Statistical Analysis Plan	
Study Code	D967MC00001
Edition Number	3.0
Date	07Feb2023

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

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Abbreviation or special term	**Explanation**
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BAL	Broncho-alveolar lavage
BMI	Body mass index
BP	Blood pressure
CEAS	Centrally-determined Efficacy Analysis Set
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CR	Complete response
CRF	Case Report Form
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTC	Common terminology criteria
CTCAE	Common terminology criteria for adverse event
ctDNA	Circulating tumor deoxyribonucleic acid
DAE	Discontinuation of investigational product due to adverse events
DBL	Database lock
DCO	Data cut-off
DCR	Disease control rate
DLCO	Diffusing capacity of the lungs for carbon monoxide
DM	Data Management
DoR	Duration of response
d.p.	Decimal place
DS	Disposition
ECG	Electrocardiogram
ECHO	Echocardiograms

Abbreviation or special term	**Explanation**
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of Treatment
EGFR	Epidermal growth factor receptor
FAS	Full analysis set
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FEV6	Forced expiratory volume in 6 seconds
FFPE	Formalin-fixed and paraffin-embedded
FVC	Forced vital capacity
HER2	Human epidermal growth factor receptor 2
HER3	Human epidermal growth factor receptor 3
HRCT	High resolution CT
ICF	Informed Consent Form
ICR	Independent central review
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IP	Investigational product
IPD	Important protocol deviation
ISH	In situ hybridization
LD	Longest diameter
LVEF	Left ventricular ejection fraction
MAAA-1181, MAAA-1181a	Deruxtecan
MDAS	Measurable disease analysis set
MDASI	MD Anderson Symptom Inventory
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MUGA	Multiple gated acquisition scans
NA	Not applicable
nAb	Neutralizing antibody
NCI	National Cancer Institute
NE	Not evaluable
NGS	Next-generation sequencing

Abbreviation or special term	**Explanation**
NSCLC	Non-small cell lung cancer
NTL	Non-target lesions
OAE	Other significant adverse event
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase Chain Reaction
PD	Progressive disease
PEF	Peak expiratory flow
PFS	Progression free survival
PFT	Pulmonary function test
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetics
PK-PD	Pharmacokinetic-pharmacodynamic
PR	Partial response
PRO	Patient reported outcome
PS	Performance status
PT	Preferred term
PTT/aPTT	partial thromboplastin time /activated partial thromboplastin time
q3w	Every 3 weeks
q6w	Every 6 weeks
qPCR	Quantitative Polymerase Chain Reaction
QTcF	QT interval by Fridericia's formula
RDI	Relative dose intensity
RECIST v1.1	Response Evaluation Criteria In Solid Tumors, version 1.1
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Stable disease
SGRQ-I	St George's Respiratory Questionnaire for patients with Idiopathic Pulmonary Fibrosis
SOC	System organ class
SpO_2	Saturation of peripheral oxygen
T-DXd	Trastuzumab Deruxtecan
TEAE	Treatment emergent adverse event

Abbreviation or special term	**Explanation**
TL	Target lesion
TLC	Total lung capacity
TMB	Tumor mutational burden
TNM	Tumor, node, metastasis
ULN	Upper limit of normal
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

AMENDMENT HISTORY

CATEGORY: Change refers to	**Date**	**Description of change**	**In line with CSP? Yes (version) / No / NA**	**Rationale**
N/A	20Oct2020	Initial approved SAP	N/A	N/A
Abbreviations	17Mar2022	Additional abbreviations –are added. QTcF and RECIST v1.1 abbreviations are updated.		
	07Feb2023	Additional abbreviations –are added. CRF, DM and DS abbreviations are updated.	NA	Consistency with the body text.
1.1.3 Exploratory objectives	07Feb2023	The analyes of the exploratory endpoint for the comparison of local HER2 mutation test results with retrospective central HER2 mutation results will not be reported in the clinical study report (CSR) due to unavailability of this data at the time of database lock.	No	Not required for CSR.
2.1 Definition of analysis sets	07Feb2023	The centrally determined-efficacy analysis set (CEAS) is removed from summary for efficacy data.	No	Retrospective central testing result for HER2 mutations will not be available at database lock so will not be included in CSR.
2.1.3 Centrally determined-efficacy analysis set (CEAS)	07Feb2023	CEAS population will not be derived and presented in the outputs for the clinical study report.	No	Retrospective central testing result for HER2 mutations will not be available at database lock so will not be included in CSR.
2.2 Protocol deviations	17Mar2022	Added text to indicate that only the IPDs deemed applicable to the statistical analyses will be summarized.	NA	Clarification that only IPDs deemed applicable to the statistical analysis will be summarized.
		Protocol deviation codes updated and additional corporate IPD added (code 3.1-3.4).	NA	Updated to align with current protocol deviation plan and corporate IPD standards.
		The listing and tabulation of other study deviations captured from the CRF module for inclusion/exclusion criteria is deleted	NA	Not required for CSR

	07Feb2023	All IPDs specified in the protocol deviation plan will be summarized and listed in the CSR.	NA	Updated wording for alignment with reporting requirements per the latest Oncology SAP template.
3.1.4 Independent central review	17Mar2022	'No evidence of disease [NED]' included.	NA	Included to cover a scenario if there is no evidence of disease.
3.2.3 Best Objective Response (BoR)	17Mar2022	The assessment window for patients who die with no evaluable RECIST assessments is updated from 7 to 13 weeks.	NA	Correction
		Text on exploratory endpoint of BoR added.	NA	Additional summary requested.
3.2.5 Progression free survival (PFS)	07Feb2023	Additional text on exploratory endpoint of BoR in the scenario where patient has a confirmed PR and an unconfirmed CR.	NA	Clarified on the response to be used for the analysis in the given scenario.
		Additional clarification provided to document the handling of the patients that are alive at the time of final database lock and the analyses.	NA	Updated for clarification on data handling.
3.3.1 Treatment exposure	17Mar2022	Text on 'Delays, reductions and interruptions' added to clarify the analysis of the delays, reductions and interruptions and the summary of infusion interruptions.	NA	Clarification of derivation of variables.
3.3.2 Dose intensity	17Mar2022	RDI derivation updated to calculate in mg rather than mg/kg. For the calculation of the intended dose, +/- 10% weight adjustment is applied.	NA	For consistency with project approach.
		The window for dosing was corrected from 2 days to 3 days when accounting for the calculation of intended cumulative dose	Yes (V1)	Correction
3.3.3 Adverse events	17Mar2022	The TEAE definition previously included SAEs with onset or worsening 48 days or more after the last dose of study drug if considered related to the study treatment - although these SAES were not included in summary tables. These SAEs will no longer be considered TEAEs, so the relevant text has been deleted.	No	Change from protocol. At a project level patient safety have agreed these SAEs will no longer be considered TEAEs in future studies. For consistency, the TEAE definition in this SAP has been updated. Summaries are not affected as the events were not included anyway.

3.3.7 Electrocardiograms	17Mar2022	Additional text added to help clarify the programming for the ECG parameters.	NA	Clarification of derivation.
3.3.9 Vital Signs and SpO2	17Mar2022	The section title updated to include SpO2 along with the vital signs	NA	Updated section heading for clarification
3.3.11.1 Pulmonary function test	17Mar2022	FiO2 deleted from the list of parameters since, it is not collected.	Yes (V1)	Correction for alignment with CSP
		DLCO formula and derivation is added.	NA	Added details on derivation and conversion factors for DLCO as this is collected in different units.
3.5.1 Baseline characteristics	17Mar2022	Repeated text for ethnicity removed	NA	Removed for redundancy
		Description of tumor types is added	NA	Clarification of derivation
3.5.2 Prior, concomitant medications and procedures	17Mar2022	The definition of concomitant medications was updated, and terminology changed to 'medications' rather than 'therapies'.	NA	Updated for consistency with the data reporting in the CSR
		The definition of concomitant procedure was removed.	NA	Not required as concomitant procedures are not summarized.
3.5.3 Immunogenicity variables	17Mar2022	Definition of treatment-boosted ADA modified from 4-fold to 2-fold	NA	T-DXd project definition uses 2-fold rather than 4-fold.
3.5.4 Biomarker variables	17Mar2022	Added text to clarify how IHC and ISH data will be reported.	NA	Updated for clarification on data handling
	07Feb2023	Added summarized grouped categories for pre-specified HER2 activation mutations with a positive result (local testing).	NA	Additional summary request.
		Added text that data from retrospective central testing will not be summarized.	No	Retrospective central testing result for HER2 mutations will not be available at database lock so will not be included in CSR.
		Updated HER2 status categorizations for local and central testings.	NA	Additional summary request

3.6.1 Time windows for safety data	17Mar2022	Added text to clarify how safety data that are collected during the study pre-infusion and post-infusion will be included in summaries. Added text to clarify the reporting of the minimum/maximum values for summaries.	NA	Updated for clarification on data handling
4.1 General principles	17Mar2022	For continuous data, additional text added 'Where presented, quartiles will be rounded to 1 additional decimal place compared to the original data.' For categorical data, the percentages of 100.0 will be presented as 100 with no decimal.	NA	Updated for consistency with the project/AZ standards..
4.2.3 Demographic and other baseline characteristics	17Mar2022	'Extent of disease at screening' changed to 'Extent of disease at baseline'. Pulmonary function test at baseline changed to screening.	Yes (V1)	Updated to align with CSP.
	07Feb2023	Data from restrospective central testing for HER2 mutations will not be summarized in the tables, figures and listings of the CSR.	No	Retrospective central testing result for HER2 mutations will not be available at database lock so will not be included in CSR.
		Removed TNM classification at screening in the summary and updated the wording in some categories.	NA	Consistency with data collected.
		Updated the disease-related treatment modalities to anti-cancer therapy by ATC classification and generic drug name and replaced "chemotherapy" with "anti-cancer therapy".	NA	Updated to include all prior therapies in the summary.
		Grouped categories will be summarized along with pre-specified HER2 activating mutations for local testing.	NA	Added per request.
		Removed HER2 mutant (central testing) from baseline biomarker status summary.	NA	Consistency with data collected.
		Removed text for summarizing the discrepancies between central and local HER2 mutation test results.	No	Not required for CSR.

		Baseline HER2 testing, baseline HER2 expression (IHC), HER2 status (grouped) and HER2 amplification (ISH) for central HER2 testing will also be presented.	NA	Added for clarification.
4.2.4 Prior and concomitant medications and procedures	17Mar2022	'Procedures' removed from the list. Summary of prior medications is removed	NA	Not required for CSR.
4.3 Analysis of efficacy	17Mar2022	The text 'for the ORR endpoint' added after 'All individual efficacy response data will be listed' for clarity.	NA	Clarification of listings to be produced.
	07Feb2023	Text for CEAS may be used for sensitivity analyses on efficacy endpoints is removed.	No	Retrospective central testing result for HER2 mutations will not be available at database lock so will not be included in CSR.
		Added duration of response for patients who have confirmed responses to ORR endpoint listing.	NA	Added for clarification.
4.3.2 Duration of response	17Mar2022	The description of spider plot added.	NA	Additional summary requested.
4.3.3 Best objective response	17Mar2022	The text 'SD for at least 11 weeks' removed since, it will not be presented.	NA	Summary will not be produced.
		Additional analysis is added - exploratory summary of BoR and summary of onset of confirmed response in relation to study treatment.	NA	Additional summaries requested.
	07Feb2023	Additional BoR category of no evidence of disease (NED) will be summarized if applicable for ICR data.	NA	Added for clarification.
4.3.5 Progression-free survival	17Mar2022	Additional analysis is added – summary of the number of patients who received/not received subsequent anti-cancer therapy.	NA	Additional summaries requested.

4.3.6 Overall survival	17Mar2022	The range of 'Duration of follow-up' presented instead of 95%CI.	NA	Correction on what will be presented in summary table.
4.3.7 Sensitivity analysis	17Mar2022	The list of anticipated tumor types is removed and Section 3.5.1 referenced for details of tumor types'.	NA	New text in Section 3.5.1 contains details of tumor types
		Additional subgroups added.	NA	Additional summaries requested.
	07Feb2023	New category added for grouped HER2 mutations.	NA	Additional summaries requested.
		Retrospective central testing data for HER2 mutations will not be summarized for CSR.	No	A change to protocol specified analysis.
		Summary table of DoR presented for subgroups instead of Kaplan Meier plots. Kaplan Meier plot only presented for HER2 mutation grouping.	NA	Due to small group sizes the Kaplan Meier plots are not easily interpreted.
		The text about "CEAS may be used for sensitivity analyses on efficacy endpoints" is removed.	No	A change to protocol specified analysis.
		Removed prior adjuvant/neoadjuvant therapy, prior treatment with taxane chemotherapy, and presence of liver metastasis at baseline from subgroup analyses. Added region, race, and HER2 expression by central testing, and HER2 amplification by central testing to subgroup analyses.	NA	Changes to subgroups requested by clinical team.
		Prior lines of systemic is replaced by Prior regimens of anticancer.	NA	Updated for consistent wording.
		HER2 status (grouped) by central testing is updated to include IHC 0 as a stand alone category andand ISH equivocal results has been added and will be combined with ISH unknown.	NA	Additional summary requested by clinical team.
4.4.1 Adverse events	17Mar2022	Dose modification category added. 'Most common non-serious AEs (frequency of >5%) (in accordance with the requirements of the FDA)' removed.	NA	Additional summaries requested and clarification of other items.

