Statistical Analysis Plan	
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A Single-arm Study of Trastuzumab Deruxtecan (T-DXd) Monotherapy for Patients with HER2-expressing Locally Advanced or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma Who Have Received 2 or More Prior Regimens (DESTINY-Gastric06)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below the limit of quantification
BoR	Best objective response
BP	Blood pressure
CHF	Congestive heart failure
CI	Confidence interval
COVID-19	Coronavirus 2019-nCoV, also referred to as severe acute respiratory syndrome coronavirus 2
CR	Complete response
CrCl	Creatinine clearance
CRO	Contract research organisation
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DBL	Database lock
DCO	Data cut-off
DCR	Disease control rate
DLCO	Diffusing capacity of the lungs for carbon monoxide
DoR	Duration of response
d.p.	Decimal place
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form

Abbreviation or special term	Explanation
EOT	End of treatment
FAS	Full analysis set
FEV1	Forced expiratory volume in 1 second
FEV6	Forced expiratory volume in 6 seconds
FiO_2	Fraction of inspired oxygen
FVC	Forced vital capacity
GEJ	Gastroesophageal junction
HER2	Human epidermal growth factor receptor 2
HRCT	High resolution CT scan
ICF	Informed consent form
ICR	Independent central review
IHC	Immunohistochemistry
ILD	Interstitial lung disease
ISH	In situ hybridisation
ITT	Intention to treat
IV	Intravenous
LD	Longest diameter
LLOQ	Lower limit of quantification
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition scan
NA	Not applicable
nAb	Neutralising ADAs
NC	Not calculable
NCI	National Cancer Institute
NE	Not evaluable
NED	No evidence of disease
NQ	Not quantifiable
NTL	Non-target lesion
NYHA	New York Heart Association
OAE	Other significant adverse events
ORR	Objective response rate

Abbreviation or special term	Explanation
OS	Overall survival
PD	Progressive disease
PD plan	Protocol Deviation plan
PEF	Peak expiratory flow
PFS	Progression-free survival
PI	Principal investigator
PK	Pharmacokinetics
PR	Partial response
PS	Performance status
PT	Preferred term
QTc	Corrected QT interval
QTcF	QT interval corrected by Fridericia's formula
RDI	Relative dose intensity
RECIST 1.1	Response Evaluation Criteria in Solid Tumours, Version 1.1
RES	Response evaluable set
SAE	Serious adverse events
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Stable disease
SoA	Schedule of Activities
SOC	System organ class
$Sp0_2$	Pulse oximetry
T-DXd	Trastuzumab deruxtecan
TEAE	Treatment emergent adverse events
TL	Target lesion
TLC	Total lung capacity
ULN	Upper limit of normal
WHO-DD	World Health Organisation Drug Dictionary

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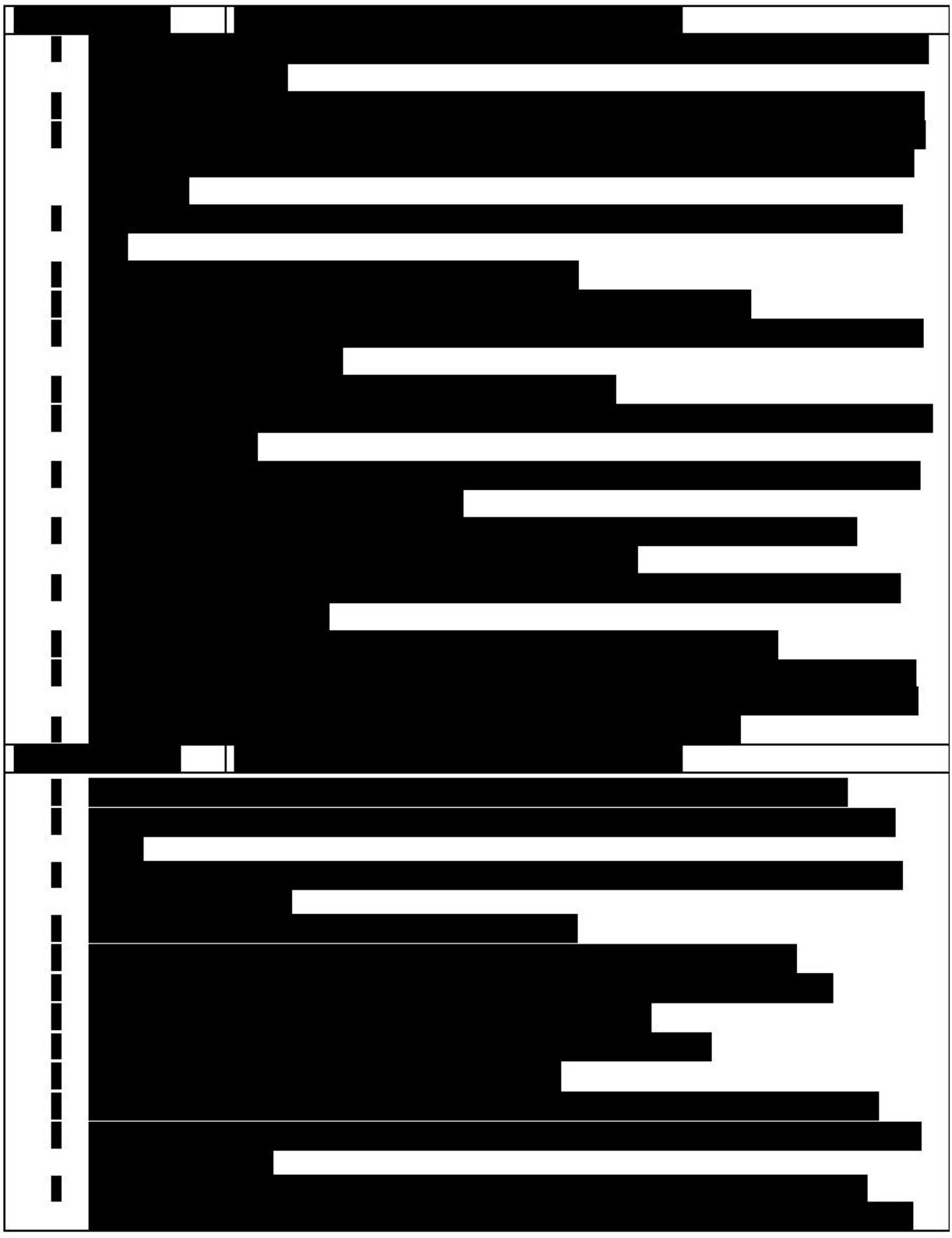
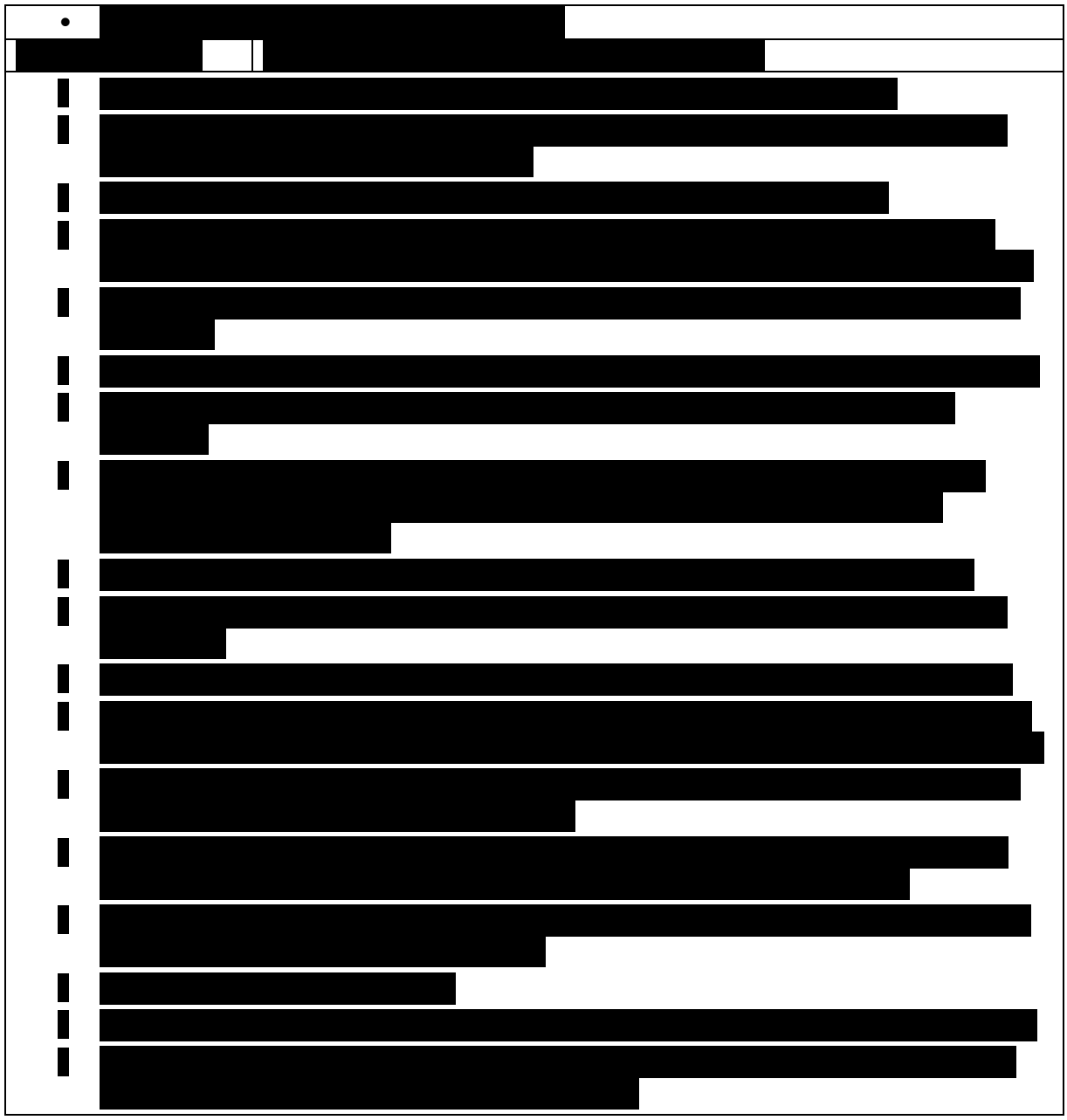




1 STUDY DETAILS

This statistical analysis plan (SAP) contains a more detailed description of the analyses in the clinical study protocol (CSP). This SAP is based on version 2.0 of the CSP.

