Statistical Analysis Plan	
Study Code	D9266C00001
Edition Number	2.0
Date	30Aug2023

Phase 1/2, Multicentre, Open-label, Multiple-cohort Study of Dato-DXd in Chinese Patients With Advanced Non-small-cell Lung Cancer, Triple-negative Breast Cancer, Gastric/Gastroesophageal Junction Cancer, Urothelial Cancer, and Other Solid Tumours

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation or Special Term	Explanation
ADA	anti-drug antibody
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse event of special interest
AGA	actionable genomic alteration
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-}17d}$	area under the curve from 0 to 17 days
AUC_{tau}	area under the plasma concentration-time curve during the dosing interval
BOR	best overall response
BP	blood pressure
CI	confidence interval
CL	total body clearance
C_{max}	maximum observed concentration
COVID-19	coronavirus 2019-nCoV
CR	complete response
CRF	case report form
CrCL	creatinine clearance
CRO	Contract Research Organisation
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	computed tomography
CTCAE 5.0	National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0
Dato-DXd	datopotamab deruxtecan
DCO	data cut-off
DCR	disease control rate
DFI	disease-free interval
DoR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram

Abbreviation or Special Term	Explanation
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
FAS	full analysis set
GEJ	gastroesophageal junction
HL	Hy's Law
HRCT	high-resolution CT
ICF	informed consent form
ICR	independent central review
iCRO	imaging CRO
ILD	interstitial lung disease
IPD	important protocol deviation
IRR	infusion-related reaction
LLOQ	Lower Limit of Quantification
LVEF	left ventricular ejection fraction
MAAA-1181a	Released drug in datopotamab deruxtecan
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MUGA	multigated acquisition
NAbs	neutralising antibodies
NA	not applicable
NE	not evaluable
NED	no evidence of disease
NSCLC	non-small-cell lung cancer
NTL	non-target lesion
OAE	other significant adverse events
OCP	oral care plan
ORR	objective response rate
OS	overall survival
PD	progression of disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PK	Pharmacokinetic(s)

Abbreviation or Special Term	Explanation
PR	partial response
PT	Preferred Term
Q3W	every 3 weeks
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 event
SAP	Statistical Analysis Plan
SD	stable disease
SoA	Schedule of Activities
SoC	standard of care
SpO_2	peripheral capillary oxygen saturation
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
TL	target lesion
T_{max}	time to C_{max}
TMG	toxicity management guideline
TNBC	triple-negative breast cancer
TROP2	trophoblast cell surface protein 2
TTR	time to response
ULN	upper limit of normal
WHO	World Health Organisation

AMENDMENT HISTORY

Date	Brief description of change
30Aug2023	• Derivation of RECIST visit responses by investigator review is updated according to AZ latest guidance. The TL visit responses subsequent to CR and overall visit response derivation has been updated. • On treatment definition has been added to section 3.3.9.1, to clarify the analysis period for summarising safety data. • The dose delay window has been update to +3 days according to CSP V4.0 SoA. • Safety follow-up duration calculation has been updated according to AZ latest guidance. • Weight and BMI group has been clarified for summary of patient characteristics at baseline. • AUCtau and Ctrough were added for PK analysis. • Death with no evaluable RECIST assessment will be considered as NE if occurred after > [redacted] days after first dose of study treatment. • Definition of immunogenicity variables have been updated in section 3.5. • Updated the subgroup analyses in section 4.2.1, to indicate that subgroup analyses may be conducted for Cohort 1. • The definition of PFS 2 missed visit has been updated in table 8.

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 3.0 of the CSP.

1.1 Study objectives

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

Table 1 Study objectives and corresponding endpoints

Objectives	Endpoints
Primary	
To estimate the effectiveness of Dato-DXd by assessment of confirmed ORR by ICR.	Confirmed ORR is defined as the proportion of participants in each cohort who have a confirmed CR or confirmed PR, as assessed by ICR per RECIST 1.1. The measure of interest is the estimate of confirmed ORR.
Secondary	
To estimate the effectiveness of Dato-DXd by assessment of confirmed ORR by investigator assessment.	Confirmed ORR is defined as the proportion of participants in each cohort who have a confirmed CR or confirmed PR, as determined by investigator assessment per RECIST 1.1.
To estimate the effectiveness of Dato-DXd by assessment of DoR.	Duration of response is defined as the time from the date of first documented response (which is subsequently confirmed) until date of documented progression per RECIST 1.1, as assessed by ICR and by investigator, or death due to any cause.
To estimate the effectiveness of Dato-DXd by assessment of DCR.	Disease control rate is defined as the percentage of participants who have a confirmed CR or PR or who have SD per RECIST 1.1, as assessed by ICR and by investigator.
To estimate the effectiveness of Dato-DXd by assessment of BOR.	Best overall response is defined as participant's best confirmed response during their participation in the study, but prior to starting any subsequent anticancer therapy, up until RECIST 1.1-defined PD or the last evaluable assessment in the absence of RECIST 1.1-defined progression. Best overall response will be assessed by ICR and by investigator per RECIST 1.1.

Objectives	Endpoints
To estimate the effectiveness of Dato-DXd by assessment of TTR.	Time to response is defined as the time from the date of the first dose of study intervention until the date of first documented objective response, which is subsequently confirmed per RECIST 1.1, as assessed by ICR and by investigator.
To estimate the effectiveness of Dato-DXd by assessment of PFS.	Progression-free survival is defined as time from the date of the first dose of study intervention until progression per RECIST 1.1, as assessed by ICR and by investigator, or death due to any cause.
To estimate the effectiveness of Dato-DXd by assessment of OS.	Overall survival is defined as the time from the date of the first dose of study intervention to the date of death due to any cause.
To assess the safety and tolerability of Dato-DXd.	Safety and tolerability are evaluated in terms of TEAEs, AESIs including ILD evaluated by an independent adjudication committee, vital signs, and clinical laboratory, ECG, ECHO/MUGA parameters, and ophthalmologic findings.
To evaluate the PK of Dato-DXd.	Plasma concentrations and appropriate PK parameters of Dato-DXd, total anti-TROP2 antibody, and MAAA-1181a (DXd) will be calculated for participants with PK samples if data permit.
To investigate the immunogenicity of Dato-DXd.	The presence of ADAs against Dato-DXd will be evaluated. Titre will be determined when ADA is positive.
Exploratory	
To investigate the association of a biomarker (TROP2) with response (ORR, PFS, and OS) to Dato-DXd.	Expression of TROP2 will be measured in tumour samples.

1.2 Study design

This is a Phase 1/Phase 2, multicentre, open-label, multiple-cohort study, which is designed to evaluate the efficacy, safety, PK, and immunogenicity of Dato-DXd in adult Chinese participants with advanced or metastatic solid tumours. It is a single-arm study with no blinding.

This study is divided into cohorts of participants with the same tumour type. The starting cohorts are Cohort 1 (NSCLC) and Cohort 2 (TNBC). Future cohorts will consist of other advanced or metastatic solid tumour types, including, but not limited to, advanced/unresectable or metastatic gastric or GEJ adenocarcinoma or urothelial carcinoma that is refractory or intolerant to SoC therapy or for which no SoC therapy is available.

Cohort 1 and Cohort 2 will be prioritised for immediate enrolment and the CSP will be amended as needed for the future cohorts.

