaluation using RECIST 1.1 are provided in Appendix G.

8.1.1.1 Central Reading of Scans

All images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed iCRO for quality control (QC), storage, and for BICR. Guidelines for image acquisition, de-identification, storage of digital copies at the investigative site as source documents, and electronic transfer to the iCRO will be provided in a separate document. A BICR of images will be performed at the discretion of AstraZeneca. Results of these independent reviews will not be communicated to Investigators, and results of Investigator RECIST 1.1 assessments will not be shared with the central reviewers. The management of patients will be based upon the results of the RECIST 1.1 assessment conducted by the Investigator. Further details of the BICR will be documented in the Independent Review Charter (IRC).

8.1.2 Overall Survival (OS)

Assessments for survival must be made every 3 months (±14 days) from the date of 40-day

(+7 days) follow-up visit, until death, withdrawal of consent, or study closure, whichever occurs first. Survival information may be obtained via telephone contact with the patient or the patient's family, or by contact with the patient's current physician. The details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected.

In addition, patients on treatment or in survival follow-up will be contacted following the DCO for the final PFS analysis and all subsequent survival analyses to provide complete survival data. These contacts should generally occur within 7 days of the DCO.

8.1.3 PFS2

PFS2 is defined as time from randomization 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 Investigator according to RECIST 1.1 assessment, patients will continue to be followed at the 40-day (+7 days) follow-up visit, and every 3 months (± 14 days) thereafter for documentation of progression on subsequent anticancer therapy.

8.1.4 Patient-Reported Outcome (PRO) Measures

PRO measures will be used to examine the impact of treatment on symptoms, functioning, HRQoL and overall health status, patient-perceived treatment tolerability, and benefit/risk from the patients' perspective. PROs have become increasingly important in evaluating the efficacy and tolerability of study treatments in clinical studies as part of the overall benefit/risk evaluation (Kluetz et al 2018). The PROs included in this study are as follows and will be administered in this order:

- EORTC QLQ-C30
- EORTC QLQ-BR45
- EQ-5D-5L
- Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)
- Patient Global Impression–Severity (PGIS)
- Patient Global Impression–Change (PGIC)
- Patient Global Impression–Treatment Tolerability (PGI-TT)
- Patient Global Impression – Benefit/Risk (PGI-BR)

The PROs will be assessed in accordance with the SoA (see Section 1.3). The individual questionnaires are provided in Appendix J.

8.1.4.1 EORTC QLQ-C30

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group to assess HRQoL, functioning, and symptoms in cancer clinical trials (see Appendix J). It has undergone extensive testing and validation as well as detailed cross-cultural testing and validation (Aaronson et al 1993). It is a 30-item self-administered questionnaire for all cancer types. Questions are grouped into 5 multi-item functional scales (physical, role, emotional, cognitive, and social), 3 multi-item symptom scales (fatigue, pain, and nausea/vomiting), a 2-item global QoL scale, 5 single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, and diarrhea), and 1 item on the financial impact of the disease. All but 2 questions have 4-point scales: "Not at All," "A Little," "Quite a Bit," and "Very Much." The 2 questions concerning global health status and QoL have 7-point scales with responses ranging from "Very poor" to "Excellent." For each of the 15 domains, final scores are transformed such that they range from 0 to 100, where higher scores indicate better functioning, better HRQoL, or greater level of symptoms (Aaronson et al 1993).

8.1.4.2 EORTC QLQ-BR45

The EORTC QLQ-BR45 is an updated version of the BR23, a validated breast cancer-specific module used in conjunction with the core QLQ-C30 to assess breast cancer-specific HRQoL (Bjelic-Radisic et al 2020, Sprangers et al 1996) (see Appendix J). New breast cancer treatments and diagnostics prompted the update of the QLQ-BR23 to include an additional 22 items. The self-administered instrument includes the original 23-items yielding 5 multi-item scores (body image, sexual functioning, arm symptoms, breast symptoms, and systemic therapy side effects). The additional 22 items yield four additional multi-item scales (breast satisfaction, endocrine therapy symptoms, skin mucosis symptoms, and endocrine sexual symptoms). In addition, single items assess sexual enjoyment, future perspective and being upset by hair loss. Items are scored on a 4-point verbal rating scale: "Not at All," "A Little," "Quite a Bit," and "Very Much." Scores are transformed to a 0 to 100 scale, where higher scores for functioning scales or items indicate better functioning, whereas higher scores for symptom scales or items represent a higher level of symptoms. The free text item in the EORTC QLQ-BR45 instrument is not included in the study, as the utility of this information and the analysis method have not been established.

8.1.4.3 EQ-5D-5L

The EQ-5D-5L will be used to explore the impact of treatment and disease state on health state utility. The EQ-5D-5L, developed by the EuroQol Group, is a generic questionnaire that provides a simple descriptive profile of health and a single index value for health status for economic appraisal (van Reenen et al 2014) (see Appendix J). The questionnaire comprises six questions that cover five dimensions of health (mobility, self-care, usual activities,

pain/discomfort and anxiety/depression). Respondents also assess their health today using the EQ-VAS (visual analogue scale), which ranges from 0 (worst imaginable health) to 100 (best imaginable health).

8.1.4.4 PGIS

The PGIS item is included to assess how a patient perceives the overall severity of cancer symptoms over the past week. This is a single-item questionnaire (Appendix J), and patients will choose the response that best describes the severity of their overall cancer symptoms with options ranging from "No Symptoms" to "Very Severe."

8.1.4.5 PGIC

The PGIC item is included to assess how a patient perceives their overall change in health status since the start of study treatment. This is a single-item questionnaire (Appendix J), and patients will choose from response options ranging from "Much Better" to "Much Worse."

8.1.4.6 PGI-TT

The PGI-TT item is included to assess how a patient perceives the overall tolerability of the study treatment. This is a single-item questionnaire (Appendix J), and patients will rate the bother associated with any treatment-related symptoms using response options ranging from "Not at all" to "Very much."

8.1.4.7 PGI-BR

The PGI-BR is a 5-item questionnaire assessing the patient's perception of the overall benefits and risks of treatment (Appendix J). The 5 items assess: overall trial experience, efficacy, side effects, convenience and overall assessment of the benefits and harms of treatment. Items are rated on 5- or 6-point verbal rating or Likert-type scales.

8.1.4.8 PRO-CTCAE

The PRO-CTCAE, developed by the NCI is included to address tolerability from the patients' perspective (Appendix J). The PRO-CTCAE will only be administered in those countries where a linguistically validated version is available. All applicable translations available during the study will be used. PRO-CTCAE is an item library of symptoms experienced by patients while undergoing treatment of their cancer. The items pre-selected for this study are based on a review of the treatment-related symptoms of T-DXd, capecitabine, paclitaxel and nab-paclitaxel and in consideration of symptoms that are already captured in the other PRO instruments with a view to minimize burden. The free text item in the PRO-CTCAE instrument is not included in the study, as the utility of this information and the analysis method have not been established.

8.1.4.9 Administration of Patient-Reported Outcome Measures

The PRO measures will be self-administered by patients using a handheld electronic device in accordance with the SoA (see Section 1.3). In case of handheld device failure, patients may complete the PRO measures using a web-based version or an appropriate back-up option may be considered with prior approval from AstraZeneca. PROs will be provided in the language of the country in which it will be administered. However, the PRO-CTCAE will only be administered in the languages where a linguistically validated version is already available.

Patients will complete PRO assessments at home or at the study sites if the assessment timepoint coincides with a scheduled site visit. Similarly, during the follow-up period, patients will complete PROs at home or at the study site if a scheduled visit coincides with the timepoint. If patients have had scans or other tests at an outside facility or missed a scheduled data collection site visit, PRO questionnaires should still be completed by patients at home according to the PRO completion schedule.

While PROs may be completed at home or site visits, patients should always bring the handheld electronic device to all site visits. It will take approximately 20 to 30 minutes for patients to complete the questionnaires.

The following instructions should be followed when collecting PRO data via an electronic device:

- The research nurse or appointed site staff must explain to patients the value and relevance of study participation and inform them that these questions are being asked to find out, directly from them, how they feel. The research nurse or appointed site staff should also stress that the information is not routinely shared with study staff. Therefore, if patients have any medical problems, they should discuss them with the doctor or research nurse separately from the PRO assessment.
- The research nurse or appointed site staff must train the patient on how to use the PRO device, using the materials and training provided by the PRO vendor, and provide guidance on whom to call if there are problems with the device if the patient is completing the PRO at home.
- It is vital that the PRO reporting is initiated at the baseline visit (Cycle 1, Day 1), as specified in the SoA (Section 1.3) to capture the effect of study treatment. The handheld 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.
- All questionnaires must be completed using an electronic device; paper questionnaires are not allowed in this study. It is therefore very important to set up the device in advance of the patient's first treatment visit, ideally at least the day before, to ensure the device is functioning properly and to identify and address any technical issues prior to the visit.

- Study sites must ensure that patients complete baseline questionnaires before revealing the treatment arm allocated to the patient.
- PRO questionnaires completed at site visits must be completed before treatment administration and ideally before any discussions of health status to avoid biasing the patient'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.
- For PROs collected at site visits, PRO questionnaires must be completed by the patient in a quiet and private location and the patient given enough time to complete the PRO questionnaires at their own speed.
- The research nurse or appointed site staff must remind patients that there are no right or wrong answers and avoid introducing bias by not interpreting or clarifying items.
- The patient should not receive help from relatives, friends, or clinic staff to answer the PRO questionnaires. If a patient uses visual aids (e.g., glasses or contact lenses) for reading and does not have them when he or she visits the site, the patient will be exempted from completing the PROs at the visit.
- Site staff must not read the PRO questionnaires on behalf of the patient. If the patient is unable to read the questionnaire (e.g., is blind, illiterate or not fluent in the available language), that patient should be 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 available language, the AstraZeneca study team must be contacted to determine if they can be exempted. Patients exempted in this regard should be flagged appropriately by the site staff in the source documents and the Review of PRO/Questionnaire/Diary eCRF.
- Site staff must administer questionnaires available in the language that the patient speaks and understands. Questions should not be read in an available language and translated into another language for the patient.
- 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 patient could not complete assessments in the eCRF. The research nurse or appointed site staff must monitor compliance since minimizing missing data is a key aspect of study success. Compliance must be checked at each study visit and should be checked more frequently to identify problems early. If the site receives an email notification regarding the patient's compliance, a check-in call from the study site to ask the patient if they have any difficulties is highly recommended. A solution to enhance/resolve compliance should be discussed with the patient. 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 Informed Consent

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. All patients will be required to provide consent to supply a sample of their tumor for entry into this study. This consent is included in the main patient ICF.

An optional pre-screen ICF may be signed for 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 a candidate for this study based on available information (e.g., medical history, availability of required number of slides for study). The collection of additional biopsies upon progression is strongly encouraged. 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 patient. However, all results from the screening assessments must have been obtained within 28 days of randomization

Optional genetic sample will not be collected in China.

8.2.2 Physical Examinations

Physical examinations will be performed according to the assessment schedules (see Section 1.3). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, gastrointestinal, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Situations in which physical examination results should be reported as AEs are described in Section 8.3.5.

8.2.3 Vital Signs

Vital signs (blood pressure [BP], pulse rate, temperature, and respiration rate) will be evaluated according to the SoAs (see Section 1.3). Body weight is recorded at Day 1 of each Cycle, at EOT and at the 40-day (+7 days) follow-up visit.

Vital signs will be evaluated and recorded in eCRF at baseline, before infusion, end of infusion on Day 1 and before infusion on Day 8 and Day 15 of the first cycle; they will be collected before infusion and end of infusion on Day 1 of Cycles 2 and 3; starting from Cycle 4, they will be evaluated only before infusion on Day 1 of each cycle until the end of treatment. Vital signs will be evaluated at the 40-day (+7 days) follow-up visit as well.

Standard infusion time for T-DXd is over 90 minutes for first infusion and over 30 minutes thereafter if the first infusion was well tolerated; however, if there are interruptions during infusion, the total allowed infusion time should not exceed 3 hours at room temperature. Based on a 90-minute infusion period, BP and pulse rate will be collected before infusion and at the end of infusion:

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the beginning of the infusion])
- At the end of the infusion (after approximately 90 minutes ±5 minutes)

The time windows above (before infusion and at end of infusion) apply to both T-DXd and chemotherapy infusions.

If the infusion takes longer than 90 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. An 1-hour observation period is recommended after the first infusion of T-DXd and the chemotherapy drugs that are administered intravenously.

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.

8.2.4 Electrocardiograms

At screening, ECGs will be obtained in triplicate . Subsequent ECGs will be performed in triplicate only if an abnormality is noted. During the treatment period, ECGs are performed within 3 days prior to dosing (see Section 1.3). ECGs will be taken while the patient is in a supine/semi-recumbent position. Twelve-lead ECGs will be performed, and standard ECG parameters will be measured, including RR, PR, QTcF intervals, and QRS duration. All ECGs must be evaluated by Investigator or delegated physician for the presence of abnormalities. Whether or not measurement is performed, date performed, results, and findings for each parameter is to be recorded in the eCRF.

At each time point at which a triplicate ECG is required, 3 individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should be completed within 5 minutes. ECGs will be obtained after the patient has been resting. All ECGs should be recorded with the patient in the same physical position. A standardized ECG machine should be used, and the patient should be examined using the same machine throughout the study, where feasible. After ECGs have been recorded, the Investigator or designated physician will review each of the ECGs and may refer to a local cardiologist if appropriate. A paper copy should be filed in the patient's medical records. If an abnormal ECG finding at screening or pre-dose is considered to be clinically significant by the

Investigator, it should be reported as a concurrent condition. For all ECGs, details of rhythm, ECG intervals and an overall evaluation will be recorded. Any clinically significant abnormalities detected require a confirmatory ECG.

8.2.5 Clinical Safety Laboratory Assessments

Blood samples for determination of clinical chemistry, coagulation, hematology, and urine samples for urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see Section 1.3).

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. For women of childbearing potential, a negative result for serum pregnancy test must be available at the screening visit (see inclusion criterion #13). A pregnancy test (urine or serum test per institutional guideline) 72 hours before randomization is required. Within 72 hours before randomization, if a positive urine pregnancy test result is confirmed using a serum test in a female patient of child bearing potential, then the patient should not be randomized into the study. Repeat pregnancy tests (urine or serum test per institutional guideline) are performed 72 hours before treatment administration of each cycle and at EOT.

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 laboratory variables to be measured are presented in Table 12 (clinical chemistry), Table 13 (hematology), and Table 14 (urinalysis).

Other safety tests to be performed at screening include assessment for hepatitis B surface antigen, hepatitis C antibodies, and HIV antibodies (as per local regulations). Hepatitis C polymerase chain reaction (PCR) test may also be done if HCV antibody test is positive (see exclusion criterion #9).

Table 12 Clinical Chemistry

Albumin	Magnesium
ALP [a]	Potassium
ALT[a]	Sodium
AST[a]	Total bilirubin [a]
Bicarbonate (where available)	Total protein
Calcium	Blood urea nitrogen or Urea, depending on local practice.
Chloride	Lactate dehydrogenase
Creatinine [b]	

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

[a] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × upper limit of normal (and no evidence of Gilbert's syndrome), then fractionate into direct and indirect bilirubin.

[b] Creatinine clearance will be calculated by the site using Cockcroft-Gault (using actual body weight).

Table 13 Hematology

Hemoglobin	Platelet count
White blood cell count	Differential white blood cell count [a]
Hematocrit	Red blood cell count
Coagulation [b]	

[a] Differential white blood cell count: neutrophils, lymphocytes, monocytes, eosinophils, basophils. These can be recorded as absolute counts or as percentages; absolute counts will be calculated by the site.

[b] For coagulation parameters: prothrombin time (PT) or international normalized ratio (INR), and partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) are to be assessed at baseline and as clinically indicated.

Table 14 Urinalysis

Protein	Microscopy assessment (if indicated)
Blood	Specific gravity

Note: Urinalysis should be performed at baseline (screening) and as clinically indicated during the treatment period.
Note: Microscopy should be used as appropriate to investigate white blood cells and use the high-power field for red and white blood cells.

Cases where a patient shows elevation in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN will need to be reported as SAEs. Refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

All patients should have hematology and clinical chemistry tests performed at screening, Cycle 1, Day 1 (before infusion), Day 8 and Day 15 of Cycle 1, and before infusion on Day 1

of all subsequent cycles until EOT. After permanent treatment discontinuation, follow-up hematology and clinical chemistry assessments are performed at 40 days (+7 days) after last dose of study treatment (see Section 1.3). Coagulation tests and urinalysis should be performed at screening and as clinically indicated during treatment period (see Section 1.3).

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 patients with Grade 3 or 4 laboratory values at the time of completion or discontinuation from study treatment must 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.

8.2.6 Pulmonary Assessments

Pulse oximetry (SpO2) should be obtained at the timepoints specified in the SoAs (Section 1.3). SpO2 should be evaluated by Investigator or the delegate physician prior to the administration of study treatment and at the end of infusion (as applicable per SoA) at each visit.

Pulmonary function tests should include basic spirometry at a minimum with optional additional components as mentioned in Table 15.

Table 15 Spirometry Components

Required spirometry components	Optional spirometry components
FVC (L)	PEF
FVC % predicted	DLCO – see exception in the below text where DLCO is mandatory
FEV1 (L)	FEV6
FEV1 % predicted	TLC
FEV1/FVC %	RV

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

Diffusion capacity of the lungs for carbon monoxide (DLCO) will be performed (if feasible), but for patients with prior severe and/or clinically significant pulmonary disorders, DLCO is a requirement. In event of suspected ILD/pneumonitis, refer to Section 8.2.10.1 for additional pulmonary assessments.

HRCT of the chest will be performed as per the SoA at screening, and if ILD/pneumonitis is

suspected. Chest CT and/or chest HRCT scans will be reviewed separately for safety for the presence of ILD/pneumonitis prior to administration of the next scheduled dose of 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, HRCT should be performed first.(Section 1.3).

8.2.7 Echocardiograms/Multiple Gated Acquisition Scans

LVEF will be measured by either echocardiogram (ECHO) or multiple gated acquisition (MUGA) scan. ECHO/MUGA scans will be performed at screening and before infusion on Day 1 of Cycle 5 and every 4 cycles (±7 days) thereafter until the EOT (see Table 5). All ECHOs/MUGAs will be evaluated by the Investigator or delegated physician for monitoring cardiac function. The modality of the cardiac function assessments must be consistent within a patient (i.e., if ECHO is used for the screening assessment, then ECHO should also be used for subsequent scans if required). The patients should also be examined using the same machine and operator whenever possible. Patients should have high-quality, standardized 2-dimensional with Doppler echocardiographic examinations performed by an experienced sonographer. LVEF determinations will be made quantitatively based on bi-plane measurements of end-diastolic and end-systolic left ventricular volumes.

Collect blood samples for troponin (preferably high-sensitivity troponin-T) at screening and as needed based on patient reported cardiac signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of cardiac myocyte necrosis. If at any time a patient reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of myocyte necrosis, a sample should be collected for troponin testing and an ECG will be performed in triplicate. If ECG is abnormal, follow institutional guidelines. For more details on TMGs for varying troponin levels, refer to Appendix H.

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

8.2.8 ECOG Performance Status

ECOG will be assessed at the times specified in the assessment schedules (see 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 (e.g., 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.

8.2.9 Ophthalmologic Assessments

Ophthalmologic assessments including visual acuity testing, slit lamp examination, and fundoscopy will be performed at screening and as clinically indicated.

8.2.10 Other Safety Assessments

8.2.10.1 Pneumonitis (ILD) Investigation

If new or worsening pulmonary symptoms (e.g., dyspnea, cough or fever) or radiological abnormality suggestive of ILD/pneumonitis is observed, treatment with study drug should be interrupted and a full investigation is required as described in detail in the TMGs for T-DXd (Appendix H). Evaluations should include:

- High resolution CT of the chest
- Pulmonologist consultation (infectious disease consultation if clinically indicated)
- Pulmonary function tests (including FVC and CO diffusing capacity) and pulse oximetry (SpO2)
- Arterial blood gases if clinically indicated
- Bronchoscopy and bronchoalveolar lavage as clinically indicated and feasible
- COVID-19 test
- CBC, blood culture, differential WBC, CRP
- One blood sample collection for PK as soon as ILD/pneumonitis is suspected, if feasible
- Additional blood samples for plasma and serum exploratory biomarker analysis as soon as ILD/pneumonitis is suspected, if feasible
- Other tests could be considered, as needed.

