Clinical Study Protocol	
Study Intervention	Trastuzumab Deruxtecan (T-DXd, DS-8201a)
Study Code	D967MC00001
Version	1.0
Date	20 July 2020

A Phase II, Multicenter, Open-label Study to Evaluate the Efficacy and Safety of Trastuzumab Deruxtecan (T-DXd) for the Treatment of Unresectable and/or Metastatic Solid Tumors Harboring HER2 Activating Mutations Regardless of Tumor Histology

Sponsor Name: AstraZeneca AB

Legal Registered Address: 151 85 Södertälje, Sweden

Regulatory Agency Identifier Number(s)

IND number: 146993
EudraCT number: 2020-002368-30

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: D967MC00001

Amendment Number: Not applicable

Study Intervention: Trastuzumab deruxtecan (T-DXd, DS-8201a, fam-trastuzumab deruxtecan-nxki)
Study Phase: II

Short Title: A Phase II Study of T-DXd for the Treatment of Solid Tumors Harboring Specific HER2 Activating Mutations.

Acronym: DESTINY-PanTumor01

Study Physician Name and contact information will be provided separately

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase II, multicenter, open-label study to evaluate the efficacy and safety of trastuzumab deruxtecan (T-DXd) for the treatment of unresectable and/or metastatic solid tumors harboring HER2 activating mutations regardless of tumor histology.

Short Title: A Phase II Study of T-DXd for the Treatment of Solid Tumors Harboring Specific HER2 Activating Mutations.

Rationale:

Trastuzumab deruxtecan (T-DXd, DS-8201a, fam-trastuzumab deruxtecan-nxki) is a novel HER2-targeting ADC. T-DXd is approved in the United States and Japan under the tradename ENHERTU®. ENHERTU was approved for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens. T-DXd is being further developed as a therapeutic candidate for other HER2-expressing tumors including gastric cancer, NSCLC, CRC, as well as other solid tumors that have lower prevalence of HER2-expression, and for tumors that exhibit somatic specific HER2 activating mutations.

Patients with relapsed/refractory metastatic tumors that develop progressive disease after multiple prior lines of therapy including but not limited to chemotherapy and/or immunotherapy following standard of care regimens may benefit from ongoing development of not yet approved targeted therapies. Objective response rates across indications, including those that will be explored in this study, in late lines, and in the refractory, metastatic setting range from 1.6% in CRC (Mayer et al 2015), 4.0% in gastric cancer (Shitara et al 2019), 8.6% in urothelial cancer (Bellmunt et al 2009), 10.3% in pancreatic cancer (Kim et al 2015), 10.9% in melanoma (Hodi et al 2010), to 12.0% in breast cancer (Cortes et al 2011). The poor clinical outcomes associated with late lines of therapy indicate a large proportion of these patients do not benefit from existing treatment approaches.

A clear unmet need exists for this patient population as several HER2 mutant cancers have not been associated with concurrent HER2 gene amplification (Arcila et al 2012; Bose et al 2013; Mazieres et al 2013) and thus represents an important subgroup of HER2-activated tumors that may not be identified by standard analyses of HER2 positivity based on IHC or ISH techniques. Current clinical practice and consensus guidelines (eg, National Comprehensive Cancer Network, ESMO Clinical Practice Guidelines) recommend clinical studies for this difficult to treat patient population, recognizing the need for personalized treatments that can help these patients.

These data warrant further investigation of T-DXd for the treatment of adult patients with

unresectable or metastatic solid tumors harboring specific HER2 activating mutations, who have progressed following prior treatment or who have no satisfactory alternative treatment options.

Objectives and Endpoints

This study aims to evaluate the efficacy and safety of T-DXd in patients with unresectable and/or metastatic solid tumors harboring specific HER2 activating mutations.

Table 1 presents the primary, secondary and exploratory endpoints of the study.

Table 1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of T-DXd in patients with metastatic or unresectable tumors harboring specific HER2 activating mutations across tumor types.	Confirmed ORR according to RECIST v1.1, as assessed by ICR.
Secondary	
To further evaluate the efficacy of T-DXd in patients with metastatic or unresectable tumors harboring pre-specified HER2 activating mutations across tumor types.	ICR and Investigator assessments, based on RECIST v1.1, to allow the calculation of: DoR DCR PFS Proportion of patients alive and progression-free at 6 and 12 months. Confirmed ORR (Investigator assessment).
To further investigate the efficacy of T-DXd on tumors with pre-specified HER2 mutations as measured by OS across tumor types.	OS Proportion of patients alive at 6 and 12 months.
To assess the safety and tolerability of T-DXd.	Assessed by the occurrence of AEs, SAEs, and changes from baseline in laboratory parameters, vital signs, ECG and ECHO/MUGA results.
To assess the PK of T-DXd, total anti-HER2 antibody and MAAA-1181a in serum.	Serum concentration of T-DXd, total anti-HER2 antibody and MAAA-1181a.
To investigate the immunogenicity of T-DXd.	Presence of ADAs for T-DXd.

ADA, anti-drug antibodies; AE, adverse event; ctDNA, circulating tumor deoxyribonucleic acid; DCR, disease control rate; DoR, duration of response; ECG, electrocardiogram; ECHO, echocardiogram; EGFR, epidermal growth factor receptor; FFPE, formalin-fixed and paraffin-embedded; FISH, fluorescent in situ hybridization; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; ICR, independent central review; ILD, interstitial lung disease; MAAA-1181, deruxtecan; MDASI, MD Anderson Symptom Inventory; MSI, microsatellite instability; MUGA, multigated acquisition; NGS, next-generation sequencing; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PK, pharmacokinetic; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SAE, serious adverse event; SGRQ-I, St George's Respiratory Questionnaire for patients with Idiopathic Pulmonary Fibrosis; T-DXd, trastuzumab deruxtecan; TMB, tumor mutational burden;

Overall Design

This is an open-label, multi-center, single arm Phase II study to evaluate the efficacy and safety of T-DXd for the treatment of unresectable and/or metastatic solid tumors harboring specific HER2 activating mutations regardless of tumor histology.

Patients will be enrolled at approximately 20 sites globally. Adult patients with unresectable and/or metastatic solid tumors carrying pre-specified HER2 activating mutations, who have progressed following prior treatment or who have no satisfactory alternative treatment options will be enrolled. Approximately 100 patients will be treated in this study, with a maximum of approximately 20 patients per tumor type to ensure adequate representation across multiple tumor types. Anticipated tumor type enrolment in the study includes breast, colorectal, urothelial, esophagogastric, hepatobiliary, small cell lung, endometrial, melanoma, ovarian, cervical, salivary gland, pancreatic and cutaneous squamous-cell carcinoma. There is no pre-specified requirement for representation of any individual tumor type that meets the eligibility criteria.

Disclosure Statement: This is a single-arm treatment study with no blinding.

Number of Participants:

Citing approximate numbers, this study will enrol and screen 130 patients to achieve a global target of 100 patients treated with T-DXd.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study but are not assigned to study treatment are considered "screen failures", unless otherwise specified by the protocol.

Patients are assigned treatment if all of the inclusion criteria and none of the exclusion criteria are met, and all screening assessments are complete.

Intervention Groups and Duration:

Treatment in this study with T-DXd will continue until any discontinuation criteria are met, including symptomatic deterioration, radiological progression, or Investigator determination that the patient is no longer benefiting from study intervention. Each patient will be followed for efficacy, regardless of whether study treatment is discontinued, until all patients have had the opportunity for approximately 32 weeks of follow-up after treatment assignment. This will provide at least 6 months of follow-up from the anticipated median time of first response assessment. Intervention after the end of the study is described in Section 6.7.

T-DXd will be administered to patients harboring tumors with specific HER2 activating mutations at a dose of 5.4 mg/kg via IV infusion on Day 1 of each cycle, every 3 weeks (q3w).

Data Monitoring Committee:

There will be no Data Monitoring Committee for this study.

Statistical methods:

Sample size estimate:

A sample size of 100 patients has been determined to provide sufficient precision for the estimation of the ORR in this population and to allow wider representation of tumor types and selected mutations. Table 2 provides the 95% exact CI for a range of possible observed response rates out of 100 patients.

Table 2 Observed ORR and 95% Confidence Interval (CI) out of 100 Patients

Observed ORR (%)	95% exact CI
30	(21.2, 40.0)
40	(30.3, 50.3)
50	(39.8, 60.2)

CI, confidence interval; ORR, objective response rate

The study will also provide an adequate number of patients to robustly assess the safety and tolerability of T-DXd across various tumor types.

Approximately 100 patients will be treated in this study, with a maximum of approximately 20 patients per tumor type to ensure adequate representation across multiple tumor types. Anticipated tumor type enrolment in the study includes breast, colorectal, urothelial, esophagogastric, hepatobiliary, small cell lung, endometrial, melanoma, ovarian, cervical, salivary gland, pancreatic and cutaneous squamous-cell carcinoma. These will be treated as separate specific tumor types for the purposes of patient recruitment caps and interim futility evaluations.

Enrolment in a specific tumor type will be paused after 8 patients with Investigator-assessed measurable disease at baseline have been treated within that tumor type, until a decision has been made on whether to stop enrolment to that tumor type based on the interim futility evaluation. If no confirmed objective response (assessed by Investigator per RECIST v1.1) is observed among the first 8 treated patients in a specific tumor type, enrolment in that tumor type will be discontinued. See Section 9.4.6 for further details.

Statistical Analyses:

The primary endpoint is confirmed ORR assessed by ICR per RECIST v1.1 across all tumor types. Secondary efficacy endpoints include confirmed ORR by Investigator assessment per RECIST v1.1, DoR, DCR, PFS (all three by ICR and Investigator assessment), and OS across all tumor types.

Safety data will be summarized using appropriate summary statistics; further details will be provided in the SAP.

To characterize DoR, the final analysis is planned to be performed when the last patient has had the opportunity for approximately 32 weeks of follow-up after treatment assignment. This will provide at least 6 months of follow-up from the anticipated median time of first response assessment.

Five analysis sets will be defined as shown in Table 3. The primary analysis population will be the Full Analysis Set (FAS), all patients receiving at least one dose of study treatment.

Table 3 Populations for Analyses

Population/Analysis set	Description
Full Analysis Set (FAS)	All patients who received at least 1 dose of study treatment. The FAS will be used for all efficacy analyses.
Measurable Disease Analysis Set (MDAS)	All patients who received at least 1 dose of study treatment, and who have Investigator-assessed measurable disease at baseline according to RECIST v1.1. The MDAS will only be used for the 8-patient interim futility evaluation within each tumor type. All patients will have Investigator-assessed measurable disease at baseline according to inclusion criteria.
Centrally-determined Efficacy Analysis (CEAS)	All patients who received at least 1 dose of study treatment, and who were determined as HER2- mutant via retrospective central testing according to pre-specified entry criteria. Depending on the level of discrepancies between the central and local HER2 mutation test results, the CEAS may be used for sensitivity analyses on efficacy endpoints as necessary.
Pharmacokinetics (PK) Analysis Set	All patients who received at least 1 dose of study treatment and had at least 1 post-dose evaluable PK data point. The population will be defined by the study pharmacokineticist, and the statistician prior to any PK analyses being performed.
Safety Analysis Set (SAF)	All patients who received at least 1 dose of study treatment.

HER2, human epidermal growth factor receptor 2

Table 4 shows the planned statistical and sensitivity analyses.

Table 4 Pre-planned Statistical Analyses to be Conducted

Endpoints analyzed	Notes
Objective response rate (ORR)	Number and percentage of patients that achieve confirmed objective response as assessed by ICR according to RECIST v1.1 (with the associated two-sided 95% exact CI). Confirmed ORR as determined by Investigator assessment will also be presented.
Duration of response (DoR)	Kaplan-Meier median estimates and their corresponding two-sided 95% confidence intervals will be reported (ICR and Investigator assessment).
Disease control rate (DCR)	Number and percentage of patients that achieve disease control (with the associated two-sided 95% exact CI) by ICR and Investigator assessment.

Table 4 Pre-planned Statistical Analyses to be Conducted

Endpoints analyzed	Notes
Progression-free survival (PFS)	Kaplan-Meier median estimates and their corresponding two-sided 95% confidence intervals will be reported (ICR and Investigator assessment). The proportions of patients alive and progression-free at 6 and 12 months (Kaplan-Meier estimates) will also be presented.
Overall survival (OS)	Kaplan-Meier median estimates and their corresponding two-sided 95% confidence intervals will be reported. The proportions of patients alive at 6 and 12 months (Kaplan-Meier estimates) will also be presented.
Safety	Summary statistics for AEs, AESIs, SAEs, laboratory findings, vital signs, ECG, ECHO/ MUGA results, ECOG/WHO performance status and deaths

AE, adverse event; AESI, adverse event of special interest; CI, confidence interval; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; ICR, independent central review; MUGA, Multiple gated acquisition; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SAE, serious adverse event; WHO, World Health Organization

Interim Analyses:

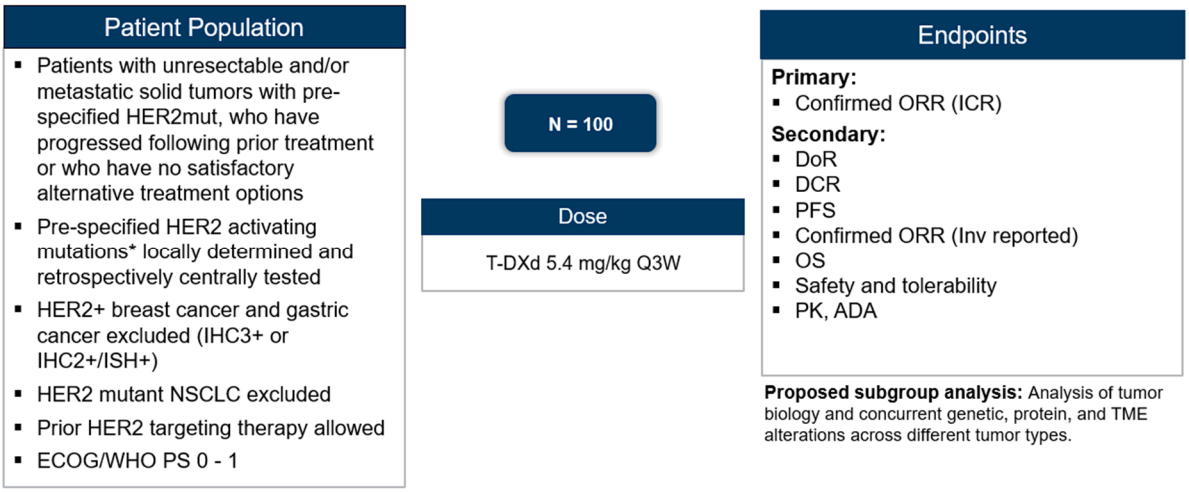
An interim futility evaluation will be performed within each tumor type after 8 treated patients with Investigator-assessed measurable disease at baseline (using the MDAS) have had 12 weeks of follow-up since first dose or have discontinued study drug. If no confirmed objective response (assessed by Investigator per RECIST v1.1) is observed among the first 8 treated patients in a specific tumor type, enrolment in that tumor type will be discontinued.

Enrolment in a tumor type will be paused, after 8 patients with Investigator-assessed measurable disease at baseline have been treated within that tumor type, until a decision has been made on whether to stop enrolment based on the futility evaluation.

Interim efficacy analyses will also be performed (using the FAS) within an individual tumor type when enrolment to the tumor type has been closed, and all treated patients have had the opportunity to complete 2 scheduled post-baseline RECIST v1.1 scans. For a tumor type with N = 20, an ORR of 40% would have 95% CI (19.1%, 63.9%); this level of activity would justify further investigation.

1.2 Schema

Figure 1 Study design



*Pre-specified HER2 activating mutations: S310F, S310Y, G660D, R678Q, D769Y, D769H, V777L, Y772_A775dup / A775_G776insYVMA, L755S, G778_P780dup / P780_Y781insGSP, T862A, and V842I
Patients with breast and gastric cancer who have received prior trastuzumab or other HER2 targeting therapy will be potentially eligible if HER2 is not overexpressed in a tissue biopsy taken after documented disease progression following trastuzumab/HER2-targeting treatment.
DoR, DCR and PFS based on ICR and Investigator assessment (see Section 4).
ADA, anti-drug antibodies; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HER2mut, HER2 mutations; ICR, independent central review; Inv, Investigator; IHC, Immunohistochemistry; ISH, In situ hybridization; N, number of patients; NSCLC, non-small cell lung cancer ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PS, performance status; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; TME, Tumor microenvironment; WHO, world health organization

1.3 Schedule of Activities

The procedures for the screening and treatment periods in this study are presented in Table 6 and the procedures for the follow-up period are presented in Table 7.

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 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, eg, PK blood sample, to occur at the timepoints indicated in the schedule of activities (Table 6).

Subsequent time between 2 consecutive doses of T-DXd cannot be less than 19 days.

Table 6 Schedule of Activities – Screening Period and Treatment Period

	Screening	Treatment period						End of treatment Visit [a]	For details, see Section
Treatment Cycle	**NA**	**C1**	**C1**	**C1**	**C2**	**C3**	**C4 to PD**		
Day	**-28 to -1**	**1**	**8**	**15**	**1**	**1**	**1**		
Window (days)	**NA**	**NA**	**(tumor assessments ± 7 days; all other procedures ± 3 days)**						
Informed consent (including consent for optional genetic sample)									
Informed consent	X								5.1, 8.2.1
Eligibility criteria	X	X							5.1, 5.2
Routine Clinical Procedures									
Demography, including baseline characteristics	X								5.1
HER2 mutation status (per local assessment)	X								5.1
Medical history (includes substance usage, past and current medical history) [b]	X								5.1
Prior anti-cancer therapy and prior surgery	X								5.1
Pulmonary function test [c]	X	If ILD/pneumonitis is suspected							8.2.8; 8.2.10.1
Pregnancy test [d]	X	X			X	X	X	X	8.2.9
Vital signs [e]	X	X	X	X	X	X	X	X	8.2.3
Full physical examination	X								8.2.2
Targeted physical examination [e]		X			X	X	X	X	8.2.2
SpO_2 [e]	X	X	X	X	X	X	X	X	8.2.8
Height	X								8.2.2
Weight	X	X			X	X	X	X	8.2.3

Table 6 Schedule of Activities – Screening Period and Treatment Period

	Screening	Treatment period						End of treatment Visit [a]	For details, see Section
Treatment Cycle	**NA**	**C1**	**C1**	**C1**	**C2**	**C3**	**C4 to PD**		
Day	**-28 to -1**	**1**	**8**	**15**	**1**	**1**	**1**		
Window (days)	**NA**	**NA**	**(tumor assessments ± 7 days; all other procedures ± 3 days)**						
WHO/ECOG Performance Score	X	X			X	X	X	X	8.2.6
12-lead ECG [f]	X	X [g]					X [g] (C5, then every 4 cycles)	X	8.2.4
HIV antibody test (as required by local regulations)	X								8.2.9
Hepatitis B / C serology	X								8.2.9
Biomarker Sampling									
Tumor tissue sample for retrospective central HER2 testing and exploratory biomarker analysis (mandatory)	X								8.6.1
Tumor tissue sample taken at pre-treatment, on-treatment, and at disease progression (optional, only if part of the SoC)	X							X [h]	8.6.2
Blood sample for plasma biomarker assessment and diagnostic development (eg, ctDNA and blood-based biomarkers) (mandatory)	X	X			X	X	X (C4 only)	X	8.6.1
Blood sample for gene expression assessment (mandatory)		X			X	X	X (C4 only)	X	8.6.1

Table 6 Schedule of Activities – Screening Period and Treatment Period

	Screening	Treatment period						End of treatment Visit [a]	For details, see Section
Treatment Cycle	**NA**	**C1**	**C1**	**C1**	**C2**	**C3**	**C4 to PD**		
Day	**-28 to -1**	**1**	**8**	**15**	**1**	**1**	**1**		
Window (days)	**NA**	**NA**	**(tumor assessments ± 7 days; all other procedures ± 3 days)**						
Blood sample for plasma exploratory clinical benefit or safety analyses (mandatory)		X					X (C4, then every 4 cycles)	X	8.6.1
Blood sample for Genomics Initiative (optional)		X							8.7
Pharmacokinetic Measurements [i]									
Pre-dose blood sample for T-DXd PK (serum) (T-DXd, total anti-HER2 antibody, and MAAA-1181)		X			X		X (C4 only)		8.5.1
Post-dose blood sample for T-DXd PK (serum) (T-DXd, total anti-HER2 antibody & MAAA-1181)		X			X		X (C4 only)	X	8.5.1
Immunogenicity Measurements									
Blood sample for T-DXd ADA assessment [j]		X			X		X (C4, then every 4 cycles)	X	8.5.2; 8.2.9
Investigational Product Administration									
Assignment of treatment [k]		X							6.3.1
T-DXd [k,l]		X			X	X	X		6.1.1
Efficacy Measurements									
Tumor assessments (RECIST v1.1) [m]	X	CT or MRI scans performed q6w (± 1w)							Appendix F,8.1.1

Table 6 Schedule of Activities – Screening Period and Treatment Period

	Screening	Treatment period						End of treatment Visit [a]	For details, see Section
Treatment Cycle	**NA**	**C1**	**C1**	**C1**	**C2**	**C3**	**C4 to PD**		
Day	**-28 to -1**	**1**	**8**	**15**	**1**	**1**	**1**		
Window (days)	**NA**	**NA**	**(tumor assessments ± 7 days; all other procedures ± 3 days)**						
Routine Safety Assessments									
High Resolution Chest CT [n]	X	If ILD/pneumonitis is suspected							8.2.8, 8.2.10.1
Clinical Chemistry [o]	X	X	X	X	X	X	X	X	8.2.9
Hematology [o]	X	X	X	X	X	X	X	X	8.2.9
Coagulation [o]	X							X	8.2.9
Troponin [p]	X	If clinically indicated						X	8.2.9
ECHO or MUGA [q]	X						X (C5, then every 4 cycles)	X	8.2.5
Ophthalmologic Assessments [r]	X	If clinically indicated						X	8.2.7
Urinalysis [s]	X	If clinically indicated							8.2.9
Concomitant Medications	X	X	X	X	X	X	X	X	6.5
Adverse Events [t]	X	X	X	X	X	X	X	X	8.3
Other Assessments and Procedures									
ePRO and pulse oximetry device allocation (ePRO device allocated only if patient does not have own compatible device) and training[u]		X							8.1.4.3
MDASI symptom diary	To be completed on C1D1 before dosing and daily thereafter								8.1.4.1
SGRQ-I	To be completed after diagnosis of ILD/pneumonitis and q7d thereafter								8.1.4.2

Table 6 Schedule of Activities – Screening Period and Treatment Period

	Screening	Treatment period						End of treatment Visit [a]	For details, see Section
Treatment Cycle	**NA**	**C1**	**C1**	**C1**	**C2**	**C3**	**C4 to PD**		
Day	**-28 to -1**	**1**	**8**	**15**	**1**	**1**	**1**		
Window (days)	**NA**	**NA**	**(tumor assessments ± 7 days; all other procedures ± 3 days)**						
At-home pulse oximetry	To be completed on C1D1 before dosing and daily thereafter (resting) To be completed on C1D1 before dosing and q7d thereafter (walking)								8.1.4.4

[a] End of treatment visit to occur within 7 days of stopping treatment.
[b] To include history, type and frequency of tobacco use, e-cigarette use, vaping (including dates).
[c] PFT as a minimum should include spirometry. [Minimum requirement of: FVC (L), FVC % predicted, FEV1 (L), FEV1 % predicted, FEV1/FVC ratio. Optional components to include: PEF, FEV6, TLC, DLCO.]. DLCO will be performed/encouraged if feasible, but for patients with prior severe and/or clinically significant pulmonary disorders, DLCO is a requirement.
[d] 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 IP. Within 72 hours before treatment assignment for all female patients of childbearing potential; a positive urine pregnancy test result must immediately be confirmed using a serum test. Perform repeat pregnancy tests (urine or serum test per institutional guideline) assignment, within 72 hours before infusion of each cycle and at end of treatment.
[e] Within 3 days before first dose of IP. Vital signs and SpO_2 should also be evaluated by Investigator or the delegate physician prior to the administration of IP at each infusion, and at end of administration.
[f] ECGs will be taken in triplicate at screening. Subsequent ECGs will be performed in triplicate in close succession only if an abnormality is noted. ECGs will be taken while in a supine/semi-recumbent position.
[g] Within 3 days before administration of IP. ECGs will be taken at every fourth cycle.
[h] Within 2 weeks of end of treatment.
[i] For patients diagnosed with COVID-19, please see Appendix I for further instructions on potential additional PK sample collections.
[j] Within 8 hours before administration on Day 1 of Cycle 1, 2 and 4, and then every 4 cycles.
[k] Treatment assignment is performed by IRT. First dose of IP must be administered within 3 days of treatment assignment.
[l] Two consecutive doses must be no less than 19 days apart.
[m] Scans must be performed q6w (± 1 week) relative to the date of first dose of IP until RECIST v1.1-defined radiological disease progression. This schedule MUST be followed regardless of any delays in dosing. Response assessment scans must be reviewed for evidence of disease progression and ILD / pneumonitis prior to administration of the next scheduled dose of T-DXd.
[n] All patients will receive a non-contrast high resolution CT (HRCT) scan of the chest at screening in addition to IV contrast-enhanced CT/MRI scans of chest/abdomen/pelvis for tumor assessments.
[o] Within 3 days prior to IP administration. Laboratory tests include: Hematology - hemoglobin, hematocrit, platelet count, white blood cell count, differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), Chemistry – serum creatinine, total bilirubin, albumin, BUN, total protein, ALP, ALT, AST, Ca, Cl, K, Na, bicarbonate, LDH, and magnesium and Coagulation – INR/PT, and either PTT or aPTT
[p] Collect blood samples for troponin (preferably high-sensitivity troponin-T) at screening, EOT, and if at any time a patient reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of myocyte necrosis.