1.1 Study objectives

1.1.1 Primary objective

The primary objective for this study and the corresponding endpoint/variable are shown in Table 1.

Table 1 Primary study objective and corresponding endpoint/variable

Objective	Endpoints/variables
To evaluate the efficacy of T-DXd by assessment of confirmed ORR by ICR in participants with HER2-positive advanced gastric or GEJ adenocarcinoma who have received at least 2 prior regimens including a fluoropyrimidine agent and a platinum agent	Confirmed ORR, defined as the proportion of patients who have a confirmed CR or confirmed PR, as determined by ICR per RECIST 1.1.

GEJ Gastroesophageal Junction; HER2 Human epidermal growth factor receptor 2; ICR Independent central review; ORR Objective response rate; RECIST 1.1 Response Evaluation Criteria in Solid Tumours, 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 evaluate the efficacy of T-DXd by assessment of confirmed ORR by investigator in participants with HER2-positive advanced gastric or GEJ adenocarcinoma who have received at least 2 prior regimens including a fluoropyrimidine agent and a platinum agent	Confirmed ORR, defined as the proportion of patients who have a confirmed CR or confirmed PR, as determined by the investigator per RECIST 1.1.
To evaluate the efficacy of T-DXd by assessment of PFS in participants with HER2-positive advanced gastric or GEJ adenocarcinoma who have received at least 2 prior regimens including a fluoropyrimidine agent and a platinum agent	PFS, defined as the time from date of enrolment until progression per RECIST 1.1 or death due to any cause, as assessed by ICR and by the investigator.

Objective	Endpoints/variables
To evaluate the efficacy of T-DXd by assessment of DCR in participants with HER2-positive advanced gastric or GEJ adenocarcinoma who have received at least 2 prior regimens including a fluoropyrimidine agent and a platinum agent	DCR, defined as the percentage of patients who have a confirmed CR/PR or SD (without subsequent anticancer therapy), as assessed by ICR and by the investigator.
To evaluate the efficacy of T-DXd by assessment of DoR in participants with HER2-positive advanced gastric or GEJ adenocarcinoma who have received at least 2 prior regimens including a fluoropyrimidine agent and a platinum agent	DoR, defined as the time from the date of first documented response until date of documented progression or death in the absence of progression, as assessed by ICR and by the investigator.
To evaluate the efficacy of T-DXd by assessment of OS in participants with HER2-positive advanced gastric or GEJ adenocarcinoma who have received at least 2 prior regimens including a fluoropyrimidine agent and a platinum agent	OS, defined as the time from date of enrolment until the date of death due to any cause.
To evaluate efficacy of T-DXd by assessment of tumour size change in participants with HER2-positive advanced gastric or GEJ adenocarcinoma who have received at least 2 prior regimens including a fluoropyrimidine agent and a platinum agent	Best percentage change from baseline in tumour size, based on the sum of diameters of target lesions, as assessed by ICR and by the investigator.
To evaluate the efficacy of T-DXd by assessment of confirmed ORR by ICR in participants with HER2-expressing advanced gastric or GEJ adenocarcinoma who have received at least 2 prior regimens including a fluoropyrimidine agent and a platinum agent	Confirmed ORR, defined as the proportion of patients who have a confirmed CR or confirmed PR, as determined by ICR per RECIST 1.1.
To evaluate the efficacy of T-DXd by assessment of confirmed ORR by investigator in participants with HER2-expressing advanced gastric or GEJ adenocarcinoma who have received at least 2 prior regimens including a fluoropyrimidine agent and a platinum agent	Confirmed ORR, defined as the proportion of patients who have a confirmed CR or confirmed PR, as determined by the investigator per RECIST 1.1.

Objective	Endpoints/variables
To evaluate the efficacy of T-DXd by assessment of PFS in participants with HER2-expressing advanced gastric or GEJ adenocarcinoma who have received at least 2 prior regimens including a fluoropyrimidine agent and a platinum agent	PFS is defined as time from date of enrolment until progression per RECIST 1.1 or death due to any cause, as assessed by ICR and the investigator.
To evaluate the efficacy of T DXd by assessment of DCR in participants with HER2-expressing advanced gastric or GEJ adenocarcinoma who have received at least 2 prior regimens including a fluoropyrimidine agent and a platinum agent	DCR is defined as the percentage of participants who have a confirmed CR/PR or SD (without subsequent anticancer therapy) as assessed by ICR and the investigator.
To evaluate the efficacy of T DXd by assessment of DoR in participants with HER2-expressing advanced gastric or GEJ adenocarcinoma who have received at least 2 prior regimens including a fluoropyrimidine agent and a platinum agent	DoR is defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression, as assessed by ICR and the investigator.
To evaluate the efficacy of T DXd by assessment of OS in participants with HER2-expressing advanced gastric or GEJ adenocarcinoma who have received at least 2 prior regimens including a fluoropyrimidine agent and a platinum agent	OS is defined as time from date of enrolment until the date of death due to any cause.
To evaluate efficacy of T-DXd by assessment of tumour size change in participants with HER2-expressing advanced gastric or GEJ adenocarcinoma who have received at least 2 prior regimens including a fluoropyrimidine agent and a platinum agent	Best percentage change from baseline in tumour size, based on the sum of diameters of target lesions, as assessed by ICR and by the investigator.
To assess the PK of T-DXd	Serum concentrations of T-DXd, total anti-HER2 antibody, and MAAA-1181a, and evaluation of appropriate PK parameters.
To investigate the immunogenicity of T-DXd	Presence of ADAs for T-DXd and Neutralising ADAs.

ADAs Anti-drug antibodies; DCR Disease control rate; DoR Duration of Response; GEJ Gastroesophageal Junction; HER2 Human epidermal growth factor receptor 2; ICR Independent central review; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; PK Pharmacokinetics; RECIST 1.1 Response Evaluation Criteria in Solid Tumours, Version 1.1; T-DXd Trastuzumab Deruxtecan.

1.1.3 Safety objective

The safety objective for this study and the corresponding endpoints/variables are shown in Table 3.

Table 3 Safety study objective and corresponding endpoints/variables

Objective	Endpoints/variables
To assess the safety and tolerability of T-DXd in participants with HER2-expressing advanced gastric or GEJ adenocarcinoma who have received at least 2 prior regimens including a fluoropyrimidine agent and a platinum agent	Assessed by the occurrence of AEs, clinical laboratory results, vital signs, physical examination findings, elevated troponin results, ECG and ECHO/MUGA results, ophthalmologic results and ADAs.

ADAs Anti-drug antibodies; AEs Adverse events; ECG Electrocardiogram; ECHO Echocardiogram; GEJ Gastroesophageal Junction; HER2 Human epidermal growth factor receptor 2; MUGA Multigated acquisition scan; T-DXd Trastuzumab Deruxtecan.