The results of the full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, SARS-CoV-2 [COVID-19] test, 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 HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) 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 pneumonitis. The results of the assessment will be collected.

- Physical examination
  - Signs and symptoms (cough, shortness of breath, and pyrexia, etc.) including auscultation for lung field will be assessed.
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:
    (i) ILD markers (KL-6, SP-D) and β-D-glucan
    (ii) Tumor markers: particular tumor markers that are related to disease progression
    (iii) Additional clinical chemistry: C-reactive protein, lactate dehydrogenase

8.3 Adverse Events and Serious Adverse Events

The 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 patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, see Section 8.3.2.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

For patients who sign the pre-screening ICF, only SAEs directly related to tissue screening procedure (i.e., if a patient undergoes a tumor biopsy) will be reported during pre-screening period. All SAEs will be recorded from the time of signing of the main ICF.

AEs and SAEs will be collected from the time of the patient signing the ICF until the

follow-up period is completed (40 [+7] days after the last dose of study treatment). 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 treatment, then it should be reported as an AE or SAE as applicable.

All SAEs will be recorded and reported to AstraZeneca or its designee within 24 hours. The Investigator will submit any updated SAE data to AstraZeneca within 24 hours of it being available.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix B.

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

The following types of events should be reported by the Investigator in eCRF electronic data capture (EDC) AE page(s) in the clinical study database within 24 hours of becoming aware for the purposes of reporting in the global safety database:

- SAEs
- All potential ILD/pneumonitis cases should be reported within 24 hours; including both serious and non-serious potential ILD/pneumonitis cases.
- Hepatic events (both serious and non-serious) which meet the potential Hy's Law criteria defined as an elevated (ALT or AST) ≥ 3 × ULN and an elevated TBL ≥ 2 × ULN that may occur either at different timepoints or simultaneously during the study.
- Overdose
- Medication error
- Pregnancy

8.3.2 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs, non-serious AEs, and AESIs (as defined in Appendix B) will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up.

Any AE that is unresolved at the patient's last AE assessment or other assessment/visit as appropriate in the study are followed up by the Investigator for as long as medically indicated (this may be beyond the 40 days after the last dose of study treatment), but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any

patient 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
- Maximum CTCAE Grade reported
- Changes in CTCAE Grade (report only the maximum CTCAE grade for a calendar day)
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product(s) (yes or no)
- Action taken with regard to study treatments
- Outcome

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

- Date the AE met criteria for SAE
- Date the 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
- Description of the SAE

The grading scales found in the revised NCI CTCAE v5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE v5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.3.3 Causality Collection

The Investigator should assess causal relationship between study treatment and each AE with respect to each study treatment (T-DXd, capecitabine, paclitaxel and nab-paclitaxel), and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that

the event may have been caused by the study treatment?'

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 Clinical Study Protocol (CSP).

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the patient 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 and vital signs will be summarized in the Clinical Study Report (CSR).

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and ECGs should therefore only be reported as AEs if they fulfil any of the SAE criteria, or are the reason for discontinuation of treatment with the investigational product or are considered to be clinically relevant as judged by the Investigator (which may include but are not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study treatment, e.g., dose adjustment or drug interruption).

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

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 patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN will need to be reported as SAEs. Refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.3.7 Disease Progression

Disease progression can be considered a worsening of a patient's condition attributable to the disease for which the investigational product 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, which are unequivocally due to disease progression, should not be reported as an AE during the study.

8.3.8 Disease Under Study

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

8.3.9 New Cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study.

8.3.10 Deaths

All deaths that occur during the study treatment period, or within the protocol-defined follow-up period after the administration of the last dose of study drug, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and 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 progression of the DUS, the AE causing the death must be reported to the Study Monitor/Physician 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 main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the eCRF. A postmortem may be helpful in

the assessment of the cause of death, and if performed, a copy of the postmortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual timeframes.

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

8.3.11 Adverse Events of Special Interest

An AESI is an AE of scientific and medical interest specific to understanding of the study treatment and may require close monitoring. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of a study treatment.

AESIs will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. AEs will be assessed by the Investigator for severity, relationship to the study treatment, possible etiologies, and whether the event meets criteria for an SAE and therefore requires immediate notification to AstraZeneca. If an AESI evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form.

Based on the available pre-clinical and clinical data, review of the cumulative literature, reported toxicities for the same class of agents and biological plausibility, ILD/pneumonitis and LVEF decrease are considered to be AESIs.

Interstitial Lung Disease/Pneumonitis

ILD/pneumonitis is considered an important identified risk based on a comprehensive cumulative review of potential ILD/pneumonitis cases reviewed by the independent ILD Adjudication 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 IB for a summary of preliminary clinical study data.

- High resolution CT of the chest and pulmonary function will be measured at baseline. If the AE is suspected to be ILD/pneumonitis during the study, treatment with study drug should be interrupted pending further evaluations. Evaluations for ILD/pneumonitis should include high resolution CT, SARS-CoV-2 (COVID-19) test, pulmonologist consultation, pulmonary function tests and pulse oximetry (SpO2), arterial blood gases if clinically indicated, bronchoscopy and bronchoalveolar lavage as clinically indicated and

feasible and one blood sample collection for PK as soon as ILD/pneumonitis is suspected, if feasible.

Refer to Appendix H for guidelines on management of drug-induced ILD.

LVEF Decrease

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

- LVEF 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 will be measured at screening and as needed based on patient reported cardiac symptoms.
- At screening, ECGs will be obtained in triplicate (3 individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should be completed within 5 minutes). Subsequent ECGs will be performed in triplicate only if abnormalities are noted. 12 lead ECGs will be performed, and standard ECG parameters will be measured, including RR, PR, QTcF intervals, and QRS duration. All ECGs must be evaluated by Investigator or delegated physician for the presence of abnormalities. Whether or not measurement is performed, date performed, results, and findings for each parameter is to be recorded in the eCRF

8.3.12 Reporting of Serious Adverse Events

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

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., 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 one calendar day i.e., 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 followed by completion of a paper SAE form.

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

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

The reference documents for definition of expectedness/listedness are the current IB for T-DXd and the Summaries of Product Characteristics (SmPC) for the investigator's choice of chemotherapy (Latest effective SmPC for Paclitaxel, Hospira UK Limited; Latest effective SmPC for Xeloda, Roche Products Limited; Latest effective SmPC for Abraxane, Celgene Limited).

8.3.13 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except:

- If the pregnancy is discovered before the patient has received any study treatment

If a pregnancy is reported during the course of study, the Investigator should inform AstraZeneca within 24 hours of learning of the pregnancy and the study treatment should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study treatment 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 patient was discontinued from the study.

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 8.3.12) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.3.13.1 Paternal Exposure

Male patients should refrain from fathering a child or donating sperm during the study treatment and during the washout period (4 months after the last dose of T-DXd, 6 months after the last dose of paclitaxel or nab-paclitaxel, and 3 months after the last dose of capecitabine) after the last dose of study treatment. Preservation of sperm should be considered prior to randomization in this study. 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 patient'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 until 4 months or as per local prescribing information (marketed products) after the last dose and as indicated by previous studies (pre-clinical and clinical) should be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

When a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant ECs/IRBs prior to use.

Patients who are permanently discontinued from further receipt of study treatment, regardless of the reason will enter follow-up (see the SoAs [Section 1.3]).

8.3.14 Management of Study Treatment-related Toxicities

The following general guidance should be followed for management of toxicities:

- Treat each of the toxicities with maximum supportive care (including withholding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the randomized study treatment along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted (See Section 6.6).
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

All toxicities will be graded according to NCI CTCAE v5.0.

8.3.14.1 Specific Toxicity Management and Dose Modification Information for T-DXd

All dose modifications (interruption, reduction and/or discontinuation) should be based on the worst preceding toxicity (CTCAE v5.0). Specific criteria for interruption, re-initiation, dose reduction and/or discontinuation of T-DXd are listed in TMGs for T-DXd (see Appendix H), which is applicable only to TEAEs that are assessed as related to use of T-DXd by the Investigator(s). A TEAE is defined as an AE that occurs, having been absent before the first dose of study drug, or has worsened in severity or seriousness after initiating the study drug until the 40-day (+7 days) safety follow-up visit.

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 I for additional information on dose modification for suspected or confirmed COVID-19 infection for patients treated with T-DXd.

ILD/Pneumonitis Management Guidance:

Refer to Appendix H for the management of DI-ILD.

ILD/pneumonitis should be ruled out if a patient 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, follow the management guidance outlined in the in the dose modification section of the study protocol (Section 6.6).

If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluations. Evaluations should include high resolution CT, pulmonologist consultation, pulmonary function tests, SARS-CoV-2 [COVID-19] test, and SpO2, arterial blood gases if clinically indicated, bronchoscopy and bronchoalveolar lavage as clinically indicated and feasible and one blood sample collection for PK as soon as ILD/pneumonitis is suspected, if feasible. Other tests could be considered, as needed. As soon as ILD/pneumonitis is suspected, corticosteroid treatment should be started promptly as per clinical treatment guidelines.

If the AE is confirmed to be ILD/pneumonitis, follow the TMGs for management of drug-induced ILD (DI-ILD)/pneumonitis (Appendix H). All events of ILD/pneumonitis regardless of severity or seriousness will be followed until resolution including after study treatment discontinuation.

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 (e.g., smoking, radiation, COPD and other

chronic lung conditions), diagnostic evaluation, treatment and outcome of the event.

LVEF Decrease Management Guidance:

LVEF 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 will be measured at screening and as needed based on patient reported cardiac signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of cardiac myocyte necrosis. If at any time a patient reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of myocyte necrosis, a sample should be collected for troponin testing and an ECG will be performed in triplicate. If ECG is abnormal, follow institutional guidelines.
- ECGs will be performed, and standard ECG parameters will be measured, including RR, PR, QTcF 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 treatment at Cycle 1 Day 1, Cycle 4 Day 1 and every 4th cycle thereafter. Whether or not measurement is performed, date performed, results, and findings for each parameter is to be recorded in the eCRF.

Dose Reduction Levels for T-DXd

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 16). More than 2 dose reductions are not allowed, and the patient will be discontinued from the study treatment if further toxicity meeting the requirement for dose reduction occurs.

Table 16 Dose Reduction Levels for T-DXd

Starting Dose	Dose Level -1	Dose Level -2
5.4 mg/kg	4.4 mg/kg	3.2 mg/kg

Dose Interruption and Modification/Toxicity Management Guidelines:

- Every effort should be made to limit T-DXd delay, however in circumstances of AE management or medical intervention, T-DXd can be held up to 18 weeks (126 days) from the last T-DXd dose. During this time scheduled CT/MRI scans should continue as per protocol, and patients should fulfil all of the following criteria:
  - T-DXd 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 scan must be done within 6 weeks prior to restarting the study drug.

- T-DXd is restarted within the guidance of the TMGs for T-DXd.
- No prohibited concomitant medications have been administered since the last dose of T-DXd.

Treatment cycles for a patient 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 discontinuation of T-DXd according to the patient's condition.

Refer to Appendix H for more detailed guidance on toxicity management.

8.3.14.2 Toxicity Management and Dose Modification Information for Investigator's Choice of Chemotherapy

Investigators should follow local standard clinical practice regarding toxicity management for the selected investigator's choice chemotherapy. Refer to the local prescribing information for paclitaxel, nab-paclitaxel and capecitabine. If a patient is assessed as requiring a dose delay of longer than 28 days, resumption of treatment must be discussed with the AstraZeneca Study Physician.

8.4 Medication Error, Drug Abuse, and Drug Misuse

8.4.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**, i.e., immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **one** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.3.12) and **within 30 days** for all other events.

8.4.2 Medication Error

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

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

8.4.3 Drug Abuse

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

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

8.4.4 Drug Misuse

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

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

8.5 Overdose

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 patient.

- 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. Use of T-DXd (20% more than the intended w/v dose), capecitabine, paclitaxel, and nab-paclitaxel (according to labels) in doses that are in excess of those specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of the study treatments used in the study, and possible symptoms of overdose are not established. Refer to the local prescribing information for treatment in cases of an overdose related to paclitaxel, capecitabine and nab-paclitaxel. The Investigator will use clinical judgement to treat any overdose. Investigators should be advised that any patient who receives a higher dose than that intended should be monitored closely, managed with appropriate supportive care, and followed up expectantly.
- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the overdose CRF module.
- An overdose without associated symptoms is only reported on the overdose CRF module and not the AE module.

If an overdose on an IMP or AstraZeneca NIMP occurs in the course of the study, the Investigator or other site personnel inform the 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 8.3.12) and **within 30 days** for all other overdoses.

8.6 Human Biological Samples

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

Outside of China, PK samples will be disposed of 6 months after issuance of the Bioanalytical Report, unless consented for future analyses.

- Pharmacokinetic samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Remaining anti-drug antibody (ADA) sample aliquots will be retained at AstraZeneca or its designee for a maximum of 5 years following issuance of the CSR. Additional use includes but is not limited to further characterization of any ADAs, 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.

In China, PK samples will be disposed within 6 months after issuance of the Bioanalytical Report and ADA samples will be disposed of within 1 year after issuance of the CSR. PK/ADA samples collected in China will be stored and disposed of according to local laws and regulations. AstraZeneca, as a Foreign Entity, will not biobank in China, in line with HGR regulations.

8.6.1 Pharmacokinetics

PK for T-DXd will be assessed as a secondary objective for this study.

Blood samples for determination of T-DXd, total anti-HER2 antibody and MAAA-1181a concentrations in serum will be obtained as according to the SoAs (see Section 1.3) and will be analyzed by a designated third party on behalf of AstraZeneca.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual. Full details of the analytical method used will be described in a separate Bioanalytical Validation Report.

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

8.6.2 Immunogenicity Assessments

Blood samples for determination of ADA in serum will be collected pre-infusion on Day 1 Cycle 1, Day 1 Cycle 2, and Day 1 Cycle 4, then on D1 of every 4 cycles, as according to the SoAs (see Section 1.3).

Samples will be measured for the presence of ADAs and also potentially for ADA-neutralizing antibodies for T-DXd using validated assays. Tiered analysis will be performed to include screening, confirmatory, and titer assay components, and positive negative cut points previously statistically determined from drug-naïve validation samples will be employed.

Full details of the methods used will be described in a separate report. ADA samples may also be further tested for characterization of the ADA response and/or other exploratory safety biomarkers.

See Laboratory Manual for further details on requirements including sample collection, and shipping.

8.7 Human Biological Sample Biomarkers

Samples and generated data may be used to support diagnostic development.

8.7.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study the patient consents to participate in the mandatory research components of the study. Samples for biomarker research are required and will be collected from all patients in this study as specified in the SoA (see Section 1.3).

The following mandatory samples will be collected from all patients including screen failures wherever possible.

- MANDATORY: A mandatory FFPE tumor sample obtained at the time of metastatic disease or later (most recent pre-randomization tumor sample) must be provided. The tumor sample(s) submitted should be of sufficient quantity to allow for assessment of HER2 status (12 slides) and for other exploratory biomarker analyses (8 slides; see below):

- Tumor tissue block is preferred. If a tissue block is unavailable, 20 freshly-cut unstained serial tumor slides from the most recently collected pre-randomization tumor sample from the time of metastatic disease or later is required. Samples with limited tumor content, fine needle aspirate specimens and specimens from metastatic bone lesions that require decalcification are not acceptable (see Lab manual for further details). If enough tumor tissue is not available from a single lesion, then the following options may be acceptable:
  - An aggregate of 20 slides from a newly acquired biopsy and a previously acquired sample from the time of metastatic disease or later can be provided (at least 12 slides must be available from one of the lesions).
  - An aggregate of 20 slides from multiple previously acquired samples from metastatic disease or later can be provided (at least 12 slides must be available from a single lesion).
  - If only one of the samples contains more than 12 slides, that sample will be used for central HER2 testing. If both submitted samples contain more than 12 slides, then the most recently collected pre-randomization tumor sample will be used for central HER2 testing.

If fewer than 20 slides are available, patients may be eligible following discussion with the AstraZeneca Study Physician.

- HER2 IHC analysis will be performed at a central reference laboratory testing service using an IHC assay, investigational for the HER2 IHC 2+, IHC1+ and IHC >0 <1+ cut-offs. Testing will be carried out in a laboratory operating to GCP and with pathology staff fully trained by the diagnostic manufacturer to score reproducibly at the HER2 IHC cut-offs under development (IHC >0 <1+ and IHC1+).
- Tumor lesions used for fresh biopsies should not be the same lesions used as RECIST 1.1 TLs, unless there are no other lesions suitable for biopsy. For patients with a single TL, if screening biopsy is collected prior to screening imaging for baseline tumor assessment, allow time for healing (e.g., 1-2 weeks) before imaging scans are acquired; and, if imaging occurs prior to biopsy, in order to ensure that lesion size is unaffected by biopsy, biopsy sampling should be no larger than core needle size.

See Laboratory Manual for further details on requirements including sample collection, and shipping.

Baseline measures will be correlated with outcomes. Note that samples will be obtained from patients randomized to each treatment arm. Comparisons will be made between baseline

measures to determine if biomarkers (or combination of markers) are prognostic or predictive of outcomes associated with treatment. The following assessments will be performed with the samples collected, where applicable.

- Tumor samples will be tested for HER2 expression by IHC at 2+, 1+ and >0 <1+ cut-offs to evaluate their association with the observed clinical responses PFS, OS, ORR to T-DXd and investigator's choice of chemotherapy.
- Tumor samples centrally confirmed to be HER2 IHC 2+ will be confirmed to be HER2 ISH negative using an approved HER2 ISH assay per manufacturers requirements
- Exploration of IHC and other assay technologies to determine tumoral HER2 expression, and IHC analysis, and expression of, but not limited to, associated family members.
- Exploration of protein expression (IHC and proteomic analysis including, but not limited to erythroblastic oncogene B (ERBB2), related family members and topoisomerase I [TOPO-1] expression).

Note: According to Human Genetic Resources (HGR) policy, tumor samples collected in China will not be used for additional exploratory biomarker studies, beyond the check of HER2 status. Please refer to China laboratory manual for sample requirements specific to China. Tumor samples collected for central HER2 testing in China will be destroyed or repatriated within 1 year of issuance of the CSR.

- MANDATORY: Blood sample for the isolation of plasma to enable the assessment, analysis and interpretation of circulating tumor DNA (ctDNA) will be collected from all patients at screening, on Day 1 of C1 to C7, then every 6 weeks (q6w ± 1 week until Week 48, and q9w ± 1 week post Week 48 until progression of disease in alignment with RECIST 1.1 assessments) and at disease progression (see Section 1.3). The buffy coat layer obtained during the plasma isolation process of the baseline sample may be retained and analyzed for germline mutations according to local regulations.
  - ctDNA samples will be analyzed for predictive biomarkers of response to treatment and may be used to develop and validate future in vitro diagnostic (IVD) tests to identify patients most likely to respond to the treatment. The sample is requested prior to treatment in order to maximize the probability of detecting ctDNA where the tumor burden is relatively high.
  - ctDNA samples taken during treatment and a final sample taken at disease progression will be used for additional exploratory research which may include but is not limited to interrogation of changes in genetic alterations as well as the dynamics of the biomarkers on treatment and potential mechanisms of resistance to treatment.

Note: These samples will not be collected in China.

- MANDATORY: Blood samples for gene expression analysis will be collected from all patients as described in SoAs (Section 1.3) to characterize molecular alterations pre-treatment and predict patients who may respond to treatment based on their molecular profiles.

Note: These samples will not be collected in China.

- MANDATORY: Blood samples for peripheral blood mononuclear cell (PBMC) analysis will be collected from the patients as described in SoAs (see Section 1.3) to assess a range of oncology and immunological biomarkers that may correlate with drug response. These biomarkers may include but are not limited to soluble biomarkers, T-cell receptor repertoire analysis and analysis of gene expression biomarkers associated with immunomodulatory effects.