[q] ECHO or MUGA scan assessments (note: the same test must be used for the patient throughout the study) will be performed at Screening and before IP administration on Day 1 of Cycle 5 and then every 4 cycles (± 7 days) (eg, Cycle 5, 9, 13), and at EOT.

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

[s] Urinalysis must be performed at screening, and as clinically indicated at other visits after screening.

[t] All adverse events AEs and SAEs (other than ILD/pneumonitis) will be collected from the time of signature of the ICF throughout the treatment period and including the safety follow-up (which is 40 +7 days after the discontinuation of all IPs). For ILD/pneumonitis, safety follow up will be continued until resolution of ILD/pneumonitis. If an event that starts post the defined safety follow up period noted above is considered to be due to a late onset toxicity to study treatment, then it should be reported as an AE or SAE as applicable.

[u] An electronic PRO device should be charged and ready for the patient prior to their arrival at the site for C1 D1 and ideally at least the day before, to ensure it is functioning properly and ready for use in case needed, in accordance with device training.

ADA, anti-drug antibodies; AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; C, cycle; Ca, calcium; Cl, chloride; CT, computed tomography; ctDNA, circulating tumor deoxyribonucleic acid; D, day; DLCO, Diffusing capacity of the lungs for carbon monoxide; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; ePRO, electronic patient reported outcome; FEV1, forced expiratory volume in 1 second; FEV6, forced expiratory volume in 6 seconds; FVC, forced vital capacity; HER2, human epidermal growth factor receptor 2; HIV, human immunodeficiency virus; HRCT, high resolution computed tomography; ICF, informed consent; ILD, interstitial lung disease; INR, international normalized ratio; IP, investigational product; IRT, interactive response technology; K, potassium; LDH, lactate dehydrogenase; MAAA-1181, deruxtecan; MDASI, MD Anderson Symptom Inventory; MRI, magnetic resonance imaging; MUGA, multigated acquisition; Na, sodium; NA, not applicable; PD, progressive disease; PEF, peak expiratory flow; PFT, pulmonary function test; PK, pharmacokinetic; PT, prothrombin time; aPTT, activated partial thromboplastin time; PTT, partial thromboplastin time; q7d, every 7 days; q6w, every 6 weeks; RECIST v1.1 Response Evaluation Criteria In Solid Tumors version 1.1; SAE, serious adverse event; SpO_2, Saturation of peripheral oxygen; SGRQ-I, St George's Respiratory Questionnaire for patients with Idiopathic Pulmonary Fibrosis; SoC, standard of care; T-DXd, trastuzumab deruxtecan; TLC, total lung capacity; WHO, World Health Organization

Table 7 Schedule of Activities – Follow-up Period for Patients Who Discontinued Study Intervention Due to Progressive Disease or Other Reason

Procedure	Follow-up period Time since last dose of study treatment					For details see Section
	40 days [a]	3 months	6 months	9 months	12+ months	
Window	**+ 7 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**	
Routine clinical procedures						
Full physical examination	X					8.2.2
WHO/ECOG performance status [b]	X					8.2.6
Vital signs	X					8.2.3
SpO_2	X					8.2.8
Weight	X					8.2.3
Pregnancy test [c]	X	As clinically indicated				8.2.9
Concomitant medications	X					6.5
Subsequent anticancer therapy	X	X	X	X	X then q3m (± 2 weeks)	8.1.3
Routine safety measurements						
Adverse events [d]	X					8.3
Clinical chemistry	X					8.2.9
Hematology	X					8.2.9
Pharmacokinetic measurements						
Blood samples for T-DXd PK assessment (T-DXd, total anti-HER2 antibody & MAAA-1181)	X					8.5.1
Immunogenicity measurements						
Blood Samples for T-DXd ADA assessment [e]	X	Additional samples may be required for patients with positive ADA at follow-up [e]				8.5.2; 8.2.9
Efficacy measurements						

Table 7 Schedule of Activities – Follow-up Period for Patients Who Discontinued Study Intervention Due to Progressive Disease or Other Reason

Procedure	Follow-up period Time since last dose of study treatment					For details see Section
	40 days [a]	3 months	6 months	9 months	12+ months	
Window	**+ 7 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**	
Tumor imaging (RECIST v1.1) [f]	CT or MRI scans q6w (± 1w)					Appendix F, 8.1.1
Survival status (phone call for patients who refuse to return for evaluations and agree to be contacted)		X	X	X	X then q3m (± 2 weeks)	8.1.3
MDASI symptom diary	For those without ILD/pneumonitis diagnosis: • To be completed daily up to and including the 40-day safety F/U For those with an ILD/pneumonitis diagnosis: • To be completed daily up to and including the first survival visit (3 months).					8.1.4.1
SGRQ-I	To be completed after diagnosis of ILD/pneumonitis and q7d thereafter, up to and including the first survival visit (3 months).					8.1.4.2
At-home pulse oximetry	For those without ILD/pneumonitis diagnosis: • To be completed daily (resting) up to and including the 40-day safety F/U • To be completed q7d relative to C1D1 (walking) up to and including the 40-day safety F/U For those with ILD/pneumonitis diagnosis: • To be completed daily (resting) up to and including the first survival visit (3 months) • To be completed q7d relative to C1D1 (walking) up to and including the first survival visit (3 months)					8.1.4.4

[a] At a minimum, telephone contact with the patient will be made 40 days (+ 7 days) following discontinuation of IP to collect new AEs and follow-up on any ongoing AEs and concomitant medications (including any subsequent anticancer therapy). See Section 7.1.2 for details.

[b] WHO/ECOG performance status should be provided when subsequent anticancer therapy information is collected, where possible.

[c] For women of childbearing potential only. A urine or serum pregnancy test is acceptable.

[d] All AEs and SAEs (other than ILD/pneumonitis) will be collected during the safety follow-up (which is 40 +7 days after the discontinuation of all IP) follow-up. For ILD/pneumonitis, safety follow-up will be continued until resolution of ILD/pneumonitis. If an event that starts post the defined safety follow-up period noted above is considered to be due to a late onset toxicity to study treatment, then it should be reported as an AE or SAE as applicable.

[e] For patients with positive ADA at the follow-up visit, additional serum ADA samples may be collected every 3 months (± 14 days) up to 1 year after the last dose of the IP, or until the ADA becomes negative, or until the ADA titer becomes less than the baseline (applicable when pre-existing ADA was observed), or until the patient starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.

[f] Patients who discontinued IP due to reason other than PD or death (regardless of whether started subsequent anticancer therapy): IV contrast-enhanced CT or MRI of the chest, abdomen, and pelvis q6w (± 1 week) relative to the date of first dose of IP, until RECIST v1.1-defined radiological disease progression.

ADA, antidrug antibody; AE, adverse event; C1D1, Cycle 1 Day1; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; F/U, follow-up; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; IP, investigational product; IV, intravenous; MAAA-1181, deruxtecan; MDASI, MD Anderson Symptom Inventory; MRI, magnetic resonance imaging; PD, progressive disease; PK, pharmacokinetic; q7d, every 7 days; q3m, every 3 months; q6w, every 6 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors Version 1.1; SAE, serious adverse event; SGRQI, St George's Respiratory Questionnaire for patients with Idiopathic Pulmonary Fibrosis; SpO_2, saturation of peripheral oxygen; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization; wk, week

2 INTRODUCTION

Trastuzumab deruxtecan (T-DXd, DS-8201a, fam-trastuzumab deruxtecan-nxki) is a novel HER2-targeting ADC. T-DXd is approved in the United States and Japan under the tradename ENHERTU. ENHERTU was approved for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens. T-DXd is being further developed as a therapeutic candidate for other HER2-expressing tumors including gastric cancer, NSCLC, CRC, as well as other solid tumors that have lower prevalence of HER2-expression, and for tumors that exhibit somatic specific HER2 activating mutations.

T-DXd consists of a humanized IgG1 monoclonal antibody with reference to the amino acid sequence of trastuzumab, that is attached by a cleavable peptide-based linker to a potent topoisomerase I inhibitor payload, deruxtecan (DXd, MAAA-1181a; MAAA-1181) (Ogitani et al 2016). T-DXd has a high drug-to-antibody ratio of approximately 8.

Following binding to HER2 on tumor cells, T-DXd undergoes internalization and intracellular linker cleavage by lysosomal enzymes that are upregulated in cancer cells. Upon release, the membrane-permeable topoisomerase I inhibitor causes DNA damage and apoptotic cell death.

2.1 Study Rationale

This study aims to evaluate the efficacy and safety of T-DXd in patients with unresectable and/or metastatic solid tumors harboring specific HER2 activating mutations, who have progressed following prior treatment or have no satisfactory alternative treatment options.

Patients with relapsed/refractory metastatic tumors that develop progressive disease after multiple prior lines of therapy including but not limited to chemotherapy and/or immunotherapy following standard of care regimens may benefit from ongoing development of not yet approved targeted therapies. Objective response rates across indications, including those that will be explored in this study, in late lines, and in the refractory, metastatic setting range from 1.6% in CRC (Mayer et al 2015), 4.0% in gastric cancer (Shitara et al 2019), 8.6% in urothelial cancer (Bellmunt et al 2009), 10.3% in pancreatic cancer (Kim et al 2015), 10.9% in melanoma (Hodi et al 2010), to 12.0% in breast cancer (Cortes et al 2011). The poor clinical outcomes associated with late lines of therapy indicate a large proportion of these patients do not benefit from existing treatment approaches.

A clear unmet need exists for this patient population as several HER2 mutant cancers have not been associated with concurrent HER2 gene amplification (Arcila et al 2012; Bose et al 2013; Mazieres et al 2013) and thus represents an important subgroup of HER2-activated tumors that may not be identified by standard analyses of HER2 positivity based on IHC or ISH techniques. Current clinical practice and consensus guidelines (eg, National Comprehensive Cancer Network, ESMO Clinical Practice Guidelines) recommend clinical studies for this

difficult to treat patient population, recognizing the need for personalized treatments that can help these patients

These data warrant further investigation of T-DXd for the treatment of adult patients with unresectable or metastatic solid tumors harboring specific HER2 activating mutations, who have progressed following prior treatment or who have no satisfactory alternative treatment options.

2.2 Background

The human epidermal growth factor receptor 2 gene (ERBB2/HER2, herein HER2) is a proto-oncogene involved in signal transduction pathways leading to tumor cell proliferation, migration, apoptosis, and differentiation.

HER2 has the ability to transform cells in a ligand-independent manner when overexpressed (Tang et al, 1999), as evident in breast, gastric, and urothelial cancers where HER2 is amplified and overexpressed (Gravalos and Jimeno, 2008; Jimenez et al, 2001; Slamon, 1987). Targeted-HER2 therapies to treat HER2-amplified and/or overexpressed breast cancers have been approved, including monoclonal antibodies trastuzumab and pertuzumab, the TKI lapatinib, and ADCs T-DM1 and T-DXd. Trastuzumab is also approved for the targeted treatment of HER2-amplifed and/or overexpressed gastric cancers.

A number of large-scale sequencing efforts and tumor-specific sequencing studies have identified somatic mutations in the extracellular, transmembrane, and kinase domains of HER2 in a wide range of cancers (Bose et al 2013; Chang et al 2018; Greulich et al 2012; Kavuri et al 2015; Ou et al 2017; Ross et al 2016; Yamamoto et al 2014; Zabransky et al 2015). HER2 overexpression has been identified as a major mechanism of HER2-driven tumorigenesis, however the relevance of HER2 somatic mutations in oncogenesis is not fully understood. Unlike other mutant oncogenes eg, BRAF or KRAS, there is no prevalence of a single HER2 mutant allele and the distribution of HER2 mutations vary by tumor type (Chang et al 2016; Hyman et al 2018). Substantial data suggest that a subset of these mutations induce ligand-independent constitutive HER2 receptor signaling and promote oncogenesis (Bose et al 2013; Jaiswal et al 2013). The mechanism of these oncogenic effects seems to differ by variant, with some causing enhanced HER2 kinase activity and others facilitating receptor dimerization (Bose et al 2013; Chumsri et al 2015).

HER2-Targeted Therapies

While some reports suggest the observed clinical activity of HER2-targeting therapies may be related to differences based on tumor type and/or specific HER2 mutations, there are no approved treatments to date for patients with solid tumors harboring HER2 activating mutations.

Recent data from the SUMMIT study in a larger breast cancer patient population treated with neratinib alone or in combination with fulvestrant, reported confirmed ORR of 17.4% in the neratinib monotherapy cohort and 28.8% in the combination therapy cohort (Smyth et al 2019). Interestingly, the SUMMIT data reported to date indicates that out of the 20 plus patients harboring non-hotspot ERBB2 mutations, only one responded to neratinib (Hyman et al 2018; Smyth et al 2019). The absence of clinical activity in most patients with non-hotspot mutations suggests that although the recurrence of a mutation is insufficient to

define it as sensitizing to a HER2 inhibitor, the absence of recurrence (mutations that do not occur at hotspot positions) provides anecdotal evidence that the alteration is unlikely to be a driver of tumorigenesis.

Afatinib, a pan-HER TKI, was investigated in tumors with specific HER2 activating mutations in Arm B of an umbrella study that assigned patients with advanced cancers to targeted therapies based on central tumor genomic testing (NCI-MATCH study, NCT02465060). Forty patients with tumor histologies in breast, colorectal, urothelial, biliary, cervix, small bowel, and others were treated with afatinib. The qualifying HER2 variants were L755S, V777L, V842I, S310F, D769Y, S310Y, and V777_G778insGSP (Bedard et al 2019). Overall, ORR was 2.7% (90% confidence interval [CI]: 0.14, 12.2) and a single confirmed PR was observed in a patient with adenocarcinoma of extra-mammary Paget disease of skin. Two unconfirmed PRs were also reported: low grade serous gynecological tract cancer and breast cancer. Although afatinib did not meet the pre-specified threshold for anti-tumor activity, a recent retrospective international series and a prospective Phase II study had demonstrated clinical activity of afatinib in patients with HER2-mutant lung cancers (Peters et al 2018, Lai et al 2019, Dziadziuszko et al 2019).

Pan-HER tyrosine kinase activity was also reported in an Investigator-led, Phase II study of the irreversible pan-ERBB inhibitor poziotinib (NCT03066206). The study included a small cohort of 12 NSCLC patients with HER2 exon 20 mutations, harboring either the Y772dupYVMA or the G778dupGSP HER2 insertions. Based on preliminary results, confirmed ORR was 42.0%, median DoR was 4.6 months, and DCR was 83.0% (Robichaux et al 2019).

The combination of mAb treatment of trastuzumab plus pertuzumab was investigated as part of the Phase II MyPathway basket study in tumors with specific HER2 activating mutations, including exon 20 insertions, deletions in amino acids 755 to 759, and several nonsynonymous amino acid substitutions without amplification or overexpression (NCT02091141). Thirty-six patients with HER2-mutant tumors received treatment and 4 patients had an objective response; the ORR was 11.0% (95% CI: 3, 26). Of the 14 patients with NSCLC, 3 patients (21.0%) had PR and 3 patients had SD (Hainsworth et al 2018). Only one out of the other 22 patients with HER2-mutant tumors responded to treatment with pertuzumab plus trastuzumab (biliary cancer).

Antibody-drug conjugates are a class of cancer therapies that combine antigen specificity and potent cytotoxicity in a single molecule, allowing greater control of drug PK and improving drug delivery to target tissue. The activity of the first-generation HER2-targeted ADC, T-DM1, was assessed in a single-center, Investigator-sponsored, Phase II basket study in a cohort of patients with HER2-mutant NSCLC (NCT02675829). Results were reported in 18 patients with HER2 mutant NSCLC. All responders had PR and the ORR was 44.0%

(95% CI: 22.0, 69.0). The median DoR of 4 months (range 2-9 months) was reported in patients with *HER2 exon 20* insertions and nonsynonymous substitution mutations in the kinase, transmembrane, and extracellular domains (Li et al 2018). Concurrent HER2 amplification was observed in 11.0% of patients, consistent with previous reports (Arcila et al 2012; Li et al 2016; Mazieres et al 2013). While the study was positive, T-DM1 activity was only reported in NSCLC carrying HER2 mutations. T-DM1 efficacy in other tumor types harboring HER2 mutations is currently unknown.

Trastuzumab deruxtecan

T-DXd is a novel next-generation ADC targeting HER2, composed of a humanized IgG1 mAb with reference to the amino acid sequence of trastuzumab, which is attached by a cleavable peptide-based linker to a potent topoisomerase I inhibitor payload (Ogitani et al 2016).

Data from the Phase I DS8201-A-J101 (Tsurutani et al 2020) and the Phase II DS8201-A-U204 (DESTINY-Lung01) studies provide encouraging preliminary evidence of antitumor activity of T-DXd in tumors with HER2 mutations. As of the DCO date of 01 February 2019 of Study DS8201-A-J101, the confirmed ORR in the HER2 mutant patients per RECIST v1.1 was 54.5% (95% CI: 23.4, 83.3) in breast cancer (N = 11), 0% in CRC (N = 6, 4 out of 6 had SD), and 73.0% (95% CI: 39.0, 94.0) in NSCLC (N = 11). Responses were observed in tumors harboring HER2 mutations in extracellular, transmembrane, and tyrosine kinase domains including D277Y, S310F, G660D, L755_T759del, E770_A771ins, Y772_A775dup, A775_G776ins, and T862A. Most of these HER2 mutations have been previously described to have oncogenic activity (Bose et al 2013; Nagano et al 2018; Ou et al 2017; Pahuja et al 2018) and have high prevalence across tumor types (Mishra et al 2017; Robichaux et al 2019).

The DCR was 81.8% in breast cancer, 66.7% in CRC, and 90.9% in NSCLC. While these data should be interpreted with caution due to the small sample sizes, they provide preliminary evidence for efficacy of T-DXd in both breast and lung tumors with HER2 mutations and suggest T-DXd could have clinically meaningful benefit across a variety of tumor types with HER2 mutations.

As of 25 November 2019, 42 patients with HER2 mutant NSCLC (Cohort 2) who had received at least one prior therapy for Stage IV disease had been enrolled in Study DS8201-A-U204 (DESTINY-Lung01). The median number of prior systemic cancer therapies was 2 [range: 1 to 6]. Thirty-eight subjects (90.5%) received prior platinum-based therapy, 23 subjects (54.8%) received prior anti-PD-1 or -PD-L1 treatment (Smit et al 2020). Central confirmation of HER2 mutation is underway. T-DXd was administered at a dose of 6.4 mg/kg to all patients. The median duration of follow-up was 8.0 months (range: 1.4-14.2 months). Treatment in 19 patients (45.2%) was ongoing at the time of DCO. The median treatment duration was 7.75 months (range: 0.7-14.3 months) The ICR-assessed confirmed

ORR was 61.9% (95% CI: 45.6, 76.4) and the median DoR was not reached. At the time of the DCO, 16 of the 26 responders remained on treatment. Responses were observed in patients with HER2 mutations, including G778_P780dup, Y772_A775dup, A775_G776ins, and G776delinsVC.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

2.3.1.1 Potential Risks of T-DXd

Based on data from clinical studies, toxicities considered to be associated with administration of T-DXd include the important identified risks of ILD/pneumonitis and neutropenia (including febrile neutropenia). Other identified risks for T-DXd are infusion-related reactions, leukopenia, lymphopenia, thrombocytopenia, anemia, pulmonary/respiratory AEs (cough, dyspnea, upper respiratory tract infection), gastrointestinal AEs (abdominal pain, constipation, decreased appetite, diarrhea, dyspepsia, nausea, stomatitis, vomiting), dry eye, alopecia, ALT and AST increase, hypokalemia, rash, dizziness, epistaxis, fatigue and headache.

Based on the available pre-clinical data, review of the cumulative literature, reported toxicities for the same class of agents, the important potential risks for T-DXd are LVEF decrease and embryo-fetal toxicity. Keratitis is considered a potential risk for T-DXd.

ILD/pneumonitis and LVEF decreased are considered to be AESIs.