		Clarification that the most common summary tables are by PT only. Details of key patient information listings added. Clarification of maximum CTCAE grade included in AE listings. AE leading to hospitalizations summary removed. Deaths section updated for clarification of summaries.		
		'Adverse events of special interest' section updated as per new AZ standards.	NA	For consistency with project standards
4.4.2 Exposure	17Mar2022	Dose modification and infusion interruptions summary added.	NA	Clarification that these will be summarized.
4.4.3 Laboratory assessments	17Mar2022	The continuous urinalysis variables (pH and specific gravity) are not summarized so any reference to urinalysis is removed.	NA	Continuous summary statistics not required for urinalysis variables.
		The text under the Hy's law section updated to clarify that the elevation in ALT or AST should precede or coincide with (that is, on the same day as) the elevation in total bilirubin.	NA	Clarification on timing of elevations (according to standards).
	07Feb2023	Laboratory parameters in CTC grade shift tables for hematology, clinical chemistry, and coagulation are updated.	NA	Align with laboratory toxicology CTCAE grading
		Removed shift table for categorical urinalysis.	NA	Consistency with data collected.
4.4.4 Electrocardiogram	17Mar2022	An additional summary table for numeric ECG data added.	NA	Additional summaries requested.
4.4.5 Vital Signs and SpO2	17Mar2022	The section heading updated to include SpO2 parameter in addition to the vital signs.	NA	Updated for clarification as SpO2 is not a vital sign.
4.5 Pharmacokinetic data	17Mar2022	Plasma concentration modified to serum concentration.	Yes (V1)	Correction for alignment with CSP
		Summary statistics for PK concentrations include the coefficient of variation and median.	NA	For consistency with project/AZ standards

	17Mar2022	This section updated to reflect the changes of analysis from the protocol.	No	Section added to specify changes from the protocol specified analysis.
6. Changes of analysis from protocol	07Feb2023	Additional update to this section to remove any reference to central testing analyses results for HER2 mutations.	No	Results will not be available at the time of database lock (DBL).
7. Reference	17Mar2022	Literature reference for DLCO conversion added	NA	Updated to include the reference to the DLCO conversion.
8. Appendix	07Feb2023	Added the definition of regions and countries in Appendix A.	NA	Additional text for clarification.

1 STUDY DETAILS

This statistical analysis plan (SAP) contains a detailed description of the analyses in the clinical study protocol (CSP). This SAP is based on version 1.0 (20 July 2020) of the CSP.

1.1 Study objectives

1.1.1 Primary objectives

The primary objectives for this study and the corresponding endpoints/variables are shown in Table 1.

Table 1: Primary study objectives and corresponding endpoints/variables

Objective	Endpoints/variables
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.

HER2, human epidermal growth factor receptor 2; ICR, independent central review; ORR, Objective response rate; RECIST v1.1, Response Evaluation Criteria In Solid Tumors, version 1.1; T-DXd, trastuzumab deruxtecan;

1.1.2 Secondary objectives

The secondary objectives for this study and the corresponding endpoints/variables are shown in Table 2.

Table 2: Secondary study objectives and corresponding endpoints/variables

Objective	Endpoints/variables
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.	

ADAs, Anti-drug antibodies; AEs, Adverse events; DCR, Disease Control Rate; DoR, Duration of response; ECG, electrocardiogram; ECHO, echocardiogram; HER2, Human epidermal growth factor receptor 2; ICR, independent central review; MAAA-1181, deruxtecan; MUGA, multigated acquisition; OS, Overall survival; PFS, Progression free survival; PK, Pharmacokinetic; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SAEs Serious Adverse Events; T-DXd Trastuzumab Deruxtecan;

1.2 Study 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, has proven to be a suitable approach (eg, pembrolizumab, larotrectinib, and entrectinib). The tumor-agnostic study design will facilitate enrollment 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 enrollment 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.

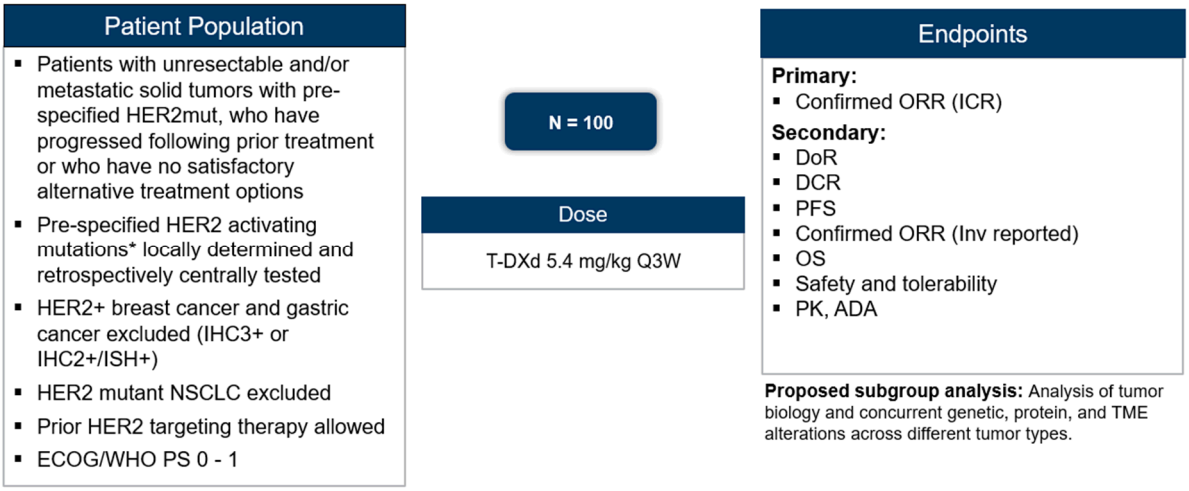
Enrollment in a specific tumor type will be paused after 8 patients with Investigator-assessed measurable disease at baseline have been treated within that tumor type, until a decision has been made on whether to stop enrolment to that tumor type based on the interim futility evaluation. If no confirmed 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 5 for further details.

The primary objective is to determine the confirmed ORR based on independent central review (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 investigational product (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.

An overview of the study design is shown in Figure 1.

Figure 1: Overview of 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 of CSP).

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 Number of patients

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 4 provides the 95% exact CI for a range of possible observed response rates out of 100 patients.

Table 4: Observed ORR and 95% Confidence Interval (CI) out of 100 Patients

Observed ORR (%)	**95% exact CI (%)** N=100
30	(21.2, 40.0)
40	(30.3, 50.3)

Observed ORR (%)	**95% exact CI (%)** N=100
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.

Enrollment 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 enrollment 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, enrollment in that tumor type will be discontinued. See Section 5 for further details.

2 ANALYSIS SETS

2.1 Definition of analysis sets

Five analysis sets are defined in this study. A summary of the analysis sets used for each outcome variable is provided in Table 5.

In a change to protocol specified analyses, the centrally determined-efficacy analysis set (CEAS) will not be used to summarise efficacy data for the CSR, see Section 2.1.3 for further details.

Table 5: 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)

Outcome variable	Populations
Safety Data	
Exposure	Safety Analysis Set
AEs	Safety Analysis Set
Laboratory measurements	Safety Analysis Set
Vital Signs	Safety Analysis Set
PK data	PK Analysis Set
ADA data	Safety Analysis Set (ADA Evaluable 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.

2.1.1 Full analysis set (FAS)

All patients who received at least 1 dose of study treatment. The FAS will be used for all efficacy analyses.

2.1.2 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.

2.1.3 Centrally-determined efficacy analysis set (CEAS)

The protocol defines the CEAS population as: 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.

In a change to the protocol specified analysis, retrospective central testing results for HER2 mutations will not be available at the time of final database lock (DBL) for the study. Therefore, the CEAS population will not be derived and presented for the tables, figures and listings of the CSR. Restrospective central testing for HER2 mutations will be reported separately when available.

2.1.4 Safety analysis set (SAF)

All patients who received at least 1 dose of study treatment.

Patients in the SAF with a non-missing baseline anti-drug antibody (ADA) result and at least one non-missing post-baseline ADA result will form a subset of the SAF, the ADA-evaluable set. All ADA analyses will be based on the ADA-evaluable set.

2.1.5 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.

2.2 Protocol deviations

All important protocol deviations (IPDs) specified in the protocol deviation plan will be programmatically identified within the clinical database by programmed edit checks or via manual validation checks. All IPDs will be summarized and listed in the clinical study report (CSR).

The IPDs deemed applicable to the statistical analysis are:

- Patient was assigned to treatment but did not receive study treatment in error (Deviation code 5.5).
- Patient was assigned to treatment but does not meet the following key inclusion criteria per the CSP (Deviation code 1):
  - Inclusion criteria 3:
    Provision of signed and dated written ICF prior to any mandatory study specific procedures, sampling, or analyses (Deviation code 1.1).
  - Inclusion criteria 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 (Deviation code 1.2).
  - Inclusion criteria 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 (Deviation code 1.3).
  - Inclusion criteria 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 (Deviation code 1.4).

  - Inclusion criteria 8:
    Has measurable target disease assessed by the Investigator based on RECIST v1.1 (Deviation code 1.5).
  - Inclusion criteria 9:
    Has an World Health Organization(WHO)/Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Deviation code 1.6).
- Patient was assigned to treatment but does not meet the following key exclusion criteria per the CSP (Deviation code 2):
  - Exclusion criteria 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 o) 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 (Deviation code 2.1).
  - Exclusion criteria 2:
    HER2 mutant NSCLC (Deviation code 2.2).
  - Exclusion criteria 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 (Deviation code 2.3).
  - Exclusion criteria 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 chronic obstructive pulmonary disease (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 (Deviation code 2.4).
  - Exclusion criteria 17:
    Patients participating in a concurrent interventional clinical study and/or previously treated with T-DXd (Deviation code 2.5).
- Baseline RECIST scan > 42 days before the date of first dose of IP (based upon a 28-day screening period plus 2 weeks allowance, so that only serious violators are identified) (Deviation code 7.1).
- No baseline RECIST v1.1 assessment on or before the date of first dose of IP (Deviation code 7.2).
- Patient received concomitant medication defined as prohibited in the CSP (Deviation code 6.1).

- Patient received their assigned study treatment at an incorrect dose (Deviation code 5.2).

The deviation codes mentioned above correspond to deviation codes from the protocol deviation plan of the study.

Deviation code 5.5 would lead to exclusion from the analysis sets described in Section 2.1. Failure to meet inclusion criteria 8 under Deviation code 1 would lead to exclusion from the MDAS. If any deviation is considered to have an impact upon PK, a patient or particular data for a patient may be excluded from the PK analysis set. None of the other deviations will lead to patients being excluded from the analysis sets.

Any other deviations from monitoring notes or reports will be reported in an appendix to the CSR.

2.3 Monitoring of important protocol deviations

The IPDs will be programmatically identified within the clinical database by programmed edit checks or via manual validation checks. A programmatically derived IPD report will be created listing all identified IPDs and the data used to identify them. This report will be reviewed at regular IPD review meetings held on at least a monthly basis. At this meeting, programmatically derived IPDs will be checked to ensure they have been correctly classified.

On an ongoing basis throughout the study, monitoring notes or summaries will be reviewed to determine any important post-entry deviations that are not identifiable via programming.

The final classification of IPDs will be made prior to DBL.

3 PRIMARY AND SECONDARY VARIABLES

3.1 Derivation of RECIST visit responses

For all patients, the RECIST tumor response data will be used to determine each patient's visit response according to RECIST version 1.1 (Appendix F of the CSP). It will also be used to determine if and when a patient has progressed in accordance with RECIST and their best objective response to study treatment.

Baseline radiological tumor assessments are to be performed no more than 28 days before the start of study treatment and should be performed as close as possible to the start of study treatment. Post-baseline tumor assessments by the Investigator will be performed at the following time points:

- Every 6 weeks (± 1 week) relative to the date of first dose of IP until RECIST v1.1-defined radiological disease progression

- Tumor assessment scans will continue if patients discontinue IP due to toxicity without progression until PD is detected.

If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimize any unintentional bias caused by some patients being assessed at a different frequency than other patients.

From the investigator's review of the imaging scans, the RECIST tumor response data will be used to determine each patient's visit response according to RECIST version 1.1. At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD or PD, using the information from target lesions (TLs), non-target lesions (NTLs) and new lesions and depending on the status of their disease compared with baseline and previous assessments. 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.

Please refer to Sections 3.1.1, 3.1.2 and 3.1.3 for the definitions of CR, PR, SD and PD.

RECIST outcomes (i.e. ORR, PFS etc.) will be calculated programmatically using the site investigator data (see Section 3.2) from the overall visit responses.