Note: These samples will not be collected in China.

- MANDATORY: Blood samples to perform exploratory safety or clinical benefit analyses to identify candidate markers which may correlate with likelihood of clinical benefit/tolerability will be collected from patients as described in the SoAs (see Section 1.3). These analyses may include but are not limited to the detection of the presence of viruses including but not limited to the SARS-CoV-2 virus and the characterization of the safety profile for patients with antibodies to the SARS-CoV-2 virus treated with T-DXd or chemotherapy compared to the safety profile of patients without evidence of immune response (antibodies) treated with T-DXd or chemotherapy.
  - Blood samples for serum isolation will be collected from the patients assigned to the investigator's choice chemotherapy arm, per the SoA; blood samples for serum isolation from patients assigned to the T-DXd arm will be taken from already collected samples (see Section 8.7.3).

8.7.2 Collection of Optional Biomarker Samples

Collection of optional samples for biomarker research is also part of this study as specified in the SoA (Section 1.3) and is subject to agreement to optional consent. These samples will not be collected in China. Collection of the following samples are optional:

- Optional tumor biopsies will be collected at time of disease progression, if consented for, and should be obtained at any point post-progression. These samples will be used to explore mechanisms of resistance to T-DXd and standard of care therapies. Biopsies on progression may be particularly valuable when there is a marked phenotypic change in a particular lesion, and Investigators are encouraged to contact AstraZeneca in these cases. The provision of tumor tissue is encouraged only if clinically appropriate and not considered detrimental to participant care.
- Paired biopsies should be collected (1) at screening or before infusion on Day 1 of Cycle 1 and (2) during the treatment period on Day 1 of Cycle 2 ([any day between Cycle 2,

Week 1, Day 2 and Cycle 2, Week 3 is allowed] recommended >4 hours post-dose) as described in SoAs (Section 1.3).

- The samples will be used for exploration of protein and RNA expression pre- and on-treatment (Immunohistochemistry and proteomic analysis including, but not limited to ERBB2, related family members and TOPO-1 expression).

See Laboratory Manual for further details on requirements including sample collection and shipping.

Procedures for withdrawal of consent for optional samples, labelling/shipping and chain of custody, refer to Appendix C.

8.7.3 Other Study Related Biomarker Research

Already collected samples may be analyzed on different biomarkers thought to play a role in efficacy outcomes including, but not limited to serum analytes, or tissue biomarkers and/or specific candidate genes/genome-wide analysis for RNA to evaluate their association with observed clinical responses to study treatments as well as analyzing whether the presence of antibodies to SARS-CoV-2 will provide any noted differences with the safety profile of patients treated with T-DXd or chemotherapy. The presence of viruses such as the SARS-CoV-2 virus may also be investigated.

A range of oncology and immunological biomarkers might also be assessed that may correlate with drug response. These biomarkers may include but are not limited to soluble biomarkers, T-cell receptor repertoire analysis and analysis of gene expression biomarkers associated with immunomodulatory effects.

Biomarker analyses will not be performed for Chinese patients, with the exception of the SARS-CoV-2-related safety profile analysis.

For storage, re-use and destruction of biomarker samples see Section 8.6.

Management of Biomarker Data

The biomarker data will be exploratory in nature and will have unknown clinical significance. AstraZeneca will not provide biomarker research results to patients, their family members, any insurance company, an employer, Study Investigator, general physician, or any other third party, unless required to do so by law. The patient's samples will not be used for any purpose other than those described in the CSP.

Individual patients will not be identified in any report or publication resulting from this work. The data and results of this research may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or

report.

8.8 Optional Genomics Initiative Sample

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA (Section 1.3) and is subject to agreement in the ICF addendum. Participation is optional. Patients who do not wish to participate in the genetic research may still participate in the study.

A blood sample will be obtained from the patients on Day 1 (first infusion day) prior to treatment administration (at or after randomization). If for any reason the sample is not drawn on Day 1, it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient.

Note: This sample will not be collected in China.

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

8.9 Medical Resource Utilization

The impact of treatment and disease on healthcare resource use will be captured in this study on an event-driven basis. The Hospital Admission (HOSPAD) module in eCRF will be used to collect information on key health care resource use that a patient receives that is not part of the study. The data may be used to support health technology assessments and payer related submissions.

At each scheduled visit, the site should review clinical notes for any non-study related hospital admissions and visits that have occurred. Where any visits have occurred, the site should complete the HOSPAD. This review should be done at every scheduled clinic visit up to and including the post-study treatment discontinuation follow-up visit. If a patient discontinues study treatment for reasons other than RECIST 1.1 progression, the HOSPAD form should continue to be administered until progression has been confirmed. Study mandated visits should not be included in the HOSPAD.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The null hypothesis for the primary and key secondary efficacy endpoints (PFS and OS) is that there is no difference in PFS/OS distribution between T-DXd and the investigator's choice chemotherapy. The intention of the study is to demonstrate the superiority of T-DXd over the investigator's choice chemotherapy, in the HER2-low population and the ITT population.

9.1.1 Multiple Testing Procedure

PFS in the HER2-low population and ITT population will be tested once, when PFS reaches approximately 65% maturity (456 events) in the HER2-low population. This is estimated to occur 29 months after the first patient is randomized (4 months after randomization is completed) assuming a non-uniform accrual of patients with a duration of 25 months. At this time, it is expected that at least 553 events (65% maturity) will have been observed in the ITT population.

OS in the HER2-low population and ITT population will be tested at two interim and one final analysis as described below:

- The first interim OS analysis will be performed at the time of the final PFS analysis. It is expected that 216 OS events (31% maturity or 41% information fraction) will have been observed in the HER2-low population and 263 OS events will have been observed in the ITT population.
- The second interim OS analysis will occur when approximately 392 OS events have been observed in the HER2-low population (56% maturity or 75% information fraction). This is anticipated to occur approximately 44 months after the first patient is randomized. It is expected that 477 OS events have been observed in the ITT population at this time.
- The final OS analysis will be performed when approximately 521 OS events have been observed in the HER2-low population (74% maturity), which is expected to occur approximately 63 months after the first patient is randomized. At this time, it is estimated that 632 OS events will have been observed in the ITT population.

To strongly control the family wise error rate at 5% in terms of the primary and key secondary endpoints, a multiple testing procedure (MTP) with the following gatekeeping strategy will be employed (Figure 1):

Step 1: Test PFS in the HER2-low population at a 5% alpha level. If significance is achieved, go to Step 2.

Step 2: Test PFS in the ITT population at a 1.5% alpha level and OS in the HER2-low population at the 3.5% alpha level. If PFS in the ITT population is significant, the 1.5% alpha will be recycled to OS in the HER2-low population. Similarly, if OS in the HER2-low population is significant at either the interim or final analysis, the 3.5% alpha will be recycled to PFS in the ITT population (i.e. PFS in the ITT population at the PFS analysis DCO will be tested at 5% alpha). If both PFS in the ITT population and OS in the HER2-low population are significant, go to Step 3.

Step 3: Test OS in the ITT population at a 5% alpha level.

The 3.5% initial alpha allocated to OS in the HER2-low population will be distributed between the two interim and final analyses using the Lan DeMets spending function that approximates the O'Brien Fleming alpha-spending approach (Lan and DeMets 1983). Under this procedure, the adjusted significance levels at the interim and final analyses are determined by the information fraction available at the time of analysis (i.e., exact number events observed), giving greater weight to analyses performed at the end of the study than those performed earlier.

If PFS in the ITT population is significant at 1.5% alpha (Step 2 above) such that this alpha is reallocated to OS in the HER2-low population, the adjusted significance levels at each of the analysis time points for OS in the HER2-low population will be updated per the Group sequential Holm variable procedure (Ye et al 2013). The Lan DeMets spending function that approximates the O'Brien-Fleming alpha-spending approach will be used to derive the updated significance levels. The same significance levels will be used for the interim OS analyses in the HER2-low population and ITT population. The significance level at the final OS analysis will be derived separately for each population and will be based on the actual number of events at the interim and final analysis, and the alpha already spent at the interim analyses for the HER2-low and ITT population, respectively.

An interim futility analysis will be performed after the first 70 patients in the HER2 IHC >0 <1+ population have been randomized and have had at least 24 weeks of follow-up from the point of randomization or withdrawn from the study. The IDMC will make a recommendation on whether or not to stop recruitment in the HER2 IHC >0 <1+ population based on the results of the interim futility analysis (Section 9.5.1). If it is decided to limit further recruitment only to the HER2-low population, tests on the ITT population will not be performed.

9.2 Sample Size Determination

The study will randomize approximately 850 patients (700 HER2 IHC 2+/ISH- and IHC 1+ [HER2-low] patients and 150 HER2 IHC >0 <1+ patients). The HER2-low (IHC 2+/ISH- and IHC 1+) strata will be closed once a total of 700 patients have been randomized in these strata. At this time, a decision will be made by AstraZeneca on whether recruitment into the HER2 IHC >0 <1+ population will be stopped if the 150-patient target has not been met.

Approximately 1417 patients will be screened with an approximate screen failure rate of 40% to achieve randomization of approximately 850 patients to the study treatment.

The study provides adequate power to show a statistically significant between-treatment difference in PFS in the HER2-low population. Based on a 2-sided significance level of 5%, a total of 456 PFS events (65% maturity) will provide at least 95% power to detect a hazard ratio of 0.55 (increase in median PFS from 5.5 to 10 months) in the HER2-low population,

assuming an exponential distribution for both treatment groups.

If PFS in the HER2-low population is significant, the study also provides sufficient power to demonstrate a statistically significant difference in OS in the HER2-low population. Based on a 2-sided alpha of 3.5% and taking into account 2 interim OS analyses, a total of 521 OS events will be required to achieve 80% power to detect a hazard ratio of 0.77 (increase in median OS from 20.5 to 26.6 months) in the HER2-low population, assuming an exponential distribution for both treatment groups. Assuming 74% maturity at the time of the final OS analysis, approximately 700 patients will need to be randomized in the HER2-low subgroup.

In addition to the 700 patients in the HER2-low population, approximately 150 patients with HER2 IHC >0 <1+ expression will be randomized, which will total up to approximately 850 patients randomized in the study.

9.3 Populations for Analyses

Table 17 defines the populations upon which the analyses are based.

Table 17 Populations for Analyses

Population/Analysis set	Description
Full analysis set (FAS) (ITT)	The ITT population, also termed as FAS, will include all randomized patients. Treatment arms will be compared on the basis of randomized study treatment, regardless of the study treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment are included in the analysis in the treatment arm to which they were randomized.
HER2-low	The HER2-low population comprises the subset of patients included in the ITT population with HER2 IHC 2+/ISH- and IHC 1+ as determined per the IRT data for HER2 IHC expression.
HER2 IHC >0 <1+	The HER2 IHC >0 <1+ population comprises the subset of patients included in the ITT population with HER2 IHC >0 <1+ as determined by central laboratory testing and who have had at least 24 weeks of follow-up at the time of the interim futility DCO (i.e. randomized ≥ 24 weeks prior to interim futility DCO).
Safety (SAF)	All patients who received at least 1 dose of study treatment. Safety data will be summarized according to the treatment received. Erroneously treated patients (e.g., those randomized to treatment A but actually given treatment B) will be summarized according to the treatment they actually received.
HER2-low SAF	The HER2-low SAF comprises the subset of patients included in the SAF with HER2 IHC 2+/ISH- and IHC 1+ as determined per the IRT data for the HER2 IHC expression.
PK	The PK analysis set will include all patients who receive at least 1 dose of T-DXd per the protocol for whom any postdose data are available.

Table 17 Populations for Analyses

Population/Analysis set	Description
ADA	All patients who receive at least 1 dose of T-DXd per the protocol, have non-missing baseline ADA and at least 1 non-missing post-baseline ADA results. All major ADA analyses will be based on the ADA evaluable set.

ADA = anti-drug antibody; DCO = data cutoff; FAS = full analysis set; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ISH = in situ hybridization; ITT = intent-to-treat; PK = pharmacokinetic; SAF = safety analysis set; T-DXd trastuzumab deruxtecan.

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be finalized before the first patient is randomized 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 key secondary endpoints (Table 18). Additional analyses to be performed at the time of the PFS and OS analyses for the HER2 IHC >0<1+ population will be specified in the SAP.

9.4.1 General Considerations

Table 18 Summary of Outcome Variables and Analysis Populations

Outcome variable	Populations
Efficacy data	
PFS	HER2-low, HER2 IHC >0 <1+ [a], and ITT
OS	HER2-low and ITT
ORR	HER2-low, HER2 IHC >0 <1+ [a] and ITT
DoR	HER2-low, HER2 IHC >0 <1+ [a] and ITT DoR will be based on the subset of patients in the HER2-low/ITT who achieved objective tumor response
DCR at 24 weeks	HER2 IHC >0 <1+ [a]
PFS2, TFST, TSST	HER2-low and ITT
PROs	HER2-low and ITT
Study population/Demography data	
Demography characteristics	HER2-low and ITT
Baseline and disease characteristics	HER2-low and ITT
Important deviations	HER2-low and ITT
Medical/surgical history	HER2-low and ITT
Previous anti-cancer therapy	HER2-low and ITT
Concomitant medications/procedures	HER2-low and ITT
Subsequent anti-cancer therapy	HER2-low and ITT

Table 18 Summary of Outcome Variables and Analysis Populations

Outcome variable	Populations
PK data	
PK data	PK analysis set
Immunogenicity data	
Immunogenicity data	Listings will be based on SAF Summaries will be based on ADA evaluable set
Safety data	
Exposure	HER2-low SAF and SAF
AEs	HER2-low SAF and SAF
Laboratory measurements	HER2-low SAF and SAF
Vital signs	HER2-low SAF and SAF
ECGs	HER2-low SAF and SAF

ADA = anti-drug antibody; AEs = adverse events; DCR = disease control rate; DoR = duration of response; ECG = electrocardiogram; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ITT = intent-to-treat population; KM = Kaplan Meier; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PFS2 = time from randomization to second progression or death; PK = pharmacokinetic; PROs = patient reported outcomes; SAF = safety analysis set; TFST = time to first subsequent treatment or death; TSST = time to second subsequent treatment or death

[a] An interim futility analysis will be performed in the HER2 IHC >0 <1+ subgroup to compare ORR between T-DXd and the investigator's choice of chemotherapy. As supportive summaries, DoR, PFS KM plot and DCR at 24 weeks by treatment arm will also be provided for the HER2 IHC >0 <1+ subgroup.

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

9.4.2 Efficacy

9.4.2.1 Primary Endpoint (PFS by BICR in the HER2-low Population)

The primary endpoint of the study is PFS by BICR according to RECIST 1.1 in the HER2-low population.

PFS is defined as the time from the date of randomization until the date of disease progression, as defined by RECIST 1.1, or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomized therapy or receives another anticancer therapy prior to progression. Patients who have not had disease progression or death 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 patient has disease progression or dies immediately after two or more consecutive missed visits, the patient will be censored at

the time of the latest evaluable RECIST 1.1 assessment prior to the two missed visits. If the patients have no evaluable visits or do not have baseline data, they will be censored at Day 1 unless they die within two visits of baseline (12 weeks plus 1 week allowing for a late assessment within the visit window).

PFS distribution will be compared between T-DXd and investigator's choice chemotherapy using a stratified log-rank test adjusting for prior CDK4/6 inhibitor use (yes vs no), HER2 IHC expression (IHC 1+ vs IHC 2+/ISH-), and prior taxane use in the non-metastatic setting (yes vs no). The stratification variables in the statistical modelling will be based on the values entered in IRT. If there are insufficient events per stratum, the strata will be pooled following a pooling strategy that will be prespecified in the SAP. The hazard ratio and its CI will be estimated from a stratified Cox Proportional Hazards model with strata being the same as the stratification variables from IRT.

Kaplan-Meier plots of PFS will be presented by treatment arm.

Sensitivity analyses for PFS will be described in the SAP.

9.4.2.2 Secondary Endpoints

PFS by Investigator Assessment in the HER2-low Population

PFS by Investigator assessment according to RECIST 1.1 in the HER2-low population will be analyzed as described for the primary endpoint (Section 9.4.2.1).

PFS by BICR in the ITT Population

PFS by BICR according to RECIST 1.1 in the ITT Population will be analyzed as described for the primary endpoint (Section 9.4.2.1), except the stratification factors will include prior CDK4/6 inhibitor use (yes vs no), HER2 IHC expression (IHC >0 <1+, IHC 1+ or IHC 2+/ISH-), and prior taxane use in the non-metastatic setting (yes vs no).

As a sensitivity analysis, PFS by Investigator assessments according to RECIST 1.1 will be analyzed in the ITT population using the same methodology as described above.

Overall Survival

OS is defined as the time from the date of randomization until death due to any cause regardless of whether the patient withdraws from randomized therapy or receives another anticancer therapy. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Analysis of OS will be performed to compare T-DXd vs investigator's choice chemotherapy in

HER2-low and ITT analysis sets using the same methodology as for PFS.

Objective Response Rate

ORR is defined as the percentage of patients with at least one visit response of complete or partial response (using RECIST 1.1) and will be based on all randomized patients. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. However, patients who receive subsequent anticancer therapy (note that for this analysis radiotherapy is not considered a subsequent anticancer therapy) after discontinuing study treatment without progression and then respond will not be included as responders in the ORR.

At the time of the formal PFS and OS analyses, the ORR (by BICR according to RECIST 1.1) will be compared between T-DXd and investigator's choice chemotherapy using logistic regression model adjusting for the same stratification factors as the primary endpoint as covariates in the model. This analysis will be performed in the HER2-low and ITT analysis sets. The ORR using Investigator assessments according to RECIST 1.1 will be analyzed using the same methodology as supportive analyses.

As a sensitivity analysis, confirmed ORR, defined as the percentage of patients with a confirmed response of CR or PR (by BICR and by Investigator assessments according to RECIST 1.1) will be analyzed using the same methodology as described above. Furthermore, ORR and confirmed ORR will also be calculated and summarized based upon the subgroup of patients with measurable disease at baseline per BICR and Investigator assessment.

At the interim futility analysis, confirmed ORR (by Investigator assessments according to RECIST 1.1) will be summarized by treatment arm using the HER2 IHC >0 <1+ analysis set. Details are described in Section 9.5.

Summaries will be produced that present the number and percentage of patients with a tumor response (complete response [CR]/partial response [PR]) for HER2-low and ITT analysis sets. Overall visit response data will be listed for all patients (i.e., the ITT). Best overall response (BOR) will be summarized by n (%) for each category (CR, PR, stable disease [SD], progressive disease [PD], and not evaluable [NE]) for each treatment arm in HER2-low and ITT analysis sets. No formal statistical analyses are planned for BOR.

Duration of Response

For patients who achieve complete or partial response per RECIST 1.1, DoR is defined as the time from the date of first documented response until date of documented progression (using RECIST 1.1) or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. If a

patient does not progress following a response, then their DoR will use the PFS censoring time.

Descriptive data will be provided for the DoR by BICR and by Investigator assessment according to RECIST 1.1 in responding patients, including the associated Kaplan-Meier curves (without any formal comparison of treatment arms or p-value attached). These summaries will be presented in the HER2-low and ITT analysis set.

Disease Control Rate (DCR) at 24 weeks

DCR at 24 weeks is defined as the percentage of patients who have a BOR of CR or PR or who have SD (without subsequent cancer therapy) for at least 23 weeks after randomization (to allow for an early assessment within the assessment window). DCR at 24 weeks will only be reported at the interim futility analysis using the HER2 IHC >0 <1+ analysis set. Similar to ORR, DCR at 24 weeks will be summarized by treatment arm.

PFS2

PFS2 is defined as time from randomization 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 and may involve any of the following: objective radiological imaging, symptomatic progression, or death. Patients alive and for whom a second disease progression has not been observed should be censored at the earliest of: date of study termination, date last known alive, DCO or, if a patient has not had a first subsequent therapy; the date last known not to have received a first subsequent therapy (TFST censoring date).

Analysis of PFS2 will be performed to compare T-DXd vs investigator's choice chemotherapy in HER2-low and ITT analysis sets using the same methodology as for PFS.

TFST

TFST is defined as time from randomization to the start date of the first subsequent anti-cancer therapy after discontinuation of randomized treatment or death due to any cause.

