Clinical Study Protocol	
Study Intervention	Trastuzumab deruxtecan (T-DXd, DS-8201a)
Study Code	D7811C00001
Version	2.0
Date	24 Feb 2022

An Open-label, Single-arm, Phase 2 Study to Evaluate the Efficacy and Safety of Trastuzumab Deruxtecan (T-DXd) for Patients with HER2-mutant Metastatic NSCLC who have Disease Progression on or after at Least One-line of Treatment (DESTINY-Lung05)

Sponsor Name: AstraZeneca AB

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This CSP has been subject to a peer review according to AstraZeneca standard procedures. The CSP is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: D7811C00001

Amendment Number: 01
Study Intervention: Trastuzumab deruxtecan (T-DXd)

The non-proprietary name of T-DXd is trastuzumab deruxtecan except in the United States where it is fam-trastuzumab deruxtecan-nxki.

Study Phase: Phase 2

Short Title: Phase 2 study of the Efficacy and Safety of Trastuzumab Deruxtecan for Patients with HER2-mutant Metastatic NSCLC who have Disease Progression on or after at least One-line of Treatment

Acronym: DESTINY-Lung05

Study Physician Name and Contact Information will be provided separately

National Co-ordinating Investigator

PPD

Employed by PPD (the "Principal Investigator")

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1 (Version 2.0)	24 Feb 2022
Original Protocol (Version 1.0)	13 July 2021

Amendment 1 (24 Feb 2022)

Overall Rationale for the Amendment:

CCI [redacted]

Additional changes implemented in this protocol amendment relate to updates or clarification to eligibility criteria, study assessments and dosing. The rationale for each of these changes is provided in the table below.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.1 Synopsis Section 1.2 Schema Section 1.3 Schedule of Activities Table 1 Section 4.1 Overall Design Section 5.1 Inclusion Criteria Section 8.1.3 Mandatory Tumour Tissue Sample Section 8.6.1 Collection of	CCI [redacted]	CCI [redacted]	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Mandatory Samples for Biomarker Analysis Appendix L List of Qualifying Activating HER2 exon 19 and 20 Mutations			
Section 1.1 Synopsis Section 1.2 Schema Section 4.1 Overall Design Section 9 Statistical considerations	CCI	CCI	Substantial
Section 1.3 Schedule of Activities Table 1 Section 8.1.4 CCI Section 8.6.1 CCI	CCI	CCI	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
[redacted]	[redacted]		
Section 1.3 Schedule of Activities Section 6.6 Dose Modification Appendix K Toxicity Management Guidelines	Deleted 49 day discontinuation criteria, updated as 126 days to be the time frame for discontinuation, the criteria for drug resuming is added	To allow longer time frame for drug discontinuation and alignment with current project safety requirements	Substantial
Section 1.3 Schedule of Activities Table 1	Clarification of timing of the Haematology and Clinical Chemistry assessments in footnote "d".	Alignment with current project safety requirements	Non-substantial
Section 1.3 Schedule of Activities Table 1	Deleted the "d" for WHO/ECOG PS	Clarification of the timing of WHO/ECOG assessment	Non-substantial
Section 1.3 Schedule of Activities Table 1	Addition of required parameters of Coagulation test at screening, including addition of new footnote "f"	Alignment with current project safety requirements	Non-substantial
Section 1.3 Schedule of Activities Table 1 Section 6.6 Dose Modification Section 8.2.3 Electrocardiograms	Addition of C1D1 timepoint of triplicate ECG testing, clarification of the timepoint of ECHO/MUGA scan assessments	Alignment with current project safety requirements	Non-substantial
Section 1.3 Schedule of Activities Table 1	Clarification of PFT, HRCT and Ophthalmologic assessments, including addition of new	Alignment with current project safety requirements	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	footnotes “i”, “j” and “k”		
Section 1.3 Schedule of Activities Table 1	Addition a note to clarify the brain scan at EoT for participants with brain metastases	Alignment with current project safety requirements	Non-substantial
Section 1.3 Schedule of Activities Table 1 Section 8.2.5.2 Pulmonary Assessments	Amended to “DLCO is strongly encouraged”	Alignment with current project safety requirements	Non-substantial
Section 2.3.1.1 Potential Risks of T-Dxd	Deleted “asthenia” And “malaise” in other identified risks for T-Dxd	Update to cover most Up to date safety information related to T-DXd	Non-substantial
Section 2.3.1.1 Potential Risks of T-Dxd	Addition of participants with severe renal impairment who has not been studied	Update to cover most up to date safety information related to T-DXd	Non-substantial
Section 5.1 Inclusion Criteria 2	Amended to state that participants must be ≥18 years at the time of signing the ICF	Clarification of the timing of calculating age	Non-substantial
Section 5.1 Inclusion Criteria 5 and 6 Section 8.1.3 Mandatory Tumour Tissue Sample	CCI [redacted]	CCI [redacted]	Non-substantial
Section 5.1 Inclusion Criteria 9	Addition of timing requirement of parameters tests	Alignment with current project safety requirements.	Non-substantial
Section 5.1 Inclusion Criteria 12	Deleted “such as 5-fluorouracil-based agents, folinate agents,	Alignment with current project requirements	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	weekly paclitaxel"		
Section 5.1 Inclusion Criteria 12	Clarification of CART and the washout period	Alignment with current project requirements	Non-substantial
Section 5.1 Inclusion Criteria 15	Clarification the starting timepoint of Refraining from fathering a child, or freezing or donating sperm	To align with current project level text and To provide clarity	Non-substantial
Section 5.2 Exclusion Criteria 2	Clarification of participants with CNS metastases must have previously completed local therapy	Alignment with context and clarification of the requirement of previous local therapy for participants with CNS metastases	Non-substantial
Section 5.2 Exclusion Criteria 11	Clarification of the eligibility of participants with past or resolved hepatitis B virus (HBV) infection	Alignment with current project requirements	Non-substantial
Section 5.2 Exclusion Criteria 11	Addition of one example of serologic evidence of viral infection	To align with current project level text and to provide clarity	Non-substantial
Section 5.2 Exclusion Criteria 12	Clarification of "mRNA and replication deficient adenoviral vaccines are not considered attenuated live vaccines"	To align with current project level text and to provide clarity	Non-substantial
Section 5.2 Exclusion Criteria 14	Clarification of chronic stable Grade 2 toxicity	To align with current project level text and to provide clarity	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 5.3 Lifestyle Considerations	Addition of requirement of donate Or retrieve ova, breastfeeding for female patients	To align with current project level text and To provide clarity	Non-substantial
Section 6.2.1 T-DXd Preparation, Administration and Storage	Added that the preparation, handling, storage, and administration instructions for T-DXd will follow the IP handling instructions	To align with current project level text and to provide clarity	Non-substantial
Section 6.2.1 T-DXd Preparation, Administration and Storage	Clarification of dose calculation method based on weight	To align with current project level text and to provide clarity	Non-substantial
Section 6.5.1 Prohibited Concomitant Medications	Addition of one example of bronchodilators	To align with current project level text and to provide clarity	Non-substantial
Section 6.6 Dose Modification	Clarification of potential ILD/pneumonitis review	To align with current project level text and to provide clarity	Non-substantial
Section 7.1 Discontinuation of Study Intervention	Clarified that subjective disease progression was one of the treatment discontinuation criteria	To align with current project level text and to provide clarity	Non-substantial
Section 7.1 Discontinuation of Study Intervention	Clarification of definition of EoT and EoT assessment when EoT is > 40 days (+ 7 days) after last treatment	To align with current project level text and to provide clarity	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 7.1 Discontinuation of Study Intervention	Clarification of continuation on Study Intervention After CNS-only Progression and added one new section 7.1.3	To align with current project level text and to provide clarity	Non-substantial
Section 8.2.3 Electrocardiograms	Amended to supine/semi-recumbent position when conducting ECG test	Alignment with current project requirements	Non-substantial
Section 8.2.4 Clinical Safety Laboratory Assessments Table 10	Amended to “INR or PT and either PTT or aPTT” including add new footnote “c”	Alignment with current project requirements and context	Non-substantial
Section 8.2.4 Clinical Safety Laboratory Assessments Table 10	Deleted leukocyte count and serum creatinine	Duplicated	Non-substantial
Section 8.2.4 Clinical Safety Laboratory Assessments Table 10	Addition of Calcium and Urea	Addition of options to conduct required tests	Non-substantial
Section 8.2.4 Clinical Safety Laboratory Assessments Section 8.3 Adverse Events and Serious Adverse Events Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy’s Law Appendix K Toxicity Management Guidelines	Amended to “TBL ≥ 2 × ULN”	Alignment with current project requirements	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 8.6.1.1 Mandatory Tumour Tissue Samples	CCI [redacted]	Based on the requirement of Laboratory Manual	Non-substantial
Section 8.6.1 Collection of Mandatory Samples for Biomarker Analysis	Clarification of handing of human biological samples with addition of one new section 8.6.1.3	Clarification of handing of human biological samples align with context	Non-substantial
Section 9.4.2.2.6	"If calculable" is added to the providing of estimate of median OS and corresponding 95%CI.	Updated in cases if median OS and corresponding 95%CI is not calculable.	Non-substantial
Section 9.4.2.2.7	Analysis of CNS-PFS updated to use appropriate Descriptive statistics based on Kaplan-Meier estimates	To ensure appropriate descriptive statistics is reported if the CNS-PFS events is relatively low.	Non-substantial
Section 9.6.1 ILD Adjudication Committee	Clarification of data collection will be triggered for adverse events reported based on a set of pre-defined list of PTs eligible for adjudication as described by the Event Adjudication Site Manual	Alignment with current project requirements and context	Non-substantial
Appendix E Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria	Deleted IV contrast-enhanced CT or MRI of the head and neck	Alignment with current project requirements and context	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
(Response Evaluation Criteria in Solid Tumours)			
Appendix L CCI [redacted]	CCI [redacted]	Duplicated	Non-substantial
Section 5.3 Lifestyle Considerations Section 6.5.1 Prohibited Concomitant Medications Section 6.6 Dose Modification Section 8.2 Safety Assessments Section 8.3 Adverse Events and Serious Adverse Events Section 8.6.1.1 Screening Tumour Tissue Samples Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law Appendix E Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria	Minor editorial changes	To align with current project level text and to provide clarity	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
(Response Evaluation Criteria in Solid Tumours) Appendix F Contraception Requirements Appendix G Concomitant Medications Appendix J Guidance for Management of Participants with Drug induced ILD/Pneumonitis Appendix K Toxicity Management Guidelines Appendix M Abbreviations Appendix L list of Qualifying Activating HER2 exon 19 and 20 Mutations Table 25			