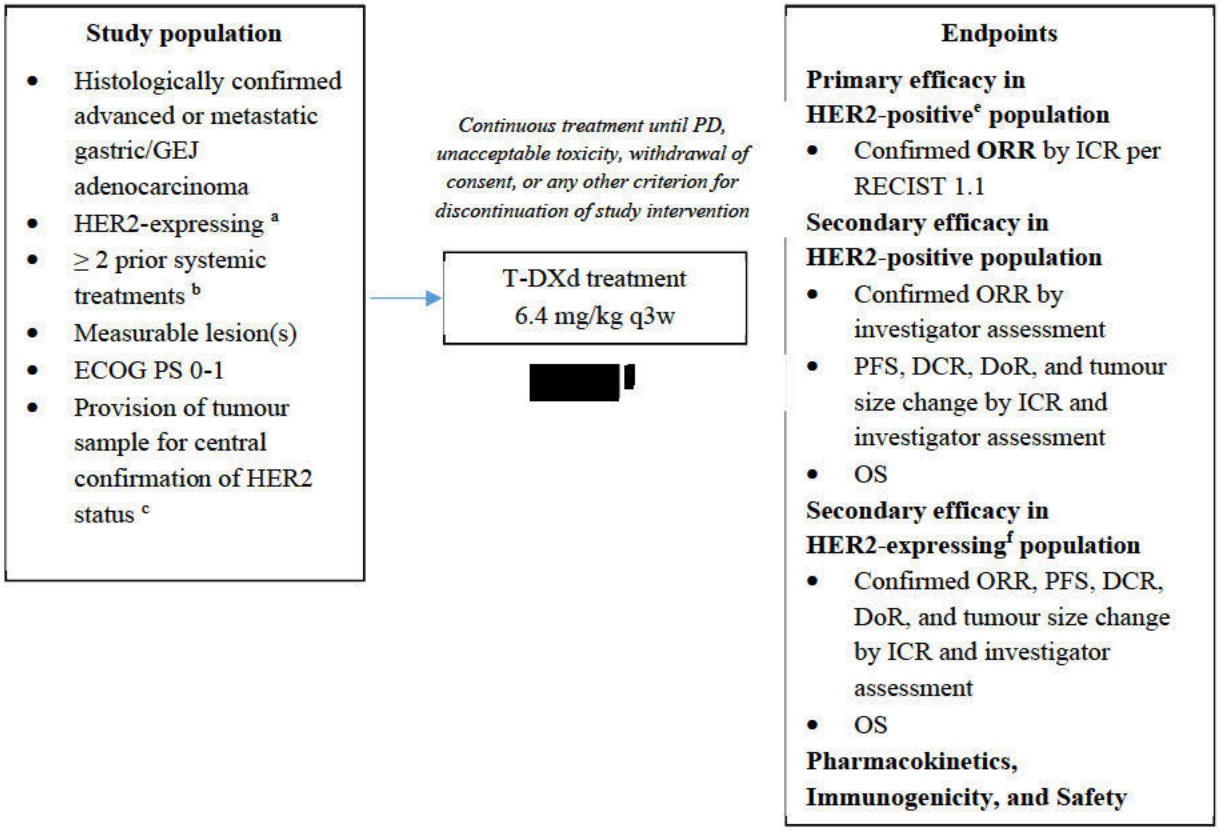
1.2 Study design

This is a Phase II, open-label, single-arm, multicentre study in China assessing the efficacy and safety of trastuzumab deruxtecan (T-DXd) in participants with human epidermal growth factor receptor 2-positive (HER2-positive), in addition to participants with HER2-expressing, advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received at least 2 prior regimens including a fluoropyrimidine agent and a platinum agent.

After signing the informed consent form (ICF), patients will begin screening procedures. Following completion of all screening procedures and documentation of all baseline assessments, eligible patients are enrolled in the study. Enrolled patients will be assigned to treatment with T-DXd monotherapy at a dose of 6.4 mg/kg administered intravenously (IV) every 3 weeks until Response Evaluation Criteria in Solid Tumours, Version 1.1 (RECIST 1.1)-defined progressive disease (PD), unacceptable toxicity, withdrawal of consent, or any other criterion for discontinuation of study intervention is met.

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

Figure 1 Overview of study design



[a] For the purposes of eligibility, HER2 status will be determined locally.
[b] Prior systemic treatment must contain fluorouracil and platinum.
[c] If the primary tumour is accessible by endoscopy or if metastatic tissue can be biopsied, a newly-acquired tumour tissue sample should be provided. If a newly acquired sample is not available, an archived sample is acceptable and should be based on the most recent archived tumour tissue sample.
[d] N = [redacted] participants who are HER2 IHC 3+ or IHC 2+ based on local laboratory report will be enrolled to ensure that approximately [redacted] participants enrolled in the study have HER2-positive status confirmed by central laboratory as these participants will form the basis of the primary analysis population. This also ensures that approximately [redacted] participants enrolled in the study have HER2-expressing status confirmed by central laboratory as these participants will form the basis of the analysis population for the secondary objectives in this population.
[e] HER2-positive is defined as IHC 3+ or IHC 2+/ISH +.
[f] HER2-expressing is defined as IHC 3+ or IHC 2+ (regardless of ISH status).
DCR disease control rate; DoR duration of response; ECOG PS Eastern Cooperative Oncology Group Performance Status; GEJ gastroesophageal junction; HER2 human epidermal growth factor receptor 2; ICR independent central review; IHC immunohistochemistry; ISH in situ hybridisation; ORR objective response rate; OS overall survival; PD progressive disease; PFS progression-free survival; q3w every 3 weeks; RECIST 1.1 Response Evaluation Criteria in Solid Tumours, Version 1.1; T-DXd trastuzumab deruxtecan.

[redacted]

[redacted]

2 ANALYSIS SETS

2.1 Definition of Analysis Sets

A summary of the analysis sets used for each outcome variable is provided in Table 4.

Table 4 Summary of outcome variables and analysis sets

Outcome variable	Analysis set
Primary Efficacy – HER2-positive	
Confirmed ORR by ICR	Primary analysis: HER2-positive Full analysis set
	Supplementary analysis: HER2-positive Response evaluable set
Secondary Efficacy – HER2-positive	
Confirmed ORR by investigator	Primary analysis: HER2-positive Full analysis set
PFS by ICR	
DCR by ICR	
DoR* by ICR	
Tumour size change by ICR	
PFS by investigator	
DCR by investigator	
DoR* by investigator	
Tumour size change by investigator	
OS	

Outcome variable	Analysis set
Secondary Efficacy – HER2-expressing	
Confirmed ORR by ICR	Primary analysis: HER2-expressing Full analysis set
Confirmed ORR by investigator	
PFS by ICR	Supplementary analysis for confirmed ORR by ICR: HER2-expressing Response evaluable analysis set
DCR by ICR	
DoR* by ICR	
Tumour size change by ICR	
PFS by investigator	
DCR by investigator	
DoR* by investigator	
Tumour size change by investigator	
OS	
Study population/Demography	
Demography characteristics	Primary analysis: HER2-positive Full analysis set
Baseline and disease characteristics	Supplementary analysis: Intention to treat analysis set
Important deviations	
Medical/surgical history	
Previous anti-cancer therapy	
Concomitant medications/procedures	
Subsequent anti-cancer therapy	
Safety data	
Exposure	Safety analysis set
AEs	
Laboratory measurements	
Vital signs	
ECGs	
PK data	PK analysis set
ADA data	T-DXd ADA evaluable set

*Patients who are evaluable for the analysis of DoR analysis are those who responded in the associated ORR analysis.
ADA Anti-drug antibody; AE Adverse event; DCR Disease control rate; DoR Duration of Response;
ECG Electrocardiogram; HER2 Human epidermal growth factor receptor 2; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; PK Pharmacokinetics; T-DXd Trastuzumab Deruxtecan.

2.1.1 Enrolled patients

Enrolled patients will be defined as all subjects who sign the ICF, have an enrolment code and have a treatment assignment number.

2.1.2 Intention to treat analysis set

The intention to treat (ITT) analysis set will include all patients who signed the ICF and are enrolled in the study.

2.1.3 HER2-Positive Full analysis set

The HER2-positive full analysis set (FAS) will include all enrolled patients with HER2 status confirmed as IHC 3+ or IHC 2+/ISH positive by central laboratory.

2.1.4 HER2-Expressing Full analysis set

The HER2-expressing FAS will include all enrolled patients with HER2 status confirmed as IHC 3+ or IHC 2+ by central laboratory.

2.1.5 HER2-Positive Response evaluable set

The HER2-positive response evaluable set (RES) will include all enrolled patients with HER2 status confirmed as IHC 3+ or IHC 2+/ISH positive by central laboratory who received at least 1 dose of study treatment and had measurable disease at baseline as assessed by ICR.

2.1.6 HER2-Expressing Response evaluable set

The HER-2 expressing RES will include all enrolled patients with HER2 status confirmed as IHC 3+ or IHC 2+ by central laboratory who received at least 1 dose of study treatment and had measurable disease at baseline as assessed by ICR.

2.1.7 Safety analysis set

The safety analysis set (SAF) will include all enrolled patients who received at least 1 dose of study treatment. Safety data will not be formally analysed but summarised using the SAF.

2.1.8 Pharmacokinetic analysis set

The pharmacokinetic (PK) analysis set will include all enrolled patients who received at least 1 dose of study treatment and had at least 1 post-dose measurable serum concentration of T-DXd.

2.1.9 T-DXd ADA evaluable set

The anti-drug antibodies (ADA) evaluable set will include all enrolled patients who received at least 1 dose of study treatment with a non-missing baseline ADA result and at least 1 non-missing post-baseline ADA result.