Cohort 1: The target population of Cohort 1 is adult Chinese participants with advanced or metastatic NSCLC with or without AGAs (ie, alterations in genes with approved therapies, such as *EGFR, ALK,* or other known AGAs). Eligible participants without AGAs will have been previously treated with platinum-based chemotherapy and anti-PD-1/anti-PD-L1 monoclonal antibody either in combination or sequentially. Participants without AGAs who received anti-PD-1/anti-PD-L1 monoclonal antibody as frontline therapy may have received the combination of platinum-based chemotherapy and anti-PD-1/anti-PD-L1 monoclonal antibody in the second-line setting. Eligible participants with AGAs will have been previously treated with one or two prior lines of an applicable targeted therapy that is approved for the participant's genomic alteration and platinum-based chemotherapy as the only prior line of cytotoxic therapy. Participants with AGAs may have received up to one anti-PD-1/anti-PD-L1 monoclonal antibody treatment alone or in combination with chemotherapy. A total of approximately 40 eligible participants in China will be enrolled in this cohort. Cohort 1 will enrol approximately 6 participants with AGAs.

Cohort 2: The target population of Cohort 2 is adult Chinese participants with inoperable locally advanced or metastatic TNBC who have received at least 2 prior chemotherapy regimens for advanced breast cancer, counting the (neo)adjuvant therapy as a prior chemotherapy regimen if progression occurred within 12 months after completion of the therapy (DFI ≤ 12 months). A total of approximately 78 eligible participants in China will be enrolled in this cohort. Cohort 2 will enrol at most around 20% (approximately N=15) of enrolled participants with a DFI ≤ 12 months.

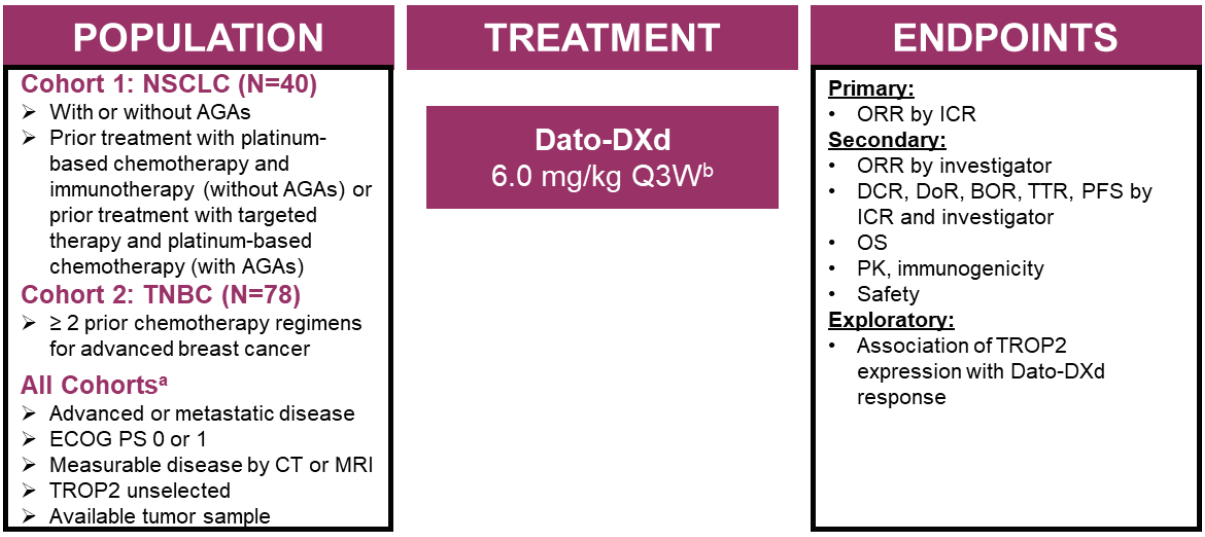
Enrolled participants will be treated with Dato-DXd at 6.0 mg/kg via an IV infusion on Day 1, Q3W.

Note: 'Screened' means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process.
'Enrolled' means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process and the participant is confirmed as eligible. Potential participants who are screened for the purpose of determining eligibility for the study, but are not enrolled, are considered 'screen failures.'

The primary objective of the study is to estimate the effectiveness of Dato-DXd by assessment of confirmed ORR by ICR.

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

Figure 1 Overview of study design



[a] Additional cohorts may include, but are not limited to, advanced/unresectable or metastatic gastric or gastrointestinal junction adenocarcinoma or urothelial carcinoma that is refractory or intolerant to SoC therapy or for which no SoC therapy is available.

[b] Study intervention will be delivered via intravenous infusion and continue until one of the criteria for discontinuation is met.

AGA, actionable genomic alteration; BOR, best overall response; CT, computed tomography; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ICR, independent central review; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; TNBC, triple-negative breast cancer; TROP2, tumour-associated calcium signal transducer 2; TTR, time to response.

1.3 CCI

Sample size justification for Cohort 1 – NSCLC

Approximately 40 eligible NSCLC participants will be enrolled to have preliminary efficacy and safety data for Dato-DXd. If the observed ORR by ICR is CCI the 95% two-sided CI based on 40 participants is CCI If the observed ORR is CCI the two-sided 95% CI is CCI If the observed ORR is CCI the two-sided 95% CI is CCI The sample size will also provide reasonable utility for safety analyses. With a sample size of 40 participants, the probability of observing one or more instances of a specific AE with a true incidence rate of 1%, 2%, and 5% is 33.1%, 55.4%, and 87.1%, respectively.

For CCI of the 40 eligible NSCLC participants without measurable disease at baseline by ICR, the information below shows the observed ORR (95% CI) based on the RES with CCI participants without measurable disease at baseline as assessed by ICR.

Number of participants in RES	Number of observed responders	Observed ORR (95% CI)
CCI of participants without measurable disease at baseline as assessed by ICR)	CCI	
CCI of participants without measurable disease at baseline as assessed by ICR)	CCI	

Sample size justification for Cohort 2 – TNBC

Approximately 78 eligible TNBC participants will be enrolled to have preliminary efficacy and safety data for Dato-DXd. Seventy-eight participants will CCI . The sample size will also provide reasonable utility for safety analyses. With a sample size of 78 participants, the probability of observing one or more instances of a specific AE with a true incidence rate of 1%, 2%, or 5% is 54.3%, 79.3%, 98.2%, respectively.

For CCI of the 78 eligible TNBC participants without measurable disease at baseline as assessed by ICR, the information below shows the observed ORR CCI based on the RES with CCI participants without measurable disease at baseline by ICR.

Number of participants in RES	Observed ORR % (n/N)	CCI
CCI of participants without measurable disease at baseline by ICR)	CCI	CCI
CCI of participants without measurable disease at baseline by ICR)	CCI	CCI

2 ANALYSIS SETS

2.1 Definition of Analysis Sets

Analysis populations for this study are defined in Table 2. A summary of the analysis populations used for each outcome variable is provided in Table 3.

Table 2 Populations for Analysis

Population/Analysis Set	Description
Enrolled	All participants who provide informed consent and the participants are confirmed as eligible irrespective of whether they received the study treatment.
FAS	Enrolled participants who have received at least one dose of treatment. Participants who were enrolled but did not subsequently receive study intervention are not included in the analysis.
RES	Enrolled participants who received at least one dose of study intervention and had measurable disease at baseline by ICR.
PK analysis set	Enrolled participants who have received at least one dose of treatment and had measurable plasma concentrations of Dato-DXd.
ADA evaluable set	Participants in the FAS with a non-missing baseline Dato-DXd ADA result and at least one post-baseline Dato-DXd ADA result.

ADA, anti-drug antibody; FAS, full analysis set; ICF, informed consent form; ICR, independent central review; PK, pharmacokinetic; RES, response evaluable set.