In vitro metabolism studies in human liver microsomes indicated that MAAA-1181a, the released drug of T-DXd, is metabolized mainly by cytochrome P450 3A4 via oxidative pathways, however, the contribution of metabolism would be minimal based on the in vivo nonclinical data and clinical study data (Study DS-8201A-A104; Section 6.4.2 of T-DXd IB). Nonclinical studies in monkeys suggested transient increases in ALT and AST, however, there were no histopathological changes in the liver with T-DXd. In clinical studies with T-DXd, elevations in liver transaminases were observed. Increases in AST and ALT are considered adverse drug reactions (ADRs) for T-DXd (Section 6.9.1 of T-DXd IB).

More detailed information about the known and expected, and potential, risks of T-DXd may be found in the IB.

2.3.2 Potential Risks of HER-2 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 monoclonal antibodies trastuzumab (HERCEPTIN®, Genentech) and pertuzumab (PERJETA®, Genentech), the antibody-drug conjugate T-DM1 (Kadcyla®, Genentech), and HER1- and 2-associated tyrosine kinase inhibitors, lapatinib (Tykerb®, Novartis), and neratinib (Nerlynx®, Puma Biotechnology). The safety profile of these HER2-targeted agents

has been well described. The main safety risks identified in patients receiving HER2-targeted products are described below; these could potentially be expected to occur in patients receiving T-DXd.

- **Cardiotoxicity**: Patients treated with trastuzumab are at increased risk for developing CHF (New York Heart Association class II to 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, although at a lower incidence than in patients receiving trastuzumab; most 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 predominantly of asymptomatic LVEF decrease. Based on the available nonclinical data, and review of the cumulative literature, LVEF decrease is considered to be an important potential risk of T-DXd.
- **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 antineoplastic 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-related 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.

2.3.2.1 Potential Risks of 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 campothecin derivative, which was previously developed by the former Daiichi Pharmaceuticals Co., Ltd. as an anticancer 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 and delayed onset 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 profiles of other topoisomerase I inhibitors, with hematological toxicities and gastrointestinal toxicities being the most significant groups of events.

ILD/pneumonitis risk is unknown in previously unexplored tumor types. In order to mitigate this risk, a prior history of ILD/pneumonitis is an exclusion criterion (Section 5.2). ILD management guidance can be found in Section 8.3.15.

2.3.3 Benefit Assessment

T-DXd is currently being developed as a therapeutic candidate for HER2-expressing tumors and for tumors that exhibit specific HER2 activating mutations. Further development of T-DXd in HER2 mutant solid tumors is supported by encouraging clinical data from studies DS8201-A-J101 and DESTINY-Lung01, which showed remarkable preliminary clinical efficacy of T-DXd across multiple HER2 mutations in breast and lung cancer, suggesting that T-DXd efficacy is being driven, in part, by mutational activation of the HER2 receptor and that this mechanism of action may be independent of histology. Confirmed ORR of 54.5% and 73.0% were reported in HER2 mutant breast and lung cancer, respectively in DS8201-A-J101(Tsurutani et al 2020), and confirmed ORR by ICR was 61.9% in NSCLC based on data from DESTINY-Lung01 (Smit et al 2020) demonstrating a much greater activity compared to other HER2-targeted agents previously used to target HER2 mutations in these indications (Hyman et al 2018, Smyth et al 2019, Peters et al 2018, Lai et al 2019, Dziadziuszko et al 2019, Li et al 2018). Whereas no objective responses were reported in CRC, the DCR was encouraging in all three tumor types examined, including CRC with 67% DCR, 82% in breast cancer, and 91% in NSCLC. Moreover, a parallel translational study performed in HER2-mutant cell lines and patient derived xenograft models showed that activating HER2 mutations (or amplification) preferentially drive internalization of receptor-ADC complex to enhance delivery of cytotoxic payload independent of HER2 protein expression levels, providing additional mechanistic and clinical rationale for targeting HER2 mutations with T-DXd (Li et al 2020).

2.3.4 Overall Benefit: Risk Conclusion

HER2-targeted therapies have transformed outcomes for HER2- amplified/overexpressed breast and gastric/GEJ cancer. However, the use of HER2 directed approaches outside of HER2- amplified/overexpressed breast and gastric cancer remains controversial. Emerging clinical data show efficacy of HER2-targeted therapies across a variety of tumor types with HER2 activating mutations (Hyman et al 2018, Smyth et al 2019, Peters et al 2018, Lai et al 2019, Dziadziuszko et al 2019, Li et al 2018), however, to date, no treatments have been approved to treat solid tumors harboring HER2 activating mutations, which highlights the unmet medical need in this patient population.

To date, the overall safety and tolerability profile of T-DXd monotherapy across the program has been acceptable and the available T-DXd efficacy data indicate that the overall benefit-risk assessment supports further clinical development. Clinical development of T-DXd in HER2 mutant cancer is further supported by encouraging preliminary efficacy data from 2 Daiichi Sankyo-sponsored studies, DS8201-A-J101 (Phase I) and DS8201-A-U204 (Phase II). In these studies, T-DXd administered at either 5.4 or 6.4 mg/kg q3w demonstrated

clinically meaningful and durable activity in patients with HER2 mutant breast and lung cancer. The lower dose of 5.4 mg/kg has been selected to maximize patient benefit-risk in previously unexplored tumor types and is consistent with the overall clinical development plan for further exploration of this dose across the program.

The study design aims to minimize and mitigate against potential risks in several ways.

Firstly, interim efficacy analyses will be performed within each tumor type to minimize subject exposure in potentially non-responding indications. If no confirmed objective response is observed among the first 8 treated patients in a specific tumor type, enrolment in that tumor type will be discontinued. The protocol also includes intensive safety monitoring with the intent of protecting patients. Furthermore, there are specific guidances for Investigators to support optimal management of risks deemed to be most likely or serious. The monitoring and management of potential risks are discussed in Section 8.3.15.

In addition, the emergence of COVID-19 presents a potential safety risk for patients and therefore, several risk mitigation factors have been implemented in this study. This includes the eligibility criteria excluding patients with active COVID-19 infections, providing guidance on the use of chloroquine and hydroxychloroquine prior to and during the study, and due to the potential overlapping impact of T-DXd and COVID-19 on the lung, also providing a dose modification and management plan for patients with confirmed or suspected COVID-19 while being treated with T-DXd (see Appendix I).

Given the data available on the efficacy and safety of T-DXd, the overall benefit/risk is considered positive. For more information on the potential benefits and an assessment of the potential and known risks for T-DXd, refer to the IB.

3 OBJECTIVES AND ENDPOINTS

Table 8 shows the objectives and endpoints for this study.

Table 8 Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of T-DXd in patients with metastatic or unresectable tumors harboring specific HER2 activating mutations across tumor types.	Confirmed ORR according to RECIST v1.1, as assessed by ICR.
Secondary	
To further evaluate the efficacy of T-DXd in patients with metastatic or unresectable tumors harboring pre-specified HER2 activating mutations across tumor types.	ICR and Investigator assessments, based on RECIST v1.1, to allow the calculation of: DoR DCR PFS Proportion of patients alive and progression-free at 6 and 12 months. Confirmed ORR (Investigator assessment).
To further investigate the efficacy of T-DXd on tumors with pre-specified HER2 mutations as measured by OS across tumor types.	OS Proportion of patients alive at 6 and 12 months.
To assess the safety and tolerability of T-DXd.	Assessed by the occurrence of AEs, SAEs, and changes from baseline in laboratory parameters, vital signs, ECG and ECHO/MUGA results.
To assess the PK of T-DXd, total anti-HER2 antibody and MAAA-1181a in serum.	Serum concentration of T-DXd, total anti-HER2 antibody and MAAA-1181a.
To investigate the immunogenicity of T-DXd.	Presence of ADAs for T-DXd.

ADA, anti-drug antibodies; AE, adverse event; ctDNA, circulating tumor deoxyribonucleic acid; DCR, disease control rate; DoR, duration of response; ECG, electrocardiogram; ECHO, echocardiogram; EGFR, epidermal growth factor receptor; FFPE, formalin-fixed and paraffin-embedded; FISH, fluorescent in situ hybridization; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; ICR, independent central review; ILD, interstitial lung disease; MAAA-1181, deruxtecan; MDASI, MD Anderson Symptom Inventory; MSI, microsatellite instability; MUGA, multigated acquisition; NGS, next-generation sequencing; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PK, pharmacokinetic; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SAE, serious adverse event; SGRQ-I, St George's Respiratory Questionnaire for patients with Idiopathic Pulmonary Fibrosis; T-DXd, trastuzumab deruxtecan; TMB, tumor mutational burden;

4 STUDY DESIGN

4.1 Overall Design

This is an open-label, multi-center, single arm Phase II study to evaluate the efficacy and safety of T-DXd for the treatment of unresectable and/or metastatic solid tumors harboring specific HER2 activating mutations regardless of tumor histology. Targeting genomic alterations that are drivers of tumorigenesis and that occur at low frequencies across different cancer types, such as specific HER2 activating mutations, have proven to be a suitable approach (eg, pembrolizumab, larotrectinib, and entrectinib). The tumor-agnostic study design will facilitate enrolment of a sufficient number of patients to evaluate the safety and efficacy of T-DXd across a number of different mutation and tumor types.

Patients will be enrolled at approximately 20 sites globally. Adult patients with unresectable and/or metastatic solid tumors carrying pre-specified HER2 activating mutations, who have progressed following prior treatment or who have no satisfactory alternative treatment options will be enrolled. Approximately 100 patients will be treated in this study with a maximum of approximately 20 patients per tumor type to ensure adequate representation across multiple tumor types. Anticipated tumor type enrolment in the study includes breast, colorectal, urothelial, esophagogastric, hepatobiliary, small cell lung, endometrial, melanoma, ovarian, cervical, salivary gland, pancreatic and cutaneous squamous-cell carcinoma. There is no pre-specified requirement for representation of any specific tumor type that meets the eligibility criteria.

Enrolment in a specific tumor type will be paused after 8 patients with Investigator-assessed measurable disease at baseline have been treated within that tumor type, until a decision has been made on whether to stop enrolment to that tumor type based on the interim futility evaluation. If no confirmed objective response (assessed by Investigator per RECIST v1.1) is observed among the first 8 treated patients in a specific tumor type, enrolment in that tumor type will be discontinued. See Section 9.5 for further details.

The primary objective is to determine the confirmed ORR based on ICR. The study will also assess DoR, DCR, PFS, OS and other outcome measures of T-DXd antitumor activity across tumor types. Tumor evaluation using RECIST v1.1 will be conducted at screening (within 28 days before first dose of study treatment) and every 6 weeks (± 1 week; relative to the date of first dose of IP) until RECIST v1.1 objective disease progression, withdrawal of consent, or death by any cause. Each patient will be followed for efficacy, regardless of whether study treatment is discontinued, until all patients have had the opportunity for approximately 32 weeks of follow-up after treatment assignment.

The imaging modalities used for RECIST assessment will be contrast-enhanced CT or MRI scans as clinically indicated. The same modality used at baseline must be used at each

subsequent follow-up assessment. Radiography (X-ray) and PET are not acceptable imaging modalities. Any other sites at which disease is suspected or known at baseline should also be imaged and additional sites of disease not covered by the protocol specified anatomy, should be followed at the same scheduled visits as the other RECIST assessments. Radiological examinations performed in the conduct of this study should be retained at site as source data and be available for collection by the Sponsor for independent central review.

Blood samples for determination of T-DXd, total anti-HER2 antibody, and MAAA-1181a concentrations in serum will be collected and analyzed by a Sponsor-designated bioanalytical laboratory on behalf of AstraZeneca. Full details of the analytical method used will be described in a separate Bioanalytical Report. All samples still within the known stability of the analytes of interest at the time of receipt by the bioanalytical laboratory will be analyzed. In addition, the PK sample concentration data may be subjected to further analyses in order to correlate PK with other primary, secondary, and exploratory endpoints in patients treated with T-DXd. Details on sample processing, handling, shipment, and storage will be provided in the laboratory manual. Blood samples for pharmacogenetic and circulating biomarker research will be obtained from consenting patients and stored for exploratory biomarker analysis (as permitted by local regulations). Patients do not have to consent to these optional samples in order to participate in the study.

4.1.1 Patient Population

Patients with unresectable and/or metastatic solid tumors harboring specific HER2 mutations who have progressed following prior treatment or who have no satisfactory alternative treatment options. Pre-specified HER2 activating mutations (S310F, S310Y, G660D, R678Q, D769Y, D769H, V777L, Y772_A775dup / A775_G776insYVMA, L755S, G778_P780dup / P780_Y781insGSP, T862A, and V842I) will be locally determined by NGS tests or a nucleic acid-based methodology (eg, qPCR, digital PCR). The local test result must be obtained from a regulated laboratory authorized to perform medical diagnostic testing ie, CLIA-certified laboratory or equivalent accredited laboratory (eg, ISO15189). These pre-specified HER2 activating mutations were selected based on overall prevalence, with special consideration given to highly prevalent mutations across multiple tumor types, as confirmed through literature review and Memorial Sloan Kettering Cancer Center database query using bioinformatic tools. Mutations were confirmed as HER2 activating mutations through OncoKB or Civic annotations. A mandatory archival tumor sample representative of the patients' disease, and preferably the same sample from which the local laboratory assessment of HER2 mutation was determined, will be required from all patients to retrospectively confirm the presence of locally identified HER2 activating mutation(s). Retrospective central test results of HER2 mutation status will not be shared with sites and will not affect patients' enrolment.

All patients must be ≥ 18 years of age (other age restrictions may apply as per local

regulations), RECIST v1.1 evaluable, and WHO/ECOG performance status of 0-1. Patients previously treated with HER2 targeting therapy will be eligible. Patients with HER2 mutant NSCLC and patients with HER2-overexpressed breast and gastric cancer, as determined by local HER2 testing will be excluded. HER2 overexpression and/or gene amplification are considered major mechanisms of HER2-driven tumorigenesis and remain the main predictive biomarker to identify patients with metastatic breast adenocarcinoma who might benefit from therapy with anti-HER2 agents or to guide selection of patients with metastatic unresectable gastroesophageal cancer to trastuzumab contained regimens. A number of reports have indicated that high HER2 levels are directly associated with response to HER2-targeted agents, which has been proposed as a marker of HER2 addiction (Di Modica et al 2017; Prat et al 2014; Triulzi et al 2015). In light of these findings, the Sponsor has opted to exclude patients with concurrent HER2 activating mutations and HER2 overexpression/amplification in indications where it is currently well established that HER2-targeted therapies exert a positive effect and have been linked with favorable clinical outcomes. Additionally, different reports have described loss of HER2 expression in patients with HER2 overexpressed/amplified gastroesophageal and breast cancer treated with trastuzumab, which may represent a mechanism of resistance to trastuzumab (Branco et al 2019; Janjigian et al 2015, Makiyama et al 2020; Mittendorf et al 2009; Niikura et al 2012; Pietrantonio et al 2016). Therefore, patients with breast and gastric cancer who have received prior trastuzumab or other HER2 targeting therapy will be potentially eligible if HER2 is not overexpressed in a tissue biopsy taken after documented disease progression following anti-HER2 treatment.

4.2 Scientific Rationale for Study Design

The primary objective of this study is to assess the efficacy of T-DXd in patients with metastatic or unresectable tumors harboring specific HER2 activating mutations across tumor types.

Antitumor activity will be primarily assessed by evaluating ORR, defined as the proportion of patients who have a confirmed CR or PR. When defined in this manner, ORR is a direct measure of the drug's antitumor activity. ORR will be supported by determination of DoR, that will show how long patients responded to, or had a positive response to, therapy, thus helping to determine the therapeutic value of T-DXd treatment. Additional secondary efficacy endpoints will be evaluated, including DCR, PFS, and OS, which are widely accepted parameters for the determination of efficacy in patients with metastatic or unresectable tumors harboring HER2 activating mutations.

The safety and tolerability of T-DXd will be assessed by the standard safety endpoints, including AEs, SAEs, clinically meaningful changes from baseline in laboratory parameters, ECG and vital signs. Careful consideration has been given to the mitigation of risks related to the mode of action and the nature of the target, which will be closely monitored during the study.

There are many potential benefits of this research, including the possibility of identifying patients most likely to benefit from treatment, explaining outliers or non-responders, and potential adverse reactions related to drug exposure.

ILD/pneumonitis-specific clinical outcome assessments will be included for exploratory purposes. ILD/pneumonitis is a known AE of T-DXd that occurs in approximately 9% of patients. Little is known about the baseline respiratory functioning of the population receiving T-DXd. Historically, ILD/pneumonitis is considered an idiopathic treatment-emergent AE, whose mechanism of action is poorly defined. Therefore, within this trial a multi-modality approach will be applied, including a digital patient diary for respiratory symptom collection, at-home pulse oximetry, and site-based PFTs. The aim of the clinical outcome assessments is to better characterize ILD/pneumonitis and the progression of these cases.

The study will help identify if T-DXd single agent therapy could help address the unmet medical need in patients with unresectable and/or metastatic solid tumors harboring specific HER2 activating mutations.

4.3 Justification for Dose

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 was not reached in the dose escalation phase of Study DS8201-A-J101. Both doses showed efficacy in different tumor types. A numerically higher incidence of AEs ≥ Grade 3 (overall and causally related), SAEs (including causally related), AEs leading to drug withdrawal (overall and causally related), and AEs leading to dose reduction (overall and causally related) were noted with 6.4 mg/kg compared to 5.4 mg/kg. PK was evaluated in 26 patients who received T-DXd in the dose escalation portion of Study DS8201-A-J101 across various tumor types. The PK exposure was approximately 20% lower in patients with gastric cancer than breast cancer at the 6.4 mg/kg dose level, and therefore a dose of 6.4 mg/kg was selected for subsequent development in gastric cancer. In the current clinical study (D967MC00001), multiple new tumor types will be evaluated, and the precedent data suggest that PK exposure and thus safety profile may differ by tumor type. Therefore, the dose planned for evaluation in this study of 5.4 mg/kg has been selected to maximize patient benefit-risk in previously unexplored tumor types and is consistent with the overall clinical development plan for further exploration of this dose across the program. Following evaluation of the initial PK and safety data, alternate dose levels may be explored via protocol amendment.

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

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

4.4 End of Study Definition

The end of the study is defined as the time of the final DCO for the final analysis. Final analysis is planned to be performed when the last patient has had the opportunity for approximately 32 weeks of follow-up after treatment assignment.

At the time of study completion the clinical database will close to new data, however SAEs must continue to be reported. Patients may be withdrawn from the study at this time; however, patients may remain on study treatment beyond closure of the database if, in the opinion of the Investigator, the patient continues to receive benefit from study treatment (Section 6.7).

The study may be stopped if, in the judgment 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 study completion in the planned timeframe.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment 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 assigned to 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. For procedures for withdrawal of incorrectly enrolled patients see Section 6.3.2.

5.1 Inclusion Criteria

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

Informed Consent

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

2 Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports the Genomic Initiative (see Appendix D).

3 Provision of signed and dated written ICF prior to any mandatory study specific procedures, sampling, or analyses.

Age

4 Male and female patients must be at least 18 years of age at the time of signing the ICF. Other age restrictions may apply as per local regulations.

Type of Participant and Disease Characteristics

5 Patients with unresectable and/or metastatic solid tumors with pre-specified HER2 mutations, who have progressed following prior treatment, or who have no satisfactory alternative treatment options including approved second line therapies in the specific tumor type. Prior HER2 targeting therapy is permitted.

6 Patients with tumors harboring any of the following HER2 mutations: S310F, S310Y, G660D, R678Q, D769Y, D769H, V777L, Y772_A775dup / A775_G776insYVMA, L755S, G778_P780dup / P780_Y781insGSP, T862A, and V842I locally determined by NGS or a validated nucleic acid-based methodology (eg, qPCR, digital PCR) on tumor tissue.

7 All patients must provide an existing FFPE tumor sample for retrospective central HER2 testing. The sample should be obtained at the time of diagnosis of metastatic or locally advanced unresectable disease. If not available, a pre-enrolment sample obtained upon diagnosis of metastatic or locally advanced unresectable disease will be accepted. New tumor samples can be obtained as part of patient's routine clinical care. Specimens with limited tumor content and fine needle aspirates are inadequate for defining tumor HER2 mutation status. Additional details on sample requirements will be provided in the laboratory manual.

8 Has measurable target disease assessed by the Investigator based on RECIST v1.1.

9 WHO/ECOG performance status 0-1.

10 LVEF ≥ 50% by either ECHO or MUGA scan within 28 days before treatment assignment.

11 Adequate organ and bone marrow function within 14 days before IP administration, defined as:

Item	Laboratory value
Platelet count	≥ 100000/mm^3. (Platelet transfusion is not allowed within 1 week prior to screening assessment)
Hemoglobin	Hemoglobin ≥ 9 g/dL. NOTE: Patients requiring ongoing transfusions or growth factor support to maintain hemoglobin ≥ 9 g/dL are not eligible. (> 8 g/dL in Gastric Cancer / Gastroesophageal Cancer Indications) (Red blood cell transfusion is not allowed within 1 week prior to screening assessment)
Absolute neutrophil count	≥ 1500/mm^3. (G-CSF administration is not allowed within 1 week prior to screening assessment)
Creatinine	Creatinine clearance ≥ 30 mL/min (as calculated using the Cockcroft and Gault equation) [a]
ALT / AST	≤ 3 × ULN, < 5 × ULN in patients with liver metastases.

Item	Laboratory value
Total bilirubin	≤ 1.5 × ULN if no liver metastases or < 3 x ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline.
Serum albumin	≥ 2.5 g/dL
INR/PT, and either PTT or aPTT	≤ 1.5 × ULN

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

ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; G-CSF, granulocyte colony-stimulation factor; INR, international normalized ratio; PTT, partial thromboplastin time; PT, prothrombin time; ULN, upper limit of normal

12 Has adequate treatment washout period before study drug treatment, defined as:

- Major surgery: ≥ 4 weeks.
- Radiation therapy including palliative stereotactic radiation therapy to chest: ≥ 4 weeks (palliative stereotactic radiation therapy to other areas ≥ 2 weeks).
- Anti-cancer chemotherapy (Immunotherapy [non-antibody-based therapy]), retinoid therapy, mBC; hormonal therapy: ≥ 3 weeks (≥ 2 weeks or 5 half-lives, whichever is longer, for small-molecule targeted agents such as 5-fluorouracil-based agents, folinate agents or weekly paclitaxel; ≥ 6 weeks for nitrosureas or mitomycin C).
- Antibody-based anti-cancer therapy: ≥ 4 weeks.
- Chloroquine / Hydroxychloroquine: > 14 days.

Reproduction

13 Evidence of post-menopausal status or negative serum pregnancy test for females of childbearing potential who are sexually active with a non-sterilized male partner.

a. 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 pregnancy test prior to each administration of IP.