2.2 Protocol deviations

The following general categories will be considered important protocol deviations and will be programmatically identified from the electronic Case Report Form (eCRF) data. These will be listed and discussed in the clinical study report (CSR) as appropriate. Additional details can be found in the Protocol Deviation plan (PD plan) V3.0:

- Patients who deviate from key inclusion entry criteria per the CSP (Deviation 1):
    - Lack of provision of informed consent prior to study related procedures.
    - Inclusion criteria 2: Pathologically documented locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma.
    - Inclusion criteria 3: Disease progression on or after ≥ 2 prior regimens for advanced/metastatic disease that included a fluoropyrimidine and a platinum.
    - Inclusion criteria 4: Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
    - Inclusion criteria 5: Documentation of HER2 IHC 3+ or IHC 2+, regardless of ISH status, during screening.
    - Inclusion criteria 6: Able to provide a tumour sample for confirmation of HER2 status by a central laboratory.
    - Inclusion criteria 7: At least 1 lesion that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes, which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and is suitable for accurate repeated measurements, as per RECIST 1.1.
    - Inclusion criteria 11: Adequate treatment washout period prior to initiation of study intervention.

- Patients who deviate from key exclusion entry criteria per the CSP (Deviation 2):
    - Exclusion criteria 4: Unresolved toxicities caused by previous anticancer therapy, defined as toxicities (excluding alopecia) not yet resolved to Grade ≤ 1 or baseline.
    - Exclusion criteria 10: Participants with a medical history of myocardial infarction (MI) within 6 months before enrolment, symptomatic congestive heart failure (CHF) (New York Heart Association [NYHA] Class II to IV), unstable angina pectoris, or a recent (< 6 months) cardiovascular event including stroke.
    - Exclusion criteria 12: History of interstitial lung disease (ILD)/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening, or other lung-specific clinically significant illnesses, or prior pneumonectomy.
    - Exclusion criteria 18: Previous treatment in the present study.
    - Exclusion criteria 19: Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) study or during follow-up period of an interventional study.
- Discontinuation criteria for study treatment met but patient not withdrawn from study treatment (Deviation 3).
- [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]

- Received prohibited concomitant medications (including other anti-cancer agents) (Deviation 6). Please refer to the CSP section 6.5.1 for those medications that are detailed as being 'excluded' from permitted use during the study. This will be used as a guiding principle for the physician review of all medications prior to database lock (DBL).

- Study procedure deviations (Deviation 7)

    - Baseline RECIST scan > 28 days before enrolment.

    - No baseline RECIST 1.1 assessment on or before date of enrolment.

The important protocol deviations will be listed and summarised. The third category of Deviation 5 would lead to exclusion from the safety analysis set and the RES. None of the other deviations will lead to patients being excluded from the analysis sets described in Section 2.1 (with the exception of the PK analysis set, if the deviation is considered to impact upon PK). A per-protocol analysis excluding patients with specific important protocol deviations is not planned. However, a 'deviation bias' sensitivity analysis may be performed on the objective response rate endpoint, excluding patients with deviations that may affect the efficacy evaluation if the deviations happen in > 10% of patients.

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

3 PRIMARY AND SECONDARY VARIABLES

3.1 Derivation of RECIST Visit Responses

For all patients, the RECIST tumour response data will be used to determine each patient's visit response according to RECIST version 1.1. 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 tumour assessments are to be performed no more than 28 days before enrolment and ideally as close as possible to the start of study treatment. Tumour assessments are then performed every 6 weeks (± 1 week) following the start of study treatment until disease progression. If a patient discontinues study treatment prior to progression, then tumour assessments continue every 6 weeks (± 1 week) for the first 48 weeks after the date of first dose, then every 12 weeks (± 1 week) thereafter until disease progression.

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 minimise 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 tumour 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 complete response (CR), partial response (PR), stable disease (SD) or progressive disease (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 tumour 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, progression-free survival [PFS] etc.) will be calculated programmatically for the site investigator data (see Section 3.2) from the overall visit responses.

3.1.1 Target lesions – site investigator data

Measurable disease is defined as having at least one measurable lesion, which is ≥ 10 mm in the longest diameter (LD), (except lymph nodes which must have short axis ≥ 15 mm) with CT or 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 TLs. A previously irradiated lesion that has shown objective progression and meets the other requirements for a measurable lesion may be considered as a TL if it is the only lesion available. If more than one baseline scan is recorded then measurements from the one that is closest and prior to the first dose of study treatment will be used to define the baseline sum of TLs. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement. In which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

All other lesions (or sites of disease) not recorded as TL should be identified as 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 5 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.

NTL Non-target lesion; 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 then all TL measurements should 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

For lymph nodes, if the size reduces to < 10mm then these 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. a 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, unless they show objective progression, meet the other requirements for measurable lesion, and is the only lesion available.

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 tumours:

- 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 74mm.

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

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

68 x 74 / 62 = 81mm

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 0cm.

Change in method of assessment of TLs

CT and MRI are the only methods of assessment that can be used in this trial. If a change in method of assessment occurs between CT and MRI, this will be considered acceptable and no adjustment within the 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 and new lesions – site investigator data

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 6 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 investigators 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)	No NTLs are recorded at baseline.

NTL Non-target lesion; 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 tumour 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 tumour.

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 tumour assessments where possible until objective disease progression is observed.

3.1.3 Overall visit response – site investigator data

Table 7 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 7 Overall visit responses

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

TARGET	NON-TARGET	NEW LESIONS	OVERALL VISIT RESPONSE
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**
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 Progressive disease; PR Partial response; SD Stable disease.

3.1.4 Independent review

A planned independent central review (ICR) of all radiological imaging data will be carried out using RECIST version 1.1. All radiological scans for all patients (including those at unscheduled visits, or outside visit windows) will be collected on an ongoing basis and sent to an AstraZeneca appointed Contract Research Organisation (CRO) for central analysis. The imaging scans will be reviewed by two 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 no programmatic derivation of visit response is necessary. (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 tumour assessment that cannot be evaluated then the patient will be assigned a visit response of NE (unless there is evidence of progression in which case the response will be assigned as PD). 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.

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, best percentage change in tumour size and DCR) 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 of all patients will be performed prior to DBL, which will cover all of the scans up to the data cut-offs (DCOs).

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

3.2 Efficacy Variables

3.2.1 Objective response rate (ORR)

ORR is defined as the percentage of patients with a confirmed response of CR or PR. The primary endpoint is confirmed ORR as assessed by ICR per RECIST 1.1.

A secondary endpoint is confirmed ORR as assessed by the investigator.

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 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 (note that for this analysis radiotherapy is not considered 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).

In the case where 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.

3.2.1.1 Best objective response (BoR)

Best objective response (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, but prior to starting any subsequent anti-cancer therapy, and up to and including RECIST progression or the last evaluable assessment in the absence of RECIST progression. Categorisation of BoR will be based on RECIST using the following response categories: confirmed CR, confirmed PR, SD, NED, PD and NE. Unconfirmed CR/PR will be included in SD. A BoR of NED applies only to those patients entering the study with no measurable disease at baseline.

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 35 days (to allow for an early assessment within the assessment window), after first dose of study treatment. 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 and prior to starting any subsequent anti-cancer therapy. It will also be determined programmatically based on RECIST using all site investigator data up until the first progression event and prior to starting any subsequent anti-cancer therapy. 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. 2*6 weeks + 1 week to allow for a late assessment within the assessment window) after first dose of study treatment, 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 study treatment then BoR will be assigned to the NE category.

A patient will be classified as a responder if the RECIST criteria for a CR or PR are satisfied at any time following first dose, prior to RECIST progression and prior to starting any subsequent cancer therapy.

3.2.2 Progression free survival (PFS)

PFS is defined as the time from date of enrolment until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the

patient withdraws from therapy or receives another anti-cancer therapy prior to progression (i.e. date of PFS event or censoring – date of enrolment + 1). PFS will be assessed using ICR assessments and using investigator assessments. 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 treatment, changing to every 12 weeks after 48 weeks following date of first dose for patients who have discontinued study treatment prior to progression) the definition of two missed visits will be as follows:

- For patients still on treatment or who discontinue due to progression or death:
    - 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 assessment + 1 week for a late assessment)
- For patients who discontinue treatment prior to progression or death:
    - 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 and <= 287 (i.e. week 41) then two missing visits will equate to 14 weeks (2 x 6 weeks + 1 week for an early assessment + 1 week for a late assessment)
    - If the previous RECIST assessment > day 287 and <= 329 (i.e. week 47) then two missing visits will equate to 20 weeks (6 weeks + 12 weeks + 1 week for an early assessment + 1 week for a late assessment)
    - If the previous RECIST assessment > day 329 then two missing visits will equate to 26 weeks (2 x 12 weeks + 1 week for an early assessment + 1 week for a late assessment)

If the patient has no evaluable 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).

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

RECIST assessments/scans contributing towards 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 investigational assessments, the date of progression will be determined based on the **earliest** of the dates of the component that triggered the progression.

- For both ICR and investigational assessments, when censoring a patient for PFS the patient will be censored at the **latest** of the 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 NTLs.

3.2.3 Disease control rate (DCR)

Disease control rate (DCR) is defined as the percentage of patients with BoR of CR, PR or SD. See Section 3.2.1.1 for the BoR definition.

DCR at 12 weeks is defined as the percentage of patient with BoR of CR or PR, or SD for at least 11 weeks (i.e., 12 weeks – 1 week to allow for an early assessment within the assessment window) after the date of the first dose of study intervention (without subsequent anticancer therapy).

3.2.4 Duration of response (DoR)

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.