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: An Open-label, Single-arm, Phase 2 Study to Evaluate the Efficacy and Safety of Trastuzumab Deruxtecan (T-DXd) for Patients with HER2-mutant Metastatic NSCLC who have Disease Progression on or after at least One-line of Treatment (DESTINY-Lung05)

Short Title: Phase 2 study of the Efficacy and Safety of Trastuzumab Deruxtecan for Patients with HER2-mutant Metastatic NSCLC who have Disease Progression on or after at least One-line of Treatment

Rationale:

NSCLC is one of the leading causes of cancer-related mortality worldwide, accounting for approximately 18% of all cancer deaths. HER2 mutations have been identified in approximately 2% to 4% of NSCLC globally including China.

Currently, there are no therapies specifically approved for patients with NSCLC whose tumours have a HER2 mutation (also referred to as HER2-mutant NSCLC). In the absence of an approved anti-HER2 therapy, treatment of patients with metastatic HER2-mutant NSCLC generally follows the treatment paradigm for those patients without an actionable mutation. For these patients, platinum-based chemotherapy combined with anti-PD-1 or anti-PD-L1 targeted immunotherapy are typically given as the front-line treatment. CCI [redacted] Docetaxel or immunotherapy (if not used in the first-line) was recommended by the CSCO as the second-line therapy for these patients, although the efficacy is also limited.

T-DXd (Enhertu®, DS-8201a) is a HER2-targeting ADC. T-DXd is being developed as a therapeutic candidate for the treatment of HER2-expressing tumours, as well as for solid tumours that exhibit somatic HER2 activating mutations including NSCLC. Clinical development of T-DXd in HER2-mutant NSCLC is supported by encouraging preliminary clinical efficacy data from 2 studies, Study DS8201 A-J101 (Phase 1) and Study DS8201-A-U204 (DESTINY-Lung01) (Phase 2).

Considering the unmet medical need and that there are currently no approved therapies for patients with HER2-mutant NSCLC in China, and based on T-DXd nonclinical and clinical data, DESTINY-Lung05 is proposed as an opportunity to bring a novel HER2 targeted therapy to this patient population; adult patients with HER2-mutant mNSCLC, with disease progression on or after at least one-line of treatment.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate confirmed ORR by ICR of T-DXd in participants with HER2-mutant NSCLC.	Confirmed ORR, defined as the proportion of participants with confirmed CR or PR, as assessed by ICR based on RECIST 1.1. The analysis will be performed on the population of participants with HER2 exon 19 or 20 mutation assessed by central laboratory.
Secondary	
To evaluate confirmed ORR by investigator assessment.	Confirmed ORR, by investigator assessment based on RECIST 1.1. The analysis will be performed on the population of participants with HER2 exon 19 or 20 mutation assessed by central laboratory.
To evaluate DoR, DCR, BOR, PFS and OS.	• DoR, defined as time from the initial confirmed response (CR or PR) until documented tumour progression or death from any cause. DoR will be assessed by ICR and by the investigator based on RECIST 1.1. • DCR, defined as the proportion of participants who achieved confirmed CR, PR, or SD during study intervention. DCR will be assessed by ICR and by the investigator based on RECIST 1.1. • BOR, is a 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 progression or the last evaluable assessment in the absence of RECIST 1.1-defined progression. BOR will be assessed by ICR and by the investigator based on RECIST 1.1. • PFS, defined as the time from date of enrolment until first objective radiographic tumour progression or death from any cause. PFS will be assessed by ICR and by the investigator based on RECIST 1.1. • OS, defined as the time from date of enrolment until death from any cause.
To evaluate CNS-PFS.	CNS-PFS, defined as the time from date of enrolment until CNS tumour progression per RECIST 1.1 as assessed by ICR or death due to any cause in the absence of CNS progression.
To evaluate the PK and immunogenicity of T-DXd.	• Serum concentrations of intact T-DXd, total anti-HER2 antibody, and DXd, and evaluation of appropriate PK parameters. T-DXd PK data will also be analysed via a PopPK approach if data allows. • Presence of ADAs against T-DXd in serum. Neutralising ADAs will also be assessed.