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

i. Women aged ≥ 50 years would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the site.

ii. Women aged ≤ 50 years would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all

exogenous hormonal treatments, had radiation-induced oophorectomy with last menses > 1 year ago, had chemotherapy-induced menopause with > 1 year-interval since last menses, or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

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 10) from the time of screening and must agree to continue using such precautions for at least 7 months after the last dose of IP. Not all methods of contraception are highly effective. Female patients must refrain from egg cell donation and breastfeeding while on study and for 7 months after the last dose of IP. Not engaging in sexual activity for the duration of the study and drug washout period is an acceptable practice; however, periodic or occasional abstinence, 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 to at least 4 months after the final dose of IP. Not engaging in sexual activity for the duration of the study and drug washout period is an acceptable practice; however, periodic or occasional abstinence, 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 to also use at least one highly effective method of throughout this period, as described in Table 10. In addition, male patients should refrain from fathering a child or freezing or donating sperm from screening, throughout the study treatment period, and for at least 4 months after the last dose of IP.

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 final study drug administration.

5.2 Exclusion Criteria

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

1 HER2 overexpressing (IHC3+ or IHC2+/ISH+) adenocarcinoma of breast, gastric or gastroesophageal junction as determined by local HER2 testing. Patients with breast, gastroesophageal and gastric cancer harboring selected specific HER2 activating mutations (See inclusion criteria 6) and who have received prior trastuzumab or other HER2 targeting therapy will be eligible if HER2 is not overexpressed (IHC3+ or IHC2+/ISH+) in in a tissue biopsy taken after documented disease progression following trastuzumab and/or HER2 targeting treatment.

2 HER2 mutant NSCLC.

3 Patients with a medical history of myocardial infarction within 6 months before randomization/enrolment, symptomatic CHF (New York Heart Association Class II to IV), unstable angina pectoris, clinically important cardiac arrhythmias, or a recent (< 6 months) cardiovascular event including stroke. 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 enrolment to rule out myocardial infarction.

4 Corrected QT interval by Fridericia's formula (QTcF) prolongation to > 470 msec (females) or > 450 msec (males) based on average of the screening triplicate 12-lead ECG.

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

6 Has a pleural effusion, ascites or pericardial effusion that requires drainage, peritoneal shunt, or Cell-free and Concentrated Ascites Reinfusion Therapy (CART). (Drainage and CART are not allowed within 2 weeks prior to screening assessment).

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

8 Receipt of live, attenuated vaccine within 30 days prior to the first dose of T-DXd. Note: Patients, if enrolled, should not receive live vaccine during the study and up to 30 days after the last dose of IP.

9 Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤ 1 or baseline. Patients with chronic Grade 2 toxicities may be eligible per the discretion of the Investigator after consultation with the Sponsor Medical Monitor or designee (eg, Grade 2 chemotherapy-induced neuropathy).

10 Multiple primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, other solid tumors curatively treated, or contralateral breast cancer.

11 Known allergy or hypersensitivity to the IP or any of the study drug excipients.

12 Pregnant or breastfeeding female patients.

13 Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals.

14 Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disorder (ie, pulmonary emboli within three months of the study enrolment, severe asthma, severe COPD, restrictive lung disease, pleural effusion etc), and any autoimmune, connective tissue or inflammatory disorders with documented or suspicious pulmonary involvement at screening (ie, rheumatoid arthritis, Sjogren's, sarcoidosis etc), and prior pneumonectomy.

15 Uncontrolled intercurrent illness, including but not limited to ongoing or active infection, uncontrolled hypertension, 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.

16 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. Patients with clinically inactive brain metastases may be included in the study. Patients 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 enrolment.

17 Patients participating in a concurrent interventional clinical study and/or previously treated with T-DXd.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

There are no meal and dietary restrictions during participation in the study.

5.3.2 Caffeine, Alcohol, and Tobacco

Use of tobacco products, e-cigarettes and vaping is strongly discouraged but not prohibited. Patients should inform their doctor about any prior or current use of these products.

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are

subsequently not assigned to treatment, as they do not meet the required eligibility (inclusion/exclusion) criteria. Screen failure only applies to patients without treatment assignment. Patients who fail to meet the eligibility criteria should not, under any circumstances, be assigned to treatment. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all eligibility criteria must not initiate treatment and must be screen-failed.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened a single time. Patients should be assigned the same patient number as the initial screening. Rescreening should be documented so that its effect on study results, if any, can be assessed.

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 publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

6 STUDY INTERVENTION

Study intervention is defined as any IP, marketed product, placebo, or medical device intended to be administered to a study patient according to the study protocol. Study treatment in this study refers to T-DXd.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

The IP to be administered in this study is shown in Table 9.

T-DXd will be administered to patients harboring tumors with specific HER2 activating mutations at a dose of 5.4 mg/kg via IV infusion on Day 1 of each cycle, every 3 weeks.

Table 9 Investigational Products

Name	Dosage Presentation	Unit Dose Strength(s)	Dosage Levels	Route of Administration	Use	Sourcing	Packaging and Labeling
T-DXd [a]	Vial	Powder for concentrate for solution for infusion 100 mg/vial	5.4 mg/kg	IV	Experimental	Provided centrally by the Sponsor	IP will be provided in a vial in carton. Each vial and carton will be labeled in accordance with GMP Annex 13 and per country requirements.

[a] Label text for trastuzumab deruxtecan (T-DXd, DS-8201a) will show "DS-8201a", depending on the agreed product name used in the respective approved study master label document. All naming conventions for these compounds are correct during this transitional period.

GMP, Good Manufacturing Practice; IP, investigational product; IV, intravenous; T-DXd, trastuzumab deruxtecan

6.2 Preparation/Handling/Storage/Accountability of Interventions

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only patients who are enrolled and subsequently assigned to treatment in the study may receive study intervention and only authorized site staff may supply or administer study intervention. T-DXd 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 intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

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

6.2.1 Administration of T-DXd

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 v1.1 disease progression, withdrawal of consent or any of the discontinuation criteria are met. Standard infusion time is over 90 minutes + 10 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.

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

6.2.2 Monitoring of T-DXd Dose Administration

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

Management of IP-related toxicities for T-DXd are described in Section 8.3.15.

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.

6.2.3 Storage

The Investigator, or an approved representative (eg, pharmacist), will ensure that all IP is stored in a secured area, at appropriate temperatures and as specified on the label and in accordance with applicable regulatory requirements. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging are to be reported to the Study Physician upon detection. Storage conditions stated in the IB may be superseded by the label storage instructions.

6.3 Measures to Minimize Bias

6.3.1 Patient Enrolment and Treatment Assignment

This is an open-label, single-arm study with no randomization or blinding, however study treatment will be centrally assigned using IRT. Before the study is initiated, instructions for the IRT will be provided to each site. The site will contact the IRT to confirm tumor type prior to the start of IP administration for each patient. IRT will provide the kit identification number to be allocated to the patient at each treatment visit.

If a patient withdraws from the study, then his/her enrolment/treatment assignment number cannot be reused. Withdrawn patients will not otherwise be replaced unless they did not receive any study treatment.

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently assigned treatment.

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

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

- Obtain signed informed consent before any study-specific procedures are performed (Section 8.2.1). If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with the consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of treatment assignment. For patients with a single target lesion, if screening biopsy is collected prior to screening imaging for baseline tumor assessment, allow approximately 2 weeks for healing before imaging scans are acquired.
- Obtain a unique 7-digit enrolment number (E-code), through the IRT in the following format: ECCNNXXX (CC being the country code, NN being the center number, and

XXX being the patient enrolment code at the center). This number is the patient's unique identifier and is used to identify the patient on the eCRFs.

- 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 assigned to treatment, the IRT should be contacted by the site to terminate the patient in the system.

Patients will begin treatment on Day 1. Treatment should start no more than 3 days after treatment assignment in IRT. Patients must not be assigned to treatment, or treatment initiated, unless all eligibility criteria have been met.

At baseline, once the patient is confirmed to be eligible, the Investigator or suitably trained delegate will obtain a unique treatment assignment number via the IRT.

6.3.2 Procedures for Handling Incorrect Enrolment or Treatment Assignment

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

When a patient does not meet all the eligibility criteria but is assigned to treatment 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.

6.4 Study Intervention Compliance

Patients will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of dose administered in the clinic will be recorded in the source documents and in the eCRF. The dose of study intervention 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 intervention. The Investigator or pharmacist must retain records of the IP administered at the site. The Study Monitor will check these records to confirm compliance with the protocol administration schedule.

The administration of IP should be recorded in the appropriate sections of the eCRF. 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 IP Storage Manager assigned by the Investigator site is responsible for managing the IP from receipt by the study site until the destruction or return of all unused IP.

Treatment compliance will be ensured by site reconciliation of IPs dispensed as described in Section 6.2.

Use of IP in doses in excess of that specified in the protocol is considered to be an overdose. Refer to Section 8.4 for procedures in case of overdose.

6.5 Concomitant Therapy

6.5.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as prohibited in Section 6.5.2.

Based on the currently available clinical safety data, it is recommended that patients receive prophylactic anti-emetic agents prior to the infusion of T-DXd and on subsequent days. Antiemetics such as 5-HT3 antagonists or NK1 receptor antagonists and/or steroids (eg, dexamethasone) might be considered and administered in accordance with the prescribing information or institutional guidelines.

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 enrolment or receives during the study must be recorded along with:

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

The AstraZeneca Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.2 Prohibited Concomitant Medications

T-DXd safety-specific restrictions are listed below.

- Patients must be instructed not to take any medications, including over-the-counter products, 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 IP.

- The following medications are prohibited during the study. The AstraZeneca Study Physician must be notified if a patient receives any of these during the study.
  - Any concurrent chemotherapy, anti-cancer IP or biologic, radiotherapy (except palliative radiotherapy) to areas other than chest, after consultation with the AstraZeneca Study Physician or hormonal therapy for cancer treatment. Concurrent use of hormones for noncancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable.
  - Trastuzumab deruxtecan cannot be administered when the patient is taking immunosuppressive medications, including corticosteroids with the following exceptions:
    - short-term courses (< 2 weeks);
    - low to moderate dose;
    - long-term, alternate-day treatment with short-acting preparations;
    - maintenance physiologic doses (replacement therapy);
    - or administered topically (skin or eyes), by aerosol, or by intra-articular, bursal, or tendon injection.
    - Treatment with corticosteroids to prevent or treat hypersensitivity reactions to radiographic contrast agents is allowed. A temporary period of steroid treatment will be allowed for different indications after discussion with the AstraZeneca Study Physician (eg, 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 IP-related AEs or in patients with contrast allergies is acceptable.
  - Immunosuppressive medications also include drugs like methotrexate, azathioprine, and tumor necrosis factor-alpha blockers.
- Concomitant treatment with chloroquine or hydroxychloroquine is not allowed during the study treatment. If treatment with chloroquine or hydroxychloroquine is absolutely required for COVID-19, study treatment must be interrupted. If chloroquine or hydroxychloroquine is administered, then a wash-out period of at least 14 days is required before restarting study treatment.

6.5.3 Other Protocol Restrictions

- Based on the currently available clinical safety data, it is recommended that patients receive prophylactic anti-emetic agents prior to infusion of T-DXd and on subsequent days. Antiemetics such as 5-HT3 antagonists or NK1 receptor antagonists and/or steroids

(eg, dexamethasone) should be considered and administered in accordance with the prescribing information or institutional guidelines.

- Hematopoietic growth factors may be used for prophylaxis or treatment based on the clinical judgment of the Investigator.
- Concomitant use of dietary supplements, medications not prescribed by the Investigator, and alternative/complementary treatments is discouraged, but not prohibited.
- Prophylactic or supportive treatment of study-drug induced adverse events will be otherwise as per investigator's discretion and institutional guidelines.
- Females of childbearing potential (defined as those who are not surgically sterile [ie, bilateral tubal ligation, 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 10) from the time of screening and must agree to continue using such precautions for at least 7 months after the last dose of IP; cessation of birth control after this point should be discussed with a responsible physician. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply.
  - Women aged ≥50 years would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels in the post-menopausal range for the site.
  - Women aged ≤ 50 years would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced oophorectomy with last menses >1 year ago, had chemotherapy-induced menopause with >1 year interval since last menses, or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Highly effective methods of contraception presented in Table 10 include copper T intrauterine device, levonorgesterel-releasing intrauterine system (eg, Mirena®), implants, hormone shot or injection, combined pill and patch.

Table 10 Methods of Contraception

Barrier/Intrauterine Methods	Hormonal Methods
Male or female condom with or without spermicide [a, b, e]	Implants [c]
Cap, diaphragm, or sponge with spermicide [a, b, e]	Hormone shot or injection [c]
Copper T intrauterine device [c]	Combined pill [c]
Progesterone T intrauterine device [d]	Minipill [a]
Levonorgestrel-releasing intrauterine system (eg, Mirena) [c, d,]	Patch [c]

[a] Not highly effective (failure rate of ≥ 1% per year)
[b] A male condom plus cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods
[c] Highly effective (failure rate of < 1% per year).
[d] Also considered a hormonal method
[e] Female partners of male patients should use an effective method of birth control.

6.6 Dose Modification

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

- Dose delays are permitted for T-DXd therapy and 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. A dose can be delayed for up to 28 days (49 days from the last infusion date) from the planned date of administration. If a patient is assessed as requiring a dose delay of longer than 28 days, the drug will be discontinued.
- For management of dose delays due to T-DXd-related events, the TMGs (Appendix G). should be followed, as applicable.

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

On improvement of an AE for which T-DXd was temporarily interrupted, T-DXd may be restarted at the same dose at the discretion of the Investigator. If a further episode of the same AE subsequently requires dose interruption, or if a different AE subsequently requires dose interruption, T-DXd may be restarted at a one dose level reduction on improvement of the AE or discontinued if the patient is receiving the lowest protocol-specified dose level (Section 8.3.15.1 and Appendix G).

Dose Modification for ILD/pneumonitis Cases

- ILD/pneumonitis Grade 1: If resolved in ≤ 28 days from day of onset, T-DXd may be resumed at the same dose. If resolved in > 28 days from day of onset, T-DXd will be resumed at a lower dose (if one is available) per Section 8.3.15.1. However, if the Grade 1

ILD/pneumonitis occurs beyond cycle Day 22 and has not resolved within 49 days from the last infusion, the drug should be discontinued.

- ILD/pneumonitis Grade 2 and higher: Permanently discontinue T-DXd. Follow-up assessments should be completed as described in the SoA (Table 7).

See Section 8.2.10.1 for tests required if ILD is suspected.

For any Grade 4 hematological toxicity with significant clinical symptoms that do not resolve with treatment within 4 weeks, treatment may be stopped.

Dose Modification Criteria for Suspected or Confirmed COVID-19

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

6.7 Intervention after the End of the Study

No intervention is planned after the end of the study (defined in Section 4.4). However, provisions will be in place for patients still ongoing at the end of the study to continue to receive study treatment if, in the opinion of the Investigator, they are still benefiting from treatment.

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 IP treatment 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 INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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

7.1 Discontinuation of Study Intervention

7.1.1 Permanent Discontinuation of IP

Patients may be discontinued from IP in the following situations. Note that discontinuation from IP is NOT the same as a complete withdrawal from the study. Patients who permanently discontinue IP will continue in follow-up assessments per the protocol (see Table 7). Patients will be permanently discontinued from the IP if the following criteria are met:

- Withdrawal by patient. The patient is free to discontinue treatment at any time, without prejudice to further treatment.

- Patients experiencing any of the following AEs will not be permitted to restart IP:
  - ILD or pneumonitis Grade 2 and higher
  - Any Grade 4 hematological toxicity with significant clinical symptoms that do not resolve with treatment within 4 weeks, treatment may be stopped.
- PD per criteria set forth in RECIST v1.1 (refer to Appendix F for details)
- Symptomatic deterioration (global deterioration of health status) without objective evidence of PD according to RECIST v1.1
- Any AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing
- Investigator decision
- Death
- Pregnancy
- Severe non-compliance with the protocol as judged by the Investigator and/or AstraZeneca Study Physician
- Patients who are incorrectly initiated on IP - after discussion between the AstraZeneca Study Physician and the Investigator. The AstraZeneca Study Physician must ensure all decisions are appropriately documented. The Investigator should document any decisions in the medical record as appropriate.
- Study terminated by Sponsor
- Patient lost to follow-up

If there is evidence that the patient is receiving benefit from treatment even though the patient has met a criterion for discontinuation as listed above, the patient may remain on study intervention after discussion with, and approval from, the AstraZeneca Study Physician.

All patients who are discontinued from IP should complete protocol-specified procedures for discontinuation of IP (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 (eg, death certificates) as allowed by local laws.

The EOT visit should be performed as soon as the patient permanently discontinues IP. See SoA (Section 1.3 and Section 7.1.2) for assessments to be performed at the EOT visit. 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 IP

At any time, patients are free to discontinue treatment with IP, and/or withdraw from the study, without prejudice to further treatment. The Investigator or designated site staff should instruct the patient to contact the site before, or at the time that, IP is permanently stopped. A

patient who decides to discontinue treatment with IP will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by the Investigator(s). The Investigator will follow-up AEs outside of the clinical study (Section 8.3).

Any patient who discontinues IP for reasons other than disease progression will continue response assessment scans every 6 weeks (± 1 week) relative to the date of first dose of IP until objective progression or withdrawal of consent. AEs must be captured as stated in the SoA (Table 7).

Note: Some assessments, such as further anticancer therapy, should continue beyond disease progression throughout the survival follow-up period (see Section 1.3). Patients who decline to return to the site for evaluations should be contacted by telephone 40 days (+ 7 days) following the discontinuation of IP as an alternative.

Permanent IP discontinuation must be recorded in the IRT and eCRF.

If a patient is withdrawn (or withdraws) from the study, see Section 7.2.

Discontinuation of IP, for any reason, does not impact on the patient´s participation in the study. Patients 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, including new AEs and follow-up on any ongoing AEs and concomitant medications. This could be a telephone contact with the patient at 40 days (+ 7 days) after IP is discontinued, contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient who agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

7.1.3 Follow-up to Progression

Patients who discontinue IP due to reasons other than objective disease progression will have tumor scans performed as per the study plan. In addition, the assessments detailed in the SoA during the follow-up period are also required (see Section 1.3).

7.1.4 Survival Follow-up

Assessments for survival will be made at 3, 6, 9, and 12 months (± 14 days), and every 3 months ± 14 days, following progression and discontinuation of IP, or where the patient has agreed only to follow-up (see Section 1.3). Survival information may be obtained via telephone contact with the patient, patient's family, or by contact with the patient's current physician or by checking publicly registries, as available and in accordance with local regulations.

Survival data will be collected up to the time of the final analysis for patients enrolled prior to the end of global recruitment. Patients should be contacted in the week following each DCO time point for analysis of survival to provide complete survival data (see Section 8.1.3).

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, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A patient who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, 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. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The patient will discontinue the study intervention and be withdrawn from the study at that time.
- If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a patient withdraws from the study, it should be confirmed if he/she is still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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, 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.

- 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 enrolled, who received at least one dose of IP. 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. Sponsor personnel will not be involved in any attempts to collect vital status information.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- The Investigator will ensure that data are recorded in the eCRFs as specified in the study protocol, and in accordance with the instructions provided. The RAVE Web Based Data Capture system will be used for data collection and query handling.
- The Investigator ensures the accuracy, completeness, legibility, 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 the AstraZeneca Study Physician immediately upon occurrence or awareness to determine if the patient should continue or discontinue treatment with IP.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened, and confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (eg, blood count), and obtained before signing of the ICF, may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- 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 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.
- Monthly SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

8.1 Efficacy Assessments

8.1.1 Antitumor Activity Using Imaging Assessments Based on RECIST v1.1

Efficacy of T-DXd in patients with tumors carrying the pre-specified HER2 mutations will be based on tumor assessments according to RECIST v1.1 (Appendix F) on scans performed by the Investigator at screening and at the intervals indicated in the SoA (Section 1.3).

The primary aim of this study is to assess the efficacy of T-DXd in patients with metastatic or unresectable tumors harboring specific HER2 activating mutations in terms of confirmed ORR, as assessed by ICR per RECIST v1.1.

Additional efficacy assessments will include confirmed ORR by Investigator assessment, DoR, DCR and PFS (all by ICR and Investigator assessment) using RECIST v1.1.

Imaging for radiological assessment of tumor burden at baseline includes CT or MRI scans of the chest, abdomen, and pelvis. Tumor assessments by Investigator are performed according to the RECIST v1.1 Guidelines (Appendix F) and are recorded in the RECIST eCRFs. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients; eg, patients with suspected brain metastases at screening should have an IV contrast-enhanced MRI of the brain prior to study entry. Brain metastases will not be recorded as RECIST Target Lesions at baseline. All on-study assessments should utilize the same modality of scanning (eg, CT or MRI) as was used at baseline for accurate comparisons. Radiologic efficacy for all patients will be assessed on images collected q6w ± 1 week relative to the date of first dose of IP until disease progression or withdrawal consent by patient. Scanning will continue if patients discontinue IP due to toxicity without progression until PD is detected.

Response assessment scans must be reviewed for evidence of disease progression and

ILD/pneumonitis prior to administration of the next scheduled dose of T-DXd.

Digital copies of all scans (scheduled and unscheduled) must be maintained at the Investigative sites as source documents, and all scans should be transferred to the central imaging vendor, with transfer preferably done electronically.

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed iCRO for QC, and storage. 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. An ICR of images will be performed. Results of these independent reviews will not be communicated to Investigators, and results of Investigator RECIST v1.1 assessments will not be shared with the central reviewers. The management of patients will be based in part upon the results of the RECIST v1.1 assessment conducted by the Investigator. Further details of the ICR will be documented in the Independent Review Charter.

8.1.2 Screening Tumor Tissue for Central HER2 Testing

All patients must provide an existing FFPE tumor sample for retrospective HER2 testing by a central laboratory designated by the Sponsor using a validated assay. The sample should be obtained at the time of diagnosis of metastatic or locally advanced unresectable disease. If not available, a pre-enrolment sample obtained upon diagnosis of metastatic or locally advanced unresectable disease will be accepted. New tumor samples can be obtained as part of patient's routine clinical care. Specimens with limited tumor content and fine needle aspirates are inadequate for defining tumor HER2 mutation status. Additional details on sample requirements will be provided in the laboratory manual.

Specimens from metastatic bone lesions are typically unacceptable unless there is a significant soft tissue component and should not be decalcified. See Section 8.6 for details of tumor sample collection.

8.1.3 Survival Assessments

Assessments for survival must be made according to the schedule in Table 7. Survival information may be obtained via telephone contact with the patient or the patient's family, by contact with the patient's current physician or by checking public registries, as available and in accordance with local regulations. 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 interim and final analysis to provide complete survival data. These contacts should generally occur within 7 days of the DCO. If the patient cannot be reached, information from

public records (as available and in accordance with local regulations) may be used for obtaining survival data.