3.2.5 Overall survival (OS)

Overall survival (OS) is defined as the time from the date of enrolment until death due to any cause regardless of whether the patient withdraws from study treatment or receives another anti-cancer therapy (i.e. date of death or censoring – date of enrolment + 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.

Note: Survival calls will be made in the week following the date of the DCO for the final 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 CRF 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). The last date for each individual patient is defined as the latest among the following dates recorded on the CRFs:

- Adverse event (AE) start and stop dates
- Admission and discharge dates of hospitalisation
- Study treatment date
- End of treatment date
- Laboratory test dates
- Date of vital signs

- Disease assessment dates on RECIST CRF
- Start and stop dates of alternative anticancer treatment
- Date last known alive on survival status CRF
- End of study date

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.

3.2.6 Change in TL tumour size

Tumour size is the sum of the longest diameters of the TLs. Baseline for RECIST is defined to be the last evaluable assessment prior to first dose. The percentage change in TL tumour size at each assessment will be obtained for each patient taking the difference between the sum of the TLs at a particular assessment (week X) and the sum of the target lesions at baseline divided by the sum of the TLs at baseline times 100 (i.e. (week X–- baseline) / baseline * 100).

The absolute change and percentage change from baseline in the sum of tumour size at each assessment will be calculated. The best change in tumour size (i.e. depth of response) is the largest decrease from baseline or the smallest increase from baseline in the absence of a reduction and will include all assessments prior to the earliest of death in the absence of progression, any evidence of progression, the start of subsequent anti-cancer therapy or the last evaluable RECIST assessment if the patient has not died, progressed or started subsequent anti-cancer therapy.

Only patients with both baseline and post-baseline values will be included in the analysis.

3.3 Safety Variables

[redacted]

[redacted]

[redacted]

[redacted]

3.3.2 Dose intensity

Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose through to the last day of dosing. 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 and D is the intended cumulative dose up to the actual last day of dosing. D is the total dose that would be delivered, if there were no modification to dose or schedule. When accounting for the calculation of intended cumulative dose 2 days should be added to the date of last dose to reflect the protocol allowed window for dosing.

When deriving actual dose administered the volume before and after infusion will also be considered:

Actual dose = actual dose per administration (initial or reduced dose level) * 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.

3.3.3 Adverse events

AEs and serious adverse events (SAEs) will be collected throughout the study, from date of informed consent throughout the treatment period and the safety follow-up period (until 40 (+7) days after the last dose of study treatment). In the case of unresolved ILD/pneumonitis, Hepatitis B reactivation or events which are considered to be due to a late onset toxicity to study treatment, collection continues during Long-term Follow-up as specified in Table 3 of the CSP. Events will be defined as treatment emergent if they onset or worsen (by investigator report of a change in severity or seriousness), during the treatment period or safety follow-up as defined in the CSP. The Medical Dictionary for Regulatory Activities (MedDRA) (using the 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 AEs (NCI CTCAE) (using CTCAE version 5).

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.

AEs of special interest

Some clinical concepts (including some selected individual preferred terms and higher-level terms) have been considered "AEs of special interest" (AESI) to the T-DXd program. AESIs represent pre-specified risks that are considered to be of importance to a clinical development program.

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

Other categories may be added as necessary or existing terms may be merged. An AstraZeneca medically qualified expert after consultation with the Global Patient Safety Physician has reviewed the AEs of interest and identified which higher-level terms and which MedDRA preferred terms contribute to each AESI. Further reviews may take place prior to DBL to ensure any further terms not already included are captured within the categories.

3.3.4 Physical examinations

Physical examinations will be performed as described in Section 8.2.1 of the CSP. Abnormalities recorded prior to the first dose of study treatment will be recorded as part of the patient's baseline signs. Abnormalities first recorded after first dose of study treatment will be recorded as AEs unless they fulfil any of the SAE criteria, are the reason for study treatment discontinuation, or are considered to be clinically relevant as judged by the investigator.

3.3.5 Vital signs

The following vital signs will be measured as described in Section 8.2.2 of the CSP: Systolic and diastolic blood pressure (BP), pulse rate, temperature and respiratory rate. 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 3.3.10.1 for visit windows, and how to handle multiple records will be used.

3.3.6 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, and at end of treatment (EOT) as described in Section 8.2.3 of the CSP. ECGs will be obtained in triplicate at screening, and subsequent ECGs will be performed in triplicate only if an abnormality is noted, otherwise single ECGs will be performed.

The following ECG variables will be collected: heart rate, RR interval, PR interval, QT interval, QT interval corrected for heart rate using Fridericia's correction (QTcF interval), QRS duration, and an overall evaluation.

The overall evaluation of an ECG will either be "normal", "abnormal" or "borderline", with abnormalities categorised as either "clinically significant" or "not clinically significant". In case of clinically significant ECG abnormalities, 2 additional ECGs will be obtained over a brief period (within 5 minutes) to confirm the finding. Where triplicate ECG results are taken, a single mean value for numeric parameters will be used, and the worst case of the three results will be used for the overall evaluation.

For the derivation of visit windows where baseline and post-baseline visits have triplicate ECGs, the date/time equal to the earliest date/time of the 3 results will be used.

Where QTcF 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:

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

3.3.7 Elevated troponin levels

Troponin will be collected at screening, when a patient reports signs or symptoms suggesting CHF, MI or other causes of myocyte necrosis, and at end of treatment (EOT). Further details regarding repeat testing are described in Section 8.2.3 of the CSP.

3.3.8 Laboratory measurements

Blood and urine samples for the determination of clinical chemistry, haematology, coagulation and urinalysis will be collected as described in Section 8.2.4 of the CSP.

For the derivation of baseline and post-baseline visit values, the rules described in Sections 4.1 and 3.3.10.1 of this document considering baseline, visit windows and how to handle multiple records will be used.

Change from baseline in haematology and clinical chemistry variables will be calculated for each post-dose visit. NCI CTCAE (version 5.0) grades will be defined at each visit according to the CTCAE grade criteria using project ranges, after conversion of lab result to corresponding project-wide preferred units. The following parameters have CTCAE grades defined for both high and low values: potassium, sodium, magnesium, glucose and corrected calcium so high and low CTCAE grades will be calculated.

Corrected calcium will be programmatically derived during the creation of the reporting database using the following formula:

Corrected calcium (mmol/L) = Total calcium (mmol/L) + ([40-albumin (g/L)] x 0.02)

Calculated creatinine clearance (CrCl) will be programmatically derived in the reporting database 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))

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

3.3.9 Other safety assessments

3.3.9.1 Echocardiograms/multigated acquisition scans

Echocardiograms (ECHO)/multigated acquisition (MUGA) scans will be performed as described in Section 8.2.5.1 of the CSP. These will be used to assess the LVEF. The LVEF % and method details will also be reported. CTCAE (version 5.0) grades will be defined at each visit according to the CTCAE grade criteria. Change from baseline of LVEF % will be calculated. LVEF % measurements will be categorised as follows:

- [redacted]

Change from baseline LVEF % values will be categorised as:

- [redacted]

3.3.9.2 Pulmonary assessments

Pulse oximetry (SpO_2) will be measured as described in Section 8.2.5.2 of the CSP.

3.3.9.3 ECOG performance status

ECOG performance status (PS) will be assessed as described in Section 8.2.5.3 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.

Any significant change from baseline or screening will be reported as an AE.

3.3.9.4 Ophthalmologic assessments

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

3.3.9.5 ILD/Pneumonitis investigation

If ILD is suspected, additional assessments are performed as described in the CSP, including pulmonary function test and high resolution CT scan (HRCT).

For the pulmonary function test, the following parameters will be measured: diffusing capacity of the lungs for carbon monoxide (DLCO) (if feasible), SpO_2, FiO_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.

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

3.3.9.6 Eligible HBV infection

Eligible patients enrolled with inactive or resolved Hepatitis B infection will be monitored for reactivation, where reactivation is as defined in Section 8.2.5.5 of the CSP.

If HBV reactivation is confirmed, T-DXd therapy must be interrupted and anti-viral therapy initiated following consultation with the local Hepatitis B expert and in accordance with local practice.

3.3.10 General considerations for safety assessments

3.3.10.1 Time windows

Time windows will be defined for any presentations that summarise values by visit. The following conventions will apply:

- The time windows will be exhaustive so that data recorded at any time point has the potential to be summarised. Inclusion within the time window will be based on the actual date and not the intended date of the visit.

- All unscheduled visit data have the potential to be included in the summaries.

- The window for the 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 earlier of the two middle days. For example, the visit windows for vital signs data are:
    - Cycle 1 Day 8, visit window 2 – 11.
    - Cycle 1 Day 15, visit window 12 – 18.
    - Cycle 2 Day 1, visit window 19 – 32.
    - Cycle 3 Day 1, visit window 33 – 53.
    - Cycle 4 Day 1, visit window 54 – 74.

- Note, for safety data that are collected during the study both pre-infusion and post-infusion (e.g. vital signs), visit summaries following the first dose 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 should 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 summarised, or the earlier, in the event the values are equidistant from the nominal visit date. The listings will highlight the value for the patient that contributed to 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 whether or not the value is closest to the scheduled visit date.