Table 3 Summary of Outcome Variables and Analysis Populations

Outcome Variable	Population(s)
Primary Efficacy Variable	
Confirmed ORR by ICR per RECIST 1.1	Primary analysis: RES Supplementary analyses: FAS
Secondary Efficacy Variables	
• Confirmed ORR by investigator assessment per RECIST 1.1 • DoR, DCR, BOR, and TTR by ICR and by investigator assessment per RECIST 1.1	Primary analysis: RES Supplementary analyses: FAS
• PFS by ICR and by investigator assessment per RECIST 1.1 • OS	Primary analysis: FAS
Baseline and Other Variables	
• Demography, baseline, and disease characteristics • Important deviations • Medical/surgical history • Previous and subsequent anticancer therapy • Concomitant medications/procedures	Primary analysis: FAS

Outcome Variable	Population(s)
Pharmacokinetics	
• Pharmacokinetics data	PK analysis set
Immunogenicity	
• Anti-drug antibodies	ADA Evaluable Set
Safety	
• Exposure to study intervention • Safety data	FAS

DoR analysis will be based on the subset of participants in the RES who achieved confirmed response.
ADA, anti-drug antibody; AEs, adverse events BOR, best overall response; DCR, disease control rate; DoR, duration of response; FAS, full analysis set; ICR, independent central review; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; RECIST 1.1, Response Evaluation Criteria in Solid Tumours Version 1.1; RES, response evaluable set.

2.2 Protocol deviations

The following general categories will be considered important protocol deviations (IPDs) and will be programmatically identified from the electronic Case Report Form (eCRF) data or detected via site monitoring. These will be listed and discussed in the clinical study report (CSR) as appropriate (see protocol deviation plan for more details):

- Patients who deviate from key inclusion criteria per the CSP (Deviation code 1): inclusion criteria 4, 12, 13, 16, 17, 18, 19, 20.
- Patients who deviate from key exclusion criteria per the CSP (Deviation code 2): exclusion criteria 6, 14, 15, 16, 18, 23, 26, 27, 29, 30.
- Discontinuation criteria for study treatment met but patient not withdrawn from study treatment (Deviation code 3).
    - RECIST 1.1-defined radiological progression as assessed by the investigator.
    - An AE that, in the opinion of the investigator or AstraZeneca, contraindicates further dosing.
    - Any AE that meets criteria for discontinuation defined in the dose modification guidelines for management of study intervention-related toxicities.
    - Pregnancy during study treatment period.
- Investigational product deviation (Deviation code 5).
    - Participant received incorrect IP.
    - Participant received incorrect dose of IP.
    - IP non-compliance (as per study specific definition):
        - Enrolled patients who will not start the assigned treatment.
        - Drug interruptions and delayed dosing for more than 4 weeks due to reasons other than AEs.

        - Drug interruptions and delayed dosing for more than 4 weeks due to AEs and the AE was not handled in accordance with TMG annex.
        - For deviations other than above, need to discuss with AZ Study Team to confirm whether the deviation is IPD.
    - Use of expired IP.
- Excluded Medications taken (Deviation code 6).
    - Participant received concomitant medication defined as prohibited in the CSP.
- Deviations to study procedure (Deviation code 7)
    - Missing baseline tumour assessment before enrolment.
    - Baseline tumour assessments performed more than 42 days Before enrolment (Except for bone imaging).
    - Baseline bone imaging performed more than 12 weeks before enrolment.
    - Chest HRCT/chest CT is not performed if ILD/pneumonitis is suspected.
    - Failure to perform the following mandatory safety assessments in ≥ 2 consecutive scheduled visit where assessment is expected:
        - Pregnancy test
        - Hematology and/or Clinical Chemistry Panel
    - Incomplete PK profile collected with which accurate PK parameters cannot be evaluated. PK sample and/or data is missing.
    - For post-baseline tumour assessment: None image scans are performed at all on 2 successive occasions.
- Other Important Protocol Deviations (Deviation code 8).
    - Any deviation considered important that was not predicted or prespecified (e.g. missing PI eCRF Signature).
    - Any study specific IPDs that are not covered by any category above (need to discuss with AZ Study Team to confirm whether the deviation is IPD).

The important protocol deviations will be listed and summarised. The first category (Enrolled patients who will not start the assigned treatment) of IP non-compliance in the Deviation code 5 would lead to exclusion from the FAS and 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. In addition, sensitivity analyses may also be performed on the objective response rate endpoint, CCI .

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 the date of the first dose of study treatment and ideally as close as possible to and prior to the start of study treatment. Tumour assessments are then performed every 6 weeks (± 1 week) from the date of the first dose of study intervention until RECIST 1.1-defined radiological PD by investigator assessment, even if the participant discontinues or delays study intervention or initiates new anticancer therapy unless they have withdrawn all consent to study related assessments. Following CCI [redacted]. The intent of CCI [redacted] The scans from all assessments of tumour response, including the follow-up assessment, will be sent for ICR review.

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, DoR, DCR, BoR, PFS and TTR) will be calculated programmatically for the ICR and 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. Note that lymph nodes also constitute an organ. 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 4 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 if any of the TLs at follow-up were not assessed or not evaluable (e.g., missing anatomy) or had a lesion intervention at this

Visit Responses	Description
	visit. 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.

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 (i.e., smallest sum of diameters in TLs since baseline tumour assessments and before current tumour assessments) 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 short axis diameter 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 i.e. if a lymph node short axis diameter increases by 20% but remains < 10mm.
- Step 3: If not all lesions are missing and those that are non-missing do not meet the CR criteria (i.e. a pathological lymph node selected as TL has short axis >10mm or the reappearance of previously disappeared lesion), then response will be set to PD.
- Step 4: If all lesions are missing the response will be set to NE.

TL too big to measure

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

TL too small to measure

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

Irradiated lesions/lesion intervention

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

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

$68 \times 74 / 62 = 81$mm

CR will not be allowed as a TL response for visits where there is missing data in non-intervened lesions. 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 or more parts

If a TL splits in two or more parts, 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 or more TLs merge, then the LD of the merged lesion should be recorded for one of the TL sizes and the other TL size should be recorded as 0mm.

Change in method of assessment of TLs

CT and MRI are the only methods of assessment that can be used 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.

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 5 NTL Visit Responses

Visit Responses	Description
Complete response (CR)	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10 mm short axis).
Progressive disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Non-CR/Non-PD	Persistence of one or more NTLs with no evidence of progression.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not applicable (NA)	No NTLs are recorded at baseline.

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

Table 6 Overall visit responses

TARGET	NON-TARGET	NEW LESIONS	OVERALL VISIT RESPONSE
CR	CR or NA	No (or NE)	**CR**
CR	Non-CR/Non-PD or NE	No (or NE)	**PR**
PR	Non-PD or NE or NA	No (or NE)	**PR**
SD	Non-PD or NE or NA	No (or NE)	**SD**
PD	Any	Any	**PD**
Any	PD	Any	**PD**
Any	Any	Yes	**PD**
NE	Non-PD or NE or NA	No (or NE)	**NE**
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 intended to assess the response to therapy or to detect disease progression 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, DoR, DCR, BoR, PFS and TTR) 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 Primary variable: Confirmed Objective response rate (ORR) by ICR

The primary variable of the study is confirmed ORR by ICR according to RECIST1.1. Confirmed ORR (per RECIST 1.1 by ICR) is defined as the number (percentage) of patients with a confirmed response of CR or PR as assessed by ICR based on RECIST 1.1.

A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit.

Data obtained up until 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.

3.2.2 Secondary Variables

3.2.2.1 Confirmed ORR by Investigator Assessment

The secondary efficacy endpoint of confirmed ORR is defined as the proportion of participants who have a confirmed CR or PR, as determined by the investigator at local site per RECIST 1.1.