Objectives	Endpoints
To evaluate the safety and tolerability of T-DXd.	Occurrence of TEAEs, SAEs and AESIs, physical examination findings, ECOG PS, vital sign measurements, standard clinical laboratory parameters, ECG parameters, ECHO/MUGA findings, and ophthalmologic findings.

ADA = anti-drug antibody; AESI = adverse event of special interest; BOR, best observed response; CNS-PFS = central nervous system progression-free survival; CR = complete response; DCR = disease control rate; DoR = duration of response; DXd = MAAA-1181a; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; HER2 = human epidermal growth factor receptor 2; ICR = independent central review; MUGA = multiple gated acquisition; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); PopPK = population pharmacokinetic(s); PR = partial response; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours, Version 1.1; SAE = serious adverse event; SD = stable disease; T-DXd = trastuzumab deruxtecan; TEAE = treatment emergent adverse event.

For tertiary/ exploratory objectives and endpoints, see Section 3 of the CSP.

Overall Design

Disclosure Statement: This is a Phase 2, open-label, single-arm, multicentre study in China assessing the efficacy and safety of T-DXd in participants with metastatic non-squamous NSCLC whose tumours have a HER2 exon 19 or 20 mutation, with disease progression on or after at least one-line of treatment.

Participant Population:

The target population of interest in this study is participants with metastatic non-squamous NSCLC whose tumours have a HER2 exon 19 or 20 mutation, with disease progression on or after at least one-line of treatment.

HER2 mutation for eligibility will be based on study qualifying activating HER2 exon 19 or 20 mutation either from a pre-existing tissue test result obtained from qualified local laboratory/assay or have the tissue HER2 mutation test result detected prospectively in a central laboratory. Retrospective central confirmation will be performed for those enrolled based on existing local HER2 mutation(s) results during study. Note: In addition, mandatory archival (preferred) or newly collected tissue samples are required for central testing. Should discordance between local and central test be higher than anticipated, enrolment by local test may be closed. If a modification to not allow further enrolment of participants on the basis of a pre-existing HER2 mutation result is made, this change will be communicated to participating sites in a timely manner. Prospective analysis of HER2 mutation status of tumor tissue using central laboratory testing is encouraged.

Number of Participants:

CCI [redacted]

CCI [redacted]

Note: Potential participants who are screened for the purpose of determining eligibility for the study but are not enrolled, are considered "screen failures", unless otherwise specified by the CSP.

Intervention Groups and Duration:

All participants will receive T-DXd at CCI [redacted] Participants will continue to receive T-DXd until PD per RECIST 1.1 as assessed by the investigator, unless unacceptable toxicity, withdrawal of consent, or other criterion for withdrawal is met (with the exception of CNS-only progression; see note below).

Note: For participants with objective radiological CNS-only progression (based on RECIST 1.1), who in the investigator's opinion, continue to receive benefit from study intervention and meet the criteria for treatment in the setting of CNS-only progression may continue to receive study intervention on study for as long as they are gaining clinical benefit and are without any discontinuation criteria, until one of the criteria in Section 6.1.1.2 is met.

Tumour evaluation scans will be performed at screening (as baseline) with follow-ups at Week 6 (±1)-week intervals from the date of enrolment for 48 weeks, and then every 9 (±1) weeks thereafter, starting at Week 57 until RECIST 1.1-defined radiological PD per investigator assessment (plus one additional follow-up scan [4 weeks later], if clinically feasible). In the case of CNS-only progression, participants continuing to receive study intervention should follow the on-treatment data collection schedule, including RECIST 1.1 tumour assessments, until a second progression (CNS or body; plus one additional follow-up scan [4 weeks later], if clinically feasible).

Intervention beyond RECIST 1.1-defined PD is not permitted in this study when the site of PD is outside of the CNS. In the setting of PD outside of the CNS, participant level risk-to-benefit ratio favours discontinuing treatment as participants are highly unlikely to derive clinical benefit post-progression and remain at risk of ILD and other toxicities if treatment is continued.

Follow-up of Participants Post-discontinuation of Study Intervention:

After study intervention discontinuation, all participants will undergo an end-of-treatment visit (within 7 days of discontinuation) and will be followed up for safety assessments 40 (+ 7) days after their last dose of study intervention (ie, the safety follow-up visit).

Participants who have discontinued study intervention in the absence of RECIST 1.1-defined

radiological progression, confirmed by investigator assessment, will be followed up with tumour assessments according to the SoA (Table 1) until RECIST 1.1-defined PD or death regardless of whether or not the participant started a subsequent anticancer therapy, unless they have withdrawn all consent to study-related assessments.

In addition, all participants will be followed up after intervention discontinuation every 3 months (± 14 days) from the date of the safety follow-up visit until death, withdrawal of consent, or the end of the study (ie, progression/survival follow-up), as per the SoA (Table 1).

See Section 6.7 for a description of assessments following DCO.

Statistical Methods

The primary endpoint of the study is confirmed ORR by ICR according to RECIST 1.1, defined as the number (percentage) of participants with confirmed CR or PR as assessed by ICR based on RECIST 1.1. ORR by ICR will be estimated with a 2-sided 95% exact CI based on the FAS who signed the ICF and were enrolled in the study.

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

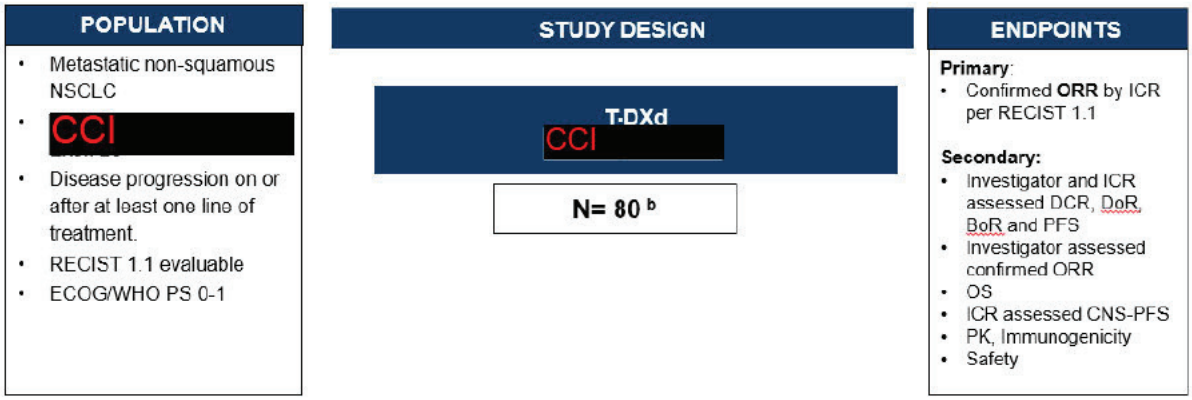
The DCO for the full final analysis of ORR by ICR will occur approximately CCI months after the last participant has initiated study intervention. Based on data from Study DS8201-A-U204, CCI months is sufficient time for participants to reach a response (median time to response was 1.4 months) and to allow DoR to be determined for responders (median confirmed DoR was 12 months). The full final analysis will report the analyses of all primary and secondary endpoints, including updated ORR and DoR, DCR, BOR, PFS, OS, CNS-PFS, PK, immunogenicity and safety.