- For summaries at a patient level, all values will be included, regardless of whether they appear in a corresponding visit based summary, when deriving a patient level statistic such as a maximum.

3.3.10.2 Missing data

Missing safety data will generally not be imputed. However, safety assessment values of the form of "< x" (i.e. below the lower limit of quantification [LLOQ]) 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.

Furthermore, for missing diagnostic dates, if day and/or month are missing use 01 and/or Jan. If year is missing, put the complete date to missing.

AE and Medication Start/Stop Dates

The original incomplete or missing dates will be presented in the listing.

- 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 AEs.

- 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.

For missing AE and medications start dates, the following will be applied:

a. Missing day – Impute the 1st of the month unless month is the same as month of the first dose of study drug then impute first dose date.

b. Missing day and month – Impute 1st January unless year is the same as first dose date then impute first dose date.

c. 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.

For missing subsequent anti-cancer therapy start dates, the following rules will be applied:

a. Missing day – If the month is the same as treatment end date, then impute to the day after treatment, otherwise 1st of the month.

b. Missing day and month – If year is the same as treatment end date, then impute to the day after treatment, otherwise 1st January of the same year as anti-cancer therapy 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).

For missing AE and medication end dates, the following will be applied:

a. Missing day – Impute the last day of the month unless month is the same as month of last dose of study treatment then impute last dose date

b. Missing day and month – Impute 31st December unless year is the same as last dose then impute last dose date.

c. 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).

Patients with a partial date of birth (i.e. for those countries where year of birth only is given) will have the 1st of the month imputed if the day is missing, and 1st Jan imputed if the day and month is missing.

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:-

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., the patient will be censored at the last known alive date).

3.4 Pharmacokinetic Variables

PK concentration data will be collected as per the CSP to assess the PK of T-DXd, total anti-HER2 antibody, and MAAA-1181a.

For PK concentration data below limit of quantification (BLQ) the following rules will apply:

- If, at a given time point, 50% or less of the serum concentrations are not quantifiable (NQ), the geometric mean, geometric CV%, mean and SD will be calculated treating the NQ as the LLOQ.
- If more than 50%, but not all, of the concentrations are NQ, the geometric mean, geometric CV%, mean, and SD will be reported as data not calculable (NC). The maximum value will be reported from the individual data, and the minimum and median will be set to NQ.
- If all the concentrations are NQ, the geometric mean, mean, minimum, median and maximum will be reported as NQ, and the geometric CV% and SD as NC.

3.5 Immunogenicity Variables

Blood samples for determination of ADAs against T-DXd and neutralising ADAs (nAb) in serum will be collected per the Schedule of Activities (SoA) in the CSP. ADA results from each sample will be reported as either positive or negative. If the sample is positive, the ADA titre will be reported as well. In addition, the presence of neutralising ADA may be tested for all ADA-positive samples using a ligand-binding assay. The nAb results will be reported as positive or negative.

The number of patients in the ADA analysis set who fulfil the following criteria will be determined. The percentage of patients in each of the categories listed below will be calculated, using the number of patients in the ADA evaluable set as the denominator.

- ADA positive at any visit; the percentage of ADA-positive patients in the ADA analysis set is known as ADA prevalence. A patient is defined as being ADA positive if a positive ADA result is available at any time, including baseline and all post-baseline measurements; otherwise ADA negative.
- 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 titre that was boosted to a 2-fold or higher level (greater than the analytical variance of the assay) following drug administration.
- Treatment-emergent ADA, defined as either treatment-induced or treatment-boosted ADA; the percentage of patients fulfilling this criterion in the ADA analysis set is known as ADA incidence.
- Treatment-emergent ADA persistently positive, defined as treatment-emergent ADA+ patients 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.
- Treatment-emergent ADA transiently positive, defined as treatment-emergent ADA+ patients having at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive.
- nAb positive at any visit (baseline or post-baseline).

3.6 [redacted]

[redacted]

[redacted]

3.7 Other variables

3.7.1 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.

For the purpose of inclusion in prior and/or concomitant mediation or therapy summaries, missing start and stop dates for medications and procedures will be handled using the rules described in Section 3.3.10.2.

Prior medications, concomitant and post-treatment medications are defined based on imputed start and stop dates as follows:

- Prior therapies are defined as those taken prior to study treatment with a stop date prior to the first dose of study treatment.
- Concomitant therapies and procedures are defined as those with a stop date on or after the first dose date of study treatment (and could have started prior to or during treatment).
- Post-treatment therapies are those with a start date after the last dose date of study treatment.

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

4 ANALYSIS METHODS

4.1 General principles

Efficacy data will be summarised and analysed using both the HER2-positive and HER2-expressing FAS for the primary analyses, both the HER2-positive and the HER2-expressing RES for supplementary analyses, and both the HER2-positive and HER2-expressing FAS for PFS and OS sensitivity analyses, as specified in Table 4. Safety and treatment exposure data will be summarised based upon the SAF. Study population and demography data will be summarised based upon the HER2-positive FAS and the ITT analysis set as specified in Table 4. PK data will be analysed using the PK analysis set. ADAs will be summarised using the T-DXd ADA evaluable set. Study day will be relative to the date of first dose of study treatment, unless a patient discontinued prior to receiving treatment, in which case study day will be relative to date of enrolment.

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

- Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, upper and lower quartiles, minimum, and maximum. For log-transformed data it is more appropriate to present geometric mean, CV, median, minimum and maximum. Categorical variables will be summarised 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.

- For categorical data, percentages will be rounded to 1 decimal place.

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

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

The last observation before the first dose of study treatment will be considered the baseline measurement. 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 CSP to be conducted before the first dose.

If two visits are equally eligible to assess status at baseline (e.g., screening and baseline assessments both on the same date with no time recorded), the average will be used as the baseline value. In the scenario where there are two assessments recorded on the same day, one with time recorded and the other without time recorded, the one with the time recorded would be selected as baseline.

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

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 (post-baseline value – baseline value) / baseline value x 100.

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 Analysis methods

4.2.1 [redacted]

[redacted]

4.2.2 Objective response rate

The ORR will be based on all scans regardless of whether they were scheduled or not. The primary endpoint, confirmed ORR as assessed by ICR based on the HER2-positive FAS, will be estimated and presented as the number (%) of patients along with the corresponding exact 95% Clopper-Pearson CI. A summary will be produced that presents the number and percentage of patients with a confirmed tumour response (CR/PR).

As a supplementary analysis to the primary endpoint. the primary analysis for the primary endpoint will be repeated for confirmed ORR as assessed by ICR based on the HER2-positive RES.

For the secondary endpoint of ORR in the HER2-positive population, the primary analysis for the primary endpoint will be repeated using investigator assessments for patients in the HER2-positive FAS.

For the secondary endpoint of ORR in the HER2-expressing population, the primary analysis for the primary endpoint will be repeated based on the HER2-expressing FAS, using both ICR and investigator assessments. The supplementary analysis for the primary endpoint will be repeated for this secondary endpoint based on the HER2-expressing RES using ICR assessments only.

Subgroup analysis

Subgroup analyses will be conducted for the primary endpoint, comparing ORR in the following subgroups of the HER2-positive FAS:

- Lines of prior systemic therapy (2 versus 3 versus ≥ 4)
- Age at enrolment (< 65 versus ≥ 65 years)
- Sex (male versus female)
- ECOG Performance status (0 versus 1)
- HER2 status by central lab (IHC 3+ versus IHC 2+/ISH positive)
- Primary tumour location (gastric versus GEJ)
- Histological subtype (intestinal versus diffuse versus others)
- Number of metastatic sites (< 2 versus ≥ 2)

- Previous total gastrectomy (yes versus no)
- Prior adjuvant/neoadjuvant therapy (yes versus no)
- Prior treatment with irinotecan or other topoisomerase I inhibitors (yes versus no)
- Prior treatment with taxane chemotherapy (yes versus no)
- Prior treatment with checkpoint inhibitor or other immuno-oncology therapy (yes versus no)
- Presence of liver metastasis at baseline (yes versus no)
- Renal impairment at baseline (normal versus mild versus moderate)
    - Renal impairment status is determined by the baseline CrCl (calculated using the Cockcroft-Gault equation) (normal renal function: CrCl ≥90 mL/min versus mild renal impairment: CrCl ≥60, <90 mL/min versus moderate renal impairment: CrCl ≥30, <60 mL/min)

This subgroup analysis will also be conducted for the secondary endpoint comparing ORR in the HER2-expressing FAS, but the HER2 status by central lab will include IHC 2+/ISH – as an additional subgroup.

4.2.2.1 Best objective response

BoR will be summarised by number (%) for each category (confirmed CR, confirmed PR, SD, NED, PD and NE). The number (%) of patients with a single visit response (i.e., an unconfirmed response) will be presented. No formal statistical analyses are planned for BoR.

The BoR summaries will be presented for the ICR and investigator assessments for the HER2-positive FAS and the HER2-expressing FAS.

Concordance of BoR between ICR and investigator assessments will be summarised in a cross tabulation presenting the number (%) in each cell for the HER2-positive FAS only.

[redacted]

4.2.3 Progression free survival

The treatment status at progression of patients at the time of analysis will be summarised. 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 a distribution of the number of days prior to progression for the patients who have discontinued treatment.