Patients alive and not known to have had a first subsequent anti-cancer treatment will be censored at the earliest of: date of study termination, date last known alive, DCO or, the last date that the patient was known not to have received a first subsequent anti-cancer treatment.

Analysis of TFST will be performed to compare T-DXd vs investigator's choice chemotherapy in HER2-low and ITT analysis sets using the same methodology as for PFS.

TSST

TSST is defined as time from randomization to the start date of the second subsequent anti-cancer therapy after discontinuation of randomized treatment or death due to any cause.

Patients alive and not known to have had a second subsequent anti-cancer treatment will be censored at the earliest of: date of study termination, date last known alive, DCO or, the last date that the patient was known not to have received a second subsequent anti-cancer treatment.

Analysis of TSST will be performed to compare T-DXd vs investigator's choice chemotherapy in HER2-low and ITT analysis sets using the same methodology as for PFS.

9.4.3 Safety

Safety summaries will be provided using the safety analysis set (SAF) and the HER2-low SAF. Safety data will be presented using descriptive statistics unless otherwise specified.

Baseline

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

Adverse Events

Adverse events will be coded using the most recent version of MedDRA that will be released for execution at AstraZeneca.

Any TEAE occurring until 47 days after the last dose of the study treatment and prior to the start of a new anticancer treatment will be included in the AE summaries. Any other AEs will be flagged in the data listings, but not included in the summaries.

An overview of TEAEs will be provided for each treatment group: the number and percentage of participants with any TEAE, TEAEs with outcome of death, serious TEAEs, and TEAEs leading to discontinuation of study treatment, as well as TEAEs leading to study treatment dose interruption, and TEAEs leading to study treatment dose reduction.

TEAEs will be presented for each treatment group by system organ class (SOC) and/or preferred term covering number and percentage of patients reporting at least one event and number of events where appropriate.

Separate TEAE tables will be provided taking into consideration the relationship of TEAE to study treatment as assessed by the Investigator, the CTCAE Grade, seriousness, death and events leading to discontinuation of study treatment as well as other action taken related to

study treatment, AESIs and other significant TEAEs (if applicable).

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

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

An AE listing will cover details for each individual AE.

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

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

Vital Signs

Vital sign parameters will be presented for each treatment group. Summary statistics for continuous variables cover number of patients (n), mean, standard deviation, median, Minimum (Min.) and Maximum (Max).

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. Summary statistics for continuous variables cover number of patients (n), mean, standard deviation, median, Min. and Max. Frequency tables and shift tables cover number and percentage of patients in the respective category.

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

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

A shift table for urinalysis will be presented with baseline assessment against the maximum on treatment category if a sufficient number of urinalysis assessments are recorded.

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

Details of laboratory analyses will be provided in the SAP.

9.4.4 Other Analyses

9.4.4.1 Patient-reported Outcomes

The main PRO endpoints identified in the secondary objectives are symptoms, functioning and HRQoL of the EORTC QLQ-C30 and EORTC QLQ-BR45. PROs are not part of the main MTP and will be analyzed as supportive endpoints. Further details of the analyses will be described in the SAP.

9.4.4.2 Healthcare Resource Utilization

An exploratory health economic analysis of hospital episodes including inpatient admissions, intensive care unit admissions, and length of stay in hospital to examine the impact of disease and treatment on resource use to primarily support the economic evaluation of T-DXd vs investigator's choice chemotherapy will be outlined in the payer analysis plan. This would include providing descriptive statistics as appropriate, including means, median, and ranges.

9.4.4.3 Pharmacokinetic Data

PK concentration data for T-DXd, total anti-HER2 antibody, and MAAA-1181a will be listed for each sampling time for each patient and each dosing day, and a summary will be provided for all evaluable patients. Descriptive statistics may be calculated.

If the data are suitable, the relationship between PK exposure and efficacy/safety parameters may be investigated graphically or using an appropriate data modeling approach.

9.4.4.4 Immunogenicity Data

Immunogenicity results will be listed by patient, and a summary will be provided by the number and percentage of patients who develop ADA for T-DXd. The immunogenicity titer and neutralizing ADA data will be listed for samples confirmed positive for the presence of T-DXd antibodies.

The effect of immunogenicity as well as the effect of its neutralizing properties on PK, pharmacodynamics, efficacy, and safety will be evaluated, if the data allow. A detailed plan will be written by the AstraZeneca Clinical Pharmacology group or designee.

9.5 Interim Analyses

9.5.1 Interim Futility Analysis

An interim futility analysis will be carried out after 70 patients have been randomized in the HER2 IHC >0 <1+ subgroup (approximately 35 per treatment group) and have had at least 24 weeks of follow-up from the point of randomization or withdrawn from the study. This is expected to occur approximately 20 months after the first patient is randomized. A non-binding stopping boundary will be applied to guide the decision of whether to limit recruitment to the HER2-low subgroup only. Confirmed ORR by Investigator assessments according to RECIST 1.1 in the HER2 IHC >0 <1+ analysis set will be used in the interim futility analysis. If the observed ORR difference (T-DXd vs investigator's choice chemotherapy) in the HER2 IHC >0 <1+ analysis set is ≤ -7%, the recommendation will be to stop enrollment in the HER2 IHC >0 <1+ subgroup. The stopping boundary was selected such that the probability of crossing the futility boundary is at most 10% if the true ORR difference (T-DXd vs investigator's choice chemotherapy) is at least 8%, assuming a 30% ORR in the chemotherapy arm. Furthermore, the probability of crossing the futility boundary is 7% if the true ORR difference is 10%, and 61%, if the true ORR difference is -10%, assuming a 30% ORR in the chemotherapy arm.

As supportive summaries, ORR, DoR, DCR at 24 weeks and PFS KM plot per Investigator assessment will also be provided using the HER2 IHC >0 <1+ analysis set. Further details will be included in the SAP.

The IDMC will make a recommendation on whether or not to stop recruitment in the HER2 IHC >0 <1+ population based on the results of the futility analysis. If recruitment in this subgroup is permanently stopped, patients already dosed may be allowed to continue treatment based on a case-by-case assessment at the discretion of the Investigator, and if the Investigator deems that a patient continues to derive clinical benefit from treatment.

9.5.2 Interim Efficacy Analysis

OS in the HER2-low population and ITT population will be tested at two interim analyses as described in Section 9.1.

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

9.6 Data Monitoring Committees

9.6.1 IDMC Committee

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. An IDMC comprised of independent experts will be convened and will meet approximately 6 months after the study

has started or after the first 60 patients have been randomized, whichever occurs first. The IDMC will review unblinded 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 and at each meeting make recommendations to continue, amend, or stop the study based on safety findings.

In addition, the IDMC will be asked to review efficacy data at pre-specified timepoints (e.g., interim futility analysis for HER2 IHC >0 <1+ subgroup). For further details on the futility analysis, see Section 9.5. Full details of the IDMC procedures, processes, and interim analyses can be found in the IDMC Charter.

9.6.2 ILD Adjudication Committee

An ILD Adjudication Committee will review all cases of potential ILD/pneumonitis. To ensure adequate evaluation, relevant additional data from within the clinical database and other sources, including imaging data, may be provided to the adjudication committee to fully characterize medical history (e.g., smoking, radiation and pulmonary history), diagnostic evaluation, treatment and outcome of the event. Further details can be found in the ILD Adjudication Charter.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., 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 patients.
- 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.

- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to AstraZeneca of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met.
- AstraZeneca 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. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- For all studies except those utilizing medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and AstraZeneca policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An investigator who receives an Investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from AstraZeneca will review and then file it along with the IB or other documents and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to the Sponsor of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A “serious breach” means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, the Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - The Sponsor will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, the Sponsor is required to enter

details of serious breaches into the EMA CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.

- The investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the Investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to the Sponsor or delegated party, through the contacts (e-mail address or telephone number) provided by the Sponsor.

A 2 Financial Disclosure

Investigators and sub-investigators will provide AstraZeneca with sufficient, accurate financial information as requested to allow AstraZeneca 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

- An optional pre-screen ICF may 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 patient or his/her legally authorized representative and answer all questions regarding the study.
- Patients 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. Patients 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 (CFR) 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) 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 patient 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.
- Patients 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 patient or the patient's legally authorized representative.

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

If a patient declines to participate in any voluntary exploratory genetic research component of

the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study.

If a patient's partner becomes pregnant during or within washout period (4 months after the last dose of T-DXd, 6 months after the last dose of paclitaxel or nab-paclitaxel, and 3 months after the last dose of capecitabine), the partner is asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Patients" and provide information about the pregnancy accordingly.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The patient will give a separate agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will indicate this in the ICF. If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analyzed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data Protection

The ICF will incorporate wording that complies with relevant data protection and privacy legislation. In some cases, such wording will be in a separate accompanying document. AstraZeneca will not provide individual genotype results to patients (with the exception of results from the optional biopsy at disease progression; these results will be provided back to the patient), their family members, their general physician, any insurance company, any employer, or any other third party, unless required to do so by law; however, AstraZeneca may share data and biosamples with research partners.

Precautions are taken to preserve confidentiality and prevent genetic data from being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and might also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files. Even so, the patient's medical information and the genetic files would remain physically separate.

- Patients will be assigned an unique identifier by AstraZeneca. Any patient records or datasets that are transferred to AstraZeneca will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

- The patient must be informed that his/her personal study-related data will be used by AstraZeneca in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the patient in the IC.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by AstraZeneca, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going 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://astrazenecagrouptrials.pharmacm.com* and *http://www.clinicaltrials.gov* as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

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

A 7 Data Quality Assurance

- All patient data relating to the study will be recorded on eCRF unless transmitted to AstraZeneca or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by 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 agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarised in the CSR.
- Monitoring details describing strategy, including definition of study-critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk

Management and Mitigation Strategies and Analytical Risk-based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are included in the internal sponsor documents like Integrated Quality Risk Management plan (IQRMP) and Monitoring Plan.

- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Medical Oversight Plan.
- AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.
- AstraZeneca assumes accountability for actions delegated to other individuals (e.g., CROs).
- Study monitors will perform ongoing source data verification as per the Monitoring Plan(s) 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 patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global Retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

A 8 Source Documents

- Source documents provide evidence for the existence of the patient 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 digital copy of all imaging scans should be stored as source documents.

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 patients.

AstraZeneca designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of AstraZeneca. 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 AstraZeneca 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, AstraZeneca's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, AstraZeneca shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

Patients 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 AstraZeneca before submission. This allows AstraZeneca to protect proprietary information and to provide comments.
- AstraZeneca will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, AstraZeneca 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 in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom (e.g., nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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 treatment has been administered.

B 2 Definitions of Serious Adverse Event

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

- Results in death
- Is immediately life-threatening
- Requires in-patient 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 patient or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events (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 judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **Non-Serious** AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumor event in question is a new malignant tumor (i.e., it is *not* the tumor for which entry into the study is a criterion and that is being treated by the investigational product 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 (e.g., 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 patient is 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 patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., 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 patient 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 judgement 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 patient or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement 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 (e.g., 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:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)

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

The grading scales found in the revised NCI CTCAE v5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE v5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

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

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

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

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

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

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

B 4 Medication Error, Drug Abuse, and Drug Misuse

B 4.1 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 drug 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 patient.

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; e.g., medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration

- Drug not taken as indicated; e.g., tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed; e.g., kept in the fridge when it should be at room temperature
- Wrong patient 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 that lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s); e.g., forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

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

B 4.2 Drug Abuse

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

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

Examples of drug abuse include but are not limited to:

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

B 4.3 Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study patient) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or

for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

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

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the patient feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

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

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

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

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca team 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

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.If a patient withdraws consent to the 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.

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 patients' 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 patient, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

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

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (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 e.g., 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 e.g., 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 patient 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 Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

Genetic variation may impact a patient's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting patients.

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.
- This optional genetic research may consist of the analysis of the structure of the patient´s DNA, i.e., the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- AstraZeneca will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on T-DXd continues but no longer than 15 years or other period as per local requirements.

D 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

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

Inclusion Criteria

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

Exclusion Criteria

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

Withdrawal of Consent for Genetic Research:

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

Collection of Samples for Genetic Research

- An optional blood sample will be obtained from the patients on Day 1 (first infusion day) prior to study treatment administration (at or after randomization). If for any reason the sample is not drawn on Day 1, it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE.

Coding and Storage of DNA Samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years from the date of last patient last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).
- The link between the patient enrollment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples

for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

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

Informed Consent

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

Patient Data Protection

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

Data Management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyze the samples.
- AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organizations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research

purposes. Researchers may see summary results, but they will not be able to see individual patient data or any personal identifiers.

- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

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 Potential Hy's Law (PHL) cases and Hy's Law (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 patient 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 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 Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the study treatment.

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

E 2 Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3×Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2×ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

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

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e., 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 patient 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 patient 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 patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient 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 patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (see Section E 6)
- 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

Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.

- For patients that met PHL criteria prior to starting study treatment, the Investigator is not required to submit a PHL SAE unless there is a significant change (see **note** below) in the patient's condition

- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up (including any further laboratory testing) and the continuous review of data

- Subsequent to this contact the Investigator will:

  – Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete follow-up SAE Form as required.
  – Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.
  – Complete the relevant Liver eCRF Modules as information becomes available

Note: 'A significant change' in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) 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 treatment, 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 patient matter experts as appropriate.

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

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a

determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

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

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

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

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

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

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

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

At the first on-study treatment occurrence of PHL criteria being met, the Investigator will determine if there has been a **significant change** in the patients' condition[#] compared with the last visit where PHL criteria were met[#]

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

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

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

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

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

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g., chronic or progressing malignant disease, severe infection or liver disease or did the patient meet PHL criteria prior to starting study treatment and at their first on-study treatment visit as described in Appendix E 6.

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

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

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

A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) 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 8 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory (Table 19). When local laboratories are used, this list may be modified according to clinical judgement. Any test result must be recorded.

Table 19 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 HBV DNA [a] 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	CD-transferrin [b]
Autoimmune hepatitis	ANA Anti-Liver/Kidney Microsomal Ab (Anti-LKM) ASMA
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin [b] Transferrin saturation

ANA = antinuclear antibody; ASMA = anti-smooth muscle antibody; CD = carbohydrate deficient; CMV = cytomegalovirus; DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; GGT = gamma glutamyl transferase; HAV = hepatitis A virus; HBc = hepatitis B core antibody; HBsAg = surface antigen of the hepatitis B virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; INR = international normalized ratio; IgG = immunoglobulin G; IgM = immunoglobulin M; LDH = lactate dehydrogenase; LKM = liver/kidney microsomal; RNA = ribonucleic acid;

[a] HCV RNA; HCV DNA are only tested when IgG anti-HCV is positive or inconclusive

[b] CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly

E 9 References

Aithal et al, 2011
Aithal et al, 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

FDA Guidance for Industry, July 2009
FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

Appendix F ASCO/CAP Guidelines on HER2 Testing in Breast Cancer

This protocol will determine human epidermal growth factor receptor 2 (HER2) status using guidelines from the American Society of Clinical Oncology (per ASCO/CAP 2018 guidelines). Per the guidelines, patients are HER2-negative if they have immunohistochemistry (IHC) 0/1+ or are fluorescent in situ hybridization (FISH) negative (Table 20).

Table 20 Summary of ASCO/CAP Guideline Recommendations 2018

Procedure	Recommendations
Optimal algorithm for HER2 testing	HER2 is positive if IHC 3+. HER2 IHC 2+ is equivocal (the revised definition of IHC 2+ [equivocal] is invasive breast cancer with "weak to moderate complete membrane staining observed in > 10% of tumor cells") and triggers ISH testing. Diagnostic criteria by ISH is defined by HER2 copy number (signals/cell) and, for dual probe assay, by HER2/CEP17 ratio: For dual probe assay, HER2-positive is defined as: • (Group 1) OR (Group 2 AND concurrent IHC 3+) OR (Group 3 AND concurrent IHC 2+ or 3+) OR (Group 4 AND concurrent IHC 3+) Where Groups 1-4 are defined: • Group 1: ratio ≥ 2.0 and ≥ 4.0 signals/cell • Group 2: ratio ≥ 2.0 and < 4.0 signals/cell • Group 3: ratio < 2.0 and ≥ 6.0 signals/cell • Group 4: ratio < 2.0 and ≥ 4.0 to < 6.0 signals/cell • Group 5: ratio < 2.0 and < 4.0 signals/cell For tumors in groups 2-4 by dual probe assay, definitive diagnosis will be made based on additional work-up as detailed in ASCO/CAP guidelines 2018. For single probe assay, HER2-positive is defined as: • (HER2 copy number ≥ 6.0 signals/cell) OR (HER2 copy number ≥ 4.0 and < 6.0 signals/cell AND concurrent IHC 3+) OR (HER2 copy number ≥ 4.0 and < 6.0 signals/cell AND concurrent dual probe Group 1). • All other tumors will be defined as HER2- as defined by ASCO/CAP 2018. 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

Procedure	Recommendations
ISH rejection criteria	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 two 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
IHC rejection criteria	Fixation for fewer than 6 hours or longer than 48 hours is not recommended Test is rejected and repeated or tested by FISH if: • 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

Procedure	Recommendations
Optimal tissue handling requirements	• Time from tissue acquisition to fixation should be as short as possible; samples for HER2 testing are fixed in 10% neutral buffered formalin for 6-72 hours. Samples should be sliced at 5-10 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 • Any exception to this process must be included in report
Optimal internal validation procedure	• Validation of test must be done before test is offered • Initial test validation requires 25-100 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 two 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
Optimal laboratory accreditation	• Onsite 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

ASCO/CAP American Society of Clinical Oncology/College of American Pathologists; CEP17, chromosome 17 centromere; FISH, fluorescent in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH in situ hybridization; QA, quality assurance.

Excerpt from: (Wolff et al 2018)

The following tables provide additional information from the ASCO/CAP Guidelines for what needs to be reported for IHC and FISH (Table 21 and Table 22).

Table 21 Reporting Elements for IHC

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 22 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)

Table 22 Reporting Elements for FISH (Local HER2 Test)

Patient identification information
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 (Response Evaluation Criteria in Solid Tumors)

Introduction

This appendix details the implementation of RECIST 1.1 guidelines. 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, Non-Target Lesions (NTLs), and New Lesions (NLs) is provided in Table 23.

Table 23 Summary of Imaging Modalities for Tumor Assessment

Target Lesions	Non-Target Lesions	New Lesions
CT	CT	CT
MRI	MRI	MRI
	Plain X-ray	Plain X-ray
	Chest X-ray	Chest X-ray
		Bone scan (Scintigraphy)
		FDG-PET/CT

CT = computed tomography; FDG-PET/CT = ^{18}F-Fluoro-deoxyglucose positron emission tomography/CT; MRI = magnetic resonance imaging.

CT and MRI

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 (i.e., for measurement of TLs, assessment of NTLs, and identification of NLs). It is essential that the same correct imaging modality, image acquisition parameters (e.g., anatomic coverage, imaging sequences, etc.), imaging facility, tumor assessor (e.g., radiologist), and method of tumor assessment (e.g., RECIST 1.1) are used consistently for each patient 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; Section 1.3), 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 (e.g., to investigate clinical signs/symptoms of progression) and the patient 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 (e.g., 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 patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, 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 timepoints are specified in the SoA (Section 1.3). 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 patients 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 patient 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 patient. 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

All patients 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 (q6w ±1 week from the date of randomization for 48 weeks, and then q9w ±1 week, starting at Week 48 thereafter until RECIST 1.1 disease progression per investigator assessment) are mandatory for all patients who were enrolled with baseline stable brain metastases, while patients without brain metastases do not need additional brain scans for subsequent tumor assessments, unless clinically indicated. Scans following investigator determined RECIST 1.1 progression should include brain scans for patients who are enrolled with baseline stable brain metastases or if 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, such as CT, be used to confirm the presence of NLs.

Plain X-ray[1]

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

All patients in this study will receive bone (scintigraphy) scans at screening/baseline. Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray at baseline should be recorded as NTLs and followed by the same method per baseline assessment (CT, MRI, or X-ray).