Safety data will be summarised descriptively.

Sparse sampling of T-DXd PK will be performed in this study to enable PopPK analysis in the treated population with measurable serum concentrations of T-DXd. Summary of intact T-DXd, total anti-HER2 antibody and DXd concentrations by visit will also be provided. Immunogenicity will be evaluated in the T-DXd treated participants in this study.

1.2 Schema

Figure 1 Study Design



[a] CCI

[b] CCI

BOR = best observed response; CNS = central nervous system; DCR = disease control rate; DoR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; HER2 = human epidermal growth factor receptor 2; ICR = independent central review; N = number of patients; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); Q3W = every 3 weeks; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours, Version 1.1; T-DXd = trastuzumab deruxtecan; WHO = World Health Organisation.

1.3 Schedule of Activities

After signing the ICF, screening and baseline procedures will commence. Screening will take place for up to about 28 days from the date of enrolment. At the end of screening and baseline procedures, participants who pass the eligibility criteria will be assigned to treatment with T-DXd.

Whenever vital signs and blood draws are scheduled for the same nominal time, the suggested order of assessments is: vital signs and then blood draws. Whenever ECGs, vital signs, and blood draws are scheduled for the same nominal time, the suggested order of assessments is: ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw, eg, PK blood sample, to occur at the time points indicated in the SoA (Table 1).

If dosing must be delayed for reasons other than treatment-related toxicity, dosing will occur as soon as feasible. If a dose is delayed for any reason, participants can be dosed in the next scheduled visit provided it is ≥ 19 days and < 18 weeks (126 days) from the date of last infusion. (see Section 6.6).

The procedures for this study are presented in the SoA (Table 1).

Table 1 Schedule of Activities

Procedure	Screening	Intervention Period [Days or Weeks, etc]						Post-intervention Follow-up Period			Notes	Details in CSP section
Treatment Cycle		C1			C2	C3	C4 and subsequent cycles until PD	EoT or E/D	Safety FU (40 + 7 days after last dose)	Progression/ survival FU (q3 months ± 14 days)		
Day		1	8	15	1	1	1					
Window (± days)	**-28 to -1 [a]**	**NA**	**± 1**	**± 1**	**± 2**	**± 2**	**± 2**	**+ 7**				
Informed consent [b]	X											5.1
Inclusion and exclusion criteria	X											5.1, 5.2
Demography	X											5.1
Full physical examination	X											8.2.1
Targeted physical examination		X [c]			X [c]	X [c]	X [c]	X	X			8.2.1
Height	X											8.2.1
Weight	X	X [c]			X [c]	X [c]	X [c]	X	X			8.2.1
Medical history (includes substance usage)	X	X [d]									Substances: tobacco. Include history, type and frequency of tobacco use, e-cigarette use, and vaping (including dates)	5.1, 5.2
Past and current medical conditions	X	X [d]										5.1, 5.2
WHO/ECOG PS	X	X [c]			X [c]	X [c]	X [c]	X	X			8.2.5.4

Table 1 Schedule of Activities

Procedure	Screening	Intervention Period [Days or Weeks, etc]						Post-intervention Follow-up Period			Notes	Details in CSP section
Treatment Cycle		C1			C2	C3	C4 and subsequent cycles until PD	EoT or E/D	Safety FU (40 + 7 days after last dose)	Progression/ survival FU (q3 months ± 14 days)		
Day		1	8	15	1	1	1					
Window (± days)	**-28 to -1 [a]**	**NA**	**± 1**	**± 1**	**± 2**	**± 2**	**± 2**	**+ 7**				
Serum/urine pregnancy test (WOCBP only) [e]	X	X			X	X	X	X	X			5.1, 5.2, 8.2.4
Hepatitis B/C serology	X											5.2, 8.2.4
HIV antibody test (as required by local regulations or IEC)	X											5.2, 8.2.4
Clinical safety laboratory assessments (clinical chemistry, haematology)	X	X [c d]	X	X	X [c]	X [c]	X [c]	X	X			8.2.4
Coagulation [f]	X	As clinically indicated										8.2.4
Urinalysis	X	As clinically indicated										8.2.4
Troponin	X	If at any time a participant reports signs or symptoms suggesting CHF, myocardial infarction, or other causes of myocyte necrosis						X				6.6, 8.2.4
12-lead ECG[g]	X	X [c]					C5 (and every 4 cycles)	X	X		Before administration and if an abnormality is detected	6.6, 8.2.3

Table 1 Schedule of Activities

Procedure	Screening	Intervention Period [Days or Weeks, etc]						Post-intervention Follow-up Period			Notes	Details in CSP section
Treatment Cycle		C1			C2	C3	C4 and subsequent cycles until PD	EoT or E/D	Safety FU (40 + 7 days after last dose)	Progression/ survival FU (q3 months ± 14 days)		
Day		1	8	15	1	1	1					
Window (± days)	**-28 to -1 [a]**	**NA**	**± 1**	**± 1**	**± 2**	**± 2**	**± 2**	**+ 7**				
ECHO or MUGA (LVEF)[g]	X						C5 (and every 4 cycles)	X				8.2.5.1
Vital signs [h]	X	X [c]	X	X	X [c]	X [c]	X [c]	X	X			8.2.2
SpO_2 [h]	X	X [c]	X	X	X [c]	X [c]	X [c]	X	X		And if ILD/pneumonitis is suspected	8.2.5.2
Pulmonary function tests (PFT)[i]	X	If ILD/pneumonitis is suspected										8.2.5.2
ILD/pneumonitis investigation		If ILD/pneumonitis is suspected										8.2.5.3
HRCT [j]	X	If ILD/pneumonitis is suspected										8.2.5.2
Ophthalmologic assessments [k]	X	As clinically indicated						X				8.2.5.5
CCI [redacted]	X											8.1.3, 8.6

Table 1 Schedule of Activities

Procedure	Screening	Intervention Period [Days or Weeks, etc]						Post-intervention Follow-up Period			Notes	Details in CSP section
Treatment Cycle		C1			C2	C3	C4 and subsequent cycles until PD	EoT or E/D	Safety FU (40 + 7 days after last dose)	Progression/ survival FU (q3 months ± 14 days)		
Day		1	8	15	1	1	1					
Window (± days)	-28 to -1 [a]	NA	± 1	± 1	± 2	± 2	± 2	+ 7				
CCI [redacted]	X											8.1.3, 8.6
Pre-dose blood sample for T-DXd PK testing		X			X	X	X (C4, 6, and 8)				Take samples within 8 hours before infusion	8.5.1
End of infusion blood sample for T-DXd PK testing		X			X	X	X (C4 only)				Take samples within 15 minutes after end of infusion	8.5.1
5 hours post-dose blood sample for T-DXd PK testing		X									Take sample within 5 (± 2) hours after start of infusion (C1D1)	8.5.1
Additional blood sample for T-DXd PK testing (if feasible)		If ILD/pneumonitis is suspected										8.2.5.3