A Kaplan-Meier plot of PFS will be presented. A summary of the number and percentage of patients experiencing a PFS event and the type of event (RECIST 1.1 or death) will be provided along with the median PFS, upper and lower PFS quartiles, and corresponding 95% cIs, calculated using the Brookmeyer-Crowley method with log-log transformation (Brookmeyer & Crowley, 1982; Klein & Moeschberger, 1997).

The percentage of patients alive and progression-free at 3-monthly intervals from first dose (Kaplan-Meier estimates) will be presented along with 95% CI.

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

The PFS summaries and plots will be presented for the ICR and investigator assessments for the HER2-positive FAS and the HER2-expressing FAS.

All of the collected RECIST 1.1 data will be listed for all enrolled patients. In addition, a summary of new lesions (i.e. sites of new lesions) will be produced.

4.2.4 Disease control rate

The DCR will be estimated and presented with the corresponding exact 95% Clopper-Pearson CI at each DCO, for both ICR and investigator assessments.

DCR at 12 weeks (as defined in Section 3.2.3) will also be summarised.

The number and percentage of patients meeting the definition of disease control will be presented for both the ICR and the investigator assessments.

These summaries for DCR will be presented for the HER2-positive FAS and the HER2-expressing FAS.

4.2.5 Duration of response

Kaplan-Meier plots of DoR will be presented. Median DoR will also be summarised calculated from the KM curve, and its corresponding 95% CI, calculated using the Brookmeyer-Crowley method with log-log transformation (Brookmeyer & Crowley, 1982; Klein & Moeschberger, 1997). Only patients who have a confirmed complete response or confirmed partial response will be included in this summary table. Swimmer plots that clearly show the profile of each patient who responds may also be produced.

Duration of response summaries will be presented for both the ICR and investigator assessments, for the HER2-positive FAS and the HER2-expressing FAS.

4.2.6 Tumour size change

The best change in TL tumour size from baseline (where best change in TL size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction) will also be summarised. The number and percentage of patients whose best percentage change data is imputed will also be presented.

Tumour size may also be presented graphically using waterfall plots, to present each patient's best percentage change in TL tumour size as a separate bar, with the bars ordered from the largest increase to the largest decrease. Reference lines at the -30% and 20% change in TL tumour size level will be added to the plots, which corresponds with the definition of 'partial response' and 'progressive disease', respectively. All progressions will be marked with a '●' or designated with patterns or colours for ORR categories. The scale in these plots will be fixed to be from -100 to 100 to avoid presenting extreme values. Values that are capped as a result of this restriction to the scale are marked with '#'. Values are ordered in descending order.

Additionally, a 'spider' plot will be produced. This depicts each patient's percentage change in TL tumour size as a line over time and progression due to non-target and/or new lesions will be indicated. Reference lines at the -30% and 20% change in TL tumour size level will be added to the plots, which corresponds with the definition of 'partial response' and 'progressive disease', respectively.

These summaries will be repeated for both the ICR and investigator assessments, for both the HER2-positive FAS and the HER2-expressing FAS.

4.2.7 Overall survival

A Kaplan-Meier plot will be presented for OS for the HER2-positive FAS. Summaries of the number and percentage of patients who have died, those still in survival follow-up, those lost

to follow-up and those who have withdrawn consent will be provided along with the median OS and corresponding 95% confidence interval, calculated using the Brookmeyer-Crowley method with log-log transformation (Brookmeyer & Crowley, 1982; Klein & Moeschberger, 1997).

The percentage of patients alive at 3-monthly intervals (Kaplan-Meier estimates) will be presented along with 95% CI.

In addition, median duration of follow-up and range of follow-up (minimum – maximum) will be summarised where duration of follow-up is defined as time from enrolment 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.

These summaries will be repeated for the HER2-expressing FAS.

4.2.8 PK

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-1181a will be summarised by nominal sample time using standard summary statistics for PK concentrations geometric mean (calculated as exp [μ], where μ is the mean of the data on a logarithmic scale), geometric standard deviation (calculated as exp[standard deviation in log scale]), geometric coefficient of variation (calculated as 100 √ [exp(s2) - 1], where s is the standard deviation of the data on a log scale), arithmetic mean, standard deviation, minimum, median, 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 modelling approach. The results of such an analysis, if conducted, will be reported in a separate report. The PK, pharmacodynamics, demographic, safety, and efficacy data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK-PD (pharmacokinetic-pharmacodynamic) methods.

Precision and Rounding Rules for Pharmacokinetic Data

For concentration data, the listings will be presented to the same number of significant figures as the data received from the bioanalytical laboratory. All descriptive statistics will be presented to 4 significant figures with the exception of the minimum and maximum which

will be presented to 3 significant figures, and n and n < LLOQ which will be presented as integers.

4.2.9 Immunogenicity

A summary of the number and percentage of patients who developed detectable ADA to T-DXd by ADA categories (see Section 3.5 for categories) will be presented based on the T-DXd ADA evaluable set.

Immunogenicity results of all patients in the SAF will be listed regardless of ADA evaluable status. ADA titre and neutralising 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 will be evaluated, if the data allow.

4.2.10 Safety

Safety and tolerability data from all cycles of treatment will be combined. The SAF will be used for reporting of safety data. Safety summaries will be descriptive only. No formal statistical analyses will be performed on the safety variables.

4.2.10.1 Adverse events

All treatment emergent AEs (TEAEs) observed on or after the date of first dose until 40 (+ 7) 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 is earlier) and AEs with an onset prior to dosing that worsened in severity or seriousness during this period are included in the summaries. This will more accurately depict AEs attributable to study treatment only, as some AEs up to 40 (+7) days following discontinuation of the study treatment are likely to be attributable to subsequent therapy. Any other AEs will be flagged in the data listings but not included in the summaries. Any AE occurring before the first dose of study treatment which does not worsen during treatment, will be referred to as ‘pre-treatment’.

All AEs, both in terms of current MedDRA preferred term and CTCAE grade, will be summarised descriptively by count (n) and percentage (%).

Summary information (the number and percent of patients) by system organ class (SOC) and/or preferred term (PT) will be tabulated for:

- All AEs

- Most common AEs
- All AEs possibly related to study treatment (*)
- AEs by maximum reported CTCAE grade (*)
- AEs with CTCAE grade 3 or higher (*)
- AEs with CTCAE grade 3 or higher possibly related to study treatment
- Most common AEs with CTCAE grade 3 or higher
- AEs with outcome of death
- AEs with outcome of death possibly related to study treatment
- All SAEs (*)
- All SAEs possibly related to study treatment
- AEs leading to discontinuation of study treatment (*)
- AEs leading to discontinuation of study treatment, possibly related to study treatment
- AEs leading to dose interruption of study treatment (*)
- AEs leading to dose interruption of study treatment, possibly related to study treatment
- AEs leading to dose reduction of study treatment (*)
- AEs leading to dose reduction of study treatment, possibly related to study treatment
- AEs leading to hospitalisation

An overview of AEs will be presented, including the number and percentage of patients in each of the categories above as well as the number and percentage of patients with dose modifications of study treatment (including discontinuation, interruption and/or reduction) The MedDRA dictionary (latest or current version) will be used for coding.

Summary information (the number and percent of patients) by Grouped Term will be presented for those categories marked with (*) for the following Grouped Terms: abdominal pain, anemia, lymphopenia, neutropenia, thrombocytopenia, stomatitis, leukopenia, upper

respiratory tract infection, headache, rash, fatigue, transaminases increased, hypokalemia, musculoskeletal pain, skin hyperpigmentation, blood bilirubin increased and vision blurred. Note that this list may be modified after review of the data. An additional overview table will be presented, tabulating the number and percentages of patients who experience the AE alongside the worst outcome experienced (as a percentage of the number reporting that AE), median time to onset and the duration of the first occurrence of that AE. Included in this table will be the Grouped Terms mentioned previously with the following selected preferred terms: constipation, decreased appetite, diarrhoea, febrile neutropenia, nausea and vomiting.

For the AE tables of most common AEs, all events will be summarised by preferred term, by decreasing frequency. A cut-off may be applied after review of the data for the CSR. 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%).

An additional AE summary will be presented for pre-treatment AEs and AEs which started more than 47 days after last dose of study treatment or after the start of subsequent anti-cancer therapy.

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. A separate listing will be created for pre-treatment AEs.

Frequencies and percentages of patients reporting each PT will be presented (i.e. multiple events per patient will not be accounted for apart from on the episode level summaries which may be produced).

Adverse events of special interest

ILD/pneumonitis and LVEF decrease are considered to be AESIs (see Section 3.3.3 for details). AESI categories will be summarised separately unless otherwise specified.

Potential ILD/pneumonitis (AESI-defined ILD cases identified based on MedDRA preferred terms) 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 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 categorised as above. Maximum CTCAE grade per adjudication committee will also be summarised 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 summarised.

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 LVEF decrease, categories will be based on preferred terms provided by the patient safety team prior to database lock. All preferred terms provided by the patient safety team will be listed and the listing will identify those present in the study.