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. NLs may be recorded in case positive hot-spots appear on a bone scan that were not present on a previous bone scan; however, a newly observed equivocal hot-spot on a bone scan that cannot be verified with correlative imaging (CT, MRI, or X-ray) of the same anatomical region shall not be the only trigger for a PD assessment at that time point.

FDG-PET/CT

^{18}F-Fluoro-deoxyglucose positron emission tomography/computed tomography/CT (FDG-PET/CT) scans may be used as a method for identifying new 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 FDG-PET scan or in a location corresponding to a NL on a companion CT/MRI collected close in time to the FDG-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 FDG-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 FDG-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

[1] In this study, a patient with non-measurable, bone-only disease assessed by X-ray at screening must have lytic or mixed lytic bone lesions; i.e., bone-only patients with exclusively sclerotic (blastic) bone lesions in the absence of measurable disease are not eligible.

[2] A positive FDG-PET scan lesion should be reported only when an uptake (e.g., SUV) greater than twice that of the surrounding tissue or liver is observed.

contrast) to a dedicated diagnostic CT scan, then the CT portion of the PET/CT can be used for RECIST 1.1 tumor assessments. Caution that this is not recommended because the PET portion of the CT introduces additional (PET) data that may bias an Investigator if it is not routinely or serially performed.

Ultrasound

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

Other Tumor Assessments

Clinical Examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will 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 (e.g., 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 complete response (all other disease disappears/reverts to normal) would be changed to PR if an effusion remains present radiologically.

Measurability of Tumor Lesions at Baseline

RECIST 1.1 Measurable Lesions at Baseline:

A tumor lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter for non-nodal lesions or ≥15 mm in short axis[3] diameter for lymph node lesions with IV contrast-enhanced CT or MRI and that is suitable for accurate repeated measurements.

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

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]
- Brain metastasis [All patients in this study will receive an intravenous (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 patients who were enrolled with baseline stable brain metastases, while patients without brain metastases do not need additional brain scans for subsequent tumor assessments, unless clinically indicated.]

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 [6].

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

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

[6] In this study, a patient with non-measurable, bone-only disease assessed by X-ray at screening must have lytic or mixed lytic bone lesions; i.e., bone-only patients with exclusively sclerotic (blastic) bone lesions in the absence of measurable disease are not eligible.

- 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 patient, these should be selected over cystic lesions as TLs.

RECIST 1.1 TL Selection at Baseline:

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

Lymph nodes, in any location (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ (e.g., adrenal glands), a segmented organ (e.g., liver), or a multilobed organ (e.g., 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 whole (integer) millimeters and calculated values should be rounded to whole numbers. 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 maximal short axis diameter of the coalesced mass should be recorded. Non-nodal lesions that coalesce should similarly be assessed by the longest axis diameter.
- Tumor lesions selected for fresh screening biopsy should not be selected as TLs, unless imaging occurred at least approximately 2 weeks after biopsy, allowing time for healing.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.

- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as a New Lesion.

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 rounded to and recorded in whole millimeters. The sum of the diameters for all TLs at each follow-up visit will be compared to the baseline sum of diameters (for response or stable disease) 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 maximal short axis diameter is recorded.
- 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 an unscheduled, non-protocol intervention, the following apply:
  - Target Lesion Intervention may include radiotherapy, embolization, excisional biopsy, surgery, etc. that is not a part of study treatment and might adversely affect the size of that Target lesion

- If an Intervention on a Target Lesion is ticked in the case report form, the diameter of the lesion is still recorded (0 mm if no longer present) and is included in the sum of diameters.
- If a Target Lesion Intervention is ticked, the Intervention must be reported for all subsequent assessments of that Target lesion.
- If a Target Lesion has an Intervention, the only Overall Visit Responses allowed to be recorded by the Investigator are NE or PD, with PD if the sum of diameters exceeds a 20% increase and at least a 5 mm absolute increase in the visit sum of diameters compared to the previous minimum (nadir) sum of diameters.
- No visit with a recorded Target Lesion Intervention can be used as the minimum (nadir) sum of diameters.

Table 24 RECIST 1.1 Evaluation of Target Lesions

Complete response (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.
Partial response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.
Stable disease (SD)	Neither sufficient decrease in the sum of diameters to qualify for PR nor sufficient increase to qualify for PD.
Progression of disease (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.
Not evaluable (NE)	Only relevant if any of the TLs at follow-up were not assessed or not evaluable (e.g., missing anatomy) or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response.
Not applicable (NA)	Only relevant if no TLs present at baseline.

CR = complete response; NE = not evaluable; PD = progression of disease; PR = partial response; RECIST 1.1 = Response Evaluation Criteria In Solid Tumors, version 1.1; 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 PR of target disease will therefore be extremely rare (Table 25).

Table 25 RECIST 1.1 Evaluation of Non-target Lesions

Complete response (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.
Progression (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.
Not evaluable (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 patients 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 (NA)	Only relevant if no NTLs present at baseline

CR = complete response; NA = not applicable; NE = not evaluable; NTL = non-target lesion; PD = progression of disease; RECIST 1.1 = Response Evaluation Criteria In Solid Tumors, version 1.1; TL = target lesion

RECIST 1.1 New Lesion (NL) Identification at Follow-up

Details, including the imaging modality, the date of scan, and the location of any new lesion (NL) will also be recorded in the case report form. The presence of 1 or more NLs is assessed as progression. The finding of a NL should be unequivocal, i.e., 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 disease progression.

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 26.

Table 26 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) [a]
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

CR = complete response; NA = not applicable (only relevant if there were no target lesions at baseline or non-target lesions at baseline), NE = not evaluable; PD = progressive disease; PR = partial response; RECIST 1.1 = Response Evaluation Criteria In Solid Tumors, version 1.1; SD = stable disease; TL = target lesion.

[a] Non-CR/Non-PD for Overall Response if only NTLs (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.

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

- For patients with TLs (at baseline): CR, PR, SD, PD, or NE
- For patients 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 QC, storage, and for BICR. Guidelines for image acquisition, de-identification, storage of digital copies at the investigative site (as source documents), and transfer to the imaging CRO will be provided in a separate document. Electronic image transfer from the sites to the iCRO is strongly encouraged. A BICR of images will be performed at the discretion of AstraZeneca. Results of these independent reviews will not be communicated to Investigators, and results of Investigator RECIST 1.1 assessments will not be shared with the central reviewers. The management of patients will be based in part upon the results of the RECIST 1.1 assessment conducted by the Investigator. Further details of the BICR will be documented in the independent review charter (IRC).

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 Toxicity Management Guidelines for T-DXd

Each of the toxicities should be treated with maximum supportive care (including withholding the agent suspected of causing the toxicity if required).

If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned study drug along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for T-DXd. In addition, guidelines for T-DXd dose modifications are provided in Section 6.6. In the event of toxicity that cannot be managed by following the toxicity management guidelines for T-DXd, consider stopping treatment with T-DXd.

All dose modifications should be documented with clear reasoning and documentation of the approach taken.

All dose modifications (interruption, reduction, and/or discontinuation) should be based on the worst preceding toxicity. Specific criteria for interruption, re-initiation, dose reduction, and/or discontinuation of T-DXd are listed in Table 27, which is applicable only to TEAEs that are assessed as related to use of T-DXd by the Investigator. For non-drug related TEAEs, follow standard clinical practice. Appropriate clinical experts should be consulted as deemed necessary.

If AE causality is possibly, probably, or definitely related to T-DXd, the most conservative toxicity guidance should be adopted. Discussion with AstraZeneca's Study Physician is recommended in such cases.

Table 27 Toxicity Management Guidelines for T-DXd

Worst toxicity CTCAE v 5.0 Grade (unless otherwise specified)	**Management guidelines for T-DXd**
No toxicity	Maintain dose and schedule
Infusion-related reaction	
Grade 1 (Mild transient reaction; infusion interruption not indicated; intervention not indicated)	If infusion related reaction (such as fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnea, and/or hypotension) is observed during administration, the infusion rate should be reduced by 50%, and patients should be closely monitored. If no other reactions appear, the subsequent infusion rate could be resumed at the initial planned rate.

Table 27 Toxicity Management Guidelines for T-DXd

Worst toxicity CTCAE v 5.0 Grade (unless otherwise specified)	**Management guidelines for T-DXd**
Grade 2 (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, and/or IV fluids); prophylactic medications indicated for ≤24 hrs)	Administration of T-DXd should be interrupted [a] and symptomatic treatment started (e.g., antihistamines, NSAIDs, narcotics, and/or IV fluids). If the event resolves or improves to Grade 1, infusion can be restarted at a 50% reduced infusion rate. Subsequent administrations should be conducted at the reduced rate.
Grade 3 or 4 (Prolonged or life-threatening consequences; urgent intervention indicated)	Administration of T-DXd should be discontinued immediately and permanently. Urgent intervention indicated. Antihistamines, steroids, epinephrine, bronchodilators, vasopressors, intravenous fluid therapy, oxygen inhalation, etc., should be administered.
Hematologic toxicity (if supportive therapy fails [as clinically indicated and according to local practice], consider additional TMG as below). For any Grade 4 hematological toxicity with significant clinical symptoms that does not resolve with treatment within 4 weeks, resuming the investigational medicinal product may be possible if the toxicity resolved, in consultation with the study physician.	
Neutrophil count decreased and/or white blood cell count decreased	
Grade 3	Delay dose [a] until resolved to ≤ Grade 2, then maintain dose
Grade 4	Delay dose [a] until resolved to ≤ Grade 2, then reduce dose 1 level
Febrile neutropenia (absolute neutrophil count < 1×10^9/L, fever > 38.3°C, or a sustained temperature of ≥ 38 °C for more than 1 hour)	Delay dose [a] until resolved, then reduce dose 1 level
Lymphocyte count decreased [b]	
Grade 1 to Grade 3 lymphopenia	No dose modification
Grade 4 (< 0.2×10^9/L)	Delay dose [a] until resolved to ≤ Grade 2: If resolved in ≤ 14 days from day of onset, then maintain dose If resolved in > 14 days from day of onset, then reduce dose 1 level
Anemia	
Grade 3 (Hemoglobin < 8.0 g/dL); transfusion indicated	Delay dose [a] until resolved to ≤ Grade 2, then maintain dose
Grade 4 Life threatening consequences; urgent intervention indicated	Delay dose [a] until resolved to ≤ Grade 2, then reduce dose 1 level

Table 27 Toxicity Management Guidelines for T-DXd

Worst toxicity CTCAE v 5.0 Grade (unless otherwise specified)	**Management guidelines for T-DXd**
Platelet count decreased	
Grade 3 (platelets < 50 to 25 × 10^9/L)	Delay dose [a] until resolved to ≤ Grade 1: If resolved in ≤ 7 days from day of onset, then maintain dose If resolved in > 7 days from day of onset, then reduce dose 1 level
Grade 4 (platelets < 25 × 10^9/L)	Delay dose [a] until resolved to ≤ Grade 1, then reduce dose 1 level
Cardiac toxicity	
Symptomatic CHF	Discontinue patient from study treatment
Decrease in LVEF 10% to 20% (absolute value), but LVEF > 45%	Continue treatment with T-DXd
LVEF 40% to ≤ 45% and decrease is < 10% (absolute value) from baseline	Continue treatment with T-DXd Repeat LVEF assessment within 3 weeks
LVEF 40% to ≤ 45% and decrease is 10% to 20% (absolute value) from baseline	Interrupt [a] T-DXd dosing Repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% (absolute value) from baseline, discontinue patient from study treatment If LVEF recovers to within 10% from baseline, resume study drug treatment
LVEF < 40% or > 20% (absolute value) drop from baseline	Interrupt [a] T-DXd dosing. Repeat LVEF assessment within 3 weeks. If LVEF < 40% or > 20% drop from baseline is confirmed, discontinue patient from study treatment If LVEF has recovered to > 40% and decrease is < 20% from baseline, follow appropriate guidance above
Electrocardiogram QTcF prolonged	
Grade 3 (Average QTcF > 500 ms or > 60 ms change from baseline)	Delay dose [a] until resolved to ≤ Grade 1 (corrected QTcF≤ 480 ms), then determine if another medication the patient was taking may be responsible and can be adjusted or if there are any changes in serum electrolytes that can be corrected. If attributed to T-DXd, reduce dose 1 level
Grade 4 (Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Discontinue patient from study treatment

Table 27 Toxicity Management Guidelines for T-DXd

Worst toxicity CTCAE v 5.0 Grade (unless otherwise specified)	Management guidelines for T-DXd
Pulmonary Toxicity	Any evidence of ILD/pneumonitis should be promptly investigated: If a patient develops radiographic changes potentially consistent with ILD/pneumonitis or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea (resting or exertional), cough, fever, unexplained fatigue or decrease in oxygen saturation, rule out ILD/pneumonitis. Evaluations should include: • High resolution CT • Pulmonologist consultation (infectious disease consultation as clinically indicated) • COVID-19 test • Blood culture and complete blood count, differential WBC count, CRP. • Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible • Pulmonary function tests (including forced vital capacity (FVC) and carbon monoxide (CO) diffusing capacity) and pulse oximetry (SpO2) • Arterial blood gases if clinically indicated • One blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible • Additional blood samples for plasma and serum exploratory biomarker analysis as soon as ILD/pneumonitis is suspected, if feasible Other tests could be considered, as needed. Appropriate management for ILD/pneumonitis should be instituted promptly as per management guideline below when ILD is suspected. If the AE is confirmed to have an etiology other than treatment-related ILD/pneumonitis, follow the management guidance outlined in the "Other Non-Laboratory Adverse Events" dose modifications. If another etiology for the AE cannot be identified and it could be related to T-DXd, then follow the ILD/pneumonitis management guidance as outlined below. Consideration should be given to the possibility of an alternate etiology occurring concurrently with DI-ILD. Whenever corticosteroids have been administered, the dose should be tapered gradually over at least 4 weeks even if an alternate etiology is confirmed. All events of ILD/pneumonitis regardless of severity or seriousness should be followed until resolution.

Table 27 Toxicity Management Guidelines for T-DXd

Worst toxicity CTCAE v 5.0 Grade (unless otherwise specified)	Management guidelines for T-DXd
Grade 1	Management: Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry, then weekly as indicated Consider follow-up imaging in 1-2 weeks (or as clinically indicated) Consider starting systemic steroids (e.g. at least 0.5 mg/kg/day prednisone/prednisolone or equivalent) until improvement, followed by gradual taper over at least 4 weeks If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines * Dose modification: The administration of T-DXd must be interrupted. T-DXd can be restarted only if the event is fully resolved to Grade 0: If resolved in ≤ 28 days from day of onset, maintain dose If resolved in > 28 days from day of onset, reduce dose 1 level Management of Grade 1 ILD/Pneumonitis: If the event Grade 1 ILD/pneumonitis occurs beyond cycle Day 22 and has not resolved within 18 weeks (126 days) from the last infusion, the drug should be discontinued. * If a patient is asymptomatic, then the patient should still be considered as Grade 1 even if steroid treatment is given.
Grade 2	Dose Modification: Permanently discontinue patient from study treatment. Management: Promptly start and treat with systemic steroids (e.g., at least 1 mg/kg/day prednisone/prednisolone or equivalent) for at least 14 days followed by a gradual taper over at least 4 weeks Monitor symptoms closely Re-image as clinically indicated If worsening or no improvement in clinical or diagnostic observations in 3-5 days, Consider increasing dose of steroids (e.g., 2 mg/kg/day prednisone/prednisolone or equivalent) and switching treatment administration to intravenous (e.g., methylprednisolone) Re-consider additional work-up for alternative etiologies as described above Escalate care as clinically indicated

Table 27 Toxicity Management Guidelines for T-DXd

Worst toxicity CTCAE v 5.0 Grade (unless otherwise specified)	**Management guidelines for T-DXd**
Grade 3 or 4	Dose modification: Permanently discontinue patient from study treatment. Management: Hospitalization required Promptly initiate empiric high-dose methylprednisolone IV treatment (e.g., 500-1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone/prednisolone (or equivalent) for at least 14 days followed by gradual taper over at least 4 weeks Re-image as clinically indicated If still no improvement within 3 to 5 days, Re-consider additional work-up for alternative etiologies as described above Consider other immunosuppressants and/or treat per local practice
Ocular	
Grade 3	Delay dose [a] until resolved to ≤ Grade 1: If resolved in ≤ 7 days from day of onset, then maintain dose If resolved in > 7 days from day of onset, then reduce dose 1 level
Grade 4	Discontinue patient from study treatment
Blood creatinine increased	
Grade 3 (> 3.0 to 6.0 × ULN)	Delay dose [a] until resolved to ≤ Grade 2 or baseline, then reduce dose 1 level
Grade 4 (> 6.0 × ULN)	Discontinue patient from study treatment
Hepatic toxicity	
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) with simultaneous blood bilirubin increased	
AST/ALT ≥ 3.0 x ULN with simultaneous total bilirubin > 2.0 × ULN	Delay study medication [a] until drug-induced liver injury can be ruled out. If drug-induced liver injury is ruled out, the patient should be treated accordingly, and resumption of study drug may occur after discussion between the Investigator and Sponsor. If drug-induced liver injury cannot be ruled out from diagnostic workup, permanently discontinue study treatment. Monitor AST/ALT and total bilirubin twice weekly until resolution or return to baseline.

Table 27 Toxicity Management Guidelines for T-DXd

Worst toxicity CTCAE v 5.0 Grade (unless otherwise specified)	Management guidelines for T-DXd
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)	
Grade 2 (> 3.0 to 5.0 × ULN if baseline was normal; > 3.0 to 5.0 × baseline if baseline was abnormal)	No action for Grade 2 AST/ALT
Grade 3 (> 5.0 to 20.0 × ULN if baseline was normal; > 5.0 to 20.0 × baseline if baseline was abnormal) In patients without liver metastases and patients with liver metastases and baseline level ≤ 3 × ULN	Repeat testing within 3 days. Delay dose[a] until resolved to ≤ Grade 1 if baseline ≤ 3 x ULN, otherwise delay dose until resolved to ≤ baseline, then: If resolved in ≤ 7 days from day of onset, then maintain dose If resolved in > 7 days from day of onset, then reduce dose 1 level
Grade 3: (> 8.0 to 20.0 × ULN if baseline was normal; > 8.0 to 20.0 × baseline if baseline was abnormal) In patients with liver metastases, if the baseline level was > 3 × ULN	Repeat testing within 3 days. Delay dose[a] until resolved to ≤ baseline level: If resolved in ≤ 7 days from day of onset, then maintain dose If resolved in > 7 days from day of onset, then reduce dose 1 level
Grade 4 (> 20 × ULN if baseline was normal; > 20.0 × baseline if baseline was abnormal)	Discontinue patient from study treatment
Blood bilirubin increased	
Grade 2 (> 1.5 to 3.0 × ULN if baseline was normal; > 1.5 to 3.0 × baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, delay dose [a] until resolved to ≤ Grade 1: If resolved in ≤ 7 days from day of onset, then maintain dose If resolved in > 7 days from day of onset, then reduce dose 1 level If documented Gilbert's syndrome or liver metastases at baseline, continue study treatment
Grade 3 (> 3.0 to 10.0 × ULN if baseline was normal; > 3.0 to 10.0 × baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose [a] until resolved to ≤ Grade 1: If resolved in ≤ 7 days from day of onset, then reduce dose 1 level If resolved in > 7 days from day of onset, then discontinue T-DXd If documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose [a] until resolved to ≤ Grade 2: If resolved in ≤ 7 days from day of onset, then reduce dose 1 level If resolved in > 7 days from day of onset, then discontinue T-DXd
Grade 4 (> 10.0 × ULN if baseline was normal; > 10.0 × baseline if baseline was abnormal)	Discontinue patient from study treatment

Table 27 Toxicity Management Guidelines for T-DXd

Worst toxicity CTCAE v 5.0 Grade (unless otherwise specified)	Management guidelines for T-DXd
Blood alkaline phosphatase increased	
Grade 3 (> 5.0 to 20.0 × ULN if baseline was normal; > 5.0 to 20.0 × baseline if baseline was abnormal) Or Grade 4 (> 20.0 × ULN if baseline was normal; > 20.0 × baseline if baseline was abnormal)	No modification unless determined by the Investigator to be clinically significant or life-threatening.
Gastrointestinal	
Nausea	
Grade 3	Delay dose [a] until resolved to ≤ Grade 1: If resolved in ≤ 7 days from day of onset, then maintain dose If resolved in > 7 days from day of onset, then reduce dose 1 level
Diarrhea/Colitis	
Grade 3	Delay dose [a] until resolved to ≤ Grade 1: If resolved in ≤ 3 days from day of onset, then maintain dose If resolved in > 3 days from day of onset, then reduce dose 1 level
Grade 4	Discontinue patient from study treatment
Other laboratory adverse events	
Grade 3	Delay dose [a] until resolved to ≤ Grade 1 or baseline level: If resolved in ≤ 7 days from day of onset, then maintain dose If resolved in > 7 days from day of onset, then reduce dose 1 level
Grade 4	Discontinue patient from study treatment
Other non-laboratory adverse events	
Grade 3	Delay dose [a] until resolved to ≤ Grade 1 or baseline: If resolved in ≤ 7 days from day of onset, then maintain dose If resolved in > 7 days from day of onset, then reduce dose 1 level
Grade 4	Discontinue patient from study treatment

AE = adverse event; ALT = alanine transaminase; AMI = acute myocardial infarction; AST = aspartate transaminase; CHF = congestive heart failure; CT = computer tomography; CTCAE = common terminology criteria for adverse events; ECG = electrocardiogram; ILD = interstitial lung disease; IV = intravenous; LVEF = left ventricular ejection fraction; NSAIDS = non-steroidal anti-inflammatory drugs; PK = pharmacokinetics; SpO2 = pulse oximetry; TMGs = toxicity management guidelines; ULN = upper limit normal

[a] See Section 6.6 Dose Modifications

[b] There will be no dose modifications for Grade 1 to Grade 3 lymphopenia

Note: All dose modifications should be based on the worst preceding toxicity

Appendix I Instructions Related to COVID-19

I 1 Concomitant Medication and T-DXd Dose Modification Relevant to COVID-19

Prior and concomitant medications

Treatment for COVID-19 is evolving, and the Investigator should consult the product label for any treatments considered.