3.1.1 Target lesions (TLs) – site investigator data

Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is ≥ 10 mm in the longest diameter (LD), (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements. A patient can have a maximum of five measurable lesions recorded at baseline with a maximum of two lesions per organ (representative of all lesions involved and suitable for accurate repeated measurement) and these are referred to as target lesions (TLs). If more than one baseline scan is recorded then measurements from the scan that is closest and prior to first dose of IP will be used to define the baseline sum of TLs. On occasion, the largest lesion may not lend itself to reproducible measurement. In such cases the next largest lesion, which can be measured reproducibly, should be selected.

All other lesions (or sites of disease) not recorded as TL should be identified as non-target lesions (NTLs) at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits.

Note: For patients who do not have measurable disease at entry (i.e. no TLs) but have non-measurable disease, evaluation of overall visit responses will be based on the overall NTL assessment and the absence/presence of new lesions (see Section 3.1.3 for further details). If a

patient does not have measurable disease at baseline then the TL visit response will be not applicable (NA).

Table 6: TL Visit Responses (RECIST 1.1)

Visit Responses	Description
Complete response (CR)	Disappearance of all TLs. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters as long as criteria for PD are not met.
Progressive disease (PD)	A ≥ 20% increase in the sum of diameters of TLs and an absolute increase of ≥ 5mm, taking as reference the smallest sum of diameters since treatment started including the baseline sum of diameters.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Not evaluable (NE)	Only relevant in certain situations (i.e. if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit; and scaling up could not be performed for lesions with interventions). Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response.
Not applicable (NA)	No TLs are recorded at baseline.

CR, Complete response; NA, Not applicable; NE, Not evaluable; PD, Progression of disease; PR, Partial response; SD, stable disease; TL Target lesion.

Rounding of TL data

For calculation of PD and PR for TLs percentage changes from baseline and previous minimum should be rounded to one decimal place (d.p.) before assigning a TL response. For example 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%.

Missing TL data

For a visit to be evaluable all TL measurements need to be recorded. However, a visit response of PD should still be assigned if any of the following occurred:

- A new lesion is recorded
- A NTL visit response of PD is recorded

- The sum of TLs is sufficiently increased to result in a 20% increase, and an absolute increase of ≥ 5mm, from nadir even assuming the non-recorded TLs have disappeared

Note: the nadir can only be taken from assessments where all the TLs had a LD recorded.

If there is at least one TL measurement missing and a visit response of PD cannot be assigned, the visit response is NE.

If all TL measurements are missing then the TL visit response is NE. Overall visit response will also be NE, unless there is a progression of non-TLs or new lesions, in which case the response will be PD.

Lymph nodes
Lymph nodes whose size reduces to < 10mm are considered non-pathological. However, a size will still be given and this size should still be used to determine the TL visit response as normal. In the special case where all lymph nodes are < 10mm and all other TLs are 0mm then although the sum may be > 0mm the calculation of TL response should be over-written as a CR.

TL visit responses subsequent to CR
Only CR, PD or NE can follow a CR. If a CR has occurred then the following rules at the subsequent visits must be applied:

- Step 1: If all lesions meet the CR criteria (i.e. 0mm or < 10mm for lymph nodes) then response will be set to CR irrespective of whether the criteria for PD of TL is also met i.e. if a lymph node LD increases by 20% but remains < 10mm.

- Step 2: If some lesion measurements are missing but all other lesions meet the CR criteria (i.e. 0mm or < 10mm for lymph nodes) then response will be set to NE irrespective of whether, when referencing the sum of TL diameters, the criteria for PD are also met.

- Step 3: If not all lesions meet the CR criteria (i.e. at least one pathological lymph node selected as TL has short axis ≥ 10mm and an absolute increase of ≥ 5mm, taking as reference the smallest short axis for the same TL since treatment started including the baseline or the reappearance of previously disappeared lesion) or a new lesion appears, then response will be set to PD.

- Step 4: If after steps 1 – 3 a response can still not be determined the response will be set to remain as CR.

TL too big to measure

If a TL becomes too big to measure this should be indicated in the database and a size ('*x*') above which it cannot be accurately measured should be recorded. If using a value of *x* in the calculation of TL response would not give an overall visit response of PD, then this will be flagged and reviewed by the study team. It is expected that a visit response of PD will remain in the vast majority of cases.

TL too small to measure

If a TL becomes too small to measure then this will be indicated as such on the case report form and a value of 5mm will be entered into the database and used in TL calculations. However a smaller value may be used if the radiologist has not indicated 'too small to measure' on the case report form and has entered a smaller value that can be reliably measured. If a TL response of PD results (at a subsequent visit) then this will be reviewed by the study team.

Irradiated lesions/lesion intervention

Previously irradiated lesions (i.e. lesion irradiated prior to entry into the study) should be recorded as NTLs and should not form part of the TL assessment.

Any TL (including lymph nodes), which has had intervention during the study (for example, irradiation / palliative surgery / embolisation), should be handled in the following way. Once a lesion has had intervention then it should be treated as having intervention for the remainder of the study noting that an intervention will most likely shrink the size of tumors:

- Step 1: the diameters of the TLs (including the lesions that have had intervention) will be summed and the calculation will be performed in the usual manner. If the visit response is PD, this will remain as a valid response category.

- Step 2: If there was no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing and if ≤ 1/3 of the TLs have missing measurements then scale up as described in the 'Scaling' section below. If the scaling results in a visit response of PD then the patient would be assigned a TL response of PD.

- Step 3: If, after both steps, PD has not been assigned, then, if appropriate (i.e. if ≤ 1/3 of the TLs have missing measurements), the scaled sum of diameters calculated in step 2 should be used, and PR or SD then assigned as the visit response. Patients with intervention are evaluable for CR as long as all non-intervened lesions are 0 (or <10mm for lymph nodes) and the lesions that have been subject to intervention have a value of 0 (or <10mm for lymph nodes) recorded. If scaling up is not appropriate due to too few non-missing measurements then the visit response will be set as NE.

At subsequent visits, the above steps will be repeated to determine the TL and overall visit response. When calculating the previous minimum, lesions with intervention should be treated as missing and scaled up (as per step 2 above).

Scaling (applicable only for irradiated lesions/lesion intervention)
If > 1/3 of TL measurements are missing (because of intervention) then the TL response will be NE, unless the sum of diameters of non-missing TL would result in PD (i.e. if using a value of 0 for missing lesions, the sum of diameters has still increased by 20% or more compared to nadir and the sum of TLs has increased by ≥5mm from nadir).

If ≤ 1/3 of the TL measurements are missing (because of intervention) then the results will be scaled up (based on the sizes at the nadir visit to give an estimated sum of diameters) and this will be used in calculations; this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the nadir sum of diameters excluding the lesions with missing measurements.

Example of scaling
Lesion 5 is missing at the follow-up visit; the nadir TL sum including lesions 1-5 was 74 mm.

The sum of lesions 1-4 at the follow-up is 68 mm. The sum of the corresponding lesions at the nadir visit is 62 mm.

Scale up as follows to give an estimated TL sum of 81 mm:

68 x 74 / 62 = 81 mm

CR will not be allowed as a TL response for visits where there is missing data. Only PR, SD or PD (or NE) could be assigned as the TL visit response in these cases. However, for visits with ≤1/3 lesion assessments not recorded, the scaled up sum of TLs diameters will be included when defining the nadir value for the assessment of progression.

Lesions that split in two
If a TL splits in two, then the LDs of the split lesions should be summed and reported as the LD for the lesion that split.

Lesions that merge
If two TLs merge, then the LD of the merged lesion should be recorded for one of the TL sizes and the other TL size should be recorded as 0mm.

Change in method of assessment of TLs
CT and MRI are the only methods of assessment that can be used within this trial. If a change in method of assessment occurs between CT and MRI, this will be considered acceptable and no adjustment within programming is needed.

If a change in method involves clinical examination (e.g. CT changes to clinical examination or vice versa), any affected lesions should be treated as missing.

3.1.2 Non-target lesions (NTLs) and new lesions – site investigator data.

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, the investigator should record an overall assessment of the NTL response. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

NTL response will be derived based on the investigator's overall assessment of NTLs as follows:

Table 7: NTL Visit Responses

Visit Responses	Description
Complete response (CR)	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10 mm short axis).
Progressive disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Non-CR/Non-PD	Persistence of one or more NTLs with no evidence of progression.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For 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 there are no NTLs at baseline.

CR, Complete response; NA, Not applicable; NE, Not evaluable; NTL, Non-target lesion; PD, Progression of disease; PR, Partial response; TL Target lesion.

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 the presence of SD or PR in TLs, the overall tumor burden has increased sufficiently to merit a determination of disease progression. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor.

New lesions will be identified via a Yes/No tick box. The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses.

A new lesion indicates progression so the overall visit response will be PD irrespective of the TL and NTL response.

If the question 'Any new lesions since baseline' has not been answered with Yes or No and the new lesion details are blank this is not evidence that no new lesions are present, but should not overtly affect the derivation.

Symptomatic progression is not a descriptor for progression of NTLs: it is a reason for stopping study therapy and will not be included in any assessment of NTLs.

Patients with 'symptomatic progression' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumor assessments where possible until objective disease progression is observed.

3.1.3 Overall visit response – site investigator data

Table 8 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 8: Overall visit response

TARGET	NON-TARGET	NEW LESIONS	OVERALL VISIT RESPONSE
CR	CR or NA	No (or NE)	**CR**
CR	Non-CR/Non-PD or NE	No (or NE)	**PR**
PR	Non-PD or NE or NA	No (or NE)	**PR**
SD	Non-PD or NE or NA	No (or NE)	**SD**
PD	Any	Any	**PD**
Any	PD	Any	**PD**
Any	Any	Yes	**PD**
NE	Non-PD or NE or NA	No (or NE)	**NE**

TARGET	NON-TARGET	NEW LESIONS	OVERALL VISIT RESPONSE
NA	CR	No (or NE)	**CR**
NA	Non-CR/Non-PD	No (or NE)	**SD**
NA	NE	No (or NE)	**NE**

CR, Complete response; NA, Not applicable; NE, Not evaluable; PD, Progression of disease; PR, Partial response; SD, stable disease; TL Target lesion.

3.1.4 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 (i.e., two reviewers review the scans and adjudication is performed by a separate reviewer in case of a disagreement). For each patient, the ICR will define the overall visit response (i.e. the response obtained overall at each visit by assessing TLs, NTLs and new lesions) data and the relevant scan dates for each timepoint (ie, for visits where response or progression is/is not identified). (For patients with TLs at baseline: CR, PR, SD, PD, NE; for patients with NTLs only: CR, SD, PD, NE; for patients with no disease identified at baseline: PD, no evidence of disease [NED], NE). 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). No programmatic derivation of visit response is necessary. RECIST assessments/scans contributing towards a particular visit may be performed on different dates and for the central review the date of progression for each reviewer will be provided based on the earliest of the scan dates of the component that triggered the progression.

Adjudication is triggered by any difference in overall timepoint response between the two primary reviewers. If adjudication is performed, the reviewer that the adjudicator agreed with will be selected as a single reviewer (note in the case of more than one review period, the latest adjudicator decision will be used). In the absence of adjudication, the records for all visits for a single reviewer will be used. The reviewer selected in the absence of adjudication will be the reviewer who read the baseline scan first. The records from the single selected reviewer will be used to report all ICR RECIST information including dates of progression, visit response, censoring and changes in target lesion dimensions. Endpoints (of ORR, PFS, DoR, etc.) will be derived programmatically from this information.

Results of this independent review will not be communicated to investigators and the management of patients will be based solely upon the results of the RECIST 1.1 assessment conducted by the investigator.

An ICR for all patients will be performed prior to database lock, covering all scans up to the DCO.

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

3.2 Efficacy variables

RECIST v1.1-based efficacy 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.

For the purposes of the efficacy variables described below, radiotherapy is not considered a subsequent anti-cancer therapy unless otherwise specified.

3.2.1 Objective response rate (ORR)

The primary endpoint is confirmed ORR assessed by the ICR per RECIST v1.1 across all tumor types. Confirmed ORR is defined as the proportion of patients who have a confirmed CR or PR, as determined by ICR per RECIST v1.1 and will be based upon all patients in the FAS.

A secondary endpoint is defined as confirmed ORR assessed by the Investigator per RECIST v1.1. Confirmed ORR is defined as the proportion of patients who have a confirmed CR or PR, as determined by the Investigator per RECIST v1.1 and will be based upon all patients in the FAS.

As a sensitivity analysis, confirmed ORR by ICR will also be defined using the ICR data to define a confirmed response of CR or PR, with the denominator defined as a subset of the FAS with measurable disease at baseline per ICR. If the selected reviewer did not consider that a patient had measurable disease then this patient should not contribute to the denominator.

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 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 anti-cancer therapy and then respond will not be included as responders in the ORR (i.e. both visits contributing to a response must be prior to subsequent therapy for the patient to be considered as a responder).