The number (%) of patients who have at least one AESI, at least one AESI causally related to study treatment, at least one AESI of grade 3 or higher, at least one serious AESI, at least one AESI with outcome of death, at least one AESI leading to discontinuation of study treatment, at least one AESI leading to drug interruption and at least one AESI leading to dose reduction 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.

Adverse events with confirmed/suspected COVID-19 infection

Summary information (the number and percent of patients) by COVID-19 Preferred Terms will be tabulated for all TEAEs with confirmed/suspected COVID-19 infection. An overview of TEAEs with confirmed/suspected COVID-19 infection will be presented, including the number and percentage of patients in each of the categories listed above. Key subject information for each and all AEs with confirmed/suspected COVID-19 infection will be listed.

Deaths

A summary of all deaths will be provided with the number and percentage of patients categorised as based on the ITT analysis set:

- Total number of deaths (regardless of date of death)
- Death related to disease under investigation only as determined by the investigator
- SAE with outcome of death only
    - Sub-category: SAE with outcome of death only and onset date > 47 days following last dose of study treatment (*)
- Death related to disease under investigation, as determined by the investigator, and AE with outcome of death
    - Sub-category: Primary cause of death due to AE.
- Other deaths

This summary will be repeated for all deaths on treatment (considered within the period from first dose of study treatment to 47 days after the last dose of study treatment). The category marked (*) will not appear in this summary.

4.2.10.2 Exposure

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

- Total exposure
- Actual exposure
- Summary statistics (mean, standard deviation, median, quartiles, minimum and maximum) of RDI
- Summary of dose infusion interruptions, reductions and cycle delays
- Number of treatment cycles.

4.2.10.3 Vital signs

Summaries of vital signs data will include all data obtained until 47 days after the last dose of study treatment. Absolute values and change from baseline for diastolic and systolic BP, pulse rate, respiratory rate, temperature and body weight will be summarised at each visit. The denominator in vital signs data should only include those patients with recorded data.

4.2.10.4 ECGs

ECG data obtained up until 47 days after the last dose of study treatment will be included in the summaries. Absolute values and change from baseline for ECG heart rate, PR interval, QRS duration, QT interval, and RR interval will be summarised at each visit.

Overall evaluation of ECG is collected in terms of normal or abnormal, and the relevance of the abnormality is termed as "clinically significant" or "not clinically significant". ECG evaluations will be summarised using a shift table of baseline to worst evaluation on-treatment during the study.

4.2.10.5 Laboratory measurements

Laboratory data obtained up until 47 days following 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 included in the summary tables.

All laboratory data will be listed. Flags will be applied to values falling outside reference ranges.

Absolute values and change from baseline for all continuous haematology and clinical chemistry laboratory parameters will be summarised 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 CTCAE grade will be produced and for specific parameters separate shift tables indicating hyper- and hypo-directionality of change will be produced. The laboratory parameters for which CTCAE grade shift outputs will be produced are:

- Haematology: Haemoglobin, platelet count, leukocytes (absolute count), differential leukocytes count (neutrophils, lymphocytes)
- Clinical chemistry: serum creatinine, total bilirubin, albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), corrected calcium (Ca) (hypo- and hyper-), potassium (K) (hypo- and hyper-), sodium (Na) (hypo- and hyper-), magnesium (hypo- and hyper-) and glucose
- Coagulation: activated partial thromboplastin time (aPTT).

For the parameters with no CTCAE grading that are listed in the CSP, shift tables from baseline to worst value on treatment will be provided if there are abnormal results. Additional summaries will include a shift table for categorical urinalysis parameters comparing baseline value to maximum value.

The denominator used in laboratory summaries of CTCAE grades will only include evaluable patients. If a CTCAE criterion involved a change from baseline, evaluable patients are those who have both a pre-dose and at least 1 post-dose value recorded. If a CTCAE criterion does not consider changes from baseline. Evaluable patients are those who have at least 1 post-dose value recorded.

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 upper limit of normal (ULN) during the study.
    - AST ≥3x – ≤5x, >5x – ≤8x, >8x – ≤10x, >10x – ≤20x, and >20x ULN during the study.
    - Total bilirubin >1.5 – ≤2x, >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 an increase in ALP: the onset date of ALT or AST elevation should be prior to or on the date of total bilirubin elevation.

Narratives may be provided in the CSR for patients who have ALT ≥3x ULN plus total bilirubin ≥2x ULN or AST ≥3x ULN plus 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) will be plotted. Individual patient data where ALT or AST plus total bilirubin are elevated at any time will be listed also.

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.

4.2.10.6 WHO/ECOG performance status

All WHO/ECOG performance status data will be listed. A shift table will be presented, from baseline to worst evaluation during treatment.

4.2.10.7 Pulmonary assessments

SpO_2 will be summarised for each visit.

4.2.10.8 Eligible HBV infection

A summary of patients with Hepatitis B at baseline will be presented, as well as a summary of first on-study reactivation for patients with reactivation. Hepatitis B reactivation will also be listed, including time to principal investigator (PI) confirmation (including any repeating episodes [PI confirmations]), length of delay to treatment, duration on drug after restart, and RECIST assessments during the delay.

4.2.10.9 Other safety assessments

ECHO/MUGA scan results and ophthalmologic findings will be listed.

Summaries of data collected for suspected ILD/pneumonitis investigation may be presented in patient narratives.

A summary of baseline LVEF % will be presented, both continuous and categorical (see Section 3.3.9.1). [redacted] Absolute value and change from baseline for the minimum LVEF value post-baseline will be presented, both continuous and categorical (see Section 3.3.9.1).

4.2.11 Demographics and baseline characteristics

The following will be summarised and/or listed for all patients in the HER2-positive FAS and the ITT analysis set (as appropriate):

- Patient disposition (including screening failures and reason for screening failure)
- Important protocol deviations
- Inclusion in analysis sets

- Demographics (age, age group[<50, ≥ 50 - < 65, ≥ 65 - < 75 and ≥ 75 years], sex, race and ethnicity)
- Patient characteristics at baseline (height, weight, weight group, BMI group)
- Patient recruitment by centre
- Previous disease-related treatment modalities
- Prior systemic therapy lines
- Disease characteristics at baseline (ECOG performance status, primary tumour location, histology type, tumour grade, AJCC stage, time from diagnosis to start of study treatment and overall disease classification)
- Extent of disease at baseline
- TNM classification at baseline
- Disease related medical history (past and current)
- Relevant surgical history
- Post-discontinuation cancer therapy
- Nicotine use, categorised (never, current, former)
- Pulmonary function test at baseline
- Pulmonary medical history
- Baseline HER2 status (IHC/ISH) from local and central testing.
- Sum of diameters at baseline based on ICR

The medications will be coded using the latest version of MedDRA.

4.2.12 Concomitant and other treatments

Information on any treatment within the four weeks prior to initiation of study drug and all concomitant treatments given up to 47 days after discontinuation of study treatment, or objective disease progression (whichever is later), with reasons for the treatment, will be

recorded in the eCRF. Thereafter, only subsequent regimens of anti-cancer therapy will be recorded in the eCRF.

Other anti-cancer therapies, investigational agents, and radiotherapy should not be given while the patient is on study drug.

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 summarised for the FAS, RES and ITT analysis set (as appropriate) by ATC classification codes.

The following summaries will be produced for the HER2-positive FAS and the ITT analysis set:

- 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.

4.2.13 COVID-19

Summaries of data relating to patients diagnosed with coronavirus 2019-nCoV (COVID-19), and the impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued study treatment, and other protocol deviations) may be generated, including:

- Disposition (discontinued study treatment due to COVID-19 and withdrew study due to COVID-19)
- Deviations (overall deviations plus if due to COVID-19 and not due to COVID-19)
- Summary of COVID-19 disruption (visit affected, drug affected, concomitant medication affected, or withdrew from study due to global/country situation)
- Treatment impacted due to COVID-19 (number of cycles impacted, duration of impact).
- Listing for patients affected by the COVID-19 pandemic.

- Listing for patients with reported issues in the Clinical Trial Management System due to the COVID-19 pandemic.

Additional summaries and sensitivity analyses may be conducted to investigate the impact of COVID-19 on study endpoints. In these sensitivity analyses, any patient who had a death with primary or secondary cause as COVID-19 infection will be censored at their COVID-19 infection death date. COVID-19 deaths will be identified by primary/secondary cause of death.

4.2.14 [redacted]

[redacted]

5 [redacted]

[redacted]

6 CHANGES OF ANALYSIS FROM PROTOCOL

Supplementary analyses based on the RES will only be presented for confirmed ORR by ICR, for both the HER2-positive RES and the HER2-expressing RES.

An additional analysis of best overall response will be conducted, including unconfirmed response (PR and CR) as a response.

[redacted]

No sensitivity analyses will be performed for PFS or OS.

SAEs which onset or worsen after the end of safety follow-up and are considered to be related to the study treatment will not be defined as treatment emergent AEs.

7 REFERENCES

Brookmeyer, R., & Crowley, J. A. (1982). Confidence Interval for the Median Survival Time. *Biometrics*, 38:29-41.

Klein, J., & Moeschberger, M. (1997). *Survival Analysis: Techniques for Censored and Truncated Data.* New York: Springer-Verlag.

8 APPENDIX

Not applicable.

[redacted]

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