Dose modification criteria

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

All confirmed or suspected COVID-19 infection events must be recorded in the eCRF. If a subject presents to the clinic with symptoms suggestive of COVID-19, infection should be confirmed via NAAT (nucleic acid amplification test such as RT-PCR) or rapid antigen testing. SARS-CoV-2 antigen testing can be used to confirm infection, but not to rule it out. 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 and report COVID-19-related AEs.

Dose modification criteria for suspected or confirmed COVID-19

If asymptomatic or symptomatic COVID-19 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, manage COVID-19 per local guidance until recovery from COVID-19 (no respiratory signs/symptoms of COVID 19, and completely or nearly resolved chest CT findings which are equivalent to CT Severity Score of 1 or 2 (CT Severity Score of 1 = Subtle Ground Glass Opacities and very few findings; CT Severity Score of 2 = Several Ground Glass Opacities and/or subtle reticulation)*.
  * *Luger AK, et al. Chest CT of lung injury 1 year after COVID-19 Pneumonia: The CovILD study. Radiology 2022;304(2):462-70.*
- After recovery, then follow below dose modifications:
  - If grade 1, resume T-DXd at the same dose
  - If grade 2

- Maintain same dose if chest CT findings are completely resolved.
- Reduce dose 1 level if chest CT findings are nearly resolved (equivalent to CT Severity Score of 1 or 2).

- If grade 3
  - Reduce dose 1 level if chest CT findings are completely resolved.
  - Otherwise, discontinue study treatment if chest CT findings are **not** completely resolved.
- If grade 4, discontinue study treatment.

Closely monitor signs/symptoms after restarting T-DXd, initially with a weekly phone call or site visit for 6 weeks.

- If an event is suspected to be drug-related ILD/pneumonitis, manage per protocol ILD/pneumonitis management guideline.

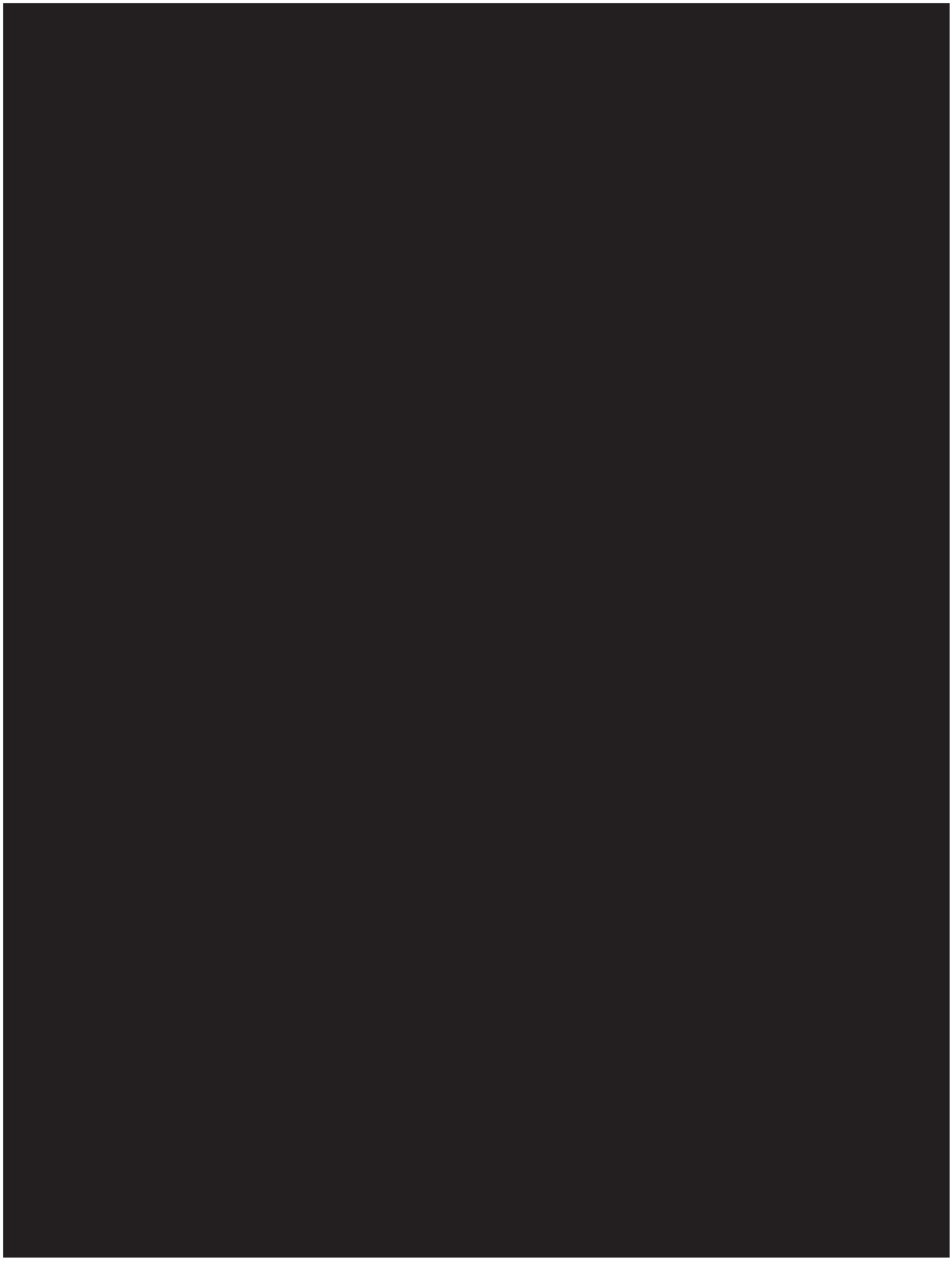
I 2 Benefit/Risk Considerations for COVID-19

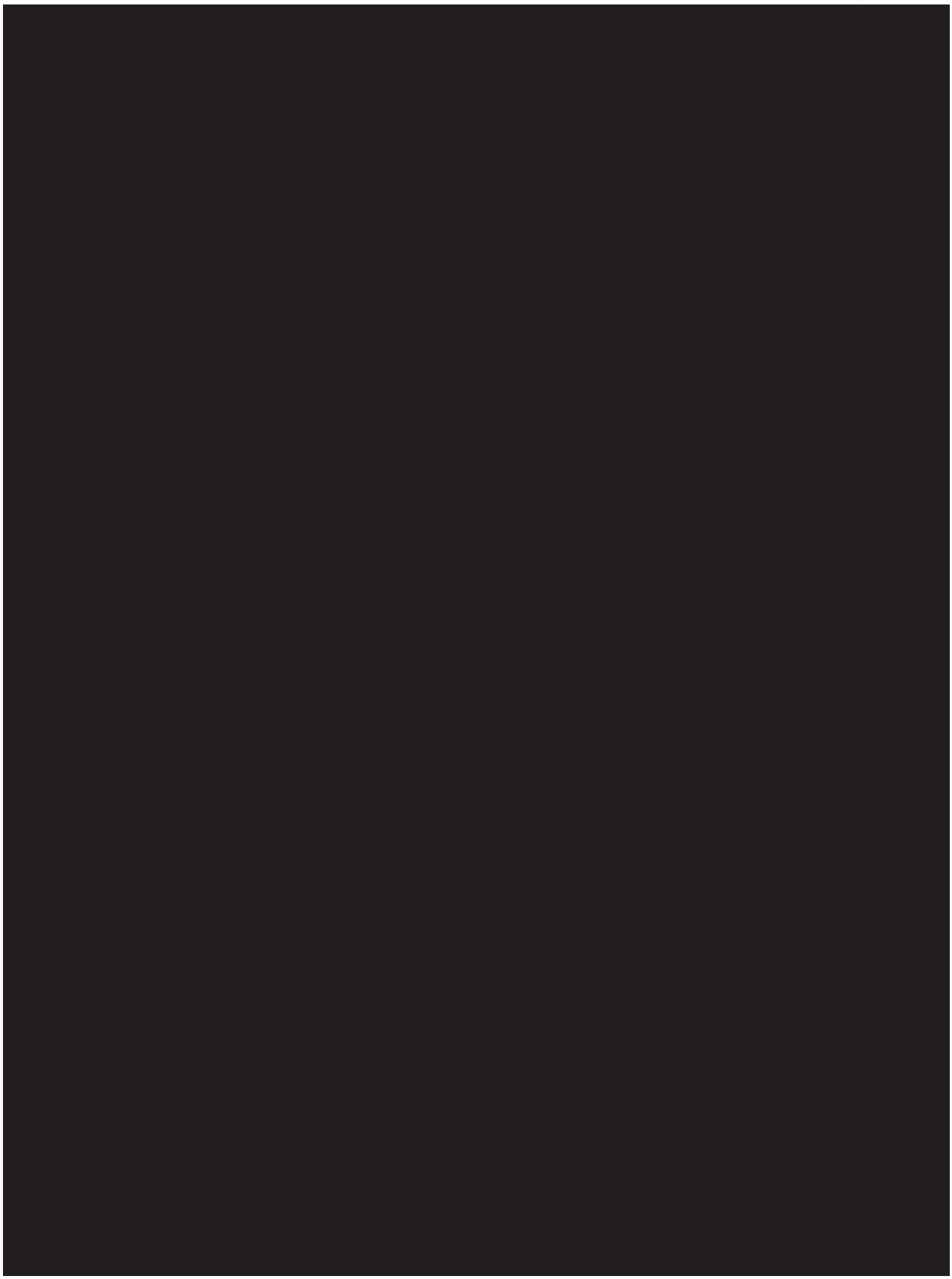
The emergence of coronavirus 2019-nCoV (COVID-19) infection presents a potential safety risk for patients, therefore, several risk mitigation factors have been implemented in this study. Notably, the eligibility criteria exclude patients with COVID-19 infections (see Section 5.2).

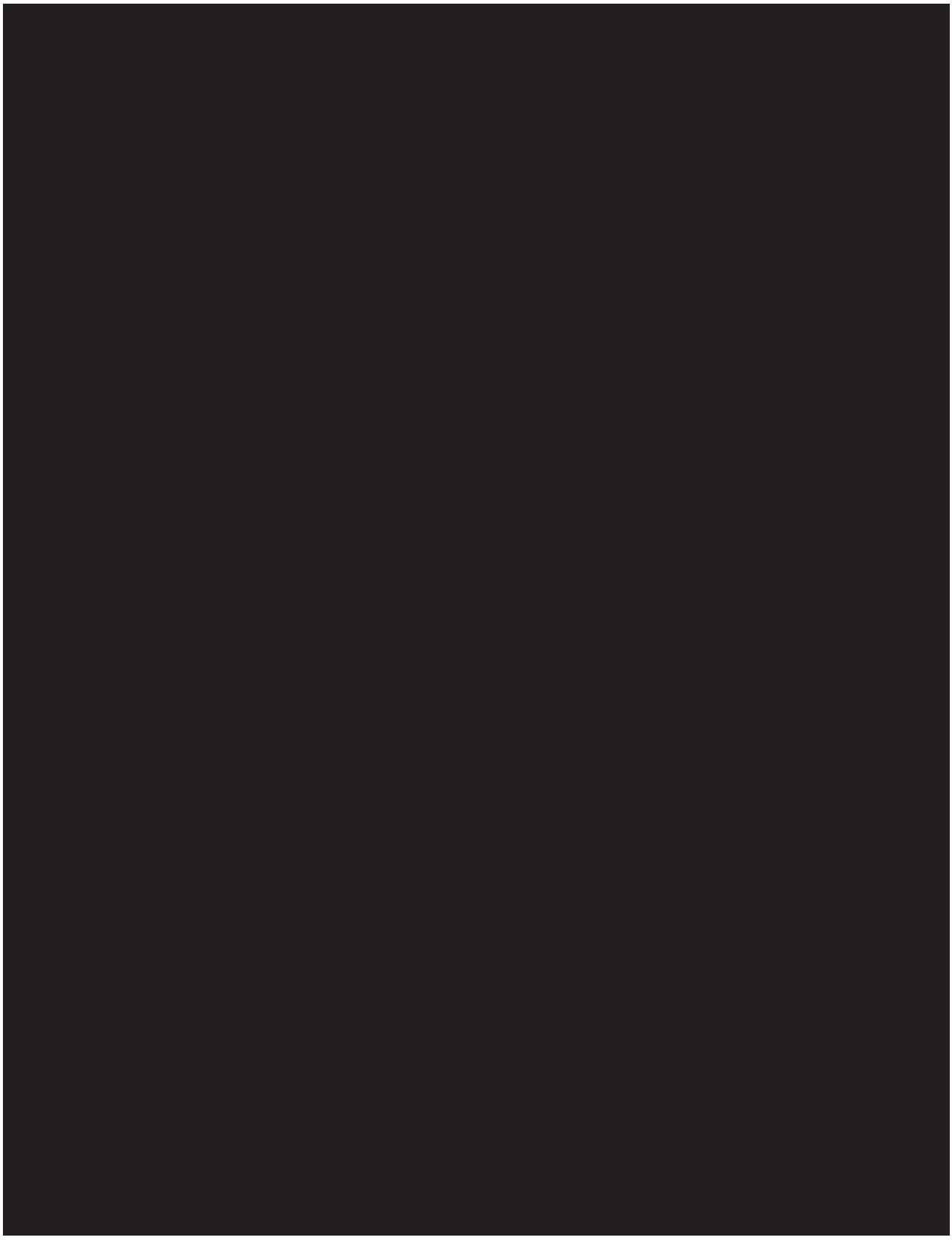
Due to the potential overlapping impact of T-DXd and COVID-19 on the lung, the Sponsor has also provided in this appendix, a dose modification and management plan for patients with confirmed or suspected COVID-19 who are being treated with T-DXd.

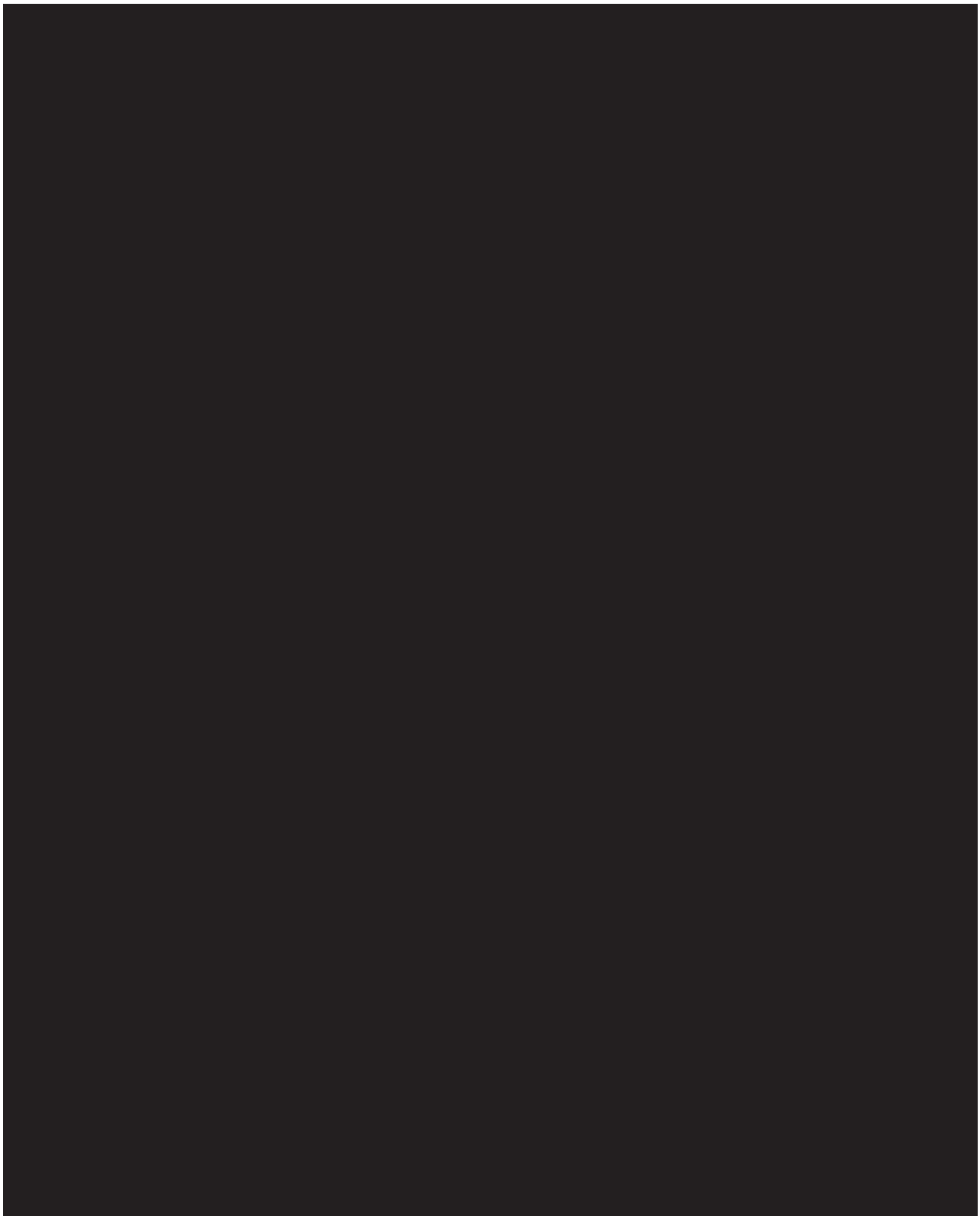
With these measures in place, it is considered the anticipated potential benefits for the patients enrolled in this study outweigh the potential risks.