8.1.4 ILD/Pneumonitis-specific Clinical Outcome Assessments

Clinical Outcome Assessments will be used for exploratory purposes to better characterize ILD/pneumonitis and the progression of ILD/pneumonitis cases. A multi-modal digital approach will be employed involving completion of electronic PRO questionnaires and at-home pulse oximetry. The PRO questionnaires will include a daily symptom diary (3 MDASI items: cough, shortness of breath and chest tightness/heaviness), and for those who are diagnosed with ILD/pneumonitis, the SGRQ-I.

PRO questionnaires and at-home pulse oximetry will be completed according to the SoA in Section 1.3.

More details on the PRO questionnaires and at-home pulse oximetry are provided below. The PRO questionnaires are provided in Appendix J.

8.1.4.1 MDASI Symptom Diary (cough, shortness of breath, chest heaviness/tightness)

The MDASI is a validated, multi-item, cancer-specific PRO questionnaire capturing symptom severity and interference (Cleeland et al 2000). The MDASI symptom library allows for specific symptom items to be selected to create a tailored instrument to address a specific research need. Three items from the MDASI symptom library will be used to capture the core ILD/pneumonitis symptoms of cough, shortness of breath, and chest heaviness/tightness. Each item is rated on an 11-point numeric rating scale, with higher scores indicating greater symptom severity.

8.1.4.2 SGRQ-I

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

8.1.4.3 Administration of PRO Questionnaires

PRO questionnaires will be self-administered by patients using their own electronic device via a mobile app. In cases where a patient does not have access to a compatible device to allow the use of the app, an electronic handheld device will be provided to the patient. PRO questionnaires will be completed at the time-points indicated in the SoA in Section 1.3.

Patients will complete the PRO questionnaires at home at approximately the same time each day. If the allowable window to complete the PRO questionnaires overlaps with a study site visit, the assessment may also be completed at the visit.

The time to complete the MDASI symptom diary is approximately 2 minutes, and the time to complete the SGRQ-I is approximately 10 minutes.

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

- The research nurse or appointed site staff must explain to patients the importance of completing the questionnaires 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 download and use the app, and in cases where a device is provided, the use of the PRO device, using the materials and training provided by the ePRO vendor. Guidance also should be provided on who to call if there are problems with the app or device when completing the questionnaires at home.
- PRO symptom diary reporting will be initiated at the Cycle 1, Day 1 visit before dosing, as specified in the SoA (Section 1.3). It is important to have a device set up in advance of each patient's first treatment visit, ideally at least the day before, to ensure that a charged and functioning device is available in case the patient needs to use a provisioned device.
- All questionnaires must be completed using an electronic device (patient's own device or a device provided by the site). Paper questionnaires are not allowed in this study.
- PRO questionnaires completed at Cycle 1, Day 1 or at the time of a visit 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 PRO questionnaires completed at a site visit, the patient should complete them in a quiet and private location and with time to complete them at their own speed.
- The research nurse or appointed site staff must remind patients that there are no right or wrong answers and must not interpret or clarify the meaning of items to avoid bias.
- The patient should not receive help from relatives, friends, or clinic staff to choose answers on the PRO questionnaires.
- If the patient is unable to read the questionnaire (eg, 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.

- 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.
- Patients will receive reminders to ensure compliance with the assessment schedules.
- If baseline (Cycle 1 Day 1) questionnaires are not completed, the reason for not completing the assessment should be documented 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 regularly and at each study visit to identify problems early. If the site receives a notification regarding the patient's compliance, a check-in call from the study site to ask the patient if he or she has 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.

8.1.4.4 At-home Pulse Oximetry

An electronic, wireless pulse oximetry device will be provided to each patient at the Cycle 1 Day 1 visit. The research nurse or appointed site staff will train patients on the use of the device. The patient will complete a resting and walking assessment at the Cycle 1 Day 1 visit before dosing. At-home pulse oximetry testing will be performed by the patient once daily while resting at approximately the same time each day and once weekly while walking, in accordance with the SoA in Section 1.3.

For the walking assessment, patients will walk in their homes for 3 minutes. Patients will walk at their own pace on level ground and with any walking aid they would normally use. Patients should wear the pulse oximeter for one minute before walking for a baseline reading, remove the pulse oximeter during the walking assessment and then take another reading immediately after the 3-minute walking period, before the pulse rate drops. The walk should be discontinued if at any time the patient experiences severe shortness of breath, anterior chest pain, or if the patient feels that he or she is unable to continue walking.

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

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. Provision of informed consent of study procedures prior to the 28-day screening window is permitted; in these circumstances the screening period will commence from the date of the first screening procedure. Refer to Appendix A 3.

If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with the consent of the patient. However, all such results must have been obtained within 28 days before first dose of IP.

8.2.2 Physical Examinations

Physical examinations will be performed according to the SoA (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. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 8.3.6.

8.2.3 Vital Signs

Vital signs (blood pressure, pulse rate, temperature, respiration rate, and SpO_2) and body weight will be evaluated according to the SoA (Section 1.3). Body temperature, pulse rate, respiratory rate, SpO_2, and blood pressure will be assessed.

- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by ≥ 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones).

8.2.4 Electrocardiograms

12-lead ECGs will be obtained as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures Pulse Rate, QRS, and QT intervals.

- ECGs will be performed at screening, before Cycle 1 infusion (within 3 days of administration) and then every 4 cycles and if an abnormality is detected and at EOT.

- Triplicate ECGs will be performed at screening. 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, Pulse Rate, QT intervals, and QRS duration.
- All ECGs must be evaluated by Investigator or designated physician for the presence of abnormalities. Whether or not measurement is performed, date performed, results, and findings for each parameter are to be recorded in the eCRF.
- ECGs will be obtained after the patient has been resting. All ECGs should be recorded with the patient in a supine/semi-recumbent 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.
- A proportion of ECG data may also be collected digitally and may be transferred electronically for central analysis as described in the study-specific ECG manual (if applicable). Heart rate, Pulse rate, RR, QRS and QT intervals may be determined and reviewed by an external cardiologist.

8.2.5 Echocardiograms/Multigated Acquisition Scans

Echocardiograms/MUGA scans will be performed at screening, as clinically indicated throughout the study, and at additional timepoints indicated in SoAs (Section 1.3). The modality of the cardiac function assessments must be consistent within a patient (ie, if ECHO is used for the screening assessment, then ECHO should also be used for subsequent scans if required). The patients should be examined using the same machine and operator whenever possible. Patients should have high-quality, standardized 2-dimensional 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.

8.2.6 WHO/ECOG Performance Status

World Health Organization/ECOG performance status will be assessed at the times specified in the SoA (Section 1.3) based on the following:

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

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

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

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

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

5 Dead

8.2.7 Ophthalmologic Assessments

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

8.2.8 Pulmonary Assessments

Saturation of peripheral oxygen should be obtained within 3 days prior to Cycle 1 Day 1, before and after each infusion, and during follow-up as per the SoA in Section 1.3. Saturation of peripheral oxygen should be evaluated by the Investigator or the delegate physician prior to the administration of IP at each visit.

Pulmonary function tests should be performed at screening, and should include basic spirometry with optional additional components as follows (Table 11):

Table 11 Pulmonary Assessment Tests

Required Spirometry Components	Optional Components
Forced vital capacity (FVC) (L)	Peak expiratory flow (PEF)
FVC % predicted	Diffusion capacity of the lungs for carbon monoxide (DLCO)
Forced expiratory volume – 1 second (FEV1) (L)	(Forced expiratory volume – 6 seconds) FEV6
FEV1 % predicted	Total lung capacity (TLC)
FEV1/FVC	

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

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

See Section 8.2.10.1 for tests required if ILD is suspected.

8.2.9 Clinical Safety Laboratory Assessments

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

Pregnancy tests may be performed at the site using a licensed test (eg, urine or serum pregnancy test). 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 IP. Within 72 hours before treatment assignment for all female patients of childbearing potential; a positive urine pregnancy test result must immediately be confirmed using a serum test. Repeat pregnancy tests must be performed (urine or serum test per institutional guideline) assignment, within 72 hours before infusion of each cycle and at end of treatment (see SoA [Section 1.3]).

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

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

be recorded on the appropriate eCRF.

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

The laboratory variables listed in Table 12 will be measured.

Other safety tests to be performed include the following (see Section 1.3 for SoA):

- Qualitative Hepatitis B Surface Antigen / Hepatitis C Antibody
- HIV antibodies (per local standards)

Table 12 Laboratory safety variables

Hematology/Hemostasis/ Coagulation (whole blood)	**Clinical Chemistry (serum or plasma)**	**Urinalysis (dipstick)**
B-Hemoglobin (Hb)	S/P-Creatinine	U-Hb/Erythrocytes/Blood
B-Hematocrit (HCT)	S/P-Bilirubin, total	U-Protein/Albumin
B-Leukocyte count	S/P-Alkaline phosphatase (ALP)	U-Glucose
B-Leukocyte differential count neutrophils, lymphocytes, monocytes, eosinophils, basophils	S/P-Aspartate transaminase (AST)	U-pH
B-Platelet count	S/P-Alanine transaminase (ALT)	U-Specific gravity
B-Prothrombin time (PT)	S/P-Albumin	
B- Partial thromboplastin time or activated partial thromboplastin time (PTT or aPTT)	S/P-Potassium	
B-international normalized ratio (INR)	S/P-Calcium, total	
	S/P-Sodium	
	S/P-Bicarbonate	
	S/P -Chloride	
	S/P-Magnesium	
	S/P-Lactate dehydrogenase (LDH)	
	S/P-Total protein	
	S/P-Urea or blood urea nitrogen (BUN), depending on local practice	
	S/P Troponin	

B, blood; S/P, Serum/plasma; U, urine

Note: In case a patient shows an AST **or** ALT ≥ 3 × ULN together with TBL >2 × ULN please refer to Appendix E. Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law, for further instructions.

- 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.
- Bicarbonate (where available), chloride, and magnesium testing are to be performed at screening, on Day 1 (unless screening laboratory assessments are performed within 3 days prior to Day 1), and if clinically indicated.
- Collect blood samples for troponin (preferably high-sensitivity troponin-T) at screening, EOT, and if at any time a patient reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of myocyte necrosis.
- ADA: Within 8 hours before infusion on Day 1 of Cycle 1, 2 and 4, and then every 4 cycles and EOT. For patients with positive ADA at the follow-up visit, additional serum ADA samples may be collected every 3 months (± 14 days) up to 1 year after the last dose of the IP, or until the ADA becomes negative, or until the ADA titer becomes less than the baseline (applicable when pre-existing ADA was observed), or until the patient starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.

8.2.10 Other Safety Assessments

8.2.10.1 Pneumonitis or ILD Investigation

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

- HRCT
- Pulmonologist consultation
- Pulmonary function tests (Section 8.2.8) and pulse oximetry (SpO_2)
- Arterial blood gases if clinically indicated
- One blood sample collection for PK as soon as ILD/pneumonitis is suspected, if feasible
- Other tests could be considered, as needed

See Appendix H for further information on the management of drug-induced ILD.

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 and 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.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

AEs and SAEs (other than ILDs) will be collected from the time of signature of the ICF throughout the treatment period and including the safety follow-up (40 + 7 days after the discontinuation of IP). For ILD/pneumonitis, safety follow-up will be continued until resolution of the event.

For patients who provide a new tumor sample, (Section 8.6.2) AEs and SAEs occurring up to and including 21 days after the new tumor biopsy procedure will be recorded.

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

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 40 + 7 days after last dose of the study drug. SAEs with an onset or worsening 40 + 7 days or more after the last dose of study drug, if considered related to the study treatment, are also TEAEs.

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 a SAE with a suspected causal relationship to the IP 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 the Sponsor.

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

- SAEs
- All potential ILD cases should be reported within 24 hours; including both serious and non-serious potential ILD cases (potential ILD will be defined by a list of preferred terms that will be provided to the sites).
- Hepatic events (both serious and non-serious) which meet the potential Hy's Law criteria defined as an elevated (ALT or AST) ≥ 3 x ULN and an elevated TBL > 2 x ULN that

may occur either at different time points or simultaneously during the study. A targeted questionnaire is built within the eCRF to collect relevant additional information for these potential cases.

- Overdose, defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. An "excessive and medically important" overdose includes any overdose in which either an SAE, a non-serious AE, or no AE occurs and is considered by the Investigator as clinically relevant, ie, 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.

Disease progression/worsening of cancer will not be recorded as an AE on the Adverse Event form of the eCRF. However, events associated with disease progression, such as thrombocytopenia or hematemesis, may be recorded as AEs. Death due to disease progression should be recorded on the DEATH module of the eCRF.

Additional relevant information regarding the AESIs ILD/pneumonitis and LVEF decrease for the T-DXd clinical program must be collected through the targeted questionnaires within the clinical study database regardless of seriousness.

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 AEs and SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up.

Any AEs that are unresolved at the patient's last AE assessment or other assessment 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 IP), 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.

8.3.3 Adverse event variables

The following variables will be collected for each AE:

- AE (verbatim)
- 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 IP (yes or no)
- Action taken with regard to IP
- Administration of treatment for the AE
- Outcome

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

- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section 8.3.4
- Description of the SAE

The grading scales found in the revised NCI CTCAE v5.0 will be utilized for all events. 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 NCI CTCAE v5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.3.4 Causality Collection

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

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

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

8.3.5 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 or since 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.

8.3.6 Adverse Events Based on Examinations and Tests

The results from the CSP-mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the IP, 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 IP, eg, dose adjustment or drug interruption).

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

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

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

8.3.7 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq$ 3 x ULN together with total bilirubin > 2 x ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.3.8 Disease Progression

Disease progression can be considered as a worsening of a patient's condition, attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as an AE during the study.

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 IP and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

8.3.10 Deaths

All deaths that occur during the study intervention period, or within the protocol-defined follow-up period after the administration of the last dose of IP, 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 disease under study, 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.
- Death 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 time frames.

Deaths occurring after the protocol-defined safety follow-up period (40 + 7 days) after the administration of the last dose of IP should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined safety follow-up period and the event is considered to be due to a late-onset toxicity to IP, then it should also be reported as an SAE.

8.3.11 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the

study procedure(s) (see Appendix B). All SAEs will be recorded in the eCRF.

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

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 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 must be undertaken immediately. Investigators or other site personnel must inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

If the EDC system is not available, then the Investigator or other study site staff must report an SAE to the appropriate AstraZeneca representative by telephone.

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

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

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

8.3.12 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca, except if the pregnancy is discovered before the study patient has received any IP.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

8.3.12.1 Maternal Exposure

If a patient becomes pregnant during the course of the study, IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP 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.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel must inform the appropriate AstraZeneca representatives within 1day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work 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 8.3.11) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

AstraZeneca must be notified of any female patients who becomes pregnant within 7 months of the last dose of study drug.

8.3.12.2 Paternal Exposure

Male patients should refrain from fathering a child or freezing or donating sperm during the study and for at least 4 months following the last dose of IP. 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 partners 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 after the last dose 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 adapt the generic ICF template in line with local procedures and submit it to the relevant ECs/IRBs prior to use.

AstraZeneca must be notified of any female partner of a male patient who becomes pregnant while receiving or within 4 months of last dose of study drug.

8.3.13 Medication error

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1-day ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 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 medication error (see Section 8.3.11) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix B.

8.3.14 Adverse Events of Special Interest

An AESI is one of scientific and medical interest specific to understanding of an IP and may require close monitoring and rapid communication to the AstraZeneca Study Physician by the Investigator. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events to characterize and understand them in association with the use of an IP.

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 IP, possible etiologies, and whether the event meets criteria for an SAE and therefore requires immediate notification to the AstraZeneca Study Physician. If an AE evolves into a condition that meets the regulatory definition of “serious,” it will be reported on the SAE Report Form.

Based on the available pre-clinical and clinical data, review of the cumulative literature, reported toxicities for the same class of agents and biological plausibility, the following events are considered to be AESIs:

Interstitial Lung Disease/Pneumonitis

Interstitial lung disease/pneumonitis is considered an important identified risk based on a comprehensive cumulative review potential interstitial lung disease (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

LVEF decrease

Left ventricular ejection fraction 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 study data.

8.3.15 Management of IP-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 assigned IP 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.

8.3.15.1 Specific Toxicity Management and Dose Modification Information - Trastuzumab Deruxtecan

All dose modifications (interruption, reduction and/or discontinuation) should be based on the worst preceding toxicity (NCI CTCAE v5.0). Specific criteria for interruption, re-initiation, dose reduction and/or discontinuation of T-DXd are listed Appendix G, which is applicable only to TEAEs that are assessed as related to use of T-DXd by the Investigator(s). For non-drug related TEAEs, follow standard clinical practice. Appropriate clinical experts should be consulted as deemed necessary.

All confirmed or suspected COVID-19 infection events must be recorded in the eCRF. Please refer to Appendix I for additional information on dose modification.

ILD Management Guidance

Please refer to the ILD management summary flow chart in Appendix H for the management of drug-induced ILD/pneumonitis. All potential ILD/pneumonitis cases should be reported within 24 hours; including both serious and non-serious potential ILD/pneumonitis cases (potential ILD/pneumonitis will be defined by the list of MedDRA preferred terms provided to sites).

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/pneumonitis, follow the management guidance outlined in the dose modification section (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 and pulse oximetry (SpO_2), arterial blood gases if clinically indicated, 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 (ILD/pneumonitis TMG).

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

All cases of potential ILD/pneumonitis will be reviewed internally by the Medical Monitor and the Study Safety Physician. Safety Knowledge Groups will also be consulted if needed. To ensure adequate and relevant evaluation, systematic additional data collection will be conducted for all cases that will be brought for evaluation. This additional data collection will cover a more in-depth relevant medical history (eg, smoking, radiation, chronic obstructive pulmonary disease, and other chronic lung conditions), diagnostic evaluation, treatment and outcome of the event. This data collection will be triggered for AEs reported using all MedDRA PTs from the current ILD Standard MedDRA Query (SMQ), plus 2 PTs of acute respiratory failure and respiratory failure.

LVEF-Decrease Management Guidance:

Left ventricular ejection fraction will be measured by either ECHO or MUGA scan. All ECHOs/MUGAs will be evaluated by the Investigator or delegated physician for monitoring cardiac function.

- Troponin-T will be measured at screening and EOT, and as needed based on patient reported cardiac signs or symptoms suggesting CHF, myocardial infarction, or other causes of cardiac myocyte necrosis. If 12-lead ECG is abnormal, follow institutional guidelines.
- ECGs will be performed, and standard ECG parameters will be measured, including RR, PR, QT intervals, and QRS duration. ECG will be performed in triplicate if 12-lead ECG is abnormal.
- All ECGs must be evaluated by Investigator or delegated physician for the presence of abnormalities prior to the injection of IMP at each cycle. Whether or not measurement is performed, date performed, results, and findings for each parameter is to be recorded in the eCRF.

Dose Reductions

Table 13 Dose Reduction Levels of T-DXd

Starting Dose	Dose Level -1	Dose Level -2
5.4 mg/kg	4.4 mg/kg Consult AstraZeneca Study Physician	3.2 mg/kg Consult AstraZeneca Study Physician

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

Dose Interruption and Modification /Toxicity Management Guidelines

A dose can be delayed for up to 28 days (49 days from the last infusion date) from the planned date of administration. If a patient is assessed as requiring a dose delay of longer than 28 days, T-DXd treatment will be discontinued.

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 discontinuations of T-DXd according to the patient's condition and after discussion with Study Physician or designee. Please refer to Appendix G for more detailed guidance on toxicity management.

8.4 Overdose

Use of IP in doses in excess of that specified in the protocol is considered to be an overdose. There is currently no specific treatment for overdose of T-DXd and possible symptoms of overdose are not established.

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

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

The designated AstraZeneca representative should work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply; see Section 8.3.11. For other overdoses, reporting must occur within 30 days.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the Study Specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - PK 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 ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue 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.

8.5.1 Pharmacokinetics

Blood samples for determination of T-DXd, total anti-HER2 antibody, and MAAA-1181a in serum will be collected as specified in the SoA (Section 1.3) and analyzed by a Sponsor-designated bioanalytical laboratory on behalf of AstraZeneca.

PK sampling on Cycle 1 will be pre-dose (should not exceed 6 hours prior to start of infusion), post-infusion (within 15 minutes after the end of T-DXd infusion), and 5 hours (± 2 hours) post-infusion. PK sampling on Cycle 2 and Cycle 4 will be pre-dose (should not exceed 6 hours prior to start of infusion) and post-infusion (within 15 minutes after the end of T-DXd infusion).

For patients diagnosed with COVID-19, please see Appendix I for further instructions on potential additional PK sample collections.

Full details of the analytical method used will be described in a separate Bioanalytical Report. All samples still within the known stability of the analytes of interest at the time of receipt by the bioanalytical laboratory will be analyzed. In addition, the PK samples may be subjected to

further analyses by AstraZeneca in order to correlate PK with other primary, secondary, and exploratory endpoints in patients treated with T-DXd.

Details on sample processing, handling, shipment, and storage will be provided in the Laboratory Manual.

8.5.1.1 Determination of Drug Concentration

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

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

8.5.2 Immunogenicity Assessments

Blood samples will be collected for determination of ADA for T-DXd.

Blood Samples will be taken within 8 hours before administration on Day 1 of Cycles 1 Cycle 2 and Cycle 4, and then every 4 cycles and EOT and Follow up. Additional details are given in Section 8.2.9.

Anti-drug antibodies will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report.

Blood samples may also be further tested for characterization of the ADA response and/or other exploratory safety biomarkers. In addition, the presence of neutralizing antibodies (nAbs) could be tested for all ADA-positive samples using a validated assay.

Details on sample processing, handling, shipment, and storage will be provided in the Laboratory Manual.

8.5.3 Pharmacodynamics

Specific pharmacodynamic samples will not be taken during the study.

8.6 Human Biological Sample Biomarkers

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

Details on sample processing, handling, shipment, and storage will be provided in the

laboratory manual.

8.6.1 Collection of Mandatory Samples for Biomarker Analysis and Diagnostic Development

By consenting to participate in the study, the patient consents to participate in the mandatory research components of the study.

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

- MANDATORY: Provision of an FFPE tumor sample obtained at the time of diagnosis of metastatic or locally advanced unresectable disease. If not available, a pre-enrolment sample obtained upon diagnosis of metastatic or locally advanced unresectable disease will be accepted. This sample will be used for retrospective HER2 central testing, exploratory biomarker analysis (as described below) and may be used to support diagnostic development.
- MANDATORY: Blood samples for plasma biomarker assessments will be collected from all patients at time points described in 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. Samples may be used to support diagnostic development.
- MANDATORY: Whole blood samples for gene expression analyses will be obtained from all patients as described in Section 1.3. This sample might be used to characterize pre-treatment molecular alterations and predict patients who may respond to treatment based on their molecular profiles.
- 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 (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 compared to the safety profile of patients without evidence of immune response (antibodies) treated with T-DXd. Blood samples for plasma isolation will be collected from all the patients as per SoA.