Table 1 Schedule of Activities

Procedure	Screening	Intervention Period [Days or Weeks, etc]						Post-intervention Follow-up Period			Notes	Details in CSP section
Treatment Cycle		C1			C2	C3	C4 and subsequent cycles until PD	EoT or E/D	Safety FU (40 + 7 days after last dose)	Progression/ survival FU (q3 months ± 14 days)		
Day		1	8	15	1	1	1					
Window (± days)	**-28 to -1 [a]**	**NA**	**± 1**	**± 1**	**± 2**	**± 2**	**± 2**	**+ 7**				
Pre-dose blood sample for immunogenicity testing		X			X		X (C4, then every 4 cycles)		X		Take samples (within 8 hours before infusion during intervention period) at time points indicated	8.5.2
AE [m]	X	At every visit and may be conducted by phone if not tied to a visit.						X	X			8.3
Concomitant therapy including medication, surgery and radiation therapy	X	At every visit and may be conducted by phone if not tied to a visit						X	X			6.5
Tumour imaging (RECIST 1.1)	X		Every 6 weeks (±7 days) from the date of enrolment for 48 weeks and then every 9 weeks (±7 days) thereafter, starting at Week 57, until RECIST 1.1-defined radiological PD. Plus an additional follow-up scan at least 4 weeks after RECIST 1.1-defined radiological PD if clinically feasible. [n]									8.1.1
Brain tumour imaging (RECIST 1.1) [o]	X		Participants with brain metastasis every 6 weeks (± 7 days) from the date of enrolment for 48 weeks and then every 9 weeks (±7 days) thereafter, starting at Week 57, until RECIST 1.1-defined radiological PD, or as needed based on neurological symptoms for all participants. [p]									8.1.1
Survival status									X	X		7.1.2, 8.1.5

Table 1 Schedule of Activities

Procedure	Screening	Intervention Period [Days or Weeks, etc]						Post-intervention Follow-up Period			Notes	Details in CSP section
Treatment Cycle		C1			C2	C3	C4 and subsequent cycles until PD	EoT or E/D	Safety FU (40 + 7 days after last dose)	Progression/ survival FU (q3 months ± 14 days)		
Day		1	8	15	1	1	1					
Window (± days)	**-28 to -1 [a]**	**NA**	**± 1**	**± 1**	**± 2**	**± 2**	**± 2**	**+ 7**				
Subsequent anticancer therapy									X	X		7.1.1
Any pre-existing tumour-specific markers [q]	X											
Study intervention administered (IV infusion) [r]		T-DXd at CCI [redacted]										6

[a] 28 days for screening period is recommended, if any case is out of this time window due to the central HER2 exon 19 and 20 mutation testing for defining eligibility or ophthalmologic assessments, the site should confirm with AstraZeneca on a case-by-case basis before moving to Cycle 1Day 1.

[b] Written informed consent and any locally required privacy act document authorisation must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations.

[c] Within 3 days before administration.

[d] If screening assessments (except for Haematology and Clinical Chemistry) have been performed within 28 days prior to starting study intervention, they do not have to be repeated at Cycle 1 Day 1 if the participant's condition has not changed. Haematology and Clinical Chemistry taken within 3 days before administration do not need to be repeated at C1D1.

[e] Pregnancy tests will be conducted within 72 hours before enrolment for all WOCBP; a positive urine pregnancy test result must immediately be confirmed using a serum test. Repeat pregnancy tests (urine or serum test per institutional guideline) should be performed 72 hours before infusion of each cycle, at EoT and safety FU visit.

[f] Coagulation tests performed only at screening include INR and aPTT.

[g] ECG will be taken in triplicate at screening and before infusion on C1D1. Subsequent ECGs will be performed in triplicate in close succession only if an abnormality is noted. ECGs will be taken while in a supine/semi-recumbent position. ECGs will then be taken prior to administration on Day 1 of Cycle 5 (then every 4 cycle, ie C9, 13…), EoT, and the safety follow-up visit. If ECG is abnormal follow institutional guidelines. ECHO or MUGA scan assessments (note: the same test must be used for the subject throughout the study) will be performed at Screening and before infusion on Day 1 of Cycle 5 and then every 4 cycles (within 7 days of administration) (e.g. Cycle 5, 9, 13…), and at EOT. See Section 8.2.3 (ECG) and Section 8.2.5.1 (ECHO/MUGA) for the detailed requirements.

[h] Assessment should be conducted prior to and at the end of infusion on Day 1 of each Cycle.

[i] PFT as a minimum should include spirometry.[Minimum requirement of: FVC (L), FVC % predicted, FEV1 (L), FEV1 % predicted, FEV1/FVC %. Optional components to include: PEF, FEV6, TLC, DLCO, RV.]. DLCO will be performed/encouraged if feasible, but for participants with prior severe and/or clinically significant pulmonary disorders, DLCO is strongly encouraged.

[j] HRCT is preferred and recommended. CT Scan should be used only when HRCT is not available.

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

[l] CCI [redacted]

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

[n] Scans must be performed every 6 weeks (± 7 days) from the date of enrolment for 48 weeks, and then every 9 weeks (±7 days) thereafter, starting at Week 57 until RECIST 1.1-defined radiological PD per investigator assessment (plus one additional follow-up scan [4 weeks later], if clinically feasible). This schedule MUST be followed regardless of dose delays. Response assessment scans must be reviewed for evidence of disease progression and ILD/pneumonitis prior to the administration of the next scheduled dose of T-DXd. In the case of CNS-only progression, participants continuing to receive study intervention should follow the on-treatment data collection schedule, including RECIST 1.1 tumour assessments, until a second progression (CNS or body; plus one additional follow-up scan [4 weeks later], if clinically feasible), see Section 6.1.1.2. Scans should continue to be performed if discontinuation takes place for a reason other than PD (AE).

[o] Brain and body RECIST 1.1 CT or MRI scan procedures should be performed on the same day where feasible.

[p] Brain imaging – MRI is preferred unless contraindicated. All participants will have brain scan at screening and EoT. In addition, participants with confirmed brain metastases will have brain scans, using the same modality as at baseline as part of each RECIST 1.1 tumour assessment visit, every 6 weeks (± 7 days) from the date of enrolment for 48 weeks and then every 9 weeks (±7 days) thereafter, starting at Week 57, until RECIST 1.1-defined radiological PD per investigator assessment (plus one additional followup scan [4 weeks later], if clinically feasible). All participants may be scanned (as needed) based on neurological symptoms or suspected brain metastases. Note: participants with brain metastases are not required to undergo an additional brain scan at EoT if the latest brain assessment was within 4 weeks of EoT or if they discontinue study intervention prior to RECIST 1.1-defined radiological progression per investigator.

[q] Pre-existing HER2 mutation results assessed by local lab will be collected. Mutation status of any other tumour-specific markers (including EGFR, ALK, ROS 1, BRAF, NTRK MET, KRAS, RET or other driver mutation), and PD-L1 expression status collected by enquiry only (previously tested), no sample needed.

[r] Every effort should be made to minimise the time between enrolment (confirmation of eligibility) and starting study intervention (ie, within 3 days). Participants should continue to receive T-DXd until PD per RECIST 1.1 as assessed by the investigator, unless unacceptable toxicity, withdrawal of consent, or other criterion for withdrawal is met. Participants with objective radiological CNS-only progression (based on RECIST 1.1), who in the investigator's opinion, continue to receive benefit from study intervention and meet the criteria for treatment in the setting of CNS-only progression may continue to receive study intervention on study for as long as they are gaining clinical benefit and are without any discontinuation criteria, until one of the criteria in Section 6.1.1.2 is met.