If a patient has two non-consecutive visit responses of PR, then, as long as the time between the 2 visits of PR is greater than 4 weeks and there is no PD between the PR visits, the patient will be defined as a responder. Similarly, if a patient has visit responses of CR, NE, CR, then, as long as the time between the 2 visits of CR is greater than 4 weeks, then a best response of CR will be assigned.

3.2.2 Duration of response (DoR)

DoR according to ICR and Investigator per RECIST 1.1 will be derived programmatically.

DoR will be defined as the time from the date of first documented response (which is subsequently confirmed) until date of documented progression or death in the absence of disease progression (i.e. date of PFS event or censoring – date of first response + 1). The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit that was CR or PR that was subsequently confirmed.

If a patient does not progress following a response, then their DoR will use the PFS censoring time (Section 3.2.5).

3.2.3 Best Objective Response (BoR)

BoR according to ICR and Investigator per RECIST 1.1 will be derived programmatically.

BoR is calculated based on the overall visit responses from each RECIST assessment, described in Section 3.1.3. It is the best response a patient has had following first dose of IP, but prior to starting any subsequent cancer therapy and up to and including RECIST progression or the last evaluable assessment in the absence of RECIST progression. Categorization of BoR will be based on RECIST using the following response categories: CR, PR, SD, PD and NE.

CR or PR must be confirmed. For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment will be used. SD should be recorded at least 6 weeks minus 1 week, i.e. at least 5 weeks (to allow for an early assessment within the assessment window), after first dose of IP. For CR/PR, the initial overall visit assessment that showed a response will use the latest of the dates contributing towards a particular overall visit assessment.

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

For patients whose progression event is death, BoR will be calculated based upon all evaluable RECIST assessments prior to death.

For patients who die with no evaluable RECIST assessments, if the death occurs ≤ 13 weeks (i.e. 12 weeks + 1 week to allow for a late assessment within the assessment window) after first dose of IP, then BoR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST assessments, if the death occurs > 13 weeks after first dose of IP then BoR will be assigned to the NE category.

In addition, an exploratory endpoint of BoR including unconfirmed responses (unconfirmed CR or unconfirmed PR) will be derived following the rules above (where applicable), but the CR or PR will not require confirmation to be included as a response.

For the exploratory endpoint of BoR including unconfirmed responses, if a patient has a confirmed PR but also has an unconfirmed CR then the patient will be included with a BoR of unconfirmed CR.

3.2.4 Disease Control Rate (DCR)

DCR according to ICR and Investigator per RECIST 1.1 will be derived programmatically.

DCR at 6 weeks is defined as the percentage of patients who have a best objective response of confirmed CR or PR, or who have SD (without subsequent cancer therapy), for at least 5 weeks after first dose of IP (to allow for an early assessment within the assessment window).

DCR at 12 weeks is defined as the percentage of patients who have a best objective response of confirmed CR or PR, or who have SD (without subsequent cancer therapy), for at least 11 weeks after first dose of IP (to allow for an early assessment within the assessment window).

However, any visit response which occurred after initiation of subsequent cancer therapy will not be included in the derivation of best overall response used to calculate DCR.

3.2.5 Progression free survival (PFS)

PFS according to ICR and Investigator per RECIST 1.1 will be derived programmatically.

PFS is defined as the time from first dose of IP until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from assigned therapy or receives another anti-cancer therapy prior to progression (i.e. date of PFS event or censoring – date of first dose + 1).

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 assessment. However, if the patient progresses or dies immediately after two or more consecutive missed visits, the patient

will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the two missed visits (Note: NE visit is not considered as missed visit).

Given the scheduled visit assessment scheme (i.e. every 6 weeks from the first dose of study drug), the definition of two missed visits will be as follows:

- If the previous RECIST assessment <= day 35 then two missing visits will equate to 13 weeks (2 x 6 weeks + 1 week for a late assessment)

- If the previous RECIST assessment > day 35 then two missing visits will equate to 14 weeks (2 x 6 weeks + 1 week for an early assessments + 1 week for a late assessment)

If a patient has no evaluable post-baseline visits or does not have baseline data, they will be censored at Day 1 unless they die within two visits of baseline (12 weeks plus 1 week allowing for a late assessment within the visit window), then they will be treated as an event with date of death as the event date.

The PFS time will always be derived based on scan/assessment dates and not visit dates.

RECIST 1.1 assessments/scans contributing toward a particular visit may be performed on different dates. The following rules will be applied:

- For ICR assessments, the date of progression will be determined based on the earliest of the scan dates of the component that triggered the progression for the adjudicated reviewer selecting PD or of the reviewer who read baseline first if there is no adjudication for ICR data.

- For investigator assessments, the date of progression will be determined based on the earliest of the RECIST 1.1 assessment/scan dates of the component that indicates progression. If a new lesion is equivocal and it is subsequently assessed as unequivocal, then the progression date will be determined using the date of the initial scan when the equivocal lesion was first detected.

- For both ICR and investigational assessments, when censoring a patient for PFS, the patient will be censored at the latest of the scan dates contributing to a particular overall visit assessment.

Note: for TLs, only the latest scan date is recorded out of all scans performed at that assessment for the TLs, and similarly for NTLs, only the latest scan date is recorded out of all scans performed at that assessment for the non-target lesions.

At the final DBL for the study, patients who are ongoing in the study will be instructed to complete the Disposition (DS, study withdrawal) case report form (CRF) with a subject status

of completed. This is to assist in Data Management (DM) tasks. These patients will be considered as progression free at the time of the analysis.

3.2.6 Overall survival (OS)

OS is defined as the time from the date of first dose of IP until death due to any cause regardless of whether the patient withdraws from therapy or receives another anti-cancer therapy (i.e. date of death or censoring – date of first dose + 1). 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 (SUR_DAT, recorded within the SURVIVE module of the electronic case report form (eCRF)).

Note: Survival calls will be made in the week following the date of data cut-off (DCO) for the analysis, and if patients are confirmed to be alive or if the death date is post the DCO date these patients will be censored at the date of DCO. The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of the final OS analysis should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patient's general practitioner and checking publicly-available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

Note: For any OS analysis performed prior to the final OS analysis, in the absence of survival calls being made, it may be necessary to use all relevant eCRF fields to determine the last recorded date on which the patient was known to be alive for those patients still on treatment (since the SURVIVE module is only completed for patients off treatment if a survival sweep is not performed).

If a patient is known to have died where only a partial death date is available then the date of death will be imputed as the latest of the last date known to be alive +1 from the database and the death date using the available information provided:

a. For Missing day only – using the 1st of the month

b. For Missing day and Month – using the 1st of January

If there is evidence of death but the date is entirely missing, it will be treated as missing, i.e. censored at the last known alive date.

3.3 Safety variables

3.3.1 Treatment exposure

Total (or intended) exposure
The total (or intended) exposure is the intended treatment duration (days) of a patient and is calculated using the start and stop dates of the drug and the intended dosing interval. The intended treatment duration is calculated as the number of days from date A to date B (i.e., B – A + 1) where

- A is the date of first dose of the study drug in the dosing period
- B is the earliest of:
    - The date of death
    - The date of DCO, and
    - The date when the last non-zero dose of the study drug was received (e.g. >0 mg of T-DXd) plus 20 (the scheduled number of days between doses minus one).

Actual exposure
Actual exposure is defined as the actual treatment duration (days) and will be calculated as follows:

- Actual treatment duration = intended treatment duration (days) – total duration of dose delays (days), where intended treatment duration will be calculated as above.

Since patients will receive T-DXd via IV infusion q3w (±3 days), the total duration of dose delays (for deriving actual exposure) will be calculated as follows:

Total duration of dose delays = sum for all dosing dates of positive values of [date of the dose – date of the previous dose – (21+3) days].

Dose modifications are permitted and the calculation of actual treatment duration makes no adjustment for any dose modifications that may have occurred.

Number of treatment cycles received
Exposure will also be measured by the number of treatment cycles received. A cycle corresponds to a period of 21 days. If a cycle is prolonged due to toxicity, this should still be counted as one cycle. A cycle will be counted if treatment is started even if the full dose is not delivered.

Delays, reductions and interruptions

Treatment dose delays and dose reductions are measured for study treatment. The number of infusion interruptions is also calculated.

A dose delay is indicated by a response of Yes to the treatment cycle delayed question. A dose reduction is indicated by a response of 'Dose reduced' for Action taken, study drug. An infusion interruption is indicated by a response of 'Drug interrupted' for Action taken, study drug. This is when the study drug administration is temporarily stopped for some time interval i.e. if there is an infusion interruption that occurs during the infusion.

A dose modification is defined as either a dose delay and/or a dose reduction.

Safety follow-up

- Total Safety Follow-up = min((last dose date + 47), date of withdrawal of main informed consent, date of death, date of DCO) – first dose date +1

3.3.2 Dose intensity

Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation. RDI will be defined as follows:

RDI = 100% * d/D, where:

- d is the actual cumulative dose delivered up to the actual last day of dosing for that drug, and
- D is the total dose of that drug that would be delivered, if there were no modifications to dose or schedule.

When deriving actual dose administered, the volume before and after infusion will also be considered. Such that for each dose received:

Actual dose = actual dose per administration * proportion of actual dose administrated, where the proportion of the actual dose administered will be calculated as (Volume before infusion - volume after infusion)/Volume before infusion.

For T-DXd, RDI calculations use doses measured in dose units of mg.

For the calculation of the intended dose the +/- 10% weight adjustment will be applied, by which the latest weight measurement (before dosing) will be considered in the calculation if it differs by at least 10% from the previous weight used in the calculation. The weight at screening (baseline) will be used to initially calculate the dose.

When accounting for the calculation of intended cumulative dose, 3 days should be added to the date of last dose to reflect the protocol allowed window for dosing.

3.3.3 Adverse events

AEs and SAEs will be collected throughout the study, from date of informed consent throughout the treatment period and including the safety follow-up (40 (+7) days after the discontinuation of IP). 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 (+7) days after the last dose of IP), but without further recording in the eCRF. Suspected ILD/pneumonitis cases will be followed up and recorded in the eCRF until resolution.

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

A treatment emergent adverse event (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 the last dose of study drug.

For adverse event reporting (see Section 4.4.1), AE summary tables will include TEAEs that occurred up to 47 days after last dose of study drug or before the initiation of first subsequent anti-cancer therapy following discontinuation of study treatment (whichever occurs first).

The Medical Dictionary for Regulatory Activities (MedDRA) (latest or current MedDRA version) will be used to code the AEs. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI CTCAE) version 5.0.

Missing start and stop dates for AEs will be handled using the rules described in Section 3.6.2.

Adverse events of special interest (AESI)
An AESI is an AE of scientific and medical interest specific to understanding of the study treatment and may require close monitoring. An AESI may be serious or non-serious.

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, interstitial lung disease (ILD)/pneumonitis and left ventricular ejection fraction (LVEF) decrease are considered to be AESIs.

AESIs will be identified based on MedDRA preferred terms (PTs). Preferred terms used to identify AESIs will be listed before DBL and documented in the Trial Master File.

An ILD adjudication committee and charter will also be established to review all cases of potential ILD/pneumonitis. To ensure adequate and relevant evaluation, additional data may

be collected to fully characterize medical history (e.g., smoking, radiation and pulmonary history), diagnostic evaluation, treatment and outcome of the event.

Other significant adverse events (OAE)
During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and 'Discontinuation of Investigational Product due to Adverse Events' (DAEs). Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious) or significant additional treatment.

3.3.4 Laboratory measurements

Blood and urine samples for the determination of clinical chemistry, hematology, coagulation and urinalysis will be collected as described in Section 8.2.9 of the CSP.

For the derivation of baseline and post-baseline visit values, the rules described in Section 3.6 of this document considering definition of baseline, visit windows and how to handle multiple records will be used.

Change from baseline in hematology and clinical chemistry variables will be calculated for each post-dose visit. National Cancer Institute (NCI) Common Terminology Criteria (CTC) grades will be defined at each visit according to the CTC grade criteria using project ranges, after conversion of lab result to corresponding project-wide preferred units. The following parameters have CTC grades defined for both high and low values: potassium, sodium, magnesium and corrected calcium so high and low CTC grades will be calculated.

Absolute values will be compared to the project reference range and classified as low (below range), normal (within range or on limits of range), and high (above range).

The maximum or minimum value (depending on the direction of an adverse effect) will be defined for each laboratory parameter as the maximum (or minimum) post-dose value at any time.

Local reference ranges will be used for the primary interpretation of laboratory data at the local laboratory. Project reference ranges will be used for reporting purposes.

The denominator used in laboratory abnormality summaries will include only evaluable patients (i.e., those who had sufficient data to have the possibility of an abnormality). For example:

- If an abnormality criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value recorded.
- If an abnormality criterion does not consider changes from baseline to be evaluable, the patient need only have 1 post-dose value recorded.

Analysis of Total Calcium per NCI CTC criteria
As applicable, values will be converted to standard units and will be graded using CTC v5.0. Corrected calcium(mmol/L) records will be programmatically derived from Total Calcium and Albumin and appended to the lab dataset for grading.