Investigator assessed ORR will be estimated using the same methods as those specified for ORR by ICR (see Section 3.2.1).

3.2.2.2 Duration of Response (DoR)

DoR according to RECIST 1.1 by ICR and investigator assessment will be derived programmatically.

For patients who achieved a confirmed CR or PR per RECIST 1.1, DoR is 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. DoR will not be defined for those patients who do not have documented response.

3.2.2.3 Disease Control Rate (DCR)

DCR according to RECIST 1.1 by ICR and investigator assessment will be derived programmatically.

DCR is defined as the percentage of patients who have a confirmed CR/PR or SD for at least [redacted] weeks (i.e., [redacted] to allow for an early assessment within the assessment window) after the date of the first dose of study intervention (without subsequent anti-cancer therapy, where radiotherapy is not considered as a subsequent anti-cancer therapy) per RECIST 1.1. DCR could be calculated as the percentage of patients with BoR of CR, PR or SD. See Section 3.2.2.4 for the BoR definition.

3.2.2.4 Best Overall Response (BoR)

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 (radiotherapy is not considered as a 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 disease at baseline. For patients with no evaluable RECIST assessments post randomisation, then BoR is assigned to the NE category.

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 [redacted], i.e. at least [redacted] (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 (radiotherapy is not considered as a 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 ≤ [redacted] days (i.e., [redacted] 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 > [redacted] days after first dose of study treatment then BoR will be assigned to the NE category.

3.2.2.5 Time to response (TTR)

TTR according to RECIST 1.1 by ICR and investigator assessment will be derived programmatically.

TTR is defined as the time from the date of the first dose of study intervention to the date of first documentation of confirmed objective response (CR or PR). The date of first documented response should coincide with that used for the DoR endpoint.

TTR will not be defined for those patients who do not have a confirmed response.

3.2.2.6 Progression free survival (PFS)

PFS according to RECIST 1.1 by ICR and investigator assessment will be derived programmatically.

PFS is defined as the time from date of the first dose of study intervention 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 the first dose of study intervention + 1). Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if the patient progresses or dies immediately after two or more consecutive missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the two missed visits (Note: NE visit is not considered as missed visit).

If the participant has no evaluable RECIST assessment or does not have baseline data, they will be censored at the date of first dose, unless they die within 2 scheduled scans of baseline (12 weeks + 1 week allowing for a late assessment within the visit window) in which case they are treated as an event with date of death as the event date. PFS censoring rules are described in Table 7.

Table 7 Outcome and date of event for PFS analysis

Scenario	Date of PD/ Death event or Censoring	PFS Outcome
Progression documented between scheduled visits after at most 1 missed assessment	Date of assessment of progression	Event
Death between assessment visits after at most 1 missed assessment	Date of death	Event
No baseline or evaluable RECIST assessment and death within 2 RECIST visits after the date of first dose	Date of death	Event

Scenario	Date of PD/ Death event or Censoring	PFS Outcome
No baseline or evaluable RECIST assessment and no death within 2 RECIST visits after the date of first dose	Day 1 (Date of first dose)	Censored
No PD or death at time of data cut-off	Date of last evaluable RECIST assessment*	Censored
Death or progression after two or more missed RECIST visits	Date of last evaluable RECIST assessment* prior to the 2 missed visits	Censored

*: if there are no evaluable post-baseline assessments prior to PD or death or data cut-off, participants will be censored at the date of first dose.

Given the scheduled visit assessment scheme (i.e. every 6 weeks from the first dose of study intervention until RECIST 1.1-defined radiological PD) the definition of two missed visits will change over time, as described in Table 8.

Table 8 PFS: Definition of 2 Missed Visits

Previous RECIST Assessment	Two Missed RECIST Visits Window
No evaluable RECIST visits or no baseline RECIST scan	2 x CCI
Day1	2 x CCI
>Day1	2 x CCI

Study day is calculated as (date of assessment – date of the first dose of study intervention + 1)

If the patient has no evaluable visits or does not have baseline data they will be censored at Day 1 (date of the first dose of study intervention) 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.

3.2.2.7 Overall survival (OS)

Overall survival (OS) is defined as the time from the date of the first dose of study intervention 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 the first dose of study intervention + 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 each DCO for the analysis, and if patients are confirmed to be alive or if the death date is post the DCO date these patients will be censored at the date of DCO. The status of ongoing, withdrawn (from the study) and “lost to follow-up” patients at the time of the final OS analysis should be obtained by the site personnel by checking the patient’s notes, hospital records, contacting the patient’s general practitioner and checking publicly-available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

Note: For any OS analysis performed prior to the final OS analysis, in the absence of survival calls being made, it may be necessary to use all relevant 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.

3.3 Safety Variables

3.3.1 Exposure and dose interruptions

Total (or intended) exposure of study treatment

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

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

Actual exposure of study treatment

- Actual exposure = intended exposure – total duration of dose delays, where intended exposure will be calculated as above.

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

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

Dose reductions are permitted and the actual exposure calculation makes no adjustment for any dose reductions that may have occurred.

Number of treatment cycles received

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

Safety follow-up

- Total Safety follow-up (months) = [min (date of safety follow-up assessment or if safety follow-up has not occurred then last dose of IP date + 20, date of study discontinuation, date of death, DCO date) – first dose date +1] / (365.25/12).

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.

Dose intensity – Actual cumulative dose

When deriving actual dose administered the volume before and after infusion will also be considered. For the calculation of actual cumulative dose for Dato-DXd, the proportion of volume left after the infusion will be used to calculate how much of the study drug the participant received, i.e.:

- Volume left (proportion) = $\frac{\text{Volume after infusion}}{\text{Volume before infusion}}$

- Actual cumulative dose = sum over all cycles [(1 – Volume left) x dose]
(where dose is taken from the exposure CRF page for each cycle)

Dose intensity – Intended cumulative dose

Intended cumulative dose is calculated by summing the individual doses that should have been received up to and including the last day of treatment according to the planned dose and schedule.

The intended dose for Dato-DXd is 6mg/kg on Day 1 (+/-3 days) of each 21-day cycle. The minimum of the participants last dose, date of death, date of DCO will be used to calculate the duration the participant has been on the study with dosing intended.

For the calculations below,

DUR = min (date of last dose date where dose > 0, date of death, date of DCO) – first dose date + 1

The intended cumulative dose for Dato-DXd is then calculated as:

6 * [integer ((DUR +3)/ 21) + 1]

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 CCI [redacted] after the last dose of study treatment). In the case of unresolved AESIs including CCI [redacted], 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 Section 8.4.1 of the CSP. Events will be defined as treatment emergent if they onset, or worsen (by investigator report of a change in intensity), 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 Dato-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 data, current clinical developmental program, review of the cumulative literature, reported toxicities for drugs with similar monoclonal antibody and payload of Dato-DXd and biological plausibility, ILD/pneumonitis, IRR, oral mucositis/stomatitis, mucosal inflammation other than oral mucositis/stomatitis, and ocular surface toxicity 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 8.3.1 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 `if` 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 8.3.2 of the CSP: Systolic and diastolic blood pressure (BP), pulse rate, temperature and respiratory rate. Body weight and SpO_2 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 3.3.9.2 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 within 7 days before enrolment, if an abnormality is noted, and at the End-of-Treatment Visit as described in Section 8.3.3 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 as clinically indicated during treatment.

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". Any clinically significant abnormalities detected require triplicate ECG results. At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should be completed within 5 minutes. 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 Laboratory measurements

Blood and urine samples for the determination of clinical chemistry, haematology, coagulation and urinalysis will be collected as described in Section 8.3.4 of the CSP.