Note: All assessments on treatment days are to be performed prior to study intervention administration, unless otherwise indicated. Data collection following study analysis until the end of the study is described in Section 8.

AE = adverse event; ALK = anaplastic lymphoma kinase; BRAF = v-raf murine sarcoma viral oncogene homolog B1; C = cycle; CHF = congestive heart failure; CNS = central nervous system; CSP = Clinical Study Protocol; CT = computed tomography; D = day; DLCO = diffusion capacity of the lungs for carbon monoxide; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; E/D = Early Study Intervention/Discontinuation; EGFR = epidermal growth factor receptor; EoT = End-of-Treatment; FEV = forced expiratory volume; FEV1 = FEV in 1 second; FEV6 = FEV in 6 seconds; FFPE = formalin-fixed and paraffin-embedded; FU = follow-up; FVC = forced vital capacity; HER2 = human epidermal growth factor receptor 2; HIV = human immunodeficiency virus; HRCT = high-resolution computed tomography; IEC = Independent Ethics Committee; ILD = interstitial lung disease; IV = intravenous; KRAS = kirsten rat sarcoma 2 viral oncogene homolog; L = litres; LVEF = left ventricular ejection fraction; MET = MET proto-oncogene, receptor tyrosine kinase; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition; NA = not applicable; NTRK = neurotrophic receptor tyrosine kinase; PEF = peak expiratory flow; PD = progressive disease; PFT = pulmonary function test; PK = pharmacokinetic(s); PS = performance status; q3 = every 3; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours, Version 1.1; RET = rearranged during transfection; ROS = ROS proto-oncogene receptor tyrosine kinase; RV = residual volume; SAE = serious adverse event; SpO2 = pulse oximetry; T-DXd = trastuzumab deruxtecan; TLC = total lung capacity; WHO = World Health Organisation; WOCBP = women of childbearing potential.

2 INTRODUCTION

T-DXd is a HER2-targeting ADC in development as a candidate therapy for breast cancer and other tumour types including lung cancer.

2.1 Study Rationale

NSCLC is one of the leading causes of cancer-related mortality worldwide, accounting for approximately 18% of all cancer deaths (Jemal et al 2011). HER2 mutations have been identified in approximately 2% to 4% of NSCLC globally including China (Arcila et al 2012, Mazieres et al 2013, Tomizawa et al 2011, Wei et al 2020).

Currently, there are no therapies specifically approved for patients with NSCLC whose tumours have a HER2 mutation (also referred to as HER2-mutant NSCLC). In the absence of an approved anti-HER2 therapy, treatment of patients with metastatic HER2-mutant NSCLC generally follows the treatment paradigm for those patients without an actionable mutation. For these patients, platinum-based chemotherapy combined with anti-PD-1 or anti-PD-L1 targeted immunotherapy are typically given as the front-line treatment. CCI [redacted] Docetaxel or immunotherapy (if not used in the first-line) was recommended by the CSCO as the second-line therapy for these patients, although the efficacy is also limited (CSCO 2020, NSCLC Guideline).

CCI [redacted]

Considering the unmet medical need and that there are currently no approved therapies for patients with HER2-mutant NSCLC in China, and based on T-DXd nonclinical and clinical data, DESTINY-Lung05 is proposed as an opportunity to bring a novel HER2 targeted therapy to this patient population; adult patients with HER2-mutant mNSCLC, with disease progression on or after at least one-line of treatment.

T-DXd is expected to be beneficial in a similar population to Study U204 in Chinese patients, given that the disease prevalence, progress and treatment practice for NSCLC are similar between China and Western countries, and that T-DXd is considered ethnically insensitive.

2.2 Background

A detailed description of the chemistry, pharmacology, mechanism of action, efficacy, and safety of T-DXd is provided in the T-DXd IB.

As of 28 March 2019, AstraZeneca and Daiichi Sankyo Company, Limited (Daiichi Sankyo) entered into a joint global development and collaboration agreement for T-DXd.

Due to incorporation of a novel linker, T-DXd achieves a higher DAR of approximately 8 with homogeneous conjugation of DXd, compared with other currently approved ADCs, which have a DAR of 3 to 4 (Ogitani et al 2016). In addition, the cleavable linker in T-DXd is stable in plasma, conferring a favourable safety profile as observed in nonclinical toxicology rat and monkey studies.

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

There are completed and ongoing clinical studies with T-DXd, either alone or in combination, across multiple HER2-expressing tumour types including breast cancer, gastric cancer, NSCLC, and colorectal cancer (please refer to the T-DXd IB for a list of completed and ongoing trials and most recent patient exposure data).

2.2.1 Background on HER2-mutant NSCLC

Lung cancer is the most common cancer, with an estimated 2.09 million new cases in 2018 globally, and was also the most common cause of death from cancer in 2018, with 1.8 million deaths, 18.4% of the total cancer deaths (International Agency for Research on Cancer 2019). At the time of diagnosis, approximately 70% of patients with NSCLC already have advanced or metastatic disease not amenable to surgical resection (Bray et al 2018). The 5-year survival

rate for all NSCLC, independent of the stage, is 24%. For mNSCLC the 5-year survival rate is 6% (American Cancer Society 2020, Howlader et al 2020).

NSCLC represent approximately 84% of all lung cancers (American Cancer Society 2021). The 2 predominant NSCLC histological phenotypes are adenocarcinoma (~50%) and squamous cell carcinoma (~40%) (Davidson et al 2013, Langer et al 2010).

Tobacco smoking remains the main cause of lung cancer and the geographics and patterns of the disease largely reflect tobacco consumption during the previous decades (Ordonez-Mena et al 2016). An increase in the proportion of NSCLC in never-smokers has been observed, especially in Asian countries (Toh et al 2006). These new epidemiological data have resulted in 'non-smoking-associated lung cancer' being considered a distinct disease entity, where specific molecular and genetic tumour characteristics have been identified (Couraud et al 2015).

Recently, in-depth analyses of lung cancer genomes and signalling pathways have further defined NSCLCs as a group of distinct diseases with genetic and cellular heterogeneity (Chen et al 2014, Langer et al 2010). Recurrent mutations and amplifications in many potentially targetable oncogenes have since been identified in lung adenocarcinomas, including HER2 (also known as ERBB2), MET, FGFR1 and FGFR2, as well as fusion oncogenes involving ALK, the ROS1 receptor tyrosine kinase, NRG1, NTRK1 and RET14-22 among others. Subtype analysis of NSCLC has come full circle now that EGFR, ALK, and ROS1 mutations are not only identifiable but their targeted treatment results in responses better than that with standard chemotherapy (Sholl 2015). Approximately 15% to 30% of non-Asian patients and 30% to 60% of Asian patients with adenocarcinoma have a mutation of the EGFR gene. The ALK gene mutations present in 2% to 7% of US patients with NSCLC; ROS1 rearrangements are identified in 1% to 2% of NSCLC patients (Bergethon et al 2012). The improved response to TKIs specific to these mutations has led the College of American Pathologists Guideline to recommend testing for EGFR and ALK mutations in all advanced-stage adenocarcinomas, mixed cancers, and those with NSCLC in whom an adenocarcinoma component cannot be excluded (Lindeman et al 2013). Patients without targetable mutations are currently receiving an immuno-based treatment based on their PD-L1 status (Pabani and Butts 2018).