The following investigations may be performed with the samples collected, where applicable:

- HER2 activating mutations for eligibility will be based on local assessment. Patients who are eligible based on local assessment will also have HER2 status confirmed by retrospective central testing.
- Quantification of HER2 protein expression and/or heterogeneity through alternative technologies (eg, Digital Pathology/Image Analysis).
- Mutational analysis in qualifying alterations in 300 to 500 genes by NGS including *EGFR, HER3, PI3K, Ras,* TMB and MSI signatures. Quantitative targeted protein expression analysis (20-30 unique proteins including HER2, HER3, TOP1, SLFN11, Efflux Receptors) and global semi-quantitative (~7000 unique proteins) protein expression analysis by mass spectrometry will be conducted as well.
- Comparison of mutational and protein expression changes between pre-treatment and progression samples.
- Assessment of morphological characteristics and immune cell profiling via image analysis/machine learning on H&Es and by multiplexed-immunofluorescence.
- Explore change in ctDNA quantity, including but not limited to changes in allele frequency, between baseline and on-treatment as a predictive marker for clinical outcomes as well as early ctDNA dynamics as marker of recurrence (informed by mutational analysis of pre-treatment samples).
- Immune cell profiling by fluorescent IHC analysis in most recent FFPE tissue.
- Immune profiling in baseline tissue and blood (DNA/RNA) sample, and on-treatment early timepoints.
- T-cell receptor analysis at baseline and on-treatment early timepoints.
- Comparison of morphology changes between pre-treatment and progression samples.

Based on emerging scientific knowledge further analyses yet to be defined may be undertaken.

8.6.2 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.

- OPTIONAL: pre-treatment or on-treatment biopsy done as part of patient's routine medical care should be provided if available.
- OPTIONAL: The provision of a tumor biopsy upon disease progression if taken as part of the patient's standard of care is strongly encouraged.

8.6.3 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, plasma analytes, tissue biomarkers and/or specific candidate genes/genome-wide analysis for RNA, to evaluate their association with observed clinical responses to study interventions 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.

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, Investigators, 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 study protocol.

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.

For storage, re-use and destruction of biomarker samples, see Section 8.5.

8.7 Optional Genomics Initiative Sample

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA (1.3) and is subject to agreement in the ICF addendum.

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

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

For storage and destruction of genetic samples see Appendix D.

8.8 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

There are no formal statistical hypotheses for this study.

9.2 Sample Size Determination

A sample size of 100 patients has been determined to provide sufficient precision for the estimation of the ORR in this population and to allow wider representation of tumor types and selected mutations. Table 14 provides the 95% exact CI for a range of possible observed response rates out of 100 patients.

Table 14 Observed ORR and 95% Confidence Interval (CI) out of 100 Patients

Observed ORR (%)	95% exact CI
30	(21.2, 40.0)
40	(30.3, 50.3)
50	(39.8, 60.2)

CI, confidence interval; ORR, objective response rate

The study will also provide an adequate number of patients to robustly assess the safety and tolerability of T-DXd across various tumor types.

Approximately 100 patients will be treated in this study, with a maximum of approximately 20 patients per tumor type to ensure adequate representation across multiple tumor types. Anticipated tumor type enrolment in the study includes breast, colorectal, urothelial, esophagogastric, hepatobiliary, small cell lung, endometrial, melanoma, ovarian, cervical, salivary gland, pancreatic and cutaneous squamous-cell carcinoma. These will be treated as separate specific tumor types for the purposes of patient recruitment caps and interim futility evaluations. There is no pre-specified requirement for representation of any individual tumor type that meets the eligibility criteria.

Enrolment in a specific tumor type will be paused after 8 patients with Investigator-assessed measurable disease at baseline have been treated within that tumor type, until a decision has been made on whether to stop enrolment to that tumor type based on the interim futility evaluation. If no confirmed objective response (assessed by Investigator per RECIST v1.1) is observed among the first 8 treated patients in a specific tumor type, enrolment in that tumor type will be discontinued. See Section 9.5 for further details.

9.3 Populations for Analyses

Five analysis populations are defined as shown in Table 15.

Table 15 Populations for Analyses

Population/Analysis set	Description
Full Analysis Set (FAS)	All patients who received at least 1 dose of study treatment. The FAS will be used for all efficacy analyses.
Measurable Disease Analysis Set (MDAS)	All patients who received at least 1 dose of study treatment, and who have Investigator-assessed measurable disease at baseline according to RECIST v1.1. The MDAS will only be used for the 8-patient interim futility evaluation within each tumor type. All patients will have Investigator-assessed measurable disease at baseline according to inclusion criteria.
Centrally-determined Efficacy Analysis (CEAS)	All patients who received at least 1 dose of study treatment, and who were determined as HER2- mutant via retrospective central testing according to pre-specified entry criteria. Depending on the level of discrepancies between the central and local HER2 mutation test results, the CEAS may be used for sensitivity analyses on efficacy endpoints as necessary.
Pharmacokinetics (PK) Analysis Set	All patients who received at least 1 dose of study treatment and had at least 1 post-dose evaluable PK data point. The population will be defined by the study pharmacokineticist, and the statistician prior to any PK analyses being performed.
Safety Analysis Set (SAF)	All patients who received at least 1 dose of study treatment.

Definitions of the analysis sets for each outcome variable are provided in Table 16.

Table 16 Summary of Outcome Variables and Analysis Populations

Outcome variable	Populations
Demography	Full Analysis Set
Efficacy Data	
ORR, DoR [a], DCR, PFS and OS	Full analysis Set, Measurable Disease Analysis Set (8-patient interim futility evaluation only), Centrally-determined Efficacy Analysis Set (CEAS)
Safety Data	
Exposure	Safety Analysis Set
AEs	Safety Analysis Set
Laboratory measurements	Safety Analysis Set
Vital Signs	Safety Analysis Set

Table 16 Summary of Outcome Variables and Analysis Populations

Outcome variable	Populations
PK data	PK Analysis Set
ADA data	Safety Analysis Set

[a] DoR analysis will be based on the subset of patients in the appropriate analysis set who achieved objective response
ADA, anti-drug antibody; AE, adverse event; DCR, disease control rate; DoR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics.

9.4 Statistical Analyses

Analyses will be performed by AstraZeneca or its representative. To characterize DoR, the final analysis is planned to be performed when the last patient has had the opportunity for approximately 32 weeks of follow-up after treatment assignment. This will provide at least 6 months of follow-up from the anticipated median time of first response assessment. A comprehensive SAP will be finalized prior to FSI and will describe the patient populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary, and exploratory endpoints. Any deviations from this plan will be reported in the CSR.

9.4.1 General Considerations

Table 17 details the endpoints to be summarized.

Table 17 Pre-planned Statistical Analyses to be Conducted

Endpoints analyzed	Notes [All endpoints derived from RECIST use ICR and Investigator assessment]
Objective response rate (ORR)	Number and percentage of patients that achieve confirmed objective response as assessed by ICR according to RECIST v1.1 (with the associated two-sided 95% exact CI). Confirmed ORR as determined by Investigator assessment will also be presented.
Duration of response (DoR)	Kaplan-Meier median estimates and their corresponding two-sided 95% confidence intervals will be reported (ICR and Investigator assessment).
Disease control rate (DCR)	Number and percentage of patients that achieve disease control (with the associated two-sided 95% exact CI) (ICR and Investigator assessment).
Progression-free survival (PFS)	Kaplan-Meier median estimates and their corresponding two-sided 95% confidence intervals will be reported (ICR and Investigator assessment). The proportions of patients alive and progression-free at 6 and 12 months (Kaplan-Meier estimates) will also be presented.

Table 17 Pre-planned Statistical Analyses to be Conducted

Endpoints analyzed	Notes [All endpoints derived from RECIST use ICR and Investigator assessment]
Overall survival (OS)	Kaplan-Meier median estimates and their corresponding two-sided 95% confidence intervals will be reported. The proportions of patients alive at 6 and 12 months (Kaplan-Meier estimates) will also be presented.
Safety	Summary statistics for AEs, AESIs, SAEs, laboratory findings, vital signs, ECG, ECHO/ MUGA results, ECOG/WHO performance status and deaths.

AE, adverse event; AESI; adverse event of special interest; CI, confidence interval; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; ICR, independent central review; MUGA, multiple gated acquisition; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SAE, serious adverse event; WHO, World Health Organization

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

The FAS will be used for all efficacy analyses, apart from the 8-patient interim futility evaluation within each tumor type which will use the MDAS. Depending on the level of discrepancies between the central and local HER2 mutation test results, the CEAS may be used for sensitivity analyses on efficacy endpoints as necessary.

9.4.2.1 RECIST v1.1-based Endpoints

RECIST v1.1-based endpoints will be assessed by ICR and determined by Investigator assessment.

For the 8-patient interim futility evaluation within each tumor type, endpoints will be determined by Investigator assessment (ICR assessed endpoints may be considered in addition to support interpretation of results). For other interim analyses and the final analysis, both ICR and Investigator assessed endpoints will be presented.

Investigator-based assessments

All RECIST 1.1 assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a patient discontinues study treatment or receives another anticancer therapy, unless otherwise stated for that parameter/analysis.

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, or PD depending on the status of their disease compared with baseline and previous

assessments. Baseline will be assessed within the 28 days prior to treatment. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is evidence of progression, in which case the response will be assigned as PD).

Independent Central Review

An ICR of all radiological imaging data will be carried out using RECIST version 1.1. All images will be collected centrally. The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and will be adjudicated, if required. For each patient, the ICR will define the overall visit response data (CR, PR, SD, PD, or NE) and the relevant scan dates for each timepoint (ie, for visits where response or progression is/is not identified). If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE; unless there is evidence of progression, in which case the response will be assigned as PD). Endpoints (of PFS) will be derived from the overall visit response date and the scan date.

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

9.4.2.2 Primary Endpoint(s)

The primary endpoint is confirmed ORR assessed by ICR per RECIST v1.1 across all tumor types.

ORR is defined as the proportion of patients who have a confirmed CR or PR, as assessed by ICR per RECIST v1.1. A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. Data obtained up until disease progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who discontinue treatment without progression, receive a subsequent anticancer therapy, and then respond, will not be included as responders in the ORR. The point estimate and corresponding two-sided 95% exact CI will be reported across tumor types.

9.4.2.3 Secondary Endpoint(s)

Secondary efficacy endpoints include confirmed ORR by Investigator assessment per RECIST v1.1, DoR (ICR and Investigator assessment), DCR (ICR and Investigator assessment), PFS (ICR and Investigator assessment), and OS across all tumor types.

Confirmed ORR as determined by Investigator assessment per RECIST v1.1 across all tumor types will be summarized (using the same methodology as for confirmed ORR assessed by ICR, Section 9.4.2.2).

DCR (ICR and Investigator assessment) is defined as the percentage of patients who have a

confirmed CR or PR or who have SD (without subsequent cancer therapy) after the date of first dose of IP. Summaries of DCR will be presented across all tumor types, including two-sided 95% exact CI.

PFS (ICR and Investigator assessment) is defined as time from the date of first dose of IP until progression per RECIST v1.1, or death due to any cause. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST v1.1 assessment. A Kaplan-Meier plot of PFS will be presented. The median PFS with 95% CI will be estimated based on the Kaplan-Meier curve.

The proportions of patients alive and progression-free at 6 and 12 months will also be summarized (using the Kaplan-Meier method).

DoR (ICR and Investigator assessment) is defined as the time from the date of first documented response (CR or PR) until the date of documented progression, or death in the absence of disease progression. Only patients who have achieved OR (confirmed CR or confirmed PR) will be evaluated for DoR. Duration of response will be summarized using the same methodology as for PFS.

OS is defined from the date of first dose of IP until the date of death due to any cause. 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. OS will be summarized using the same methodology as for PFS.

The proportions of patients alive at 6 and 12 months will also be summarized (using the Kaplan-Meier method).

9.4.2.4 Sensitivity Analyses

Consistency of effect will be investigated by tumor type and select mutations. To demonstrate consistency of the estimates, descriptive summaries for ORR (ICR and Investigator assessment) as outlined above (Section 9.4.2.2) will also be presented by both tumor type and select mutations. A forest plot will be used to evaluate homogeneity of effect across both tumor types and selected HER2 mutations.

A Kaplan-Meier plot of DoR (ICR and Investigator assessment) will be presented by tumor type and select HER2 mutations. The median DoR with 95% CI for each tumor type will be estimated based on the Kaplan-Meier curves, and a forest plot will be used to evaluate homogeneity of effect across tumor types and select HER2 mutations.

Depending on the level of discrepancies between the central and local HER2 mutation test results, the CEAS may be used for sensitivity analyses on efficacy endpoints as necessary.

9.4.3 Safety

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

Baseline

In general, the baseline value for statistical analysis is the last non-missing value prior to administration of the first dose of IP.

Adverse Events

- AEs will be coded using the most recent version of MedDRA that will have been released for execution at AstraZeneca.
- AEs will be presented by system organ class and/or PT, covering number and percentage of patients reporting at least one event and number of events where appropriate.
- AEs occurring prior to start of IP, TEAEs and post-treatment AEs will be presented separately.
- An overview of AEs will present the number and percentage of patients with any AE, AEs with outcome of death, serious AEs, AEs leading to discontinuation of IP, AEs leading to IP dose interruptions, and AEs leading to IP dose reduction, as well as the number of individual occurrences in those categories.
- Separate AE tables will be provided taking into consideration relationship as assessed by the Investigator, CTCAE grade, seriousness, death, and events leading to discontinuation of IP as well as other action taken related to IP, AESIs, other significant AEs, and timing of events.
- An additional table will present the number and percentage of patients with the most common AEs. Most common will be defined in the SAP.
- In accordance with the requirements of the FDA, a separate table will present non-serious AEs occurring in more than 5% of patients.
- Key patient information will be presented for patients with AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP.
- An AE listing for the SAF will cover details for each individual AE.
- Treatment emergent: The following events are considered treatment emergent:
  - AEs with an onset date on or after first dose of IP
  - Worsening of pre-existing events on or after first dose of IP

Vital Signs

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

Laboratory Parameters

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 summarized and reported appropriately if potential cases have been identified during the course of the study.

A frequency table for urinalysis will present the number of patients reporting at least one treatment emergent increase in baseline category. A shift table for urinalysis will present the baseline assessment against the maximum on-treatment category

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

9.4.4 Other Analyses

PK data will be summarized using the PK Analysis Set. ADA data will be summarized using the SAF.

9.4.4.1 Immunogenicity Data

Immunogenicity results will be listed by patient, and a summary will be provided by the number and percentage of patients who develop detectable ADAs for T-DXd at multiple timepoints until the end of each patient's follow-up.

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

9.4.4.2 Pharmacokinetics

Individual patient data and descriptive statistics will be provided for serum concentration data at each time point for T-DXd, total anti-HER2 antibody, and MAAA-1181a.

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

The results of such an analysis, if conducted, will be reported in a separate report. The PK, pharmacodynamics, demographic, safety, and efficacy data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK/PD methods.

9.4.4.3 Biomarker Data

Summaries and analyses for exploratory biomarkers will be documented in a separate analysis plan and will be reported outside the CSR in a separate report.

9.4.5 Exploratory Analysis

Analyses to address the exploratory objectives, including subgroup investigations by biomarker status, will follow the approaches described for the primary and secondary endpoints, and be described in more detail in the SAP.

9.4.6 ILD/Pneumonitis-related Clinical Outcome Assessments

PRO questionnaires and at-home pulse oximetry are included for exploratory purposes only to further characterize ILD/pneumonitis. The analyses may be described in a separate analysis plan and presented in a separate report.

9.5 Interim Analyses

An interim futility evaluation will be performed within each tumor type after 8 treated patients with Investigator-assessed measurable disease at baseline (using the MDAS) have had 12 weeks of follow-up since first dose or have discontinued study drug. If no confirmed objective response (assessed by Investigator per RECIST v1.1) is observed among the first 8 treated patients in a specific tumor type, enrolment in that tumor type will be discontinued. Enrolment in a tumor type will be paused, after 8 patients with Investigator-assessed measurable disease at baseline have been treated within that tumor type, until a decision has been made on whether to stop enrolment based on the futility evaluation. Table 18 provides the probability of stopping (ie, observing zero responses) for a range of true ORR values given 8 treated patients.

Table 18 Probability of Stopping an Individual Tumor Type for a Range of True ORR Values

True ORR	Probability of stopping
10%	43.0%
20%	16.8%
30%	5.8%
40%	1.7%
50%	0.4%

ORR, objective response rate

Interim efficacy analyses will also be performed (using the FAS) within an individual tumor type when enrolment to the tumor type has been closed, and all treated patients have had the

opportunity to complete 2 scheduled post-baseline RECIST scans. For a tumor type with N = 20, an ORR of 40% would have 95% CI (19.1%, 63.9%); this level of activity would justify further investigation.

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

9.6 Data Monitoring Committee

There will be no Data Monitoring Committee for this study. The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

9.6.1 ILD Adjudication Committee

An ILD Adjudication Committee and Charter will be established to review all cases of potential ILD/pneumonitis. To ensure adequate evaluation, relevant additional data from within the clinical database may be provided to the adjudication committee to fully characterize medical history (eg, 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 Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study 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.

Regulatory Reporting Requirements for SAEs

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

A 2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the 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 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.
- If a patient declines to participate in a 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 4 months after the last dose of IP, the partner will be asked to sign the 'Adult Study Informed Consent Form for Pregnant Partners of Study Patients' and to provide information about the pregnancy accordingly. Also refer to Section 8.3.12.2.

Patients who are rescreened will resign and date their original ICF(s), next to their original signature and date, or according to local or site-specific procedures.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The Investigator or authorized designee will explain to each patient the objectives of the analysis to be done on the samples

and any potential future use. Patients will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor 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 the Sponsor 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 informed consent.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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.

An ILD adjudication committee will review all cases of potential ILD/pneumonitis.

A 6 Dissemination of Clinical Study Data

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

A 7 Data Quality Assurance

- All patient data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of 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 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the 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.
- Definition of what constitutes source data can be found in the Central Monitoring Plan.

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, ie, the date of opening of the first site.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies

have been collected and a study-site closure visit has been performed.

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the 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 the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a co-ordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence 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 (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the 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 IP has been administered.

B 2 Definitions of Serious Adverse Event

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

- Results in death
- Is immediately life-threatening
- Requires in-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 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 (ie, it is *not* the tumor for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B cell chronic lymphocytic leukaemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

Life threatening

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

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the 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 as 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 (eg, neutropenia or anaemia 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 above. 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 above. 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 above.

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

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

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 patient received the drug
- Did not occur, but circumstances were recognized that could have led to an error

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

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

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

- Errors related to or resulting from IRT - including those which lead to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AstraZeneca product

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

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

The Investigator at each center keeps full traceability of collected biological samples from the 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 during for the remainder of the sample life cycle.

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

C 2 Withdrawal of Informed Consent for Donated Biological Samples

If a 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 patient's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that 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

LABELING 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 eg, 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 eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name.

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

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

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

Appendix D Optional Genomics Initiative Sample

D 1 Use/analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting patients.
- This optional genetic research may consist of the analysis of the structure of the patient´s DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on 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

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

Coding and storage of DNA samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain 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 enrolment/treatment assignment number and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

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

Informed consent

- The genetic component of this study is optional and the 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 centre. 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 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 analyse 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 including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

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

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether 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 IP.

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) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) > 2 x 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 ≥ 3x ULN **together with** TBL > 2 x ULN, where no other reason, other than the IP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

E 3 Identification of Potential Hy's Law Cases

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

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL > 2xULN

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 IP, the Investigator is not required to submit a PHL SAE unless there is a significant change[#] 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. Completes follow-up SAE Form as required.
  – Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.
  – Complete the three Liver eCRF Modules as information becomes available

[#]**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 IP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

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

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

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

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

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

E 6 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 eg, 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 Section E 6 of this Appendix?

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

If **Yes**: Determine if there has been a significant change in the 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

Table E1 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	Carbohydrate deficient transferrin (CD-transferrin) [b]
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin [b] Transferrin saturation

[a] HCV RNA; HCV DNA are only tested when IgG anti-HCV is positive or inconclusive
[b] CD-transferrin and Transferrin are not available in China.

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 Guidelines for Evaluation of Objective Tumor Response Using RECIST v1.1 Criteria (Response Evaluation Criteria in Solid Tumors)

Introduction

This Appendix details the implementation of Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) guidelines (Eisenhauer et al 2009). Investigator assessments will use the RECIST v1.1 guidelines described in this Appendix.

Imaging modalities and acquisition specifications for RECIST v1.1

A summary of the imaging modalities that can be used for tumor assessment of Target Lesions (TLs), Non-Target Lesions (NTLs), and New Lesions (NLs) is provided in the Table F1.

Table F1 Summary of Imaging Modalities for Tumor Assessment

Target Lesions	Non-Target Lesions	New Lesions
CT MRI	CT MRI Plain X-ray Chest X-ray	CT MRI Plain X-ray Chest X-ray Bone scan (Scintigraphy) FDG-PET/CT

CT, Computed tomography; FDG-PET/CT, ^{18}F-Fluoro-deoxyglucose positron emission tomography/CT; MRI, Magnetic resonance imaging.

CT and MRI

Computed tomography (CT) with IV contrast is the preferred imaging modality (although MRI with IV contrast is acceptable if CT is contraindicated) to generate reproducible anatomical images for tumor assessments (ie, for measurement of TLs, assessment of NTLs, and identification of NLs). It is essential that the same correct imaging modality, image acquisition parameters (eg, anatomic coverage, imaging sequences, etc), imaging facility, tumor assessor (eg, radiologist), and method of tumor assessment (eg, RECIST v1.1) 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 (eg, 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 (eg, heart, major blood vessels, breathing) associated with MRI. Magnetic resonance imaging 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.

Chest X-ray

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

Plain X-ray

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

Isotopic bone scan

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

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions may be recorded in case positive hot-spots appear on a bone scan that were not present on a previous bone scan; however, a newly

observed equivocal hot-spot on a bone scan that cannot be verified with correlative imaging (CT, MRI, or X-ray) of the same anatomical region shall not be the only trigger for a PD assessment at that time point.

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 v1.1 assessments according to the following algorithm: NLs will be recorded where there is positive ^{18}F-Fluoro-deoxyglucose uptake[1] not present on baseline or prior 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 v1.1. In exceptional situations, if a site can document that the CT performed, as part of a PET/CT examination, is of identical diagnostic quality (with IV contrast) to a dedicated diagnostic CT scan, then the CT portion of the PET/CT can be used for RECIST v1.1 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 v1.1 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 v1.1 assessments. Tumors identified by clinical examination will

[1] A positive FDG-PET scan lesion should be reported only when an uptake (eg,SUV) greater than twice that of the surrounding tissue or liver is observed.

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 v1.1.

Results of cytological examination for the neoplastic origin of any effusion (eg, ascites, pericardial effusion, and pleural effusion) that appears or worsens during the study will not be used as part of the tumor response assessment as per RECIST v1.1.