For the derivation of baseline and post-baseline visit values, the rules described in Sections 4.1 and 3.3.9.2 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)] × 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).

For parameters with no CTCAE grading that are listed in the CSP any increase/decrease/treatment emergent laboratory change (TELC) is derived, where any increase is an increase to a value above the upper local laboratory reference limit at any time on treatment for participants with a value below the upper local laboratory reference limit at baseline, and any decrease is a decrease to any value below the local laboratory reference range limit at any time on treatment for participants with a value above the lower local laboratory reference limit at baseline. A TELC is defined as any on treatment increase or decrease from baseline.

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.

3.3.8 Other safety assessments

3.3.8.1 Echocardiograms/multigated acquisition scans

Echocardiograms (ECHO)/multigated acquisition (MUGA) scans will be performed as described in Section 8.3.5.1 of the CSP. These will be used to assess the LVEF. The LVEF % and method details will also be reported. Change from baseline of LVEF % will be calculated.

3.3.8.2 Pulmonary assessments

CCI will be measured as described in Section 8.3.5.2 of the CSP.

3.3.8.3 ILD/Pneumonitis investigation

CCI, additional assessments are performed as described in Section 8.3.5.3 of the CSP, including CCI and high resolution CT scan (HRCT).

For the CCI, the following parameters will be measured: CCI, 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.

High-resolution CT of the chest will be performed/encouraged if feasible (otherwise CT is acceptable) CCI. Chest CT and/or chest HRCT scans will be reviewed separately for safety CCI.

3.3.8.4 ECOG performance status

ECOG performance status (PS) will be assessed as described in Section 8.3.5.4 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.

3.3.8.5 IRR Including Anaphylaxis

CCI [redacted]. Participants should remain at the site for at least CCI [redacted] hour post infusion of every dose of Dato-DXd for close observation for possible allergic reaction.

3.3.8.6 Ophthalmologic assessments

Ophthalmologic assessments by a licensed eye care provider will be performed as specified in the SoA in the CSP.

The following assessments will be performed for both CCI [redacted] rescribed, if any.

The preferred method for measuring CCI [redacted] is the CCI [redacted]

CCI

Table 9 CCI

3.3.8.7 Oral Care Plan

A daily OCP will be started before study intervention initiation, and it must be maintained throughout the study. An oral care kit will be provided at study enrolment and at the beginning of each cycle thereafter until the Safety Follow-up Visit, which will include a toothbrush, toothpaste, dental floss, and an alcohol-free mouthwash. An oral care guide will also be provided to each enrolled participant before study drug initiation.

3.3.8.8 Nausea and Vomiting

Based on the currently available clinical safety data, it is recommended that participants receive CCI prior to infusion of Dato-DXd and on subsequent days, as needed.

3.3.9 General considerations for safety assessments

3.3.9.1 On treatment

For the purposes of summarising safety data assessed at visits, in addition to baseline data, only on treatment data are included in the summary tables. On treatment data is defined as

data after the first dose of IP and with assessment date up to and including the date of last IP + CCI or prior to the start of any subsequent cancer therapy, whichever occurs earlier.

3.3.9.2 Time windows

Time windows will be defined for any presentations of safety data 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. 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 1 post dose, visit window 1 – 11(for Cycle 1 Day 1, only post dose assessment will be included)
    - Cycle 2 Day 1, visit window 12 - 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.

3.3.9.3 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.

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 Dato-DXd, total anti-TROP2 antibody, and MAAA-1181a(DXd).

3.5 Immunogenicity Variables

Immunogenicity Variables

The presence of ADAs will be assessed in plasma samples taken according to the SoA in the CSP. ADA samples may be further tested for characterisation of the ADA response. ADA result from each sample is reported as either positive or negative. If the sample is positive, the ADA titre is reported as well. In addition, the presence of neutralizing antibody (nAb) will be

tested for all ADA-positive samples using a ligand-binding assay. The nAb results is reported as positive or negative.

- ADA positive at any visit (at baseline and/or post-baseline). The percentage of these participants in a population is known as ADA prevalence.
- Treatment-induced ADA positive, defined as ADA positive post-baseline and not detected at baseline (negative or missing).
- Treatment-boosted ADA positive, defined as a baseline positive ADA titre that was boosted to a 4-fold or higher-level following drug administration.
- Treatment-emergent ADA positive (TE ADA+), defined as either treatment-induced positive or treatment-boosted ADA positive. The percentage of these participants in a population is known as ADA incidence.
- Non-treatment-emergent ADA positive (non-TE ADA+), defined as being ADA positive but not fulfilling the conditions for treatment-emergent ADA positive.
- ADA positive post-baseline and positive at baseline.
- ADA not detected post-baseline and positive at baseline.
- Treatment-emergent persistently ADA positive, defined as being TE ADA+ and having at least 2 post-baseline ADA positive measurements with ≥ 16 weeks between first and last positive, or an ADA positive result at the last available post baseline assessment.
- Those who are classified as treatment-emergent persistently ADA positive based on the second criterion above (last assessment being positive) but not fulfilling the first criterion (based on duration).
- Treatment-emergent transiently ADA positive, defined as being TE ADA+ and having at least one post- baseline ADA positive measurement but not fulfilling the conditions for persistently positive.
- nAb positive at any visit (at baseline and/or post-baseline).

3.6 Biomarker Variables

Samples for the determination of biomarkers will be taken from all enrolled patients according to the schedule described in Section “8.7 Human Biological Sample Biomarkers” of CSP V4.0.

Tumour samples obtained from the primary tumour or from a metastatic site (excluding bone) before enrolment are mandatory for all enrolled participants in this study based on local regulatory approval. Samples will be tested for TROP2 protein measured by immunohistochemistry.

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 3.3.9.2.

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 or ongoing (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

The efficacy, safety, treatment exposure, PK and ADA data will be summarised and analysed using analysis set accordingly, as specified in Table 3 for details. 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 in corresponding analysis set.
- 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. Note, percentages of 100.0 will be presented as 100 with no decimal.
- 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.

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

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

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

For efficacy endpoints the last observed measurement prior to first dose of study treatment is considered the baseline measurement. For time to event endpoints such as PFS and OS and for calculation of the number of days on study, the start date (Day 1) will be the date of the first dose of study treatment.

For all other variables, baseline will be the last evaluable assessment of the variable under consideration prior to the intake of the first dose of IP. Assessments on the day of the first dose where neither time nor a nominal pre-dose indicator are captured are considered prior to the first dose if such procedures are required by the protocol to be conducted before the first dose. For continuous laboratory variables, ejection fraction measurements, ECG and vital signs, if two visits are equally eligible to assess subject status at baseline (e.g. two assessments

both on the same date with no time recorded), the average will be used as the baseline value. For non-numeric laboratory tests (i.e. some of the urinalysis parameters) where taking the average is not possible, the best value (value closest to none/normal/negative) is used as baseline as this is most conservative. In the scenario where there are two assessments on the day 1, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline. Where safety data are summarized over time, time on study will be calculated in relation to date of first study treatment.

In all summaries change from baseline variables are calculated as the post-treatment value minus the value at baseline. The percentage change from baseline is 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 Objective response rate

The ORR will be based on all scans regardless of whether they were scheduled or not. The confirmed ORR as assessed by ICR (based on the RES) 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 supplementary analyses to the primary endpoint, summaries presenting the confirmed ORR as assessed by ICR based on the FAS will also be produced.

For the secondary endpoint of ORR by investigator assessment, will be analysed in the RES and FAS using the same methods as described in the primary analysis for the primary endpoint.