Corrected calcium product will be derived using the following formula:

Corrected calcium (mmol/L) = Total calcium (mmol/L) + ([40 – albumin (G/L)] × 0.02)

3.3.5 Physical examinations

Physical examinations will be performed as described in Section 8.2.2 of the CSP. Abnormalities recorded prior to the first dose of study treatment will be recorded as part of the patient's baseline signs and symptoms. Abnormalities first recorded after first dose of study treatment will be recorded as AEs unless unequivocally related to the disease under study.

3.3.6 Ophthalmologic assessments

Opthalmologic assessments including visual acuity testing, slit lamp examination and fundoscopy will be performed at screening and end of treatment (EOT), and as clinically indicated.

3.3.7 Electrocardiograms

Resting 12-lead electrocardiograms (ECGs) will be recorded at screening, before Cycle 1 infusion (within 3 days of administration), and then every 4 cycles, if an abnormality is detected, and at EOT as described in Section 8.2.4 of the CSP. ECGs will be obtained in triplicate at screening and subsequent ECGs will be performed in triplicate if an abnormality is noted.

The following ECG variables will be collected: heart rate, RR interval, PR interval, QT interval, QTcF interval, QRS duration, and an overall evaluation.

The overall evaluation of an ECG will either be "normal", "abnormal" or "borderline", with abnormalities categorized as either "clinically significant" or "not clinically significant".

Triplicate ECGs will be handled according to the following approach:

- The mean of the 3 ECG assessments will be used to determine the values of ECG parameters at that time point.
- The worst overall evaluation will be used to determine the overall ECG evaluation at that time point.
- For the derivation of baseline and of post-baseline visit values, the triplicate ECG will be considered as a single assessment with date/time equal to the earliest date/time of the 3 ECGs.

Where QTcF (Fridericia) is not collected, it will be calculated programmatically using the reported ECG values (RR and QT) as follows (where RR are in seconds):

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

Alternatively, RR (or QT) can be programmatically derived if not collected but QTcF and QT (or RR, respectively) is collected. RR can be calculated as follows:

$$RR = \left(\frac{QT}{QTcF}\right)^3$$

The following relationship between RR and heart rate (with RR expressed in seconds and heart rate in bpm) will be used to derive programmatically the missing parameter in case only one of these variables is available:

$$\text{RR} = \frac{60}{\text{heart rate}}$$

Where ECG parameters are calculated programmatically these will also be used (alongside collected ECG parameters) when determining the mean of ECG assessments if applicable.

3.3.8 Echocardiograms/multiple gated acquisition scans and LVEF

Echocardiograms/multiple gated acquisition (ECHO/MUGA) scans will be performed as described in Section 8.2.5 of the CSP. These will be used to assess the LVEF. The LVEF % and method details will also be reported. Change from baseline of LVEF % will be calculated.

3.3.9 Vital signs and SpO_2

The following vital signs will be measured as described in Section 8.2.3 of the CSP: Systolic and diastolic blood pressure (BP), pulse rate, temperature, respiration rate and Saturation of peripheral oxygen (SpO_2). Body weight will also be recorded along with vital signs.

For the derivation of baseline and post-baseline visit values, the definitions and rules described in Section 3.6 for visit windows, and how to handle multiple records will be used.

3.3.10 World Health Organization/Eastern Cooperative Oncology Group performance status

World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status (PS) will be assessed as described in Section 8.2.6 of the CSP as the following:

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

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

2. Ambulatory and capable of self-care, but unable to carry out any 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

3.3.11 Additional safety assessments

If interstitial lung disease (ILD) is suspected, additional assessments are performed as described in the CSP.

3.3.11.1 Pulmonary function test

Pulmonary function test (PFT) results will be collected at screening for all patients and if ILD/pneumonitis is suspected. The following parameters will be measured: diffusing capacity of the lungs for carbon monoxide (DLCO) (if feasible), SPO_2, whether the patient has received oxygen treatment, oxygen treatment start and stop dates and method provided, forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1% predicted, FVC % predicted, peak expiratory flow (PEF), forced expiratory volume in 6 seconds (FEV6), total lung capacity (TLC), FEV1/FVC ratio.

DLCO
DLCO may be collected in units of mmol/kPa x min, mL/min/mmHg and %. Data are collected as 3 separate variables.

No derivations/conversions will be performed for DLCO with units %.

If DLCO data is collected for both mmol/kPa x min and mL/min/mmHg the values will be used as reported in the CRF. If DLCO data is collected for only mmol/kPa x min or mL/min/mmHg the following data will be derived (Graham et al 2017):

- *DLCO (mmol/kPa x min) multiplied by 2.987 = DLCO (mL/min/mmHg)*
- *DLCO (mL/min/mmHg) divided by 2.987 = DLCO (mmol/kPa x min)*

3.3.11.2 High resolution CT scan

An overview of the high resolution CT (HRCT) radiological findings will be collected at screening for all patients and if ILD/pneumonitis is suspected.

3.3.11.3 Laboratory measurements

If ILD/pneumonitis is suspected, the following laboratory measurements will be collected: Sialylated Carbohydrate Antigen KL-6, Surfactant Protein A, 1,3-Beta-D-Glucan, C-Reactive Protein, Lactate Dehydrogenase, Carcinoembryonic Antigen, Surfactant Protein D, Surfactant Protein D.

Further ILD/pneumonitis assessments that may be conducted include broncho-alveolar lavage (BAL) examinations, analytes testing and collection of ILD/pneumonitis symptoms and findings as per the ILDIS eCRF form.

3.4 Pharmacokinetic variables

Pharmacokinetic concentration data will be collected as described in Section 8.5.1 of the CSP.

3.5 Other variables

3.5.1 Baseline characteristics

Baseline characteristics that will be collected or derived are:

- Demographics: Age (years), sex, race and ethnicity.
- Patient characteristics: Weight, height and body mass index (BMI)
    - BMI will be calculated as: weight (kg)/height $(m)^2$.
- Disease characteristics at initial diagnosis: Diagnosis date, primary tumor location, primary tumor laterality, primary tumor type, histology type, tumor grade, TNM classification, American Joint Committee on Cancer (AJCC) staging
- WHO/ECOG performance status

- Extent of disease upon entry to study: Stage (locally advanced, metastatic, both) and site of local/metastatic disease, recent progression date, evaluation method, radiological assessment

- Medical history: Name of past and/or concomitant diseases (verbatim and coded using the latest or current version of the MedDRA dictionary), start and stop dates

- Relevant surgical history: Surgical procedure (verbatim and coded using the latest or current version of the MedDRA dictionary) and date of surgery

- Relevant pulmonary medical history: pulmonary medical history condition and response

- Prior radiotherapy: Site/region treated location, treatment setting, site/region laterality, radiotherapy technique, start and stop dates

- Prior cancer therapy: Therapy class, agent route of administration, number of cycles, treatment status, best response, start and stop dates

- Pregnancy status and report for applicable patients only: Test date and result (positive or negative)

- Nicotine use: category (current, former or never), type of substance, current substance use specification, start and stop dates

Tumor Types

Patients are grouped into 'tumor type' categories as part of the screening process. Tumor type categories on the GROUP eCRF include breast, colorectal, urothelial, esophagogastric, hepatobiliary, small cell lung, endometrial, melanoma, ovarian, cervical, head and neck squamous cell carcinoma, salivary gland/head and neck adenocarcinoma, pancreatic, cutaneous squamous-cell carcinoma, adenocarcinoma of unknown primary, soft tissue sarcoma, other neuroendocrine tumors, prostate, peripheral nerve cell tumors, germ cell tumors, renal cell carcinoma, thyroid cancer, squamous anogenital tumors and small intestinal adenocarcinoma. Additional tumor type groups may be added as necessary (added, following medical review, to the tumor type groups available to select in the IRT system during screening).

Tumor type categories will be reported based on data recorded on the GROUP eCRF. For additional categories created in IRT during the study these will be specified as 'Other' on the GROUP form and further details to specify the tumor type category will be collected as free text (in the variable RAW.GROUP.ASMGROTH). These further details will be used as the

tumor type category when 'Other' is selected (hence 'Other' will not be the tumor type for these patients). The GROUP eCRF data will be checked as part of the data cleaning process against the tumor type selected in the IRT system at treatment assignment to ensure consistency.

3.5.2 Prior and concomitant medications and procedures

All therapies (drug and non-drug), including herbal preparations, whether prescribed or over-the-counter, that are used during the study will be recorded on the eCRF. Details include generic and/or brand names of the medications, World Health Organisation Drug Dictionary (WHO-DD) encoding (latest or current version), reason for use, route, dose, dosing frequency, and start and end dates.

Procedures performed during the study will be recorded on the eCRF and details include the procedure name, WHO-DD encoding (latest or current version), reason for the procedure, and start and end dates.

Prior medications are defined as those taken prior to study treatment with a stop date prior to the first dose of study treatment.

Concomitant medications are defined as those that are ongoing at first IP dose date or started after first dose of IP either prior to or on the date of last IP dose.

Post-study treatment medications are those with a start date after the last dose date of study treatment.

Allowed and disallowed medications are defined as detailed in the protocol Sections 6.5.1 and 6.5.2 respectively.

Missing start and stop dates for medications and procedures will be handled using the rules described in Section 3.6.2.

3.5.3 Immunogenicity variables

Blood samples will be collected for determination of ADA for T-DXd. ADA data will be collected at scheduled visits shown in the CSP (Section 8.5.2). ADA results from each sample will be reported as either positive or negative. If the sample is positive, the ADA titer will be reported as well. In addition, the presence of neutralizing antibody (nAb) may be tested for all ADA-positive samples using a ligand-binding assay. The nAb results will be reported as positive or negative.

The following ADA outcomes will be determined:

- ADA positive at any visit (at baseline or post-baseline).
- ADA positive post-baseline and positive at baseline.

- ADA not detected post-baseline and positive at baseline.
- Treatment-induced ADA, defined as ADA positive post-baseline and not detected at baseline.
- Treatment-boosted ADA, defined as a baseline positive ADA titer that was boosted to a 2-fold or higher-level following drug administration.
- Treatment-emergent ADA, defined as either treatment-induced or treatment-boosted ADA.
- Persistently positive ADA, defined as having at least 2 post-baseline ADA positive measurements with at least 16 weeks (112 days) between the first and last positive measurement or an ADA positive result at the last available assessment. The category may include patients meeting these criteria who are ADA positive at baseline.
- Transiently positive ADA, defined as having at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive. The category may include patients meeting these criteria who are ADA positive at baseline.
- nAb positive at any visit (at baseline or post-baseline), if available.

3.5.4 Biomarker variables

Samples for the determination of biomarkers will be taken from all enrolled patients according to the schedule described in Section 8.6 of the CSP.

Summaries and analyses for exploratory biomarkers (other than what is specified below) will be documented in a separate analysis plan and will be reported outside the CSR in a separate report.

HER2 activating mutations
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). Local test results will be collected as positive, negative, unknown, or not done.

In addition, the number of pre-specified HER2 activating mutations with a positive result will be derived for each patient.

Patients with pre-specified HER2 activating mutations with a positive result (local testing) will also be summarized based on the grouped categories as follows:

- Extracellular domain mutations: includes S310F and S310Y
- Transmembrane domain mutations: includes R678Q only
- Kinase domain mutations: all other pre-specified mutations

For subgroup analyses, the grouping will be called 'HER2 mutations by local testing (grouped)'.

Based on the HER2 activating mutations listed above, patients will be defined as:

- HER2-mutant (local testing): A patient who has a positive result for any protocol-specified HER2 activating mutation

The pre-specified HER2-activating mutations (as listed above) will also be determined by retrospective central testing. However results from this retrospective central testing will not be available at the time of DBL for the study, so in a change to the protocol specified analysis, this data will not be summarized in the tables, figures and listings of the CSR. Restrospective central testing for HER2 mutations will be reported separately when available.

Other potential baseline HER2 mutations
Where local test results indicate a patient has another potential HER2 mutation (not included in the protocol defined list of pre-specified HER2 activating mutations) this information will be collected on the eCRF. Inclusion of a mutation in the MUTTYPO variable (free text field) of the SC eCRF indicates that a patient has the additional HER2 mutation(s).

Baseline HER2 status (IHC and ISH assessed by local testing)
Local HER2 test results will only be available for certain tumor types.

HER2 expression by IHC local test results (where applicable for a tumor type) will be collected as IHC 0, IHC 1+, IHC 2+, IHC 3+, or unknown.

For HER2 ISH testing based on local assessment (where applicable for a tumor type), results will be collected as positive, negative, unknown or not done.

For breast and esophagogastric tumor types, HER2 status is considered in terms of both IHC and ISH results (where available): HER2-overexpression (IHC 3+), HER2 equivocal (IHC 2+), or HER2 low (IHC 1+); patients with HER2 IHC2+ will be grouped as HER2 overexpressed if they are also ISH+, or HER2 low if they are also ISH- (where local test ISH results are available). To facilitate this, data will be categorized using both IHC and ISH results, e.g.:

- IHC 3+
- IHC 2+ ISH +
- IHC 2+ ISH –
- IHC 2+ ISH unknown
- IHC 1+
- IHC 0
- IHC unknown

Note, in breast and esophagogastric tumour types ISH local testing results are not expected when the IHC category is IHC 1+ or IHC 0 or IHC unknown.