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

Measurability of Tumor Lesions at Baseline

RECIST v1.1 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[2] diameter for lymph node lesions with IV contrast-enhanced CT or MRI and that is suitable for accurate repeated measurements.

Non-measurable lesions at baseline:

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

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

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

- Previously irradiated lesions[4]
- Brain metastasis

Special considerations regarding lesion measurability at baseline:

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

RECIST v1.1 TL selection at baseline:

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

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

The site and location of each TL should be documented, as well as the longest axis diameter for non-nodal lesions (or short axis diameter for lymph nodes). All measurements should be recorded in whole (integer) millimeters and calculated values should be rounded to whole

[4] 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.

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 time was allowed for any bleeding to subside (eg, 1 to 2 weeks) before imaging scans are acquired.
- 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.

RECIST v1.1 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 v1.1 TL assessment at follow-up

This section defines the criteria used to determine objective tumor visit response for RECIST v1.1-defined TLs. The imaging modality, location, and scan date of each TL identified previously at baseline should be documented at follow-up visits with the long axis diameter for non-nodal lesions or short axis diameter for lymph node lesions. All measurements should be recorded in 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 a 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. The choice of "Too large to measure" in the case report form will trigger an overall visit response of PD.
- 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 F2 RECIST v1.1 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.

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.
Not evaluable (NE)	Only relevant if any of the TLs at follow-up were not assessed or not evaluable (eg, missing anatomy) or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD 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; SD, stable disease; TL, Target lesion

RECIST v1.1 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 stable disease or partial response 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 stable disease (SD) or partial response (PR) of target disease will therefore be extremely rare.

Table F3 RECIST v1.1 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; TL, Target lesion

RECIST v1.1 NL identification at follow-up

Details, including the imaging modality, the date of scan, and the location of any new lesions (NLs) 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, ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor. If a NL is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the previously (pre-existing) new lesion 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 v1.1 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 F4.

Table F4 RECIST v1.1 Overall Visit Response

Target Lesions	Non-Target Lesions	New lesions	Overall visit response
CR	CR	No	CR
CR	NA	No	CR
CR	Non CR/Non PD [a]	No	PR
CR	NE	No	PR
PR	Non PD or NE or NA	No	PR
SD	Non PD or NE or NA	No	SD
NE	Non PD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[a] Non-CR/Non-PD for Overall Response if only non-target lesions (no TLs) are present at baseline.

Note: An overall assessment of Complete Response (all other disease disappears/reverts to normal) would be changed to Partial Response if ascites remains present radiologically.

CR, Complete response; NA, Not applicable (only relevant if there were no non-target lesions at baseline), NE, Not evaluable; PD, progressive disease; PR, Partial response; SD, stable disease; TL, Target Lesion.

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

- For patients with TLs (at baseline): complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD), or not evaluable (NE)

Central imaging

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed imaging Contract Research Organization (iCRO) for QC, and storage. 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. An independent central review (ICR) of images will be performed. Results of these independent reviews will not be communicated to Investigators, and results of Investigator RECIST v1.1 assessments will not be shared with the central reviewers. The management of patients will be based in part upon the results of the RECIST v1.1 assessment conducted by the Investigator. Further details of the ICR will be documented in the Independent Review Charter.

Appendix G Toxicity Management Guidelines for Trastuzumab Deruxtecan

All dose modifications (interruption, reduction and/or discontinuation) should be based on the worst preceding toxicity (CTCAE version 5.0). Specific criteria for interruption, re-initiation, dose reduction and/or discontinuation of T-DXd are listed in Table G1, which is applicable only to TEAEs that are assessed as related to use of T-DXd by the Investigator(s). For non-drug related TEAEs, follow standard clinical practice. Appropriate clinical experts should be consulted as deemed necessary.

All confirmed or suspected COVID-19 infection events must be recorded in the eCRF. Please refer to Appendix I for additional information on dose modification.

ILD/pneumonitis management Guidance: Please also refer to the ILD/pneumonitis management summary flow chart in Appendix H.

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/pneumonitis, follow the management guidance outlined in the designated "Other Non-Laboratory Adverse Events" dose modification section of the study protocol.

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 and pulse oximetry (SpO_2), arterial blood gases if clinically indicated, 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 (ILD/pneumonitis TMG).

If the AE is confirmed to be ILD/pneumonitis, follow the management guidance outlined in the designated dose modification section (Section 8.3.15.1). The summary flow chart for management of drug-induced ILD is also available in Appendix H of this document. All events of ILD/pneumonitis regardless of severity or seriousness will be followed until resolution including after drug discontinuation.

All cases of potential ILD/pneumonitis will be reviewed internally by the Medical Monitor and Study Safety Physician. Safety Knowledge Groups will also be consulted if needed. To ensure adequate and relevant evaluation, systematic additional data collection will be conducted for all cases that will be brought for evaluation. This additional data collection will cover a more in-depth relevant medical history (eg, smoking, radiation, COPD and other chronic lung conditions), diagnostic evaluation, treatment and outcome of the event. This data collection will be triggered for AEs reported using all MedDRA preferred terms from the

current ILD Standard MedDRA Query (SMQ), plus 2 preferred terms of acute respiratory failure and respiratory failure.

LVEF decrease Management Guidance:

Left ventricular ejection fraction will be measured by either ECHO or MUGA scan. All ECHOs/MUGAs will be evaluated by the Investigator or delegated physician for monitoring cardiac function.

Troponin-T will be measured at screening and EOT, 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 a 12-lead ECG is abnormal, follow institutional guidelines.

ECGs will be performed and standard ECG parameters will be measured, including RR, PR, QT intervals, and QRS duration. All ECGs must be evaluated by the Investigator or delegated physician for the presence of abnormalities prior to the injection of IP at each cycle. Whether or not measurement is performed, date performed, results, and findings for each parameter is to be recorded in the eCRF.

Table G1 Dose Reduction Levels of Trastuzumab Deruxtecan

Starting Dose	Dose Level -1	Dose Level -2
5.4 mg/kg	4.4 mg/kg Consult AZ Study Physician	3.2 mg/kg Consult AZ Study Physician

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

Dose Interruption and Modification /Toxicity Management Guidelines:

A dose can be delayed for up to 28 days (49 days from the last infusion date) from the planned date of administration. If a patient is assessed as requiring a dose delay of longer than 28 days, the study treatment will be discontinued.

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.

Table G2 Toxicity Management Guidelines for T-DXd

Worst toxicity CTCAE v5.0 Grade (unless otherwise specified)	Management Guidelines for trastuzumab deruxtecan
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, 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.
Grade 2 (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs.)	Administration of trastuzumab deruxtecan should be interrupted and symptomatic treatment started (eg, antihistamines, NSAIDs, narcotics, IV fluids). If the event resolves or improves to Grade 1, infusion can be re-started 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 trastuzumab deruxtecan 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)	
Neutrophil Count Decreased and/or White Blood Cell Count Decreased	
Grade 3	Delay dose until resolved to ≤ Grade 2, then maintain dose
Grade 4	Delay dose until resolved to ≤ Grade 2, Reduce dose 1 level
Febrile Neutropenia (absolute neutrophil count < 1 x 10^9/L, fever > 38.3°C or a sustained temperature of ≥ 38 °C for more than one hour)	Delay dose until resolved, Reduce dose by 1 level
Lymphocyte Count Decreased[a]	
Grade 1 to Grade 3 Lymphopenia	No dose modification
Grade 4 (< 0.2 x 10^9/L)	Delay dose until resolved to ≤ Grade 2: - If resolved in ≤ 14 days from day of onset, maintain dose - If resolved in > 14 days from day of onset, reduce dose 1 level
Anaemia	
Grade 3 (Hemoglobin (Hb) < 8.0 g/dL); transfusion indicated	Delay dose until resolved to ≤ Grade 2, then maintain dose
Grade 4	Delay dose until resolved to ≤ Grade 2, then reduce dose 1 level

Worst toxicity CTCAE v5.0 Grade (unless otherwise specified)	**Management Guidelines for trastuzumab deruxtecan**
Life threatening consequences; urgent intervention indicated	
Platelet Count Decreased	
Grade 3 (platelets < 50 – 25 x 10^9/L)	Delay dose until resolved to ≤ Grade 1: - If resolved in ≤ 7 days from day of onset, maintain dose - If resolved in > 7 days from day of onset, reduce dose 1 level
Grade 4 (platelets < 25 x 10^9/L)	Delay dose until resolved to ≤ Grade 1, then reduce dose 1 level
Cardiac Toxicity	
Symptomatic congestive heart failure (CHF)	Discontinue patient from study treatment
Decrease in Left ventricle ejection fraction (LVEF) 10-20% (absolute value), but LVEF > 45%	Continue treatment with trastuzumab deruxtecan
LVEF 40% to ≤ 45% and decrease is < 10% (absolute value) from baseline	Continue treatment with trastuzumab deruxtecan Repeat LVEF assessment within 3 weeks
LVEF 40% to ≤ 45% and decrease is 10-20% (absolute value) from baseline	Interrupt trastuzumab deruxtecan 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 treatment with study drug
LVEF < 40% or > 20% (absolute value) drop from baseline	Interrupt trastuzumab deruxtecan dosing Repeat LVEF assessment within 3 weeks. If LVEF < 40% or > 20% drop from baseline is confirmed, discontinue patient from study treatment
Electrocardiogram QTc Prolonged	
Grade 3 (Average QTc > 500 ms or > 60 ms change from baseline)	Delay dose until resolved to ≤ Grade 1 (corrected QT ≤ 480 ms), 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, then if attributed to trastuzumab deruxtecan, reduce dose 1 level
Grade 4 (Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Discontinue patient from study treatment

Worst toxicity CTCAE v5.0 Grade (unless otherwise specified)	Management Guidelines for trastuzumab deruxtecan
Pulmonary Toxicity	Work-up of suspected ILD/pneumonitis: 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, cough or fever, rule out ILD/pneumonitis Evaluations should include: • High resolution CT • Pulmonologist consultation (Infectious Disease consultation as clinically indicated) • Blood culture and CBC. Other blood tests could be considered as needed • Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible • Pulmonary function tests and pulse oximetry • Arterial blood gases if clinically indicated • One blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible Other tests could be considered, as needed. 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 trastuzumab deruxtecan, then follow the ILD/pneumonitis management guidance as outlined below. All events of ILD/pneumonitis, regardless of severity or seriousness, should be followed until resolution.
Grade 1	Management: • Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry • Consider follow-up imaging in 1-2 weeks (or as clinically indicated). • Consider starting systemic steroids (eg, at least 0.5 mg/kg/day prednisone 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.*

Worst toxicity CTCAE v5.0 Grade (unless otherwise specified)	**Management Guidelines for trastuzumab deruxtecan**
	Dose modification: The administration of trastuzumab deruxtecan must be interrupted. Trastuzumab deruxtecan 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 However, if the event Grade 1 ILD/pneumonitis occurs beyond cycle Day 22 and has not resolved within 49 days from the last infusion, the drug should be discontinued.

Grade 2	Dose Modification:
	Permanently discontinue patient from study treatment.
	
	Management:
	• Promptly start and treat with systemic steroids (eg, at least 1 mg/kg/day prednisone or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, then 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 5 days,
	  • Consider increasing dose of steroids (eg, 2 mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (eg, methylprednisolone).
	  • Re-consider additional work-up for alternative etiologies as described above.
	  • Escalate care as clinically indicated.

Grade 3 or 4	Dose modification: Permanently discontinue patient from study treatment. Management: • Hospitalization required. • Promptly initiate empiric high-dose methylprednisolone IV treatment (eg, 500-1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) for at least 14 days or until complete resolution of clinical symptoms and chest CT findings, then followed by a gradual taper over at least 4 weeks. • Re-image as clinically indicated.

Worst toxicity CTCAE v5.0 Grade (unless otherwise specified)	Management Guidelines for trastuzumab deruxtecan

	• If still no improvement within 3 to 5 days,
	  • Re-consider additional work-up for alternative etiologies as described above.
	  • Consider other immuno-suppressants and/or treat per local practice.

Ocular	
Grade 3	Delay dose until resolved to ≤ Grade 1: If resolved in ≤ 7 days from day of onset, maintain dose If resolved in > 7 days from day of onset, reduce dose 1 level
Grade 4	Discontinue patient from study treatment
Blood creatinine increased	
Grade 3 (> 3.0 to 6.0 x upper limit of normal [ULN])	Delay dose until resolved to ≤ Grade 2 or baseline, then reduce dose 1 level
Grade 4 (> 6.0 x 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 TBL > 2.0 x ULN	Delay study medication 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 TBL twice weekly until resolution or return to baseline.
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)	
Grade 2 (> 3.0 - 5.0 x ULN if baseline was normal; > 3.0 - 5.0 x baseline if baseline was abnormal)	No action for Grade 2 AST/ALT
Grade 3 (> 5.0 - 20.0 x ULN if baseline was normal; > 5.0 - 20.0 x baseline if baseline was abnormal) In patients without liver metastases and patients with liver metastases and baseline level ≤ 3 x ULN	Repeat testing within 3 days. Delay dose 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, maintain dose If resolved in > 7 days from day of onset, reduce dose 1 level
Grade 3: (> 8.0 - 20.0 x ULN if baseline was normal; > 8.0 - 20.0 x baseline if baseline was abnormal) In patients with liver metastases, if the baseline level was > 3 x ULN	Repeat testing within 3 days. Delay dose until resolved to ≤ baseline level, then: If resolved in ≤ 7 days from day of onset, maintain dose If resolved in > 7 days from day of onset, reduce dose 1 level
Grade 4 (> 20.0 x ULN if baseline was normal; > 20.0 x baseline if baseline was abnormal)	Discontinue patient from study treatment
Blood bilirubin increased	

Worst toxicity CTCAE v5.0 Grade (unless otherwise specified)	Management Guidelines for trastuzumab deruxtecan
Grade 2 (> 1.5 - 3.0 x ULN if baseline was normal; > 1.5 - 3.0 x baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, delay dose until resolved to ≤ Grade 1: - If resolved in ≤ 7 days from day of onset, maintain dose - If resolved in > 7 days from day of onset, reduce dose 1 level If documented Gilbert's syndrome or liver metastases at baseline, continue study treatment
Grade 3 (> 3.0 - 10.0 x ULN if baseline was normal; > 3.0 - 10.0 x baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to ≤ Grade 1: - If resolved in ≤ 7 days from day of onset, reduce dose 1 level - If resolved in > 7 days from day of onset, discontinue trastuzumab deruxtecan If documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to ≤ Grade 2: - If resolved in ≤ 7 days from day of onset, reduce dose 1 level - If resolved in > 7 days from day of onset, discontinue trastuzumab deruxtecan
Grade 4 (> 10.0 x ULN if baseline was normal; > 10.0 x baseline if baseline was abnormal)	Discontinue patient from study treatment
Blood Alkaline Phosphatase Increased	
Grade 3 (> 5.0 - 20.0 x ULN if baseline was normal; > 5.0 - 20.0 x baseline if baseline was abnormal) or Grade 4 (> 20.0 x ULN if baseline was normal; > 20.0 x 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 until resolved to ≤ Grade 1 If resolved in ≤ 7 days from day of onset, maintain dose If resolved in > 7 days from day of onset, reduce dose 1 level
Diarrhoea/Colitis	
Grade 3	Delay dose until resolved to ≤ Grade 1 If resolved in ≤ 3 days from day of onset, maintain dose If resolved in > 3 days from day of onset, reduce dose 1 level
Grade 4	Discontinue patient from study treatment
Other Laboratory Adverse Events	
Grade 3	Delay dose until resolved to ≤ Grade 1 or baseline level: If resolved in ≤ 7 days from day of onset, maintain dose If resolved in > 7 days from day of onset, reduce dose 1 level

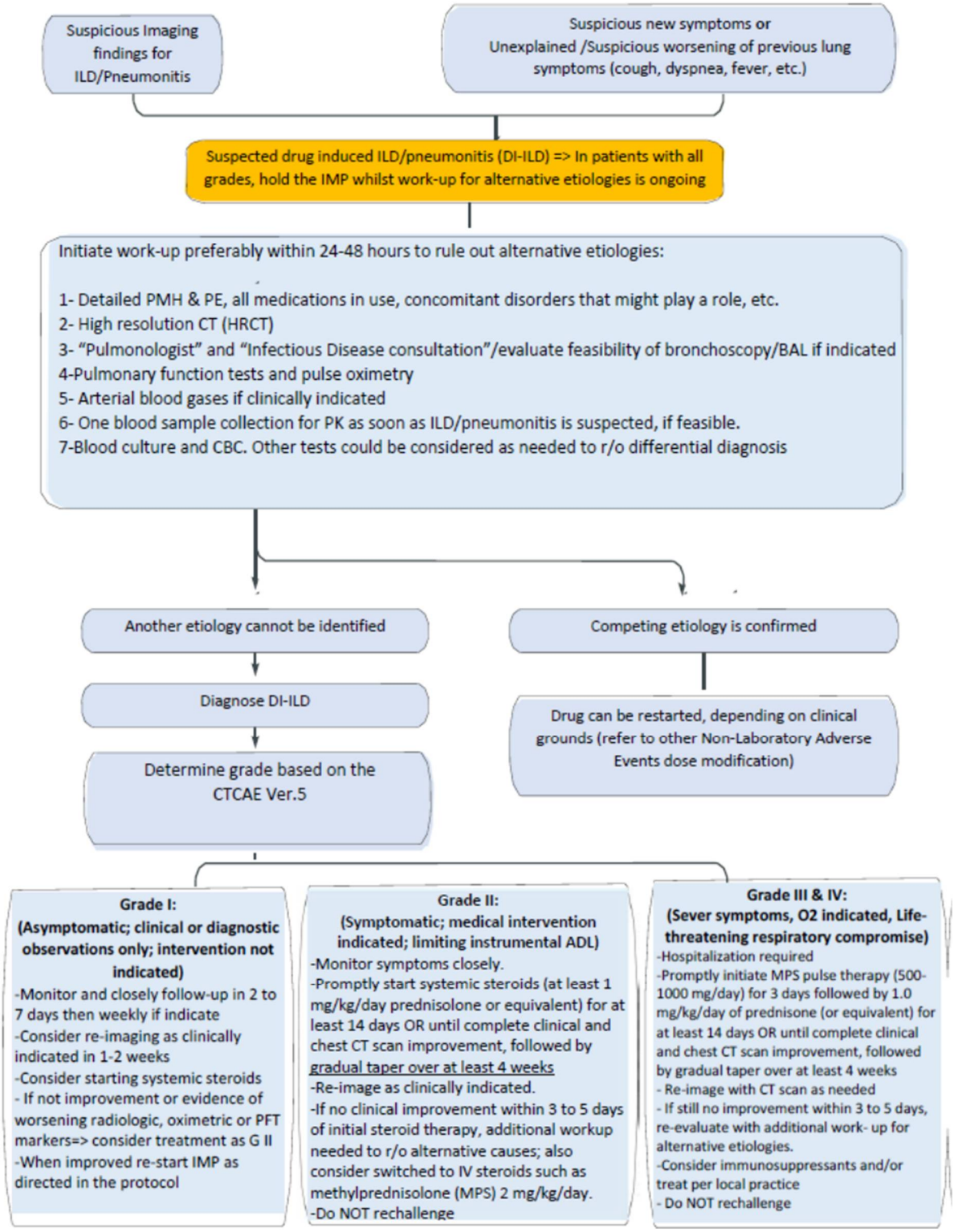
Worst toxicity CTCAE v5.0 Grade (unless otherwise specified)	Management Guidelines for trastuzumab deruxtecan
Grade 4	Discontinue patient from study treatment
Other Non-Laboratory Adverse Events	
Grade 3	Delay dose until resolved to ≤ Grade 1 or baseline: If resolved in ≤ 7 days from day of onset, maintain dose If resolved in > 7 days from day of onset, reduce dose 1 level
Grade 4	Discontinue patient from study treatment

[a] There will be no dose modifications for Grade 1 to Grade 3 lymphopenia.
All dose modifications should be based on the worst preceding toxicity.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; CHF, congestive heart failure; CT, Computed tomography; CTCAE: Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; IV, intravenous; LVEF, left ventricular ejection fraction; NCI, National Cancer Institute; NSAID, non-steroidal anti-inflammatory drug; QTc, QT interval; TBL, total bilirubin; T-DXd, trastuzumab deruxtecan; TMG, toxicity management guidelines; ULN, upper limit of normal

In addition, Investigators may consider dose reductions or discontinuations of the study drug according to the patient's condition and after discussion with the Medical Monitor or designee.

Appendix H Management of Drug-Induced ILD

Figure H1 Flow Chart for Management of Drug-Induced ILD



Appendix I Instructions related to COVID-19

Benefit-Risk Considerations for COVID-19

The emergence of the coronavirus 2019-nCoV (COVID-19) presents a potential safety risk for patients. Several risk mitigation factors have been implemented in this study. Notably, the eligibility criteria exclude patients with COVID-19 infections (see protocol Section 5.2).

Moreover, with the outbreak of COVID-19, there is the potential for increased use of chloroquine and hydroxychloroquine to treat severely symptomatic patients, or even for prophylactic use. Chloroquine and hydroxychloroquine have been shown in vitro to substantially affect the pH of the lysosome, a key intracellular compartment involved in the trafficking and payload release of T-DXd. As it is unknown whether chloroquine/ hydroxychloroquine may affect the safety and efficacy of T-DXd, to be eligible for this clinical study, use of chloroquine and hydroxychloroquine treatment must be completed 14 days prior to the first dose of T-DXd (See protocol Section 5.1). During study treatment, chloroquine and hydroxychloroquine are considered prohibited concomitant medications. However, in case treatment with chloroquine or hydroxychloroquine treatment is absolutely required for COVID-19, study treatment must be interrupted. After chloroquine or hydroxychloroquine is administered for COVID-19, then a wash-out period of at least 14 days is required before restarting study treatment.

Lastly, due to the potential overlapping impact of T-DXd and COVID-19 on the lung, the Sponsor has also provided in this Appendix, a dose modification and management plan for 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.

Prior and Concomitant Medications

Concomitant treatment with chloroquine or hydroxychloroquine is not allowed during the study treatment. If treatment with chloroquine or hydroxychloroquine treatment is absolutely required for COVID-19, study treatment must be interrupted. If chloroquine or hydroxychloroquine is administered, then a wash-out period of at least 14 days is required before restarting study treatment.

Dose Modification Criteria

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

Dose modification criteria for suspected or confirmed COVID-19

If COVID-19 infection is suspected, delay T-DXd and rule out COVID-19 per local guidance.

- If COVID-19 is ruled out, follow study protocol.
- If COVID-19 is confirmed or diagnosis is suspected after evaluation, manage COVID-19 per local guidance until recovery of COVID-19 defined as no signs/symptoms, at least 1 negative RT-PCR test result*, and nearly or completely resolved chest CT findings. 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.
  - If Grade 3
    - Reduce dose 1 level if chest CT findings are completely resolved.
    - Otherwise, discontinue study treatment.
  - If Grade 4, discontinue study treatment.