Despite advances in the diagnosis, imaging, staging and treatment of NSCLC, the estimated overall 5-year survival for patients continues to be low, being improved to approximately 16% in recent years (Pabani and Butts 2018) and the median PFS still less than 12 months even with the latest trial results from promising combinations (Gandhi et al 2018, Mok et al 2019, Reck et al 2016).

HER2 alterations (mutation, gene amplification and protein overexpression) have been identified as a possible target in NSCLC, however there is currently an unmet medical need

for new treatment options to further improve outcomes.

In China in 2010, 605900 patients were diagnosed and 486600 patients died of lung cancer and the mortality of lung cancer has dramatically increased over the last 3 decades (Chen et al 2015). The SoC treatment for patients with mNSCLC is currently based on molecular characterisation and matched targeted therapy for specific driver-mutated subsets (Heigener et al 2019). For mNSCLC patients without EGFR or ALK genomic tumour aberrations, platinum doublet chemotherapy with anti-PD-1/anti-PD-L1 targeting immunotherapy is the SoC based on results from KEYNOTE189 (Gandhi et al 2018).

Although HER2 alterations have been widely studied as a predictive biomarker in breast cancer, with multiple therapeutic options having been developed against them, there have yet to be any approved therapies for HER2 alterations in mNSCLC.

A number of large-scale sequencing efforts and tumour-specific sequencing studies have identified somatic mutations in the extracellular, transmembrane, and kinase domains of HER2 in a wide range of cancers, including NSCLC (Bose et al 2013, Chang et al 2018, Greulich et al 2012, Kavuri et al 2015, Ou et al 2017, Ross et al 2016, Yamamoto et al 2014, Zabransky et al 2015). HER2 activating mutations are causally implicated in oncogenesis, can promote HER2 protein gain of function (Cocco et al 2019, Zabransky et al 2015), and have been described in at least 25 different tumour types with mutation hotspots varying by malignancy (Robichaux et al 2019). These mutations confer an invasive growth advantage on neoplastic cells with positive selection in the tumour microenvironment (Bose et al 2013). Nonclinical data also indicate that HER2 activating mutations lead to increased dimerisation and/or activation at the C-terminal kinase domain (Greulich et al 2012, Wang et al 2006). HER2 mutations are a not associated with HER2 amplification suggesting a distinct therapeutic target (Li et al 2016).

HER2 mutations have been identified in approximately 2% to 4% of NSCLC (Arcila et al 2012, Mazieres et al 2013, Tomizawa et al 2011, Wei et al 2020). The most common HER2 mutations are exon 20 insertions found in the tyrosine kinase domain; their frequency, as a group, has been reported to range from 35% to 70% of all HER2 mutations in NSCLC (Ou et al 2019, Singh et al 2020, Wei et al 2020). More rarely, HER2 mutations are observed in the extracellular domain (eg, S310F, S310Y in exon 8), outside of exon 20 in the tyrosine kinase domain (eg, L755P in exon 19), and in the transmembrane domain, representing approximately 25%, 16%, and 10% of HER2 mutations, respectively (Robichaux et al 2019).

In general, HER2-mutant NSCLC is more commonly associated with female patients, non-smokers, and adenocarcinoma histology (Arcila et al 2012). HER2 mutations and other driver oncogene abnormalities are reported to be mutually exclusive (Mazieres et al 2013, Pillai et al 2017), although rare cases of non-tyrosine kinase domain HER2 mutations have been observed with concurrent EGFR mutations (Ou et al 2019, Wei et al 2020). Tumour

protein 53 has been described as a frequent co-mutation and other mutations including KEAP1, STK11, and KRAS have also been observed (Wei et al 2020). HER2 co-amplification has been described in approximately 5% to 15% of HER2-mutant NSCLC (Ou et al 2019, Singh et al 2020).

2.2.2 Relevance of HER2-mutant NSCLC

HER2 is a member of the HER superfamily that initiates signal transduction via the PI3K/protein kinase b (Akt) and Ras/mitogen-activated protein kinase pathways (Archer et al 1995). In human advanced solid tumours, expression of HER2 protein has been reported in various tumour tissues and in a variety of cultured tumour cell lines including lung cancer (Li et al 2012) among others like breast cancer (Ross et al 2009) and gastric cancer (Gravalos and Jimeno 2008).

HER2 alterations in mNSCLC are usually a marker of poor prognosis and fall into 3 distinct mechanistic categories: HER2 mutations (2% to 4%) (Hirsch et al 2017), HER2 gene amplification (1% to 20%) and HER2 protein overexpression (6% to 35%) (Hirsch et al 2017, Li et al 2016, Mar et al 2015, Mazieres et al 2013, Ou et al 2019, Singh et al 2020).

HER2 mutations are predominantly mutually exclusive of other actionable oncogenic drivers (such as EGFR, KRAS and ALK alterations) and in lung cancer are associated with a poor prognosis (Arcila et al 2012, Li et al 2016, Mazieres et al 2013, Pillai et al 2017).

2.2.3 Therapies in mNSCLC and HER2-mutant mNSCLC

Until recently, common first-line treatment regimens for advanced NSCLC in major global markets were typically platinum-based doublets and include carboplatin and paclitaxel (eg, nab paclitaxel [Abraxane®]), carboplatin and gemcitabine (squamous only), carboplatin and pemetrexed (non-squamous only), cisplatin and gemcitabine (squamous only), and cisplatin and pemetrexed (non-squamous only). Maintenance therapy, with pemetrexed has been shown to improve OS and PFS, particularly in non-squamous histology (Ciuleanu et al 2009, Paz-Ares et al 2019).

More recently, the treatment landscape has changed based on targetable molecular characterisation. Approximately, 10% of Caucasian patients and up to 50% of Asian patients with NSCLC will harbour a targetable activating EGFR mutation, the most common of which are L858R and deletions in exon 19 (Ettinger et al 2019). For these patients, the third generation EGFR TKI osimertinib (Tagrisso) has been approved as a first-line treatment option after the Phase 3 FLAURA study (NCT02296125) demonstrated a statistically significant improvement in PFS (18.9 months) compared to either erlotinib or gefitinib (10.2 months) in patients with EGFR-mutated mNSCLC (Soria et al 2018). Recently, the FLAURA study (NCT02296125) reported updated results with a median OS rate of 38.6 months in the osimertinib group compared to 31.8 months in the comparator group

(Ramalingam et al 2020). Moreover, for patients lacking EGFR or ALK/ROS1 mutations, immune checkpoint inhibitors were found to be more efficacious and better tolerated than first-line platinum-based chemotherapy.

Among patients with a tumour proportion score for PD-L1 of 50% or greater, pembrolizumab as a monotherapy is considered a first-line treatment of choice (Gandhi et al 2018). For patients with a lower expression of PD-L1, the treatment of choice is platinum doublet chemotherapy with anti-PD-1/PD-L1 targeting immunotherapy (Pabani and Butts 2018) Two recent studies (CHECKMATE 227 [NCT02477826] and CHECKMATE-9LA [NCT03215706]) have demonstrated benefit for nivolumab plus ipilimumab, with or without chemotherapy, versus chemotherapy alone, in advanced mNSCLC (Hellman et al 2019, Reck et al 2016). Based on these data, nivolumab plus ipilimumab has been approved by the FDA for adult patients with mNSCLC without EGFR or ALK genomic tumour alterations with PD-L1 expression ≥ 1 %; nivolumab plus ipilimumab is also approved with 2 cycles of platinum-based chemotherapy in tumours lacking EGFR and ALK alterations, irrespective of PD-L1 expression (FDA 2020).