For local HER2 results, the ISH results will only be combined with IHC results for IHC 2+.

HER2 status (IHC and ISH assessed by central testing)
HER2 expression based on retrospective central testing will also be defined. Restrospective central testing will be performed for all tumor types. Data will be categorized by IHC (3+/2+/1+/0/unknown) and associated ISH (+/-/equivocal/unknown) results. The following parameters will be defined:

- HER2 expression (IHC results only)
- HER2 amplification (ISH results only)
- HER2 status (IHC and ISH results combined)

For central HER2 results, the ISH results will be combined with IHC results for all categories of IHC when defining HER2 status.

In addition the following grouped categories will be defined:

- IHC 3+ or IHC 2+ ISH+
- IHC 2+ ISH- or IHC 1+
- IHC 2+ ISH Equivocal/Unknown
- IHC 0
- IHC Unknown

Other baseline biomarkers
In addition to the baseline biomarkers described above, local test results for other biomarkers will be collected at screening (where applicable and available). Local test results will be collected as positive, negative, unknown, or not done. These biomarkers include:

- FGFR mutation
- HPV [HPV Antigen, HPV DNA PCR, HPV ISH Stain]
- ER [Estrogen Receptor H-Score; Estrogen Receptor, Qual]
- PR
- dMMR
- BRCA Mutation
- BRCA1 Mutation
- BRCA2 Mutation
- HRD [Homologous Recombination Deficiency Score; Homologous Recombination Deficiency Status]

For HPV, ER and HRD, an overall category will also be defined (positive or negative), where any positive result from the individual results would be positive overall, in the absence of a positive result then any negative result would be negative overall.

Other biomarkers will also be collected (where applicable and available) with local testing results indicating whether a genetic abnormality was detected (including but not limited to):

- KRAS mutation detected
- BRAF mutation detected
- EGFR mutation positive status
- Microsatellite instability

3.5.5 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 collected as described in Section 8.1.4 of the CSP. Summaries and analyses for this data will be documented in a separate analysis plan and may be presented in a separate report.

3.6 Other information regarding the derivation of primary and secondary variables

3.6.1 Time windows for safety data

Time windows will be defined for all presentations of safety data that summarize values by visit according to the following conventions:

- The time windows should be exhaustive so that data recorded at any time point (scheduled or unscheduled) has the potential to be summarized. Inclusion within the time window should be based on the actual date and not the intended date of the visit.

- For reporting, summaries of post-dose laboratory parameters, vital signs, ECGs, SpO2, LVEF and ECOG performance status will be based on data collected from date/time of the first dose of study treatment up to 47 days following last dose of study treatment and before the initiation of the first subsequent anti-cancer therapy (palliative radiotherapy is not considered a subsequent cancer therapy), whichever occurs first.

- The window for visits following baseline will be constructed in such a way that the upper limit of the interval falls half-way between the two visits (the lower limit of the first post baseline visit will be Day 2). If an even number of days exists between two consecutive visits, then the upper limit will be taken as the midpoint value minus 1 day. For demonstration purposes, Table 9 shows the visit windows for clinical chemistry parameters up to Day 105. Assessments will continue until study end as defined in the CSP.

Table 9: Analysis visits and visit windows

Cycle	Scheduled day	Analysis window (day)
1	Day 1	NA
	Day 8	2 to 11
	Day 15	12 to 18
2	Day 22	19 to 32
3	Day 43	33 to 53
4	Day 64	54 to 74
5	Day 85	75 to 95
6	Day 106	96 to 116

- Note, for safety data that are collected during the study pre-infusion and post-infusion (e.g. vital signs) post-dose visit summaries will present the pre-infusion and post-infusion timepoints separately. The pre-infusion timepoint will not be presented at Cycle 1 as any pre-infusion data at Cycle 1 are included in the derivation of baseline.

- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval).

- Listings will display all values contributing to a time point for a patient

- For visit-based summaries, if there is more than one value per patient within a time window then the closest value to the scheduled visit date will be summarized. If the values are equidistant from the nominal visit date, then the earlier value will be used. If two values are recorded on the same day and the parameter is CTCAE gradable then the record with the highest toxicity grade should be used. Alternatively, if two records are recorded on the same day and the toxicity grade is the same (or is not calculated for

the parameter), then the average of the two records should be used. Data listings will highlight the values used in the summary table, wherever feasible. Note: in summaries of extreme values, all post-baseline values collected are used including those collected at unscheduled visits regardless of which value is closest to the scheduled visit date

- For summaries at patient level, all values will be included when deriving a patient level statistic such as a minimum/maximum regardless of whether or not they appear in the corresponding visit-based summary

3.6.2 Handling of missing data

Missing data will generally not be imputed.

Safety assessments of the form of "<x" (i.e., below the lower limit of quantification) or ">x" (i.e., above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but will be displayed as "<x" or ">x" in the listings.

Additionally, adverse events that have missing causality (after data querying) will be assumed to be related to study drug.

AE and Medication Start/Stop Dates
The original incomplete or missing dates will be presented in the listings.

- Adverse events: all AEs will be considered as treatment-emergent unless the opposite can be clearly stated. Imputation will be done only in the context of identifying treatment-emergent adverse events.
- Concomitant medications: all medications will be considered as concomitant unless the opposite can be clearly stated. Imputation will be done only in the context of identifying concomitant medications.

In practice, for AEs and medications, original incomplete or missing start dates will be imputed as below:

- Missing day: impute the 1st of the month unless month is same as month of first dose of study drug then impute first dose date.
- Missing day and month: impute 1st January unless year is the same as first dose date then impute first dose date.
- Completely missing: impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.

When imputing a start date, ensure that the new imputed date is sensible (i.e., is prior to the end date of the AE or medication).

Original incomplete or missing stop dates for adverse events and medications/therapies will be imputed as below:

- Missing day: impute the last day of the month unless month is same month as last dose of study drug then impute last dose date.
- Missing day and month: impute 31st December unless year is the same as last dose date then impute last dose date.
- Completely missing:
    - AE: since there is no ongoing flag recorded in CRF, then assume that AE is still present (i.e., do not impute a date).
    - Medication: if the ongoing flag is missing then assume that medication is still being taken (i.e., do not impute a date). If the medication has stopped and start date of medication is prior to first dose date then impute the first dose date, if the medication started on or after first dose date then impute a date that is after the last dose date.

When imputing a stop date, ensure that the new imputed date is sensible (i.e., is after the start date of the AE or medication).

Flags will be retained in the database indicating where any programmatic imputation has been applied, and in such cases, any durations would not be calculated.

Date of Death
If a patient is known to have died where only a partial death date is available, then the date of death will be imputed as the latest of the last date known to be alive +1 from the database and the death date using the available information provided:

- For missing day only: using the 1st of the month.
- For missing day and month: using the 1st of January.

If there is evidence of death but the date is entirely missing, it will be treated as missing (i.e., the patient will be censored at the last known alive date).

4 ANALYSIS METHODS

4.1 General principles

The below mentioned general principles will be followed throughout the study:

- All analysis and reporting will be across tumor types, unless otherwise specified.

- All safety data will be summarized using the SAF. Evaluations of safety and tolerability will include, but may not be limited to, analyses of the safety variables detailed in Section 3.3 using appropriate summary statistics.

- 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.

- PK data will be summarized using the PK analysis data set.

- ADAs will be summarized using the ADA evaluable set.

- Baseline characteristics and demography data will be summarized based upon the FAS.

- The analyses will be descriptive, and no inferential analysis will be performed based on statistical tests.

- Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized by frequency counts and percentages for each category.

- Unless otherwise stated, percentages will be calculated out of the population total.

- For continuous data, the mean and median will be rounded to 1 additional decimal place compared to the original data. The standard deviation will be rounded to 2 additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data. Where presented, quartiles will be rounded to 1 additional decimal place compared to the original data.

- For categorical data, percentages will be rounded to 1 decimal place. Note, percentages of 100.0 will be presented as 100 with no decimal.

- SAS® version 9.4 or higher will be used for all analyses

- Exact 95% CIs for binomial proportions will be calculated using the Clopper-Pearson method.

- For percentiles of survival times based on the Kaplan-Meier method (e.g., median survival), CIs will be calculated using the default method available in the SAS LIFETEST procedure (i.e. the Klein and Moeschberger extension of the Brookmeyer-Crowley method).

- For point-estimates of survival based on the Kaplan-Meier method, CIs will be calculated using the default method available in the SAS LIFETEST procedure (i.e., using Greenwood's estimate of standard-error and a log-log transformation).

Baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of IP (i.e., the latest result obtained prior to the start of study treatment). For ECGs, if the last assessment prior to first dose of IP was performed as a triplicate ECG, then the average of the triplicate will be considered baseline.

For continuous laboratory variables, LVEF measurements, ECG, and vital signs, if two visits are equally eligible to assess patient status at baseline (e.g., screening and baseline assessments both on the same date prior to first dose with no washout or other intervention in the screening period), the average will be used as the baseline value.

For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose. Assessments on the day of the first dose where neither time nor a nominal pre-dose indicator are captured will be considered prior to the first dose if such procedures are required by the protocol to be conducted before the first dose. In the scenario where there are two nominal pre-dose assessments on the Day 1, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline.

Where safety data are summarized over time, time on study will be calculated in relation to date of first dose of IP.

In all summaries, change from baseline variables will be calculated as the post-treatment value minus the value at baseline. The percentage change from baseline will be calculated as 100 x (post-baseline value - baseline value) / baseline value.

When calculating time to an event or duration, the default unit will be days unless otherwise specified. If an analysis requires days be converted to weeks, the time to event or duration will be divided by 7. If an analysis requires days be converted to months, the time to event or duration will be divided by (365.25/12).

4.2 Study population

4.2.1 Disposition of patients

The following will be presented:

- Number and percentage of patients who were screened, assigned to treatment, who received and did not receive study medication, who discontinued treatment and the reason for discontinuation, and who withdrew from the study and reasons for withdrawal.

- Number and percentage of patients in each analysis set.
- Patient recruitment by region (Asia, Europe, North America), country and center.

4.2.2 Protocol deviations

Important protocol deviations are defined in Section 2.2 and will be listed for all patients assigned to treatment and summarized for all patients in the FAS.

The number and percentage of patients with any IPD will be summarized for each IPD category. Patients with more than one deviation in the same IPD category will be counted once for that IPD category. Any patients who have deviations in more than one IPD category will be counted once in the overall summary.

4.2.3 Demographic and other baseline characteristics

Demographic and other baseline characteristics (see Section 3.5.1) will be listed for all FAS patients and the following will be summarized for the FAS (unless otherwise specified):

- Demographics (age, age group[< 65, ≥ 65 - < 75 and ≥ 75 years], sex, race and ethnicity).
- Patient characteristics at baseline (height, weight, weight group [<70, ≥70 – ≤90, >90 kg] and BMI group [Underweight (<18.5), Normal (18.5 - <25.0), Overweight (25.0 - <30.0) and Obese (>=30.0)]).
- Previous anti-cancer therapy by ATC classification and generic drug name.
- Previous anti-cancer therapy prior to this study (including number of prior regimens).
- Disease characteristics at screening/baseline (ECOG performance status, primary tumor location, histology type, tumor grade, AJCC stage, time from diagnosis to start of study treatment and overall disease classification).
- Disease characteristics at time of diagnosis (primary tumor location, histology type, tumor grade, AJCC stage).
- Extent of disease at baseline .
- TNM classification at time of diagnosis.
- Disease related medical history (past and current).
- Relevant surgical history.
- Nicotine use, categorized (never, current, former) and number of pack-years.
- Pulmonary function test at screening.
- Pulmonary medical history.

Medical history (past and current) and surgical history are coded using MedDRA (latest or current version) and will be summarized by System Organ Class (SOC) and Preferred Term (PT).

Baseline Biomarker Status
The baseline biomarker status (see Section 3.5.4) will be summarized for the FAS.

The number (%) of patients who are HER2-mutant (local testing) will be summarized. In addition, test results for each of the pre-specified HER2 activating mutations and grouped categories (as described in Section 3.5.4) will be summarized (number and percentage of patients) for local testing. Patients with more than one positive HER2 activating mutation result within a grouped category will only be counted once per category. The number of pre-specified HER2 activating mutations with a positive result per patient will be summarized (i.e., 1, 2, 3, etc.; number and percentage of patients) for local testing, as an indicator of patients reporting multiple HER2 mutations. In addition, for local testing, the number (%) of patients reporting other potential HER2 mutations (other than the protocol defined pre-specified HER2 activating mutations) will be summarized for all additional HER2 mutations reported.

In addition, the number and percentage of patients with a positive result for each of the 12 pre-specified HER2 activating mutations will be summarized for each tumor type (for local testing).

In a change to the planned analysis, data from restrospective central testing for HER2 mutations will not be summarized in the tables, figures and listings of the CSR.