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

- If an event is suspected to be drug-related ILD/pneumonitis, manage per protocol ILD/pneumonitis management guideline.

* If PCR testing is not available, the patient must not have any sign/symptoms for at least 2 weeks, in addition to meeting the requirement for chest CT imaging.

Pharmacokinetic sampling

In addition to the PK samples specified in the SoA (see Section 1.3), patients who receive chloroquine or hydroxychloroquine during the treatment period should have T-DXd PK blood samples taken at the following timepoints:

- On the day that chloroquine/hydroxychloroquine treatment starts, before any chloroquine/hydroxychloroquine is administered
- Before chloroquine/hydroxychloroquine dosing on Day 3 or 4
- On the last day of chloroquine/hydroxychloroquine treatment
- Pre-dose on the day of restarting T-DXd treatment, if T-DXd is restarted

The PK sample should be taken within 4 hours prior to chloroquine/hydroxychloroquine dose.

Following the above blood PK draws, if T-DXd is restarted, routine T-DXd PK blood sample collection will continue per the SoA in Section 1.3.

Appendix J Patient-reported Outcomes

MDASI

Daily Symptom tracker	Not Present										As bad as you can imagine
Your coughing at its worst	0	1	2	3	4	5	6	7	8	9	10
Your shortness of breath at its worst	0	1	2	3	4	5	6	7	8	9	10
Your chest heaviness or tightness at its worst	0	1	2	3	4	5	6	7	8	9	10

SGRQ-I

THE ST GEORGE'S RESPIRATORY QUESTIONNAIRE
IDIOPATHIC PULMONARY FIBROSIS VERSION
The SGRQ-I

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problem, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Name: ..... Date: .....

ID Number: .....

Age: ..... Sex: Male/Female

Please tick in one box to show how you describe your current health:-

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

SGRQ-I Current Health Status
Version 1.0 August 2012

Part 1

Questions about how much chest trouble you currently have. Please tick in one box for each question.

	Almost every day	Only with chest infections	Not at all
1. I cough:	☐	☐	☐
2. I bring up phlegm (sputum):	☐	☐	☐
3. I have shortness of breath:	☐	☐	☐
4. I have attacks of wheezing:	☐	☐	☐

5. In a typical week how many attacks of chest trouble do you have? Please tick (✓) one:

More than 1 attack ☐
No attacks ☐

6. In a typical week how often do you have good days? Please tick (✓) one:

None ☐
A few days ☐
Every day is a good day ☐

Part 2

Section 1:
If you have ever had paid employment:

Please tick (✓) one:

My lung condition interferes or made me stop work ☐

My lung problem does not affect my job ☐

Section 2: Questions about what activities usually make you feel breathless. Please tick in each box that applies to you <u>these days</u>.

Please tick (✓) in *each box* that applies to you *these days*:

		True	False
1.	Getting washed or dressed	☐	☐
2.	Walking around the home	☐	☐
3.	Walking outside on the level	☐	☐
4.	Walking up a flight of stairs	☐	☐
5.	Playing sports or games	☐	☐

Section 3: Some more questions about your cough and breathlessness. Please tick in each box that applies to you <u>these days</u>.

Please tick (✓) in *each box* that applies to you *these days*:

		True	False
1.	My cough hurts	☐	☐
2.	My cough makes me tired	☐	☐
3.	I am breathless when I talk	☐	☐
4.	I am breathless when I bend over	☐	☐
5.	My cough or breathing disturbs my sleep	☐	☐
6.	I get exhausted easily	☐	☐

Section 4: Questions about other effects that your chest trouble may have on you. Please tick in each box that applies to you <u>these days</u>.

Please tick (✓) in *each box* that applies to you *these days*:

		True	False
1.	My cough or breathing is embarrassing in public	☐	☐
2.	My chest trouble is a nuisance to my family, friends or neighbours	☐	☐
3.	I get afraid or panic when I cannot get my breath	☐	☐
4.	I feel that I am not in control of my chest problem	☐	☐
5.	Exercise is not safe for me	☐	☐
6.	Everything seems too much of an effort	☐	☐

SGRQ-I Current health status 3
Version 1.0 August 2012

Section 5: These are questions about how your activities might be affected by your breathing. Please tick in each box which you think applies to you <u>because of your breathing</u>

	True	False
1. Jobs such as housework take a long time, or I have to stop for rests	☐	☐
2. If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
3. If I hurry or walk fast, I have to stop or slow down	☐	☐
4. My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐
5. My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	☐	☐

Section 6: We would like to know how your chest <u>usually</u> affects your daily life. Please tick in each box that applies to you <u>because of your chest trouble</u>

	True	False
1. I cannot play sports or games	☐	☐
2. I cannot go out of the house to do the shopping	☐	☐
3. I cannot do housework	☐	☐
4. I cannot move far from my bed or chair	☐	☐

Now, would you tick in the box (one only) which you think best describes how your chest affects you:-

It does not stop me doing anything I would like to do	☐
It stops me doing one or two things I would like to do	☐
It stops me doing most of the things I would like to do	☐
It stops me doing everything I would like to do	☐

Appendix K Abbreviations

Abbreviation or special term	Explanation
5-HT3	5-hydroxytryptamine receptor
ADA	Anti-drug antibody
ADC	Antibody-drug conjugate
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
Anti-LKM	Anti–liver-kidney microsomal antibody
ASMA	Anti-smooth muscle antibody
AST	Aspartate aminotransferase
AZ	AstraZeneca
BUN	Blood urea nitrogen
CART	Cell-free and concentrated ascites reinfusion therapy
CBC	Complete blood count
CEAS	Centrally-determined Efficacy Analysis Set
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus 2019-nCoV
CR	Complete response
CRC	Colorectal cancer
CRF	Case report form
CRO	Clinical research organization
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor deoxyribonucleic acid

Abbreviation or special term	Explanation
DCO	Data cutoff
DCR	Disease control rate
DILI	Drug induced liver injury
DLCO	Diffusing capacity of the lungs for carbon monoxide
DNA	Deoxyribonucleic acid
DoR	Duration of response
DS-8201a	Trastuzumab deruxtecan
DXd	Deruxtecan
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EOT	End of treatment
ePRO	electronic patient-reported outcome
ERBB2	erb-b2 receptor tyrosine kinase 2
ESMO	European Society for Medical Oncology
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAS	Full analysis set
FDA	US Food and Drug Administration
FDG-PET	Fluoro-deoxyglucose positron emission tomography
FEV1	Forced expiratory volume in 1 second
FEV6	Forced expiratory volume in 6 seconds
FFPE	Formalin-fixed and paraffin-embedded
FISH	Fluorescent in situ hybridization
FSI	First subject in
FVC	Forced vital capacity
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulation factor
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
H & E	Hematoxylin and eosin stain
Hb	Hemoglobin
HbsAg	Hepatitis B surface antigen

Abbreviation or special term	Explanation
HBV DNA	Hepatitis B virus DNA
HCT	Hematocrit
HCV	hepatitis C virus
HER	Human epidermal growth factor receptor
HER2	Human epidermal growth factor receptor 2
HER3	Human epidermal growth factor receptor 3
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HL	Hy's Law
HRCT	High-resolution computed tomography
HRQoL	health-related quality of life
IATA	International Airline Transportation Association
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council on Harmonization
ICR	Independent central review
iCRO	imaging Contract Research Organization
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IND	Investigational new drug
INR	International Normalized Ratio
IP	Investigational product
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board
IRT	Interactive response technology
ISH	in situ hybridization
IV	Intravenous(ly)
K	Potassium
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MAAA-1181, MAAA-1181a	Deruxtecan

Abbreviation or special term	Explanation
mAb	Monoclonal antibody
MDAS	Measurable disease analysis set
MDASI	MD Anderson Symptom Inventory
MedDRA	Medical Dictionary for Regulatory Activities
min	Minutes
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MUGA	Multiple gated acquisition
Na	Sodium
NA	Not applicable
NCI	National Cancer Institute
NE	Not evaluable
NGS	Next-generation sequencing
NK1	Neurokinin-1
NL	New lesion
NSAID	nonsteroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
NTL	Non-target lesion
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PEF	Peak expiratory flow
PET	Positron emission tomography
PFT	Pulmonary function test
PFS	Progression-free survival
PHL	Potential Hy's Law
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetic(s)
PK/PD	Pharmacokinetic/pharmacodynamic
PR	Partial response
PRO	Patient reported outcome

Abbreviation or special term	Explanation
PT	Prothrombin time
PTT/aPTT	partial thromboplastin time /activated partial thromboplastin time
q7d	Every 7 days
q3m	Every 3 months
q3w	Every 3 weeks
q6w	Every 6 weeks
QC	Quality control
qPCR	Quantitative polymerase chain reaction
QTcF	QT interval by Fridericia's formula
RECIST v1.1	Response Evaluation Criteria In Solid Tumors, version 1.1
RNA	Ribonucleic acid
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SGRQ-I	St George's Respiratory Questionnaire for patients with Idiopathic Pulmonary Fibrosis
SLFN11	Schlafen Family Member 11
SMQ	Standard MedDRA Query
SoA	Schedule of Activities
SpO_2	Saturation of peripheral oxygen
SUSAR	Suspected unexpected serious adverse reactions
SUV	Standardized uptake value
TBL	Total bilirubin
T-DM1	ado-trastuzumab emtansine
T-DXd	Trastuzumab deruxtecan
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TL	Target lesion
TLC	Total lung capacity
TMB	Tumor mutational burden
TME	Tumor microenvironment
TMG	Toxicity management guidelines
TOP1	DNA topoisomerase 1

Abbreviation or special term	Explanation
ULN	Upper limit of normal
US	United States
WHO	World Health Organization

11 REFERENCES

Arcila et al 2012
Arcila ME, Chaft JE, Nafa K, Roy-Chowdhuri S, Lau C, Zaidinski M et al. Prevalence, clinicopathologic associations, and molecular spectrum of ERBB2 (HER2) tyrosine kinase mutations in lung adenocarcinomas. Clin Cancer Res. 2012;18(18):4910-8.

Bedard et al 2019
Bedard PL, Li S, Wisinski KB, Yang ES, Limaye SA, Mitchell EP et al. Abstract CT139: NCI Molecular Analysis for Therapy Choice (NCI-MATCH EAY131) arm B: Phase II study of afatinib in patients (pts) with HER2 (ERBB2) activating mutations. Cancer Research. 2019;79(13 Supplement):CT139-CT.

Bellmunt et al 2009
Bellmunt J, Theodore C, Demkov T, Komyakov B, Sengelov L, Daugaard G et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol. 2009;27(27):4454-61.

Bose et al 2013
Bose R, Kavuri SM, Searleman AC, Shen W, Shen D, Koboldt DC et al. Activating HER2 mutations in HER2 gene amplification negative breast cancer. Cancer Discov. 2013;3(2):224-37.

Branco et al 2019
Branco FP, Machado D, Silva FF, Andre S, Catarino A, Madureira R et al. Loss of HER2 and disease prognosis after neoadjuvant treatment of HER2+ breast cancer. Am J Transl Res. 2019;11(9):6110-6.

Chang et al 2016
Chang MT, Asthana S, Gao SP, Lee BH, Chapman JS, Kandoth C et al. Identifying recurrent mutations in cancer reveals widespread lineage diversity and mutational specificity. Nat Biotechnol. 2016;34(2):155-63.

Chang et al 2018
Chang MT, Bhattarai TS, Schram AM, Bielski CM, Donoghue MTA, Jonsson P et al. Accelerating Discovery of Functional Mutant Alleles in Cancer. Cancer Discov. 2018;8(2):174-83.

Chumsri et al 2015
Chumsri S, Weidler J, Ali S, Balasubramanian S, Wallweber G, DeFazio-Eli L et al. Prolonged Response to Trastuzumab in a Patient With HER2-Nonamplified Breast Cancer With Elevated HER2 Dimerization Harboring an ERBB2 S310F Mutation. J Natl Compr Canc Netw.

2015;13(9):1066-70.

Cleeland et al 2000
Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle MT, Morrissey M et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. Cancer. 2000;89(7):1634-46.

Cortes et al 2011
Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011;377(9769):914-23.

Di Modica et al 2017
Di Modica M, Tagliabue E, Triulzi T. Predicting the Efficacy of HER2-Targeted Therapies: A Look at the Host. Dis Markers. 2017;20177849108.

Dziadziuszko et al 2019
Dziadziuszko R, Smit EF, Dafni U, Wolf J, Wasąg B, Biernat W et al. Afatinib in NSCLC With HER2 Mutations: Results of the Prospective, Open-Label Phase II NICHE Trial of European Thoracic Oncology Platform (ETOP). J Thorac Oncol. 2019;14(6):1086-94.

Eisenhauer et al 2009
Eisenhauer E, Therasse P, Bogaerts J, Schwartz L, 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.

Greulich et al 2012
Greulich H, Kaplan B, Mertins P, Chen TH, Tanaka KE, Yun CH et al. Functional analysis of receptor tyrosine kinase mutations in lung cancer identifies oncogenic extracellular domain mutations of ERBB2. Proc Natl Acad Sci USA. 2012;109(36):14476-81.

Hainsworth et al 2018
Hainsworth JD, Meric-Bernstam F, Swanton C, Hurwitz H, Spigel DR, Sweeney C et al. Targeted Therapy for Advanced Solid Tumors on the Basis of Molecular Profiles: Results From MyPathway, an Open-Label, Phase IIa Multiple Basket Study. J Clin Oncol. 2018;36(6):536-42.

Hodi et al 2010
Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711-23.

Hyman et al 2018
Hyman DM, Piha-Paul SA, Won H, Rodon J, Saura C, Shapiro GI et al. HER kinase inhibition

in patients with HER2- and HER3-mutant cancers. Nature. 2018;554(7691):189-94.

Jaiswal et al 2013
Jaiswal BS, Kljavin NM, Stawiski EW, Chan E, Parikh C, Durinck S et al. Oncogenic ERBB3 mutations in human cancers. Cancer Cell. 2013;23(5):603-17.

Janjigian et al 2015
Janjigian YY, Riches JC, Ku GY, Imtiaz T, Capanu M, Chou JF et al. Loss of human epidermal growth factor receptor 2 (HER2) expression in HER2-overexpressing esophagogastric (EG) tumors treated with trastuzumab. J Clin Oncol. 2015;33(3_suppl):63-.

Kancha et al 2011
Kancha RK, von Bubnoff N, Bartosch N, Peschel C, Engh RA, Duyster J. Differential sensitivity of ERBB2 kinase domain mutations towards lapatinib. PLoS One. 2011;6(10):e26760.

Kavuri et al 2015
Kavuri SM, Jain N, Galimi F, Cottino F, Leto SM, Migliardi G et al. HER2 activating mutations are targets for colorectal cancer treatment. Cancer Discov. 2015;5(8):832-41.

Kim et al 2015
Kim JH, Lee SC, Oh SY, Song SY, Lee N, Nam EM et al. Attenuated FOLFIRINOX in the salvage treatment of gemcitabine-refractory advanced pancreatic cancer: a phase II study. Cancer Commun (Lond). 2018;38(1):32.

Lai et al 2019
Lai WV, Lebas L, Barnes TA, Milia J , Ni A , Gautschi O et al. Afatinib in patients with metastatic or recurrent HER2-mutant lung cancers: a retrospective international multicentre study. Eur J Cancer. 2019;109:28-35.

Li et al 2016
Li BT, Ross DS, Aisner DL, Chaft JE, Hsu M, Kako SL et al. HER2 Amplification and HER2 Mutation Are Distinct Molecular Targets in Lung Cancers. J Thorac Oncol. 2016;11(3):414-9.

Li et al 2018
Li BT, Shen R, Buonocore D, Olah ZT, Ni A, Ginsberg MS et al. Ado-Trastuzumab Emtansine for Patients With HER2-Mutant Lung Cancers: Results From a Phase II Basket Trial. J Clin Oncol. 2018;36(24):2532-7.

Li et al 2020
Li BT, Michelini F, Misale S, Cocco E, Baldino L, Cai Y et al. HER2-mediated internalization of cytotoxic agents in ERBB2 amplified or mutant lung cancers. Cancer Discov. 2020.

Makiyama et al 2020
Makiyama A, Sukawa Y, Kashiwada T, Kawada J, Hosokawa A, Horie Y et al. Randomized, Phase II Study of Trastuzumab Beyond Progression in Patients With HER2-Positive Advanced Gastric or Gastroesophageal Junction Cancer: WJOG7112G (T-ACT Study). J Clin Oncol. 2020;38:1919-27.

Mayer et al 2015
Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015;372(20):1909-19.

Mazieres et al 2013
Mazieres J, Peters S, Lepage B, Cortot AB, Barlesi F, Beau-Faller M et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. J Clin Oncol. 2013;31(16):1997-2003.

Mishra et al 2017
Mishra R, Hanker AB, Garrett JT. Genomic alterations of ERBB receptors in cancer: clinical implications. Oncotarget. 2017;8(69):114371-92.

Mittendorf et al 2009
Mittendorf EA, Wu Y, Scaltriti M, Meric-Bernstam F, Hunt KK, Dawood S et al. Loss of HER2 amplification following trastuzumab-based neoadjuvant systemic therapy and survival outcomes. Clin Cancer Res. 2009;15(23):7381-8.

Nagano et al 2018
Nagano M, Kohsaka S, Ueno T, Kojima S, Saka K, Iwase H et al. High-Throughput Functional Evaluation of Variants of Unknown Significance in ERBB2. Clin Cancer Res. 2018;24(20):5112-22.

Niikura et al 2012
Niikura N, Liu J, Hayashi N, Mittendorf EA, Gong Y, Palla SL et al. Loss of Human Epidermal Growth Factor Receptor 2 (HER2) Expression in Metastatic Sites of HER2-overexpressing Primary Breast Tumors. J Clin Oncol 2012 Feb 20;30(6):593-9.

Ogitani et al 2016
Ogitani Y, Aida T, Hagihara K, Yamaguchi J, Ishii C, Harada N et al. DS-8201a, A novel HER2-targeting ADC with a novel DNA topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1. Clin Cancer Res. 2016;22(20):5097-108.

Ou et al 2017
Ou SI, Schrock AB, Bocharov EV, Klempner SJ, Haddad CK, Steinecker G et al. HER2 Transmembrane Domain (TMD) Mutations (V659/G660) That Stabilize Homo- and Heterodimerization Are Rare Oncogenic Drivers in Lung Adenocarcinoma That Respond to

Afatinib. J Thorac Oncol. 2017;12(3):446-57.

Pahuja et al 2018
Pahuja KB, Nguyen TT, Jaiswal BS, Prabhash K, Thaker TM, Senger K et al. Actionable Activating Oncogenic ERBB2/HER2 Transmembrane and Juxtamembrane Domain Mutations. Cancer Cell. 2018;34(5):792-806 e5.

Peters et al 2018
Peters S, Curioni-Fontecedro A, Nechushtan H, Shih J, Liao W, Gautschi O et al. Activity of Afatinib in Heavily Pretreated Patients With ERBB2 Mutation-Positive Advanced NSCLC: Findings From a Global Named Patient Use Program. J Thorac Oncol. 2018;13(12):1897-905.

Pietrantonio et al 2016
Pietrantonio F, Caporale M, Morano F, Scartozzi M, Gloghini A, De Vita F et al. HER2 loss in HER2-positive gastric or gastroesophageal cancer after trastuzumab therapy: Implication for further clinical research. Int J Cancer. 2016;139(12):2859-64.

Prat et al 2014
Prat A, Bianchini G, Thomas M, Belousov A, Cheang MC, Koehler A et al. Research-based PAM50 subtype predictor identifies higher responses and improved survival outcomes in HER2-positive breast cancer in the NOAH study. Clin Cancer Res. 2014;20(2):511-21.

Robichaux et al 2019
Robichaux JP, Elamin YY, Vijayan RSK, Nilsson MB, Hu L, He J et al. Pan-Cancer Landscape and Analysis of ERBB2 Mutations Identifies Poziotinib as a Clinically Active Inhibitor and Enhancer of T-DM1 Activity. Cancer Cell. 2019;36(4):444-57 e7.

Ross et al 2016
Ross JS, Gay LM, Wang K, Ali SM, Chumsri S, Elvin JA et al. Nonamplification ERBB2 genomic alterations in 5605 cases of recurrent and metastatic breast cancer: An emerging opportunity for anti-HER2 targeted therapies. Cancer. 2016;122(17):2654-62.

Shitara et al 2019
Shitara K, Iwata H, Takahashi S, Tamura K, Park H, Modi S et al. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive gastric cancer: a dose-expansion, phase 1 study. Lancet Oncol. 2019;20(6):827-36.

Smit et al 2020
Smit EF, Nakagawa K, Nagasaka M, Felip E, Goto Y, Li BT, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-mutated metastatic non-small cell lung cancer (NSCLC): Interim results of DESTINY-Lung01. J Clin Oncol. 2020;38(15):9504.

Smyth et al 2019
Smyth LM, Piha-Paul SA, Won HH, Schram AM, Saura C, Loi S et al. Efficacy and

Determinants of Response to HER Kinase Inhibition in HER2-Mutant Metastatic Breast Cancer. Cancer Discov. 2019.

Triulzi et al 2015
Triulzi T, De Cecco L, Sandri M, Prat A, Giussani M, Paolini B et al. Whole-transcriptome analysis links trastuzumab sensitivity of breast tumors to both HER2 dependence and immune cell infiltration. Oncotarget. 2015;6(29):28173-82.

Tsurutani et al 2020
Tsurutani J, Iwata H, Krop I, Janne PA, Doi T, Takahashi S et al. Targeting HER2 with Trastuzumab Deruxtecan: A Dose-Expansion, Phase I Study in Multiple Advanced Solid Tumors. Cancer Discov. 2020;10(5):688-701.

Wang et al 2006
Wang SE, Narasanna A, Perez-Torres M, Xiang B, Wu FY, Yang S et al. HER2 kinase domain mutation results in constitutive phosphorylation and activation of HER2 and EGFR and resistance to EGFR tyrosine kinase inhibitors. Cancer Cell. 2006;10(1):25-38.

Yamamoto et al 2014
Yamamoto H, Higasa K, Sakaguchi M, Shien K, Soh J, Ichimura K et al. Novel germline mutation in the transmembrane domain of HER2 in familial lung adenocarcinomas. J Natl Cancer Inst. 2014;106(1):djt338.

Yorke et al 2010
Yorke J, Jones PW, Swigris JJ. Development and validity testing of an IPF-specific version of the St George's Respiratory Questionnaire. Thorax. 2010;65(10):921-6.

Zabransky et al 2015
Zabransky DJ, Yankaskas CL, Cochran RL, Wong HY, Croessmann S, Chu D et al. HER2 missense mutations have distinct effects on oncogenic signaling and migration. Proc Natl Acad Sci USA. 2015;112(45):E6205-14.

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d967mc00001-csp-v1	
Document Title:	D967MC00001 Clinical Study Protocol version 1
Document ID:	Doc ID-004267372
Version Label:	1.0 CURRENT LATEST APPROVED

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.