Subgroup analysis

Subgroup analyses may be conducted for primary endpoint by histology type (adenocarcinoma vs. squamous cell carcinoma) for Cohort 1 (NSCLC), if data allowed.

4.2.2 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 RES and FAS.

4.2.3 Disease control rate

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

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 RES and FAS.

4.2.4 Best objective response

BoR will be summarised by number (%) for each category (confirmed CR, confirmed PR, SD, NED, PD and NE). The unconfirmed CR/PR could be displayed as subcategory under SD if needed. 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 RES and FAS.

4.2.5 Time to response

The TTR will be summarised (i.e. number of patients [%] based upon the number of responders) by the scheduled assessment timepoint that the response was first observed. The analysis will include participants who have a confirmed response. Additionally, descriptive summary statistics (i.e. minimum, maximum, median, Q1 and Q3) will also be presented. These summaries will be repeated for both the ICR and investigator assessments, for the RES and FAS.

4.2.6 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 study 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.

Kaplan-Meier plot of PFS for the FAS will be presented. Summaries of the number and percentage of patients experiencing a PFS event, the type of event (RECIST 1.1 or death) and the number and percentage of censored patients and detailed reason for censoring will be provided along with median PFS and its corresponding 95% CI, 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 the first dose of study intervention 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.

Additionally, summary statistics for the number of weeks between the time of RECIST progression and the last evaluable RECIST assessment prior to progression is presented.

Summaries of the number and percentage of participants who miss two or more consecutive RECIST assessments is presented.

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.

The PFS summaries will be presented for the ICR and investigator assessments for the FAS.

4.2.7 Overall survival

Kaplan-Meier plots will be presented for OS for the 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 (if calculable), 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 the date of the first dose of study intervention to the date of death (i.e. overall survival) or to the date of censoring (date last known to be alive) for all patients and censored patients.

4.2.8 Pharmacokinetic

PK Concentrations

Plasma PK Concentration Listings

All reportable PK concentrations, will be listed for each subject by Cohort, PK Day and Dose (if appropriate, considering potential dose change), for each analyte separately.

Plasma PK Concentration Descriptive Statistics

Three observations > LLOQ are required as a minimum for plasma concentrations to be summarised. Two observations > LLOQ are presented as minimum and maximum with the other summary statistics as NC.

For each analyte, plasma concentrations for each scheduled time-point are summarised by Cohort, PK Day and Dose (if appropriate, considering potential dose change) using appropriate descriptive statistics. Intensive PK concentration will be summarized independently.

The following descriptive statistics are presented for plasma concentrations:

- n
- n below LLOQ
- geometric mean (gmean)
- geometric coefficient of variance (%) (gCV)
- arithmetic mean (mean)
- arithmetic standard deviation (Std Dev)
- median
- minimum (min)
- maximum (max)

The gmean is calculated as $\exp(\mu)$, where μ is the mean of the data on the natural log scale.

The gCV is calculated as $100 \times \text{sqrt}[\exp(s^2)-1]$, where s is the Std Dev of the data on the natural log scale.

Where required for plots: The geometric standard deviation (gSD) is calculated as exp(σ), where σ is the standard deviation of the data on the natural log scale. The gmean ± gSD (gmean-gSD and gmean+gSD) are calculated as exp[μ ± s].

Protocol scheduled times are used to present the PK concentration summary tables and corresponding geometric mean concentration-time figures.

Individual concentrations below the LLOQ of the bioanalytical assay are reported as NQ in the listings with the LLOQ defined in the footnotes of the relevant TFLs. Individual plasma concentrations that are Not Reportable are reported as NR and those that are missing are reported as NS (No Sample) in the listings. Plasma concentrations that are NQ, NR or NS are handled as follows for the provision of descriptive statistics:

- Any values reported as NR or NS are excluded from the summary tables and corresponding figures.
- At a time point where less than or equal to 50% of the concentration values are NQ, all NQ values are set to the LLOQ, and all descriptive statistics are calculated accordingly.
- At a time point where more than 50% (but not all) of the values are NQ, the gmean and gCV% are set to Not calculable (NC). The maximum value is reported from the individual data, and the minimum and median are set to NQ.
- If all concentrations are NQ at a time point, no descriptive statistics are calculated for that time point. The gmean, minimum, median and maximum are reported as NQ and the gCV% as NC.
- The number of values below LLOQ (n < LLOQ) are reported for each time point together with the total number of collected values (n).

Graphical presentation of PK Concentration data

All mean (arithmetic mean and/or geometric mean) plots or combined plots showing all subjects are based on the PK analysis set (taking into account any exclusions from summary statistics). Individual plots by subject are based on the full analysis set (all patient's PK data).

For consistency, the plasma concentration values used in the mean (arithmetic mean and/or gmean) data graphs are those given in the descriptive statistics summary table for each time point.

For gmean concentration-time plots, NQ values are handled as described for the descriptive statistics; if the geometric mean is NQ, the value plotted is zero for linear plots and missing

for semi-logarithmic plots. Any gmean±gSD error bar values that are negative are truncated at zero on linear concentration-time plots and omitted from semi-logarithmic plots.

For individual plots, plasma concentrations which are NQ prior to the first quantifiable concentration are set to a value of zero (linear plots only). After the first quantifiable concentration, any NQ plasma concentrations are regarded as missing.

Data permitting, the following figures are presented as appropriate:

- Figures for the mean (arithmetic mean and gmean) plasma concentration-time data (with ±Std Dev or ±gSD error bars) presented on both linear and semi-logarithmic scales using scheduled post-dose time as follows:
  - By cohort with each analyte overlaid on the same plot for C1D1 (including predose for C2D1 relative to C1D1 dose). Following this rule, intensive PK plots will be plotted independently

- Individual subject plasma concentration-time data graphically presented on both linear and semi-logarithmic scales using actual time post-dose as:
  - By subject with all analytes overlaid on the same plot for C1D1 (including predose for C2D1 relative to C1D1 dose). Following this rule, intensive PK plots will be plotted independently.
  - Combined individual plots by cohort and analyte with all subjects overlaid on the same plot (including predose for C2D1 relative to C1D1 dose). Following this rule, intensive PK plots will be plotted independently.

PK Parameters

The pharmacokinetic (PK) parameters of the plasma concentration data for Dato-DXd, total anti-TROP2 antibody and MAAA-1181a will be derived using non-compartmental methods in Phoenix® WinNonlin® Version 8.3 or higher (Certara). The PK parameters only will be estimated for patients with intensive PK sampling

The following PK parameters will be determined for C1D1 according to AstraZeneca standards:

Parameter Symbol	Definition
AUCinf	Area under plasma concentration-time curve from time 0 to infinity
AUClast	Area under plasma concentration-time curve from time 0 to the last quantifiable concentration

AUCtau	Area under plasma concentration-time curve in the dose interval
Cmax	Maximum observed drug concentration
tmax	Time to reach peak or maximum observed concentration
t½λz	Terminal elimination half-life
CL	Total body clearance (Dato-DXd only)
Ctrough	The observed lowest before the next dose is administered
Vss	Volume of distribution at steady state (Dato-DXd only)
Vz	Volume of distribution based on the terminal phase (Dato-DXd only)
MRTinf	Mean residence time (Dato-DXd only)

In addition the following diagnostic PK parameters will also be determined for C1D1:

Parameter Symbol	**Definition**
AUCextr	Extrapolated area under the curve from tlast to infinity, expressed as percentage of AUCinf
λz	Terminal elimination rate constant
λz lower	Lower (earlier) t used for λz determination
λz upper	Upper (later) t used for λz determination
λzN	Number of data points used for λz determination
λz span ratio	Time period over which λz was determined as ratio of t½λz
Rsq	Statistical measure of fit for the regression used for λz determination
Rsq adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points (n obs)
tlast	Time of last observed (quantifiable) concentration

Where data allow, PK analysis will be carried out using actual elapsed times determined from the PK sampling and dosing times recorded in the database. If actual elapsed times are missing, nominal times may be used at the discretion of the PK Scientist with approval from

the AZ Clinical Pharmacology Scientist (CPS). Nominal sampling times may be used for any agreed interim PK parameter calculations.