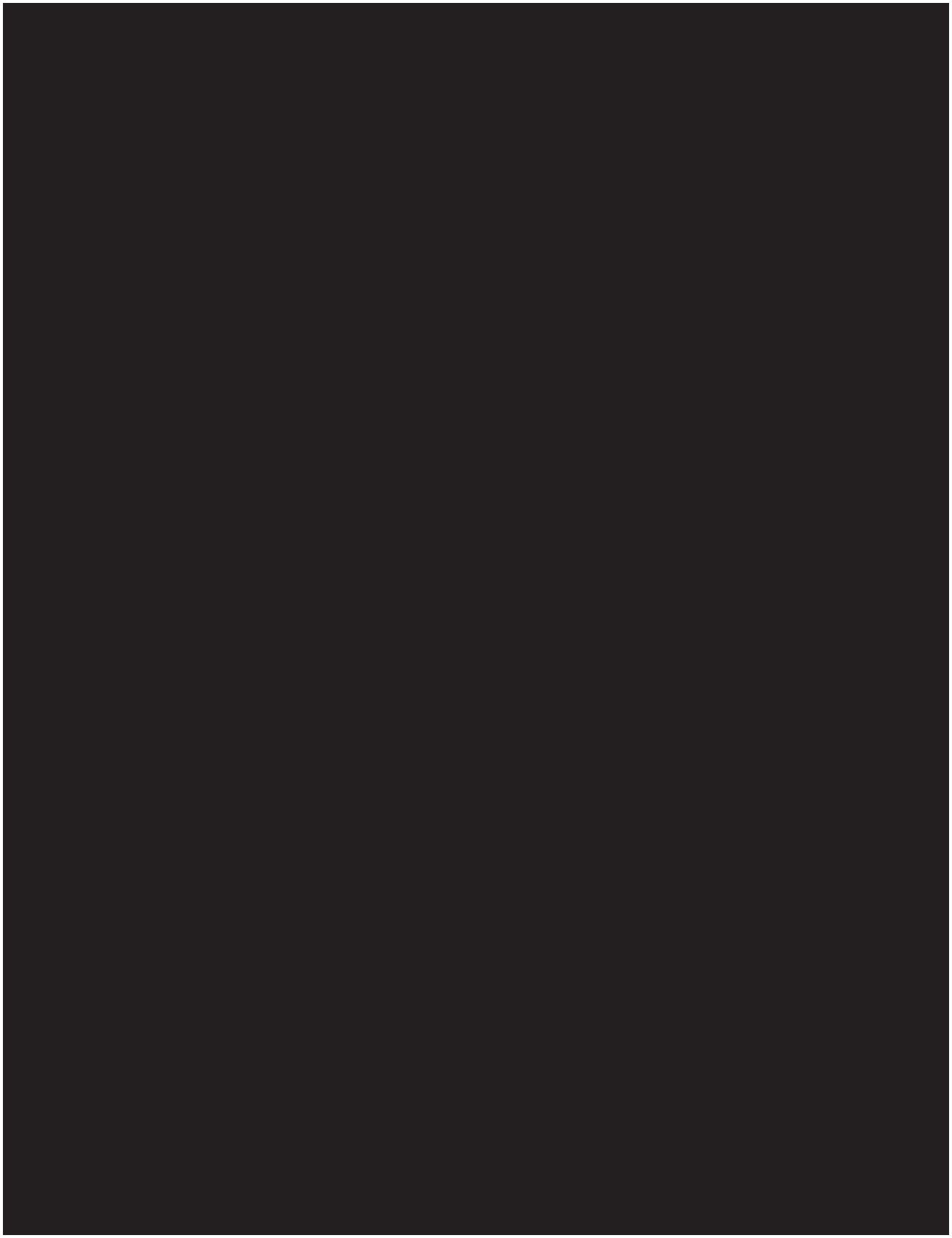
Appendix J European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 and BR45