Baseline HER2 status (IHC/ISH) will be summarized (for local testing and central testing, where available, as described in Section 3.5.4), and presented separately for tumor types of breast, esophagogastric, other tumor types (not breast or esophagogastric), and across all tumor types. For central HER2 testing, baseline HER2 expression (IHC), HER2 status (grouped) and HER2 amplification (ISH) will also be presented, as described in Section 3.5.4.

Baseline HER2 activating mutation data and HER2 expression data will be listed, including information on patients with other potential HER2 mutations not included in the protocol pre-specified list of HER2 activating mutations.

Data on other baseline biomarkers will be summarized (number and percentage of patients) and listed.

4.2.4 Prior and concomitant medications

Prior and concomitant medications will be listed for all patients in the FAS.

Medications received prior to, concomitantly, or post-treatment will be coded using the AstraZeneca Drug Dictionary Anatomical Therapeutic Chemical (ATC) classification codes. Concomitant medications will be summarized for the FAS by ATC classification codes. Patients with the same concomitant medication multiple times will be counted once per

medication. A medication that can be classified into more than one chemical and/or therapeutic subgroup will be presented in each subgroup.

The following summaries will be produced:

- Summary of disallowed concomitant medications
- Summary of allowed concomitant medications
- Summary of post study treatment cancer therapies

All concomitant and other treatment data will be listed.

Missing coding terms should be listed and summarized as "Not coded".

4.3 Analysis of efficacy

All RECIST 1.1 assessments, whether scheduled or unscheduled, will be included in the calculation of efficacy variables. Unless otherwise stated below or in Section 3.2 for that parameter/analysis, this principle applies regardless of whether a patient discontinues study treatment or receives another anti-cancer therapy.

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.

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.

Table 10: Efficacy analyses summary

Endpoints analyzed	Notes [All endpoints derived from RECIST use ICR and Investigator assessment]
Confirmed 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.

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.

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

All individual efficacy response data will be listed for the ORR endpoint, including duration of response for patients who have confirmed responses.

4.3.1 Objective response rate

The confirmed ORR as assessed by ICR and Investigator assessment (based on the FAS) will be estimated and presented as the number (%) of patients along with the corresponding exact 95% Clopper-Pearson CI.

As a sensitivity analysis, a summary presenting the confirmed ORR as assessed by ICR based on a subset of the FAS with measurable disease at baseline per ICR will also be produced.

4.3.2 Duration of response

Descriptive data will be provided for the DoR for responding patients in the FAS (Section 3.2.2), including Kaplan-Meier curves. Only patients who have achieved OR (confirmed CR or confirmed PR) will be evaluated for DoR. Summary statistics (based on Kaplan-Meier estimates) will include: lower and upper quartile and median DoR with 95% CI. A swimmer plot may be produced (sorted by tumor type) to graphically display the duration of response.

A spider plot presenting the target lesion size (percentage change from baseline) over time will be produced, including all patients in the FAS.

The DoR summaries described above will be presented for the ICR and Investigator assessment.

4.3.3 Best objective response

BoR will be summarized by number (%) for each category (CR, PR, SD, PD and NE). For ICR data only, an additional BoR category of no evidence of disease (NED) will also be summarized, if applicable. The number (%) of patients with a single visit response (i.e., an unconfirmed response) will be presented.

The BoR table will also present the number (%) of patients with SD (without subsequent cancer therapy) for at least 5 weeks after start of study treatment..

In addition, an exploratory summary of BoR including unconfirmed responses (unconfirmed CR or unconfirmed PR) as a response will be presented.

A summary table showing the onset of confirmed response in relation to study treatment and subsequent anticancer therapy will also be presented.

The BoR summaries described above will be presented for the ICR and Investigator assessment.

4.3.4 Disease control rate

The disease control rate at 6 weeks and 12 weeks will be estimated and presented with the corresponding exact 95% Clopper-Pearson CI.

The number (%) of patients meeting the definition of disease control in Section 3.2.4 will be presented. This will be repeated for a timepoint of 12 weeks, as described in Section 3.2.4.

The DCR summaries described above will be presented for the ICR and Investigator assessment.

4.3.5 Progression free survival

The treatment status at progression of patients at the time of analysis will be summarized. This will include the number (%) of patients who were on treatment at the time of progression, the number (%) of patients who discontinued study treatment prior to progression, the number (%) of patients who have not progressed and were on treatment or discontinued treatment. This will also provide distribution of number of days prior to progression for the patients who have discontinued treatment.

Kaplan-Meier plots and descriptive statistics will be provided for PFS for the FAS. Summary statistics (based on Kaplan-Meier estimates) will include: lower and upper quartile and median PFS with 95% CI.

The proportion of patients alive and progression-free at 6 and 12 months (Kaplan-Meier estimates) will be presented along with 95% CI.

The duration of follow-up for censored patients will be presented (median, minimum & maximum). In addition, the number of days from last RECIST assessment (i.e. censoring date) to DCO will be summarized for censored patients.

A summary of the number (%) of patients who received subsequent anti-cancer therapy or not will be presented, including when any subsequent anti-cancer therapy occurred in relation to RECIST progression (before/after/no progression).

The PFS summaries described above will be presented for the ICR and Investigator assessment.

4.3.6 Overall survival

The following number (%) of patients in the FAS will be presented: those who have died and those who are censored. Censored subjects will be summarized as either those still in survival follow-up or terminated prior to death. The reason for termination prior to death will be summarized.

Kaplan-Meier plots and descriptive statistics will be presented for OS for the FAS. Summary statistics (based on Kaplan-Meier estimates) will include the lower and upper quartile and median OS with 95% CI.

The proportion of patients alive at 6 and 12 months (Kaplan-Meier estimates) will be presented along with 95% CI.

In addition, median duration of follow-up and range (minimum – maximum) will be summarized where duration of follow-up is defined as time from first dose of IP to the date of death (i.e. overall survival) or to the date of censoring (date last known to be alive) for all patients and censored patients.

4.3.7 Sensitivity analyses

Consistency of effect will be investigated by tumor type and selected mutations. To demonstrate consistency of the estimates, descriptive summaries for confirmed ORR (ICR and Investigator assessment) as outlined in Section 4.3.1 will also be presented by both tumor type and selected mutations. A forest plot presenting the ORR estimates and 95% CI for each tumor type and selected HER2 mutations will be used to evaluate homogeneity of effect across both tumor types and selected HER2 mutations.

Tumor type categories will be reported based on data recorded on the GROUP eCRF (see Section 3.5.1). HER2 mutations will be based on local testing and will be reported based on the individual pre-specified HER2 activating mutations and the grouped categories (see Section 3.5.4).

In a change to the planned analysis, data from restrospective central testing for HER2 mutations will not be summarized in the tables, figures and listings of the CSR.

A summary table of DoR (ICR and Investigator assessment) will be presented by tumor type, selected HER2 mutations and other subgroups (as described below). The median DoR will be estimated based on Kaplan-Meier curves, and the minimum and maximum will also be presented. The median DoR with 95% CI for each HER2 mutation grouped category will be

estimated based on the Kaplan-Meier curves, and a forest plot presenting median DoR and 95% CI will be used to evaluate homogeneity of effect across the HER2 mutation groups.

In addition, subgroup analyses will be performed for the following subgroups (using the FAS):

- Prior regimens of anti-cancer therapy (1 versus 2 versus ≥ 3)
    - Determined using the number of prior regimens recorded on the prior cancer therapy eCRF (RAW.CAPRX. PRCHEMO).
- Age (< 65 versus ≥ 65 years)
    - Determined using the Age collected on the demography eCRF (RAW.DM.AGE).
- Sex (male versus female)
- WHO/ECOG Performance status (0 versus 1)
    - Determined using the baseline WHO/ECOG performance status.
- Region (Asia versus Europe versus North America)
    - Defined in Appendix A.
- Race (Black or African American versus Native Haiwaiian or other Pacific Islander versus American Indian or Alaska Native versus Asian versus White versus Other versus Not reported)
    - Determined using the Race collected on the demography eCRF (RAW.DM.RACE)
- HER2 expression by central testing (IHC 3+ versus IHC 2+ versus IHC 1+ versus IHC 0 versus IHC Unknown)
    - Based on retrospective central testing.
- HER2 status (grouped) by central testing
    - Based on retrospective central testing, categorized using both IHC and ISH results. Categories as defined in Section 3.5.4:
        - IHC 3+ or IHC 2+ ISH+

        - IHC 2+ ISH- or IHC 1+
        - IHC 2+ ISH Equivocal/Unknown
        - IHC 0
        - IHC Unknown
    - Note, only categories that appear in the data will be presented in the summary table.

- HER2 amplification by central testing (ISH+ versus ISH- versus ISH Equivocal/Unknown)
    - Based on retrospective central testing.
- Number of metastatic sites (≤1 versus ≥ 2)
    - Determined from the DISEXT eCRF. Any metastatic sites recorded as 'Other' will be counted as one site.
- Prior HER2 therapy (yes vs no)
    - Determined from the CAPRX eCRF. The medical team will provide a list of medications considered as HER2 therapy.
- Prior treatment with topoisomerase I inhibitors (e.g., irinotecan) (yes versus no)
    - Determined from the CAPRX eCRF. The medical team will provide a list of medications considered as topoisomerase I inhibitors.
- Prior treatment with immune checkpoint inhibitor or other immuno-oncology therapy (yes versus no)
    - Determined from the CAPRX eCRF. The medical team will provide a list of medications considered as immune checkpoint inhibitors or other immune-oncology therapy.
- Renal impairment at baseline (normal versus mild versus moderate)
    - Renal impairment status is determined by the baseline Creatinine Clearance (CrCl) (calculated using the Cockcroft-Gault equation) with categories:
        - normal renal function: CrCl ≥90 mL/min
        - mild renal impairment: CrCl ≥60, <90 mL/min
        - moderate renal impairment: CrCl ≥30, <60 mL/min)

- Calculated creatinine clearance (CrCl) will be programmatically derived in the reporting database (for this subgroup categorisation only) using the Cockcroft-Gault formula:

  Creatinine clearance (mL/min) = ([140 – age at first dose] * weight (kg) [* 0.85 if patient is female]) / (72 * serum creatinine (mg/dL))

Confirmed ORR (ICR and Investigator assessment) will be presented by subgroup using descriptive summaries (as outlined in Section 4.3.1). Forest plots will be produced presenting the ORR estimates and 95% CI for each subgroup level with a vertical line representing the ORR estimate from the primary analysis.

Descriptive results will be presented for each level of subgroup, comparative statistical analysis between subgroups will not be performed.

For completeness, the subgroup summary table will also present data for the 'Unknown' category (where applicable). These will not appear in the forest plots.

4.4 Analysis of safety

Safety and tolerability will be assessed in terms of AEs (including SAEs and AESIs), exposure, deaths, laboratory measurements, vital signs, ECG, HRCT, PFT, echocardiograms/multiple gated acquisition (ECHO/MUGA) scan and physical examinations, which will be collected for all patients.

Data from all cycles of treatment will be combined in the presentation of safety data. The SAF will be used for reporting of safety data.

4.4.1 Adverse events

TEAEs (as defined in Section 3.3.3) that occurred before the initiation of the first subsequent cancer therapy will be used for reporting in all AE summary tables, unless otherwise specified. In this definition, palliative radiotherapy is not considered a subsequent cancer therapy. This convention will more accurately depict safety findings attributable to study treatment only as opposed to presenting all TEAEs, as they may include AEs likely to be attributable to subsequent cancer therapy.

All other TEAEs and post-treatment AEs will be included in the AE listings, but not in the summary tables. AEs occurring 48 days or more after the last dose of study treatment and/or after a patient has received further therapy for cancer (following discontinuation of study treatment) will be flagged in the data listings.

For each AE preferred term included in the summary tables for each patient, the listing will include the maximum CTCAE grade up until (and including) 47 days following

discontinuation of study treatment or until the initiation of the subsequent anticancer therapy following discontinuation of study treatment (whichever occurs first).

All AEs, both in terms of MedDRA preferred term and CTCAE grade, will be listed and summarized descriptively by count (n) and percentage (%). An overview of AEs will be presented, including the number and percentage of patients with any AE, AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP, as well as AEs leading to IP dose interruptions, AEs leading to IP dose reduction, AEs leading to IP dose modification (i.e. either dose reduction or dose interruption), and other significant adverse events as well as the number of individual occurrences in those categories. The MedDRA dictionary (latest or current version) will be used for coding.

All reported AEs will be listed along with the date of onset (including study day), date of resolution (if AE is resolved), investigator's assessment of CTCAE grade and relationship to study drug. If an AE has changes in CTCAE grade, the maximum value will be presented.

Multiple events per patient will be counted once in summaries.

Summary information (the number and percent of patients) by SOC and PT (unless otherwise specified) will be tabulated for:

- All AEs.
- Most common AEs (frequency of >5%) by PT.
- Most common AEs (frequency of >5%) with CTCAE grade 3 or higher, by PT.
- All AEs possibly related to study medication (as determined by the reporting investigator).
- AEs by maximum reported CTCAE grade.
- AEs with CTCAE grade 3 or higher.
- AEs with CTCAE grade 3 or higher, possibly related to study medication (as determined by the reporting investigator).
- AEs with outcome of death.
- AEs with outcome of death possibly related to study medication (as determined by the reporting investigator).
- All SAEs.