For each PK sampling period, plasma concentrations that are non-quantifiable (NQ) from the time of pre-dose sampling (t=0) up to the time of the first quantifiable concentration will be set to a value of zero. After this time point, NQ plasma concentrations will be set to missing for all concentration profiles. Where 2 or more consecutive concentrations are NQ at the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

If an entire concentration-time profile is NQ, the profile will be excluded from the PK analysis.

Cmax, tmax and tlast are taken directly from the concentration-time profiles.

PK Parameter Listings

All reportable PK parameters, including individual diagnostic and λz related parameters, will be listed for each subject by Cohort, PK Day and Dose (if appropriate, considering potential dose change), for each analyte separately.

PK parameter descriptive statistics

All PK parameters and diagnostic parameters will summarised for each analyte by Cohort, PK Day and Dose (if appropriate, considering potential dose change)using appropriate descriptive statistics.

The descriptive statistics for the PK parameters will be presented as: n, arithmetic mean, SD, gmean, gCV%, median, min and max.

The descriptive statistics for the diagnostic PK parameters will be presented as: n, arithmetic mean, SD, median, min and max.

For tmax and tlast, the following descriptive statistics will be presented: n, median, min and max

Precision and Rounding Rules for Pharmacokinetic Data

PK concentration data

PK concentration data listings present to the same number of significant figures as the data received from the bioanalytical laboratory (usually but not always to 3 significant figures) and against the same units as received.

PK concentration descriptive statistics present 4 significant figures with the exception of the min and max which present 3 significant figures and n and n<LLOQ which present as integers.

PK parameter data

The PK parameters will all be presented to 3 significant figures with the exception of:

- Cmax/Ctrough: Present to the same number of significant figures as received from the bioanalytical laboratory
- tmax, tlast, λz lower and λz upper: present as actual time received in the data, usually to 2 decimal places
- λzN: present as integer (no decimals)

The descriptive statistics for the PK parameters will be presented to 4 significant figures with the exception of min and max which will be presented to 3 significant figures and the following:

- tmax, tlast, λz lower and λz upper: present as received in the data, usually to 2 decimal places
- λzN and number of values (n): present as integer

Additional PK analysis

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.

4.2.9 Immunogenicity data

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

A summary may be provided for the number and percentage of participants who develop detectable anti-Dato-DXd antibodies by visit (baseline and all scheduled post-baseline visits) if data allowed. Descriptive statistics for ADA titres by visit may also be included. A line plot of the percentage of participants who are ADA positive at each visit may be provided when appropriate.

If data allowed, a summary may be provided for the number and percentage of participants who are ADA positive at a post-baseline assessment for the first time and/or by visit. Descriptive statistics for ADA titres by first positive visit may also be included. A line plot of the percentage of first-positive participants at each visit may be provided when appropriate.

The effect of ADA on PK, pharmacodynamics, efficacy, and safety will be evaluated, if data allow. And neutralising antibody data may be listed, if data allow.

Immunogenicity results will be listed for all participants in SAF regardless of ADA-evaluable status. Anti-drug antibody titre and neutralising ADA data will be listed for samples confirmed positive for the presence of anti-Dato-DXd antibodies.

CCI [redacted]
CCI [redacted]

4.2.11 Safety

Safety and tolerability data from all cycles of treatment will be combined. The FAS 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.

4.2.11.1 Adverse events

Treatment emergent adverse events (TEAEs) are defined as those AEs with onset or that worsen (by investigator report of an increase in CTCAE grade relative to pre-treatment) after the first dose of study treatment and on or before the date of last dose of treatment + CCI [redacted].

All treatment emergent AEs (TEAEs) observed up until CCI [redacted] 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) are included in the summaries. This will more accurately depict AEs attributable to study treatment only, as some AEs up to

CCI 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 (%).

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

- All AEs
- Most common AEs (frequency of >5%)
- 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
- All SAEs with CTCAE grade 3 or higher
- AEs leading to dose modification of study treatment (including interruption and/or reduction)
- AEs leading to discontinuation of study treatment
- AEs leading to discontinuation of study treatment, possibly related to study treatment
- SAEs leading to discontinuation of study treatment
- SAEs 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

An overview of AEs will be presented, including the number and percentage of patients in each of the categories above in those categories. The MedDRA dictionary (latest or current version) will be used for coding.

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

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

Further details of summaries by SOC and PT are given below if a participant experienced more than one TEAE:

- The participant will be counted once for each SOC and once for each PT.
- The participant will be counted once for each SOC and once for each PT at the maximum CTCAE grade.
- The participant will be counted once for each SOC and once for each PT using the most related event
- The participant will be counted once for each SOC and once for each PT for related events at the maximum CTCAE grade.

AEs are assigned CTCAE grades and summaries of the number and percentage of participants are provided by maximum reported CTCAE grade, SOC and PT.

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, IRR including anaphylaxis (occurred within 1 day [24h] after dose infusion at any cycle), oral mucositis/stomatitis, mucosal inflammation other than oral mucositis/stomatitis, and ocular surface toxicity 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 other AESI, 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.

An AESI overview will be provided by AESI category, including any AESI, AESI causally related to study treatment, AESI with ≥Grade 3, serious AESI, AESI associated with actions taken with study treatment (discontinuation of study treatment, dose reduction, and dose interruption), AESI associated with death, and AESI outcome.

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.

Time to the first treatment-emergent AESI will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, maximum). Only subjects with the treatment-emergent AESI will be included.

Duration of the first treatment-emergent AESI will be summarised using Kaplan-Meier approach and estimates of the lower and upper quartiles and median will be calculated. For ongoing AESIs in the database, stop date is censored at the earliest of following:

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

If all of the above dates are missing, the stop date will be censored at the subject's last alive date, derived as per Section 3.2.2.7. When summarising time to and duration of the first treatment-emergent AESI for CCI events, only adjudicated drug-related events will be considered.

Deaths

A summary of all deaths will be provided with the number and percentage of patients categorised as:

- Total number of deaths (regardless of date of death)
- Death related to disease under investigation only as determined by the investigator
- AE with outcome of death only and onset date ≤ CCI following last dose of study treatment
- AE with outcome of death only and onset date > CCI following last dose of study treatment
- Death related to disease under investigation, as determined by the investigator, and AE with outcome of death
- Other deaths

4.2.11.2 Exposure

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

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

For subjects on study treatment at the time of each analysis, the DCO date will be used to calculate exposure. Total exposure and actual exposure may summarised in months in the FAS.

Details of administration of study treatment will be listed for subjects in the FAS.

4.2.11.3 Vital signs

Summaries of vital signs data will include all data obtained until CCI after the last dose of study treatment or until the initiation of the first subsequent anti-cancer therapy (radiotherapy

is not considered a subsequent anti-cancer therapy) following discontinuation of study treatment (whichever occurs first). Absolute values and change from baseline for diastolic and systolic BP, pulse rate, respiratory rate, temperature, body weight and SpO_2 will be summarised at each visit for the before infusion assessments. The denominator in vital signs data should only include those patients with recorded data. Vital signs data is also listed.