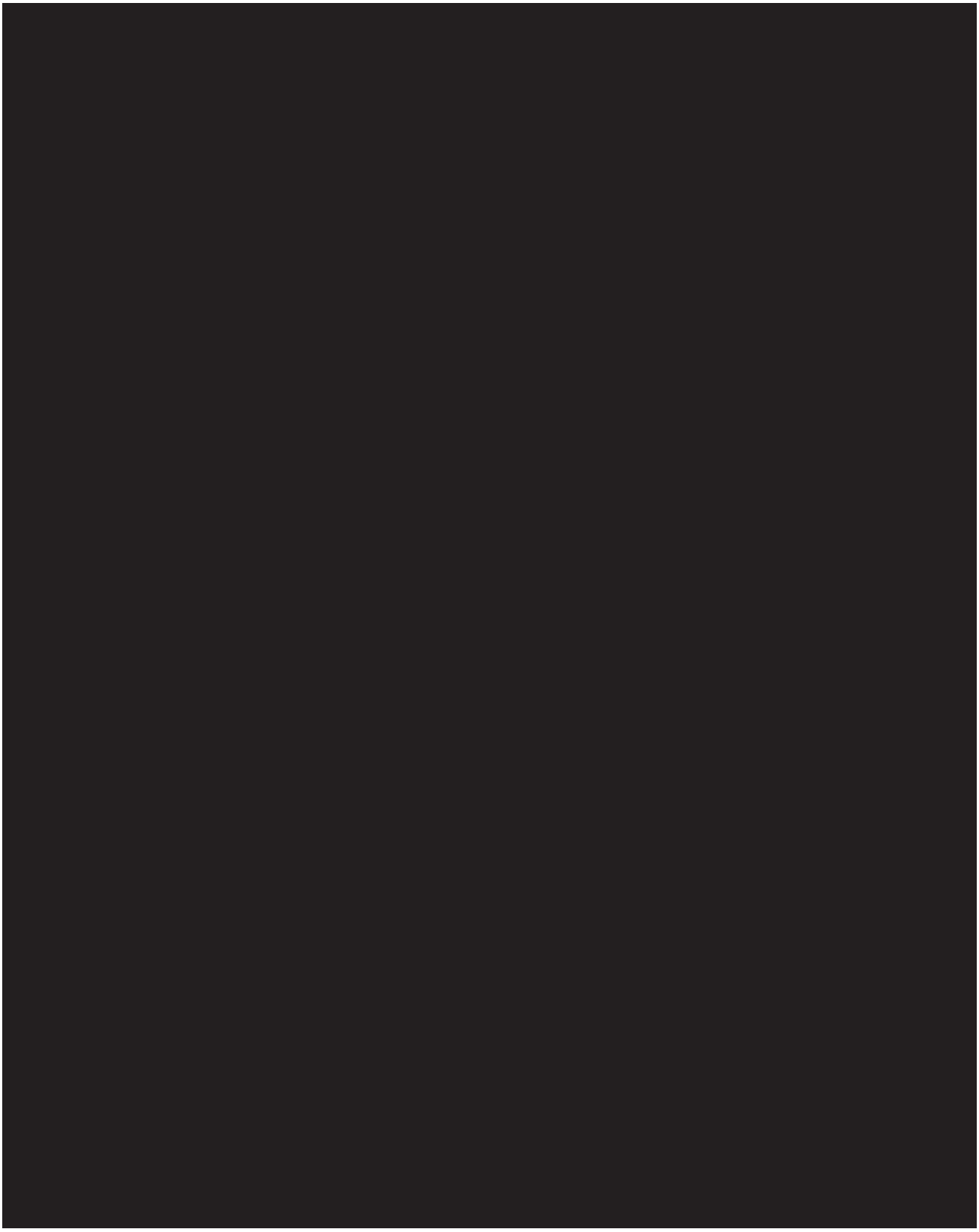


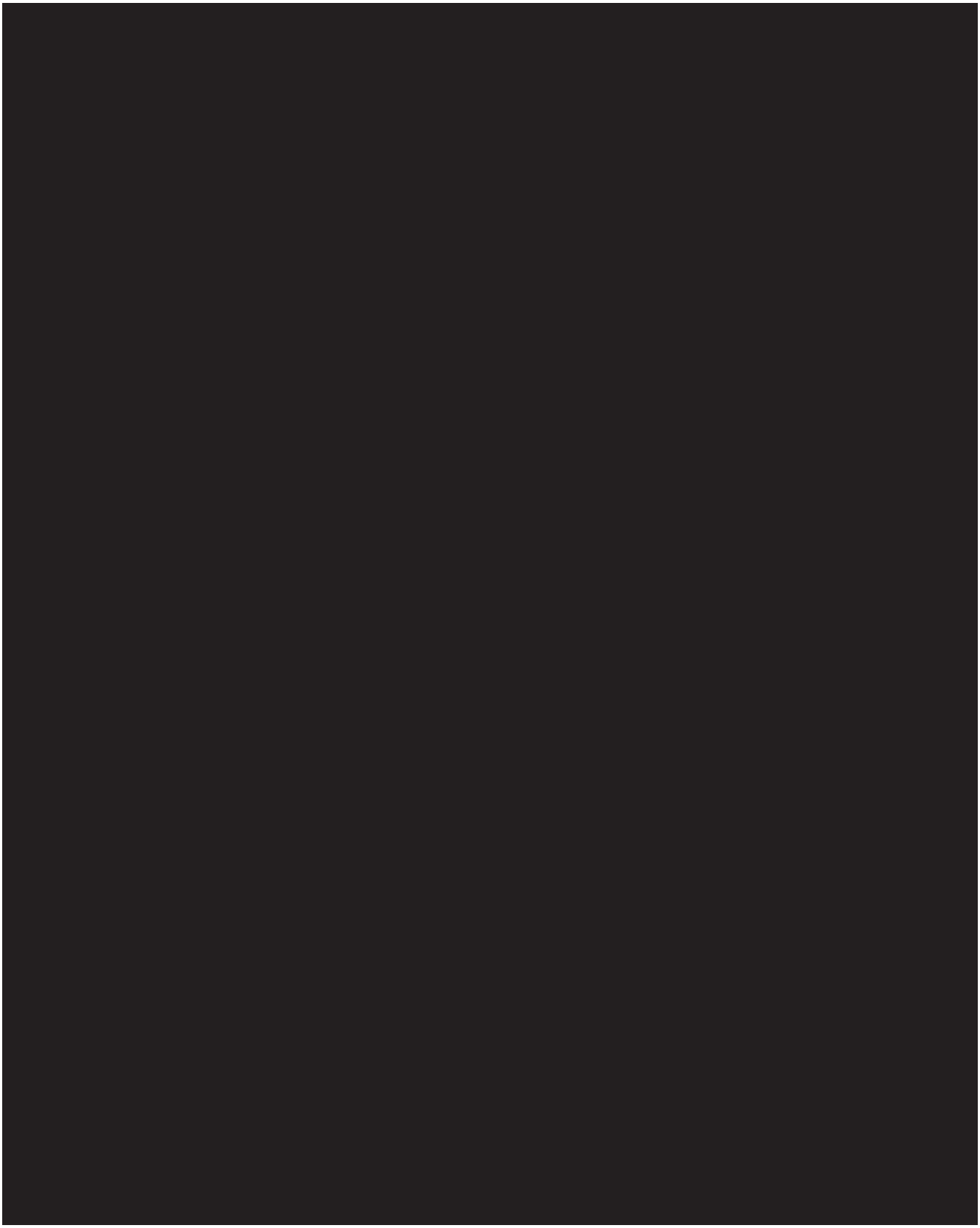


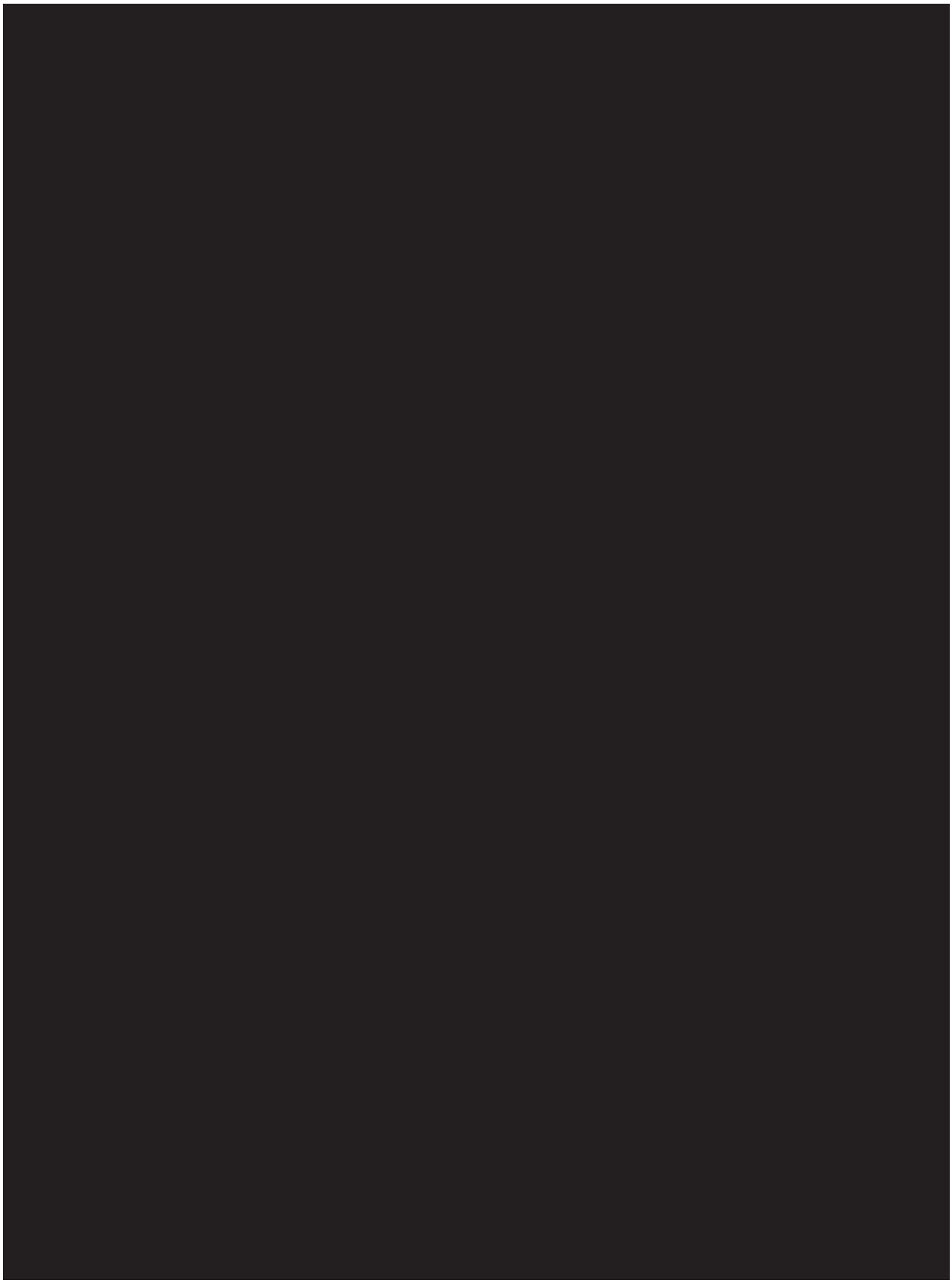


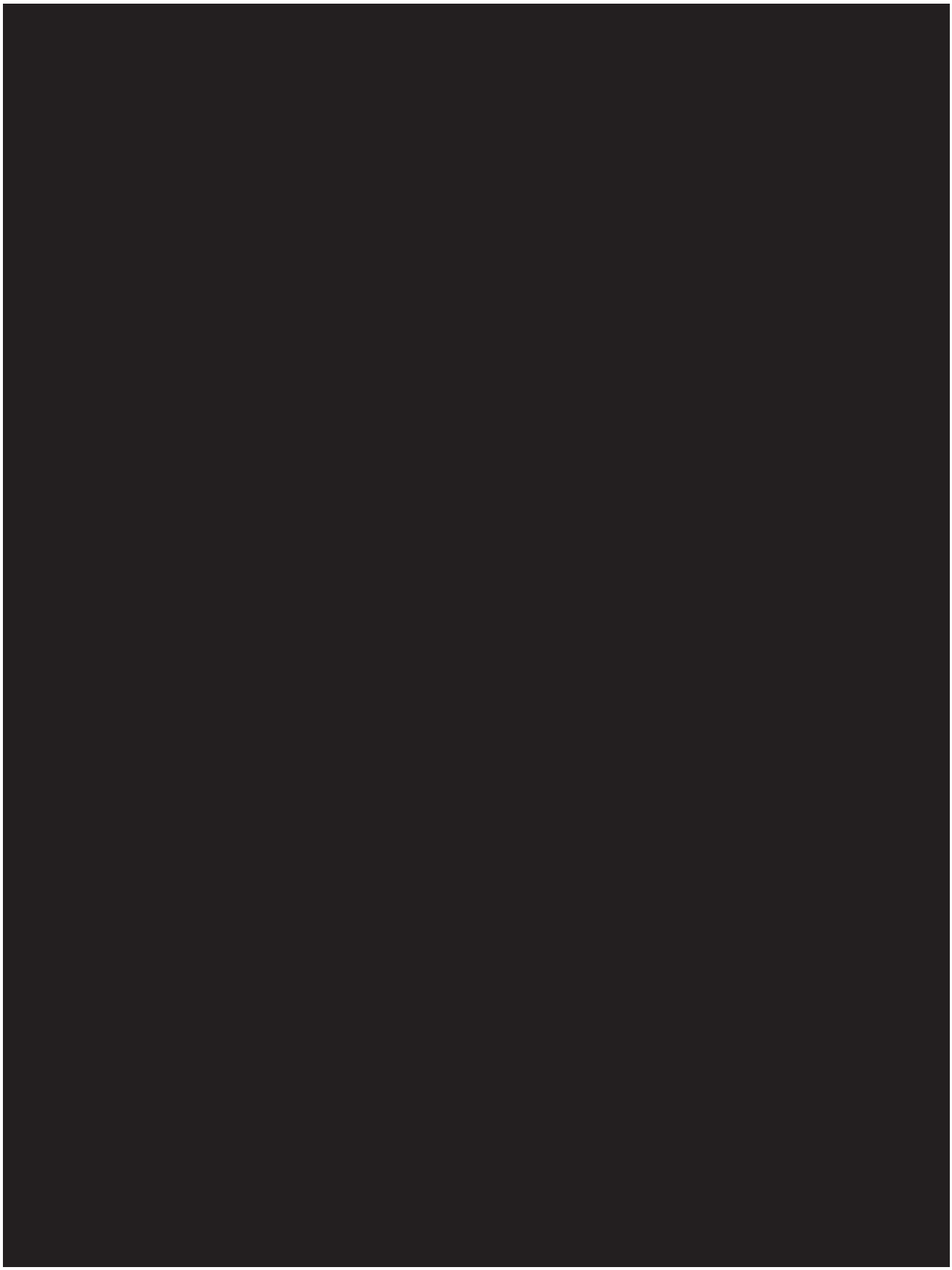


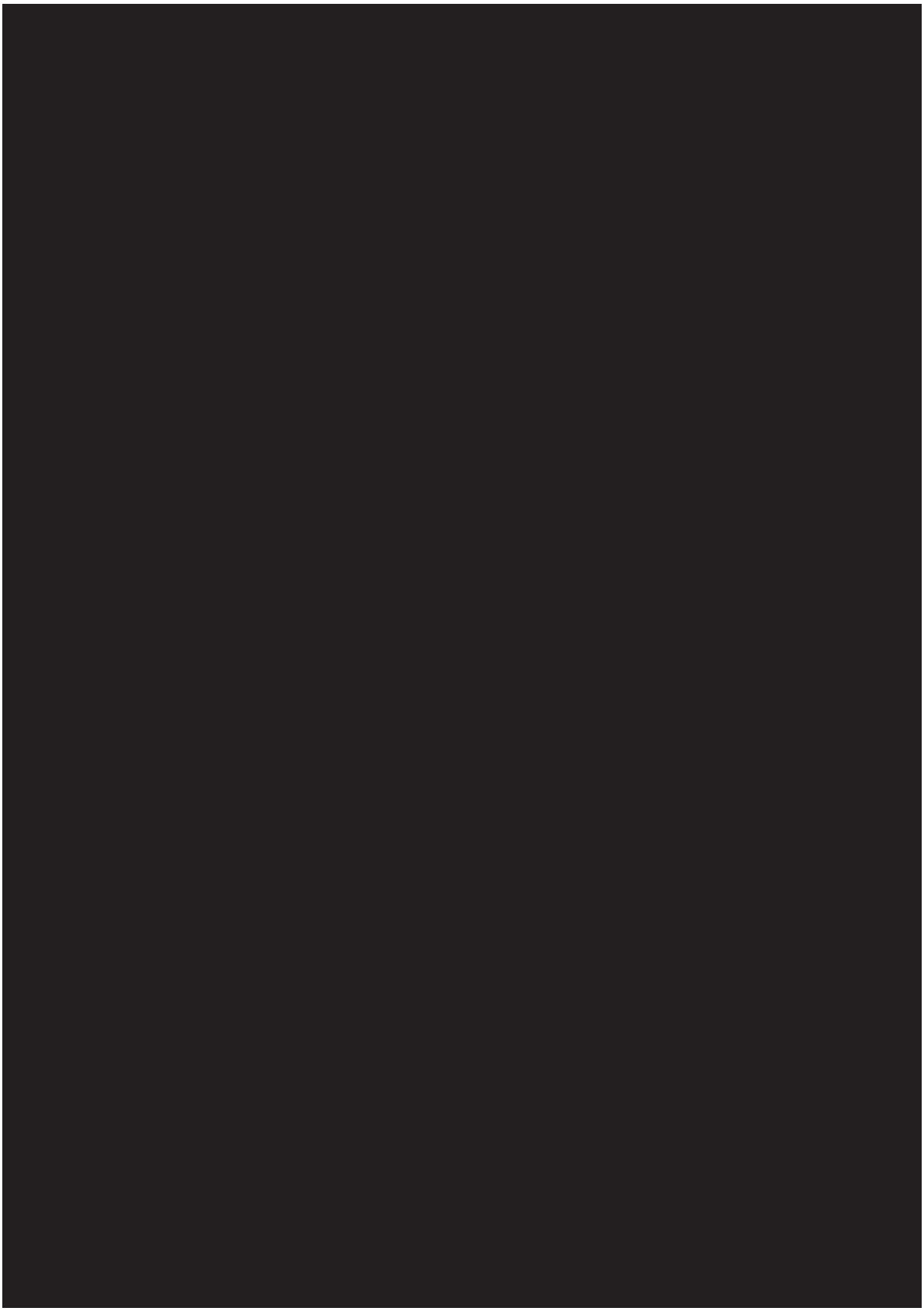


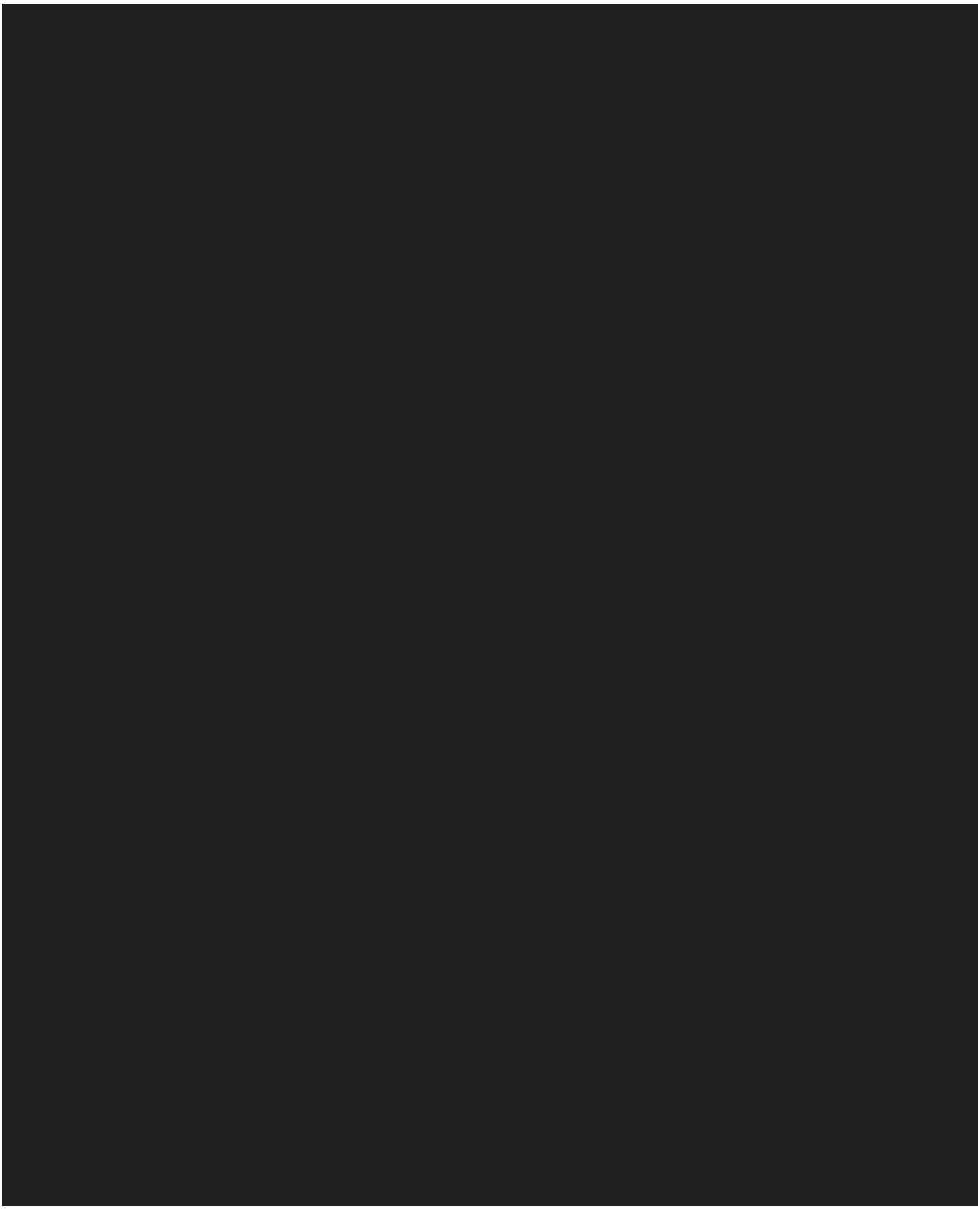


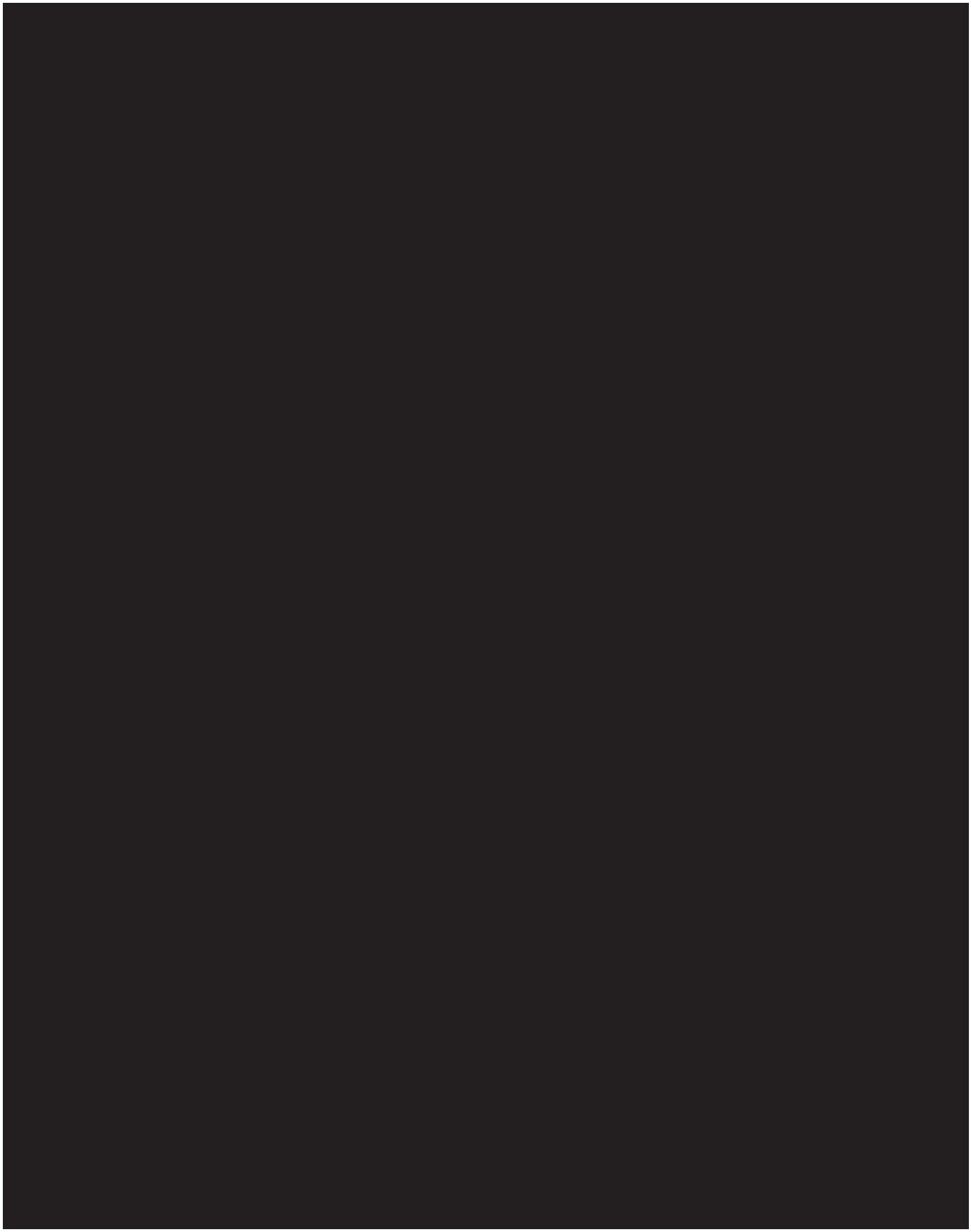


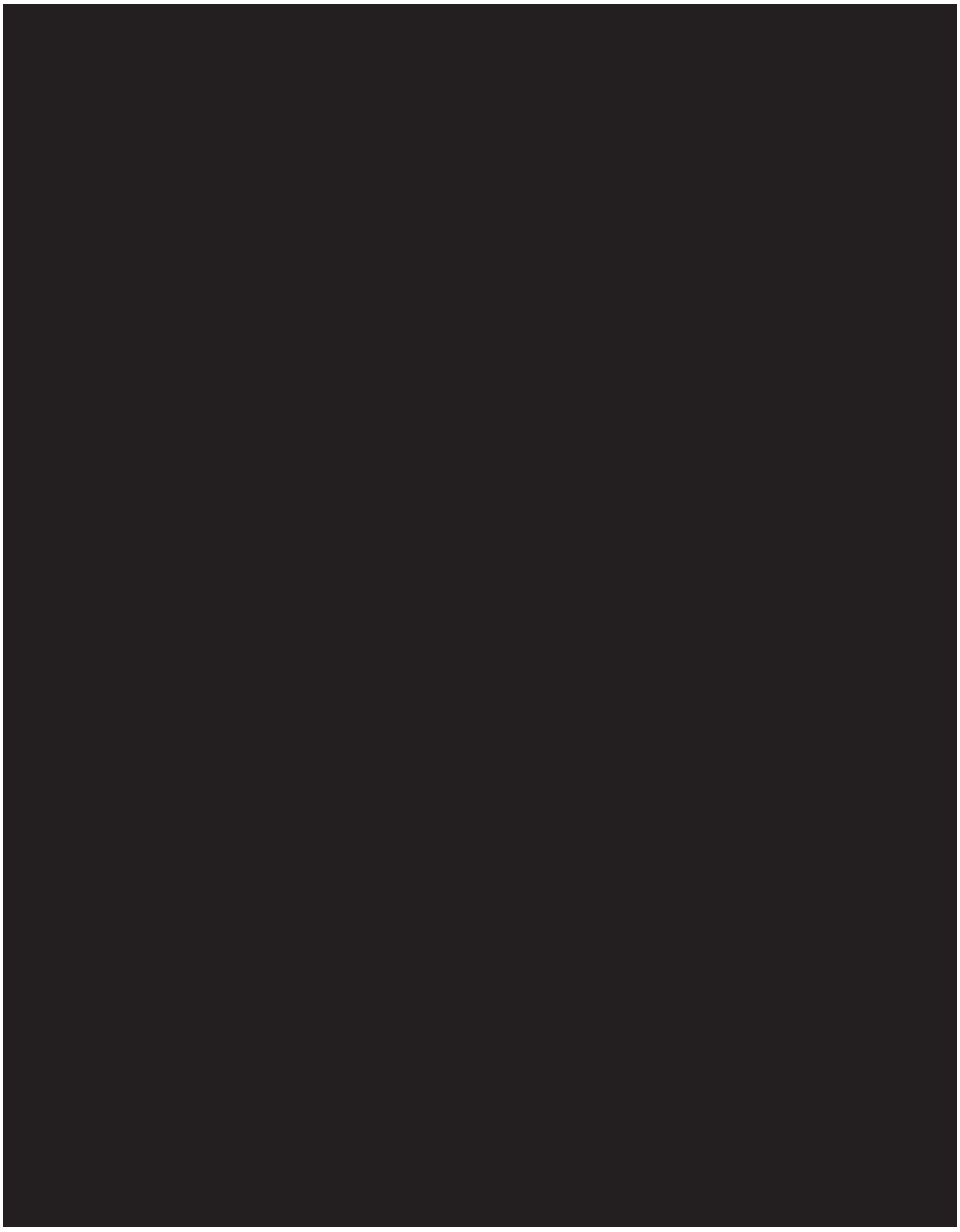












Appendix K Country-specific Protocol Information

K 1 Sweden

Clinical Study Protocol – Local Addendum Swe
Drug Substance – Trastuzumab Deruxtecan (T-DXd)
Study Code – D9670C00001 Version 1.0
Date – 02 Jun 2020

Clinical Study Protocol – Local Addendum Sweden	
Drug Substance	Trastuzumab Deruxtecan/AZD4552
Study Code	D9670C00001
Addendum Version	1.0
Date	02 Jun 2020

Sweden – Addendum

A Phase 3, Randomized, Multi-center, Open-label Study of Trastuzumab Deruxtecan (T-DXd) Versus Investigator's Choice Chemotherapy in HER2-low, Hormone Receptor Positive Breast Cancer Patients whose Disease has Progressed on Endocrine Therapy in the Metastatic Setting

(DESTINY-BREAST06)

Sponsor:

AstraZeneca AB, S-151 85 Södertälje, Sweden

CENTRES AFFECTED BY THE ADDENDUM:

This addendum affects all the Swedish centres in the study and will prevail if in conflict with any other section in the Clinical Study Protocol (CSP) (including its appendicies).

REASON FOR THIS ADDENDUM:

According to the CSP, the follow samples will be collected and stored for a maximum of 15 years from the date of the Last Subject's Last Visit (LSLV), after which they will be destroyed.

*** Storage, re-use and destruction of Pharmacokinetic samples**

Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. The results of any investigation will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication.

Page 1 of 2

*** Storage, re-use and destruction of Pharmacogenetic samples**

Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication.

*** Storage, re-use and destruction of biomarkers**

Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

LOCAL REQUIREMENT – SWEDISH BIOBANK LEGISLATION:

No information regarding storage place is described in the CSP and according to the Swedish Biobank legislation tissue samples may be sent abroad for analysis, but not for long term storage.

Any residual blood (or its derivates, e.g. plasma, serum, DNA) must, if no analyses are planned within a 24 months period after LSLV be sent to AstraZeneca's Biobank in Mölndal for long term storage, unless the samples are anonymised by pooling.

Sample stored by the Biobank in Mölndal may be requested for additional tests later, if an analysis plan is attached to the request. Samples requested can only be sent for additional tests as long as the tests are in scope of the patients consent and the approval from Ethics Committee.

It is the responsibility of the Global Study Team to ensure adherence to the requirements described above.

PERSONS WHO INITIATED THIS ADDENDUM:

The Local Study Team Leader, after approval from Global Study Team for study D9670C00001 at AstraZeneca.

K 2 Germany

Clinical Study Protocol - Addendum DEU-4	
Study Intervention	Trastuzumab Deruxtecan (T-DXd; AZD4552; DS-8201a)
Study Code	D9670C00001
Addendum Version	4.0
Date	27 May 2022

Germany Addendum

A Phase 3, Randomized, Multi-center, Open-label Study of Trastuzumab Deruxtecan (T-DXd) Versus Investigator's Choice Chemotherapy in HER2-low, Hormone Receptor Positive Breast Cancer Patients whose Disease has Progressed on Endocrine Therapy in the Metastatic Setting (DESTINY-Breast06)

Sponsor Name:

AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifier Numbers:

US IND number: 146,111

EudraCT number: 2019-004493-26

Appendix L Abbreviations

Abbreviation or special term	Explanation
ADA	anti-drug antibody
ADC	antibody drug conjugate
AE	adverse event
AESI	adverse event of special interest
AI	aromatase inhibitor
ALP	alkaline phosphatase
ALT	alanine transaminase
Anti-HBc	hepatitis B core antibody
AST	aspartate transaminase
ASCO/CAP	American Society of Clinical Oncology/College of American Pathologists
AZ	AstraZeneca
BfS	Federal Office for Radiation Protection in Germany
BICR	blinded independent central review
BOR	best overall response
CBC	complete blood count
CDK	cyclin-dependent kinase
CDK4/6i	cyclin-dependent kinase 4/6 inhibitor
CHF	congestive heart failure
CI	confidence interval
CO	carbon monoxide
COPD	chronic obstructive pulmonary disorder
COVID-19	corona virus disease 2019
CR	complete response
iCRO	imaging Contract Research Organization
CRP	C-reactive protein
CSP	Clinical Study Protocol
CSR	Clinical study report
CT	computer tomography
ctDNA	circulating tumor DNA
CTIS	Clinical Trial Information System
CTR	Clinical Trials Regulation
DAR	drug-to-antibody ratio
DCO	data cut off

Abbreviation or special term	Explanation
DI-ILD	drug-induced ILD
DLCO	diffusing capacity of the lungs for carbon monoxide
DCO	data Cut Off
DNA	deoxyribonucleic acid
DoR	duration of response
DUS	disease under study
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECHO	echocardiogram
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EOT	end of treatment
EORTC QLQ	European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D-5L	European Quality of Life 5-Domain 5-Level Scale
ER	estrogen receptor
ET	endocrine therapy
EU	European Union
FAS	Full Analysis Set
FFPE	Formalin-fixed and Paraffin-embedded
FISH	fluorescent in situ hybridization
FVC	forced vital capacity
GCP	Good Clinical Practice
HBsAg	surface antigen of the hepatitis B virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HFS	hand and foot syndrome
HIV	human immunodeficiency virus
HOSPAD	hospital admission
HR	hormone receptor
HRCT	high-resolution computed tomography
HRQoL	health-related quality of life

Abbreviation or special term	Explanation
IB	Investigator's Brochure
IDMC	Independent Data Monitoring Committee
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
ILD	interstitial lung disease
INR	international normalized ratio
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	interactive response technology
ISH	in situ hybridization
ITT	intent-to-treat population
IV	intravenous(ly)
IVD	in vitro diagnostic
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
MUGA	Multiple gated acquisition scans
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIMP	non-investigational medicinal product
NLs	new lesions
NSCLC	non-small cell lung cancer
NYHA	New York heart association
ORR	objective response rate
PBMC	peripheral blood mononuclear cell
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PFS2	time from randomization to second progression or death

Abbreviation or special term	Explanation
PFT	pulmonary function test
PGI-BR	Patient Global Impression – Benefit/Risk
PGIC	Patient Global Impression–Change
PGIS	Patient Global Impression–Severity
PGI-TT	Patient Global Impression–Treatment Tolerability
PgR	progesterone receptor
PK	pharmacokinetic
PI3-K	phosphoinositide 3-kinase
PR	partial response
PRO	patient-reported outcome
PRO-CTCAE	Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events
PT	prothrombin time
q3w	every 3 weeks
q9w	every 9 weeks
RECIST 1.1	Response Evaluation Criteria In Solid Tumors version 1.1
RNA	ribonucleic acid
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Safety Analysis Set
SD	stable disease
SmPC	Summary of Product Characteristics
SoA	Schedule of Assessments
SOC	system organ class
SpO2	pulse oximetry
TBL	total bilirubin
T-DM1	Ado-trastuzumab emtansine
TEAE	treatment-emergent adverse event
TFST	time to first subsequent treatment or death
TLs	target lesions
TMG	toxicity management guidelines
TSST	time to second subsequent treatment or death
ULN	upper limit of normal

Abbreviation or special term	Explanation
US	United States
US FDA	US Food and Drug Administration
WBC	white blood cell

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