- All SAEs possibly related to study medication (as determined by the reporting investigator).
- AEs leading to discontinuation of study medication.
- AEs leading to discontinuation of study medication, possibly related to study medication (as determined by the reporting investigator).
- AEs leading to dose interruption of study medication.
- AEs leading to dose interruption of study medication, possibly related to study medication (as determined by the reporting investigator).
- AEs leading to dose reduction of study medication.
- AEs leading to dose reduction of study medication, possibly related to study medication (as determined by the reporting investigator).
- AEs leading to dose modification of study medication.

For the truncated AE tables of most common AEs, all events that occur in more than 5% of patients overall in the SAF will be summarized by preferred term, by decreasing frequency. This cut-off may be modified after review of the data. When applying a cut-off (e.g., 5%), the raw percentage should be compared to the cut-off, no rounding should be applied first (i.e., an AE with frequency 4.9% will not appear if the cut-off is 5%).

Key patient information will also be listed for AEs with outcome of death, SAEs, AEs leading to discontinuation of study medication and other significant adverse events (see Section 3.3.3).

In accordance with the United States Food and Drug Administration (FDA) requirements, a separate table will present non-serious AEs occurring in more than 5% patients. This will not be produced as part of the CSR outputs.

Adverse events of special interest (AESI)
ILD/pneumonitis and LVEF decrease are considered to be AESIs (see Section 3.3.3 for further details). AESI categories will be summarized separately unless otherwise specified.

Potential ILD/pneumonitis will be adjudicated by the ILD Adjudication Committee as follows:

- Adjudicated as ILD/pneumonitis
    - Adjudicated as drug-related ILD/pneumonitis

    - Adjudicated as not drug-related ILD/pneumonitis
- Adjudicated as not ILD/pneumonitis
- Unable to adjudicate due to insufficient information

A summary of all potential ILD events that were submitted to the ILD adjudication committee for adjudication will be provided and categorized as above. Maximum CTCAE grade per adjudication committee will also be summarized for the events adjudicated as ILD (drug-related/not drug-related). For events unable to be adjudicated due to insufficient information, the maximum CTCAE grade per investigator assessment will be summarized.

Summaries of ILD/pneumonitis events will be primarily based on adjudicated drug-related ILD events from the ILD adjudication committee. For adjudicated ILD events, summaries of causality and CTCAE grading are as determined by the ILD Adjudication Committee.

For AESIs other than ILD/pneumonitis, categories will be based on preferred terms provided by the patient safety team prior to database lock (Section 3.3.3). All preferred terms provided by the patient safety team will be listed and the listing will highlight those present in the study.

The number (%) of patients who have at least one AESI, at least one AESI causally related to study medication, and at least one AESI leading to discontinuation of study medication will be presented.

A summary table of AESIs will be produced for each AESI category, sub-category (if applicable) and preferred term by maximum CTCAE grade.

Key patient information for each AESI occurrence will be listed. Duration of the first AESI will be summarized using KM approach and estimates of the lower and upper quartiles and median will be calculated. For ongoing AESIs in the database, the stop date is censored at the earliest of following:

- Death date.
- Start of subsequent cancer therapy.
- Last dose of study treatment + 47 days.
- Last contact date.

When summarizing duration of the first AESI for adjudicated ILD/pneumonitis events, only adjudicated drug-related events will be considered.

Deaths
Summaries of all deaths (note: all deaths on/after date of first dose of the study drug will be considered) will be provided with number (%) of patients categorized as:

- Total number of deaths (regardless of date of death).
- Death related to disease under investigation only as determined by investigator.
- Death related to disease under investigation, as determined by the investigator, and an AE with an outcome of death.
- AE with outcome of death only.
    - Sub-category AE with outcome of death only (AE start date falling after 47 days follow-up period) (*)
- Other deaths

This summary will be repeated for all deaths on treatment or within 47 days of the last dose of study medication. The category marked (*) will not appear in this summary.

A listing of all deaths will be produced.

4.4.2 Exposure

Exposure will be listed and summarized for the SAF. The following summaries will be produced:

- Total exposure
- Actual exposure
- Plot of exposure over time (percentage of patients still on treatment over time)
- Summary statistics (mean, standard deviation, median, quartiles, minimum and maximum) of RDI
- Summary of dose reductions and cycle delays, infusion interuptions and dose modifications.
- Number of treatment cycles

Swimmer plots displaying dosing over time per patient may be presented.

4.4.3 Laboratory assessments

Laboratory data obtained until 47 days after the last dose of study treatment or until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment (whichever occurs first) will be used for reporting.

Absolute values and change from baseline for all continuous hematology and clinical chemistry laboratory parameters will be summarized by visit.

Scatter plots (shift plots) of baseline to maximum/minimum value (as appropriate) on treatment may be produced for certain parameters if warranted after data review.

Box-plots of absolute values by week, and box-plots of change from baseline by week, may be presented for certain parameters if warranted after data review.

Shift tables for laboratory values by worst common toxicity criteria (CTC) grade will be produced. The laboratory parameters for which CTC grade shift outputs will be produced are:

- Hematology: Hemoglobin, platelet count, white blood cell count, differential white blood cell count (neutrophils, lymphocytes)
- Clinical chemistry: serum creatinine, total bilirubin, albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), corrected calcium (Ca), potassium (K), sodium (Na) and magnesium (Mg).
- Coagulation: activated partial thromboplastin time (aPTT)

For the parameters with no CTC grading that are listed in the CSP, shift tables from baseline to minimum and maximum value will be provided (low/normal/high categories).

Hy's law
The following summaries will include the number (%) of patients who have:

- Elevated ALT, AST, and Total bilirubin during the study.
  - ALT ≥3x – ≤5x, >5x – ≤8x, >8x – ≤10x, >10x – ≤20x, and >20x ULN during the study.
  - AST ≥3x – ≤5x, >5x – ≤8x, >8x – ≤10x, >10x – ≤20x, and >20x ULN during the study.
  - Total bilirubin ≥2x – ≤3x, >3x – ≤5x, >5x ULN during the study.
  - ALT or AST ≥3x – ≤5x, >5x – ≤8x, >8x – ≤10x, >10x – ≤20x, >20x ULN during the study.
  - Potential Hy's Law: ALT or AST ≥3x ULN and total bilirubin ≥2x ULN during the study, irrespective of serum ALP. The onset date of ALT or AST elevation should be prior to or on the date of total bilirubin elevation.

Narratives will be provided in the CSR for patients who have ALT ≥ 3x ULN concurrent or preceding total bilirubin ≥ 2x ULN or AST ≥ 3x ULN concurrent or preceding total bilirubin ≥ 2x ULN at any visit.

Liver biochemistry test results over time for patients with elevated ALT (i.e. ≥ 3x ULN) or AST (i.e. ≥ 3x ULN), and elevated total bilirubin (i.e. ≥2x ULN) (at any time during treatment i.e., between the start of treatment and up to and including 47 days following the date of last dose) will be plotted. Individual patient data where ALT or AST plus total bilirubin are elevated at

any time during treatment will be listed also. Note, the plot and listing include data for patients where the elevation in ALT or AST precedes or coincides with (that is, on the same day as) the elevation in total bilirubin.

Plots of maximum post-baseline ALT and AST vs. maximum post-baseline total bilirubin, expressed as multiples of ULN, will also be produced with reference lines at 3×ULN for ALT and AST, and 2×ULN for Total bilirubin. In each plot, total bilirubin will be in the vertical axis.

4.4.4 Electrocardiograms

Summaries of ECG data will include all data mapped in accordance with Section 3.6 and selected as defined in Section 4.4.3 for laboratory parameters.

Absolute values and change from baseline for ECG heart rate, PR interval, QRS duration, QT interval, QTcF interval and RR interval will be summarized.

The number and percentage of patients with normal and abnormal (not clinically significant and clinically significant) ECG results will be presented as a shift table from baseline to worst evaluation during the study.

4.4.5 Vital signs and SpO_2

Summaries of vital signs data will include all data mapped in accordance with Section 3.6 and selected as defined in Section 4.4.3 for laboratory parameters.

Absolute values and change from baseline for diastolic and systolic BP, pulse rate, respiration rate, temperature, body weight and SpO_2 will be summarized at baseline and over time.

4.4.6 World Health Organization/Eastern Cooperative Oncology Group performance status

Summaries of WHO/ECOG data will include all data mapped in accordance with Section 3.6 and selected as defined in Section 4.4.3 for laboratory parameters.

WHO/ECOG results will be presented as a shift table from baseline to worst evaluation during the study.

4.4.7 Suspected ILD/pneumonitis and LVEF

Summaries of data collected for suspected ILD/pneumonitis cases as per Section 3.3.11 from assessments not performed at screening or as part of the SoA may be presented in patient narratives. Where appropriate, laboratory assessments may be summarized as detailed in Section 4.4.3. By-patient listings may also be presented, including HRCT and PFT data collected at screening for all patients.

LVEF % values, as well as baseline and change from baseline, will be summarized for all assessments.

4.5 Pharmacokinetic data

PK concentration data will be listed by patient and dosing day/time and will be tabulated using summary statistics for all patients in the PK analysis set.

Serum concentrations of T-DXd, total anti-HER2 antibody, and MAAA-1181 will be summarized by nominal sample time using standard summary statistics for PK concentrations (geometric mean, geometric coefficient of variation, geometric mean ± standard deviation, arithmetric mean, standard deviation, coefficient of variation, median, minimum, maximum and n). All serum concentrations will be listed.

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

4.6 Immunogenicity analysis

A summary of the number and percentage of patients who developed detectable ADA to T-DXd by ADA categories (Section 3.5.3) will be presented based on the ADA evaluable set. Immunogenicity results of all patients in the SAF will be listed regardless of ADA evaluable status. ADA titer and neutralizing antibody data will be listed for samples confirmed positive for the presence of T-DXd antibodies. AEs in ADA positive patients by ADA positive category will be listed.

The effect of ADA on PK, pharmacodynamics, efficacy, and safety may be evaluated, if the data allow.

4.7 Exploratory analyses

4.7.1 Coronavirus Disease 2019 (COVID-19)

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. Protocol deviations will be evaluated by pre- and post- any CSP amendments once the study begins. A listing of all patients affected by a COVID-19 related study disruption by unique subject number identifier and investigational site may be generated along with the description of how the individual's participation was altered. Additional summaries may be conducted to investigate the impact of COVID-19 on study endpoints.

4.7.2 Biomarker analysis

Baseline biomarker summaries are detailed in Section 4.2.3. All other biomarker summaries and analyses for exploratory endpoints will be documented in a separate analysis plan and will be reported outside the CSR in a separate report.

4.7.3 ILD/pneumonitis

Analyses to explore the risk factors on incidence of ILD/pneumonitis cases may be performed on adjudicated results.

4.7.4 Re-challenged patients

A listing of key information of re-challenged patients may be provided (re-challenged with T-DXd). Re-challenged patients are defined as patients who had any adverse event which led to stopping scheduled dosing of T-DXd, but who could be restarted on T-DXd once the toxicity was resolved.

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, enrollment in that tumor type will be discontinued.

Enrollment 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 enrollment based on the futility evaluation. Table 11 provides the probability of stopping (ie, observing zero responses) for a range of true ORR values given 8 treated patients.

Table 11: 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 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.

6 CHANGES OF ANALYSIS FROM PROTOCOL

The statistical methods as described in the clinical study protocol version 1.0, 20 July 2020 were adopted. The following are the changes of analysis from the protocol:

- The potential Hy's law reporting will use >=2x ULN for Total Bilirubin although CSP v1 specifies >2x ULN.

- The protocol specified TEAE definition includes SAEs with onset or worsening 48 days or more after the last dose of study drug, if considered related to the study treatment. The SAP specifies that for adverse event reporting these TEAEs will not be included in AE summary tables. At project level patient safety have agreed that these SAEs will no longer be considered TEAEs in future studies. For consistency, the TEAE definition in this SAP has been updated so these SAEs will no longer be considered TEAEs, even if related to study treatment. This has no impact on AE summary tables, as the events will not be included for AE reporting according to SAP rules.

- Retrospective central testing results for HER2 mutations will not be available at the time of final DBL for the study. Therefore the CEAS population will not be used and central test results for HER2 mutations will not be presented for the tables, figures and listings of the CSR. Retrospective central testing for HER2 mutations will be reported separately when available.

7 REFERENCES

Clopper, C. J., and Pearson, E. S. (1934). "The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial." *Biometrika* 26:404–413

Graham BL, Brusasco V, Burgos F, et al (2017). "ERS/ATS standards for single-breath carbon monoxide uptake in the lung." Eur Respir J 2017; 49: 1600016

8 APPENDIX

Appendix A

Region and countryin subgroup analyses are as follows:

Region	**Country**
Asia	Japan
	South Korea
Europe	Belgium
	Denmark
	France
	Italy
	Spain
North America	Canada
	United States

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