4.2.11.4 Electrocardiograms

ECG data obtained up until CCI following the last dose of study treatment or until the initiation of the first subsequent anti-cancer therapy (radiotherapy is not considered a subsequent anti-cancer therapy) following discontinuation of study treatment (whichever occurs first) will be included in the summaries.

Absolute values at baseline and end of treatment visit and change from baseline for ECG heart rate, PR interval, QRS interval, QT interval, QTcF intervals and RR interval will be presented.

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 during the study.

In addition, the number and percentage of subjects with the following clinically notable values during the study will be summarized:

- QT and QTcF:
  - New >450 msec
  - New >480 msec,
  - New >500 msec,
  - Increase from baseline >30 msec,
  - Increase from baseline >60 msec,
  - New >480 msec and Increase from baseline >30 msec,
  - New >500 msec and Increase from baseline >60 msec.
- PR: An increase >25% from baseline and PR >200 msec.
- QRS: An increase >25% from baseline and QRS >100 msec.
- Heart rate (HR): A decrease >25% from baseline and HR <50 bpm. An increase >25% from baseline and HR >100 bpm.

Note that “New” implies a newly occurring ECG abnormality. It is defined as an abnormal ECG finding at post-baseline that is not present at baseline (e.g., QT New>480 msec implies QT>480 msec post-baseline and QT≤ 480 msec at baseline).

Note that when ECGs are collected in triplicate, analyses will be based on the average of triplicate results. If there is(are) missing value(s) in triplicates, the other non-missing value(s) in the triplicates will be used to calculate the average.

ECG data will be listed.

4.2.11.5 Laboratory measurements

Laboratory data obtained up until CCI following the last dose of study treatment or until the initiation of the first subsequent anti-cancer therapy (radiotherapy is not considered a 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, clinical chemistry and urinalysis 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, haematocrit, platelet count, leukocytes (absolute count), differential leukocytes count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
- Clinical chemistry: serum creatinine, total bilirubin, albumin, blood urea nitrogen (BUN), total protein, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), corrected calcium (Ca) (hypo- and hyper-), chloride (Cl), potassium (K) (hypo- and hyper-), sodium (Na) (hypo- and hyper-), lactate dehydrogenase (LDH), magnesium (hypo- and hyper-), glucose (hypo- and hyper-) and troponin

For parameters with no CTCAE grading that are listed in the CSP, the number and percentage of participants with any on treatment increase from baseline, any on treatment decrease from

baseline and a TELC is summarised. Percentages are based on the number of participants with a baseline value below/above the local laboratory upper/lower reference limit and an on-treatment value for the any increase/decrease summaries respectively. Percentages for a TELC are based on the number of participants with a baseline value and an on-treatment value.

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. 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.

Liver Enzyme Elevations and 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 ≥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.

4.2.11.6 Other safety assessments

4.2.11.6.1 Echocardiograms/multigated acquisition scans

Absolute values at baseline and end of treatment visit and change from baseline to end of treatment visit for LVEF results are summarised.

4.2.11.6.2 Pulmonary assessments

CCI will be summarised for each visit along with vital signs.

4.2.11.6.3 ILD/Pneumonitis investigation

The analysis details could be seen in the section 4.2.11.1 for AESI. Summaries of data collected for suspected ILD/pneumonitis investigation may be presented in patient narratives.

4.2.11.6.4 ECOG performance status

All WHO/ECOG performance status data will be listed. The number and percentage of participants in each category is summarised at each visit. A shift table will be presented, from baseline to worst evaluation during treatment.

4.2.11.6.5 Ophthalmologic assessments

Ophthalmologic assessments will be summarised at the DCO of primary analysis.

For daily use of CCI [redacted] will be reported if appropriate.

For use of CCI [redacted] will be reported if appropriate.

For CCI [redacted] will be reported if appropriate.

For CCI [redacted] will be reported if appropriate. Percentages will be based on the number of participants with a baseline result and at least one result for the corresponding visit.

For CCI [redacted] will be reported if appropriate. CCI [redacted] will be based on the number of participants CCI [redacted]

The reported diagnosis will be summarised by preferred term (PT). The following PTs will be displayed as separate categories:

- CCI [redacted]
- [redacted]
- [redacted]

The prescribed ocular treatments will be summarised by categories of CCI [redacted] if appropriate.

Listings will be produced for the following assessments: CCI [redacted] In addition, listings will be produced for medication used for eye pain, eye exam diagnosis results and eye treatments prescribed.

4.2.12 Demographics and baseline characteristics

The following will be summarised and/or listed for all patients in the FAS:

- 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 [<70, ≥70 - ≤ 90 and >90 kg], BMI group [<18.5, ≥18.5 - <24, ≥24 - <28 and ≥28 kg/m^2])
- Patient recruitment by centre
- Previous disease-related treatment modalities
- Previous anti-cancer systemic therapy and radiotherapy prior to this study
- Disease characteristics at baseline (ECOG performance status, primary tumour location, histology type, tumour grade, AJCC stage, time from diagnosis of primary cancer to start of study treatment, time from diagnosis of inoperable cancer to start of study treatment [for TNBC cohort], overall disease classification, extent of disease and TNM classification)
- Disease characteristics at time of diagnosis (primary tumour location, histology type, tumour grade, AJCC stage and TNM classification)

- Disease free interval (De novo, DFI ≤12 months, DFI >12months) (for TNBC cohort)
- Disease related medical history (past and current)
- Relevant surgical history
- Nicotine use, categorised (never, current, former)

4.2.13 Concomitant and other treatments

Information on any treatment from the time of screening to initiation of study drug and all concomitant treatments given up to CCI 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 and RES (as appropriate) by ATC classification codes.

In addition, all post-treatment anti-cancer medications and surgical procedures will be summarised for the FAS.

The following summaries will be produced:

- Summary of prior medications
- Summary of concomitant medications
- Summary of disallowed concomitant medications
- Summary of prior cancer therapies
- Summary of post study treatment cancer therapies.

Prior medications (excluding prior cancer therapies), concomitant medications (including both allowed and disallowed concomitant medications) and disallowed concomitant medications are presented by ATC classification and generic term, sorted by descending frequency of ATC group and generic term. Participants taking the same concomitant medication/procedure multiple times are counted once per ATC classification and generic term.

Prior cancer therapies, non-study cancer therapies whilst on study treatment, and post-study treatment cancer therapies are summarised by therapy class and ATC group.

All concomitant and other treatment data will be listed.

4.2.14 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 impact, drug impacted)
- 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.

4.2.15 Data Cut-offs

The DCO for the primary analysis of ORR by ICR will occur approximately 6 months after the last participant has initiated study intervention for that cohort. Duration of response, DCR, BOR, TTR, PFS, OS, and available safety, immunogenicity, and PK data will also be summarised at this time.

The DCO for the final analysis of ORR by ICR will occur approximately 12 months after the last participant has initiated study intervention for that cohort. The final analysis will report the analyses of all primary and secondary endpoints, including updated ORR and DoR, DCR, BOR, TTR, PFS, OS, PK, immunogenicity, and safety.

The statistical analysis will be performed separately for NSCLC and TNBC cohort.

5 INTERIM ANALYSES

There are no planned interim analyses for this study.

6 CHANGES OF ANALYSIS FROM PROTOCOL

Not applicable.

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.

SIGNATURE PAGE

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

Document Name: d9266c00001-sap-ed-2		
Document Title:	Statistical Analysis Plan Edition 2	
Document ID:	Doc ID-004990795	
Version Label:	2.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
11-Sep-2023 13:51 UTC	PPD	Content Approval

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