Immunotherapy with anti-PD-1 or anti-PD-L1 checkpoint inhibitors was first investigated in the Phase 1 study of nivolumab reported in 2012 (Topalian et al 2014). NSCLC patients included in this study showed responses, some of which were durable. Subsequent trials of nivolumab and other agents, eg, pembrolizumab and atezolizumab (Borghaei et al 2015, Brahmer et al 2015, Herbst et al 2016), have confirmed responses and improved survival outcomes compared with docetaxel chemotherapy in the second-line treatment setting. The benefit is seen across adenocarcinoma and squamous carcinoma histology but there are poorer outcomes in EGFR and ALK-mutant tumours, possibly related to a lower mutational tumour burden and a poorer immune infiltrate in these tumours (Peters et al 2019).

While there are no direct HER2-targeted therapies approved for NSCLC, further investigation of HER2-targeting strategies are warranted in this patient population. Results from clinical studies suggest a potential role of HER2-targeting ADC in NSCLC. Two retrospective international studies of afatinib showed modest activity in patients with HER2-mutant NSCLC (Peters et al 2018, Lai et al 2019). A study of T-DM1 in NSCLC based on HER2 IHC expression showed an ORR of 0% for IHC 2+ tumours but did demonstrate efficacy with ORR 20% in IHC 3+ tumours (Peters et al 2019). A separate T-DM1 study reported an ORR of 44% in patients with HER2-mutant NSCLC (Li et al 2018). A recent Phase 1 dose escalation study of T-DXd monotherapy in patients with advanced solid malignant tumours (NCT02564900) confirmed responses in 6 solid tumour types, including HER2-expressing and HER2-mutant mNSCLC. In the HER2-expressing or HER2-mutant mNSCLC subgroup, 55.6% (10/18) of patients had a confirmed ORR, with a median DoR of 10.7 (95% CI: 6.9, 11.5) months and the median PFS was 11.3 (95% CI: 7.2, 14.3) months. Among the subset of patients with mNSCLC with HER2-mutant disease, the confirmed ORR was 72.7% (8/11),

with a median DoR of 9.9 (95% CI: 6.9, 11.5) months (Tsurutani et al 2020). More recently, in an ongoing open-label Phase 2 study (NCT03505710), T-DXd monotherapy ([redacted]) is administered as a second-line treatment, in patients with HER2-overexpressing (Cohort 1) or HER2-mutated (Cohort 2) NSCLC. Preliminary data from an interim analysis showed promising results for Cohort 2 (n = 42) with an ORR of 61.9% and an estimated PFS of 14 months. 59.5% (n = 25) of patients showed PR and 28.6% (n = 12) showed signs of SD.

A substantial unmet medical need exists for patients with NSCLC who have received platinum-doublets and immune checkpoint inhibitors. For these patients, the mainstay of treatment has been cytotoxic chemotherapy, with modest benefit and potential for significant toxicity. Although 30% to 40% of patients initially respond to platinum-based chemotherapy, they eventually progress on or after treatment. The introduction of immunotherapeutic agents targeting PD-1/PD-L1 has changed the treatment paradigm for these patients. These immunotherapies have been shown to be superior to chemotherapy in the second-line setting (Bose et al 2013, Bray et al 2018, Borghaei et al 2015, Herbst et al 2016), and have demonstrated improved outcomes for patients with tumours expressing PD-L1 in the first-line setting (Reck et al 2016). The combination of pembrolizumab plus chemotherapy has also been established as a new first-line SoC in NSCLC regardless of PD-L1 expression (Gandhi et al 2018).

Clinical outcomes with second-line therapies like docetaxel are generally poor with ORR of approximately 10%, median PFS of less than 4 months and median OS of 7 to 9 months (Bose et al 2013, Bray et al 2018, Borghaei et al 2015).

In the randomised Phase 3 trial investigating ramucirumab plus docetaxel versus docetaxel (Garon et al 2014), patients with NSCLC who had progressed after first-line platinum-based chemotherapy regimen were treated with ramucirumab or placebo in combination with docetaxel. Patients were screened between December 2010 and January 2013 and 1253 patients were randomly assigned to treatment. In 628 patients treated with ramucirumab plus docetaxel, the median OS was 10.5 months (95% CI: 9.5, 11.2), median PFS was 4.5 months (95% CI: 4.2, 5.4), and investigator assessed ORR was 22.9% (95% CI: 19.7, 26.4). Subgroup analysis for the population with HER2-mutant NSCLC was not reported.

In the randomised open-label Phase 3 CheckMate 078 study in a predominantly Chinese patient population, patients with squamous or non-squamous NSCLC that had progressed during/after platinum-based doublet chemotherapy were treated with nivolumab or docetaxel (Wu et al 2019). Patients were enrolled between December 2015 and November 2016. Median OS was 12.0 months for patients treated with nivolumab and 9.6 months for patients treated with docetaxel. The ORR was 16.6% (95% CI: 12.8, 21.0) with nivolumab and 4.2% (95% CI: 1.7, 8.5) with docetaxel.

In the randomised open-label Phase 3 RATIONALE 303 study of the anti-PD-1 antibody

tislelizumab was compared to docetaxel as second- or third-line therapy for patients with locally advanced or mNSCLC. Interim results, which were recently published in American Association for Cancer Research 2021 (Zhou et al 2021), indicate that the median OS was 17.2 months (95% CI: 15.28, 20.04) in the tislelizumab arm compared to 11.9 months (95% CI: 10.18, 13.93) in the docetaxel arm ($p < 0.0001$), median PFS in the tislelizumab arm was 4.1 months (95% CI: 3.75, 5.03) compared to 2.6 months (95% CI: 2.17, 3.78) in the docetaxel arm (descriptive $p < 0.0001$), and ORR in the tislelizumab arm was 21.9% compared to 7.0% in the docetaxel arm, with a difference of 14.9% (95% CI: 10.26, 19.56; descriptive $p < 0.0001$) (Business Wire 2021).

However, immunotherapy has not been well studied in HER2-mutant NSCLC and the benefits seen with immunotherapy and with targeted therapies have not been replicated in patients with HER2-mutant NSCLC. To date there are no approved therapies specifically targeting HER2 activating mutations. Therefore, HER2-mutant mNSCLC represents an important unmet medical need.

To better understand clinical outcomes following systemic therapy, the nationwide (US-based) de-identified FH-FMI CG was used to analyse data for patients with HER2 mutations and HER2 wild-type in 2013 or later. In the FH-FMI CG database, among all unique advanced/metastatic non-squamous NSCLC patients who were treated with any systemic therapy in the second-line setting, the median real world PFS was 3.31 months (n = 71, 95% CI: 2.43, 4.13 months) versus 4.56 months (n = 2638, 95% CI: 4.20, 4.82 months) in patients with activating HER2 mutation versus HER2 wild-type patients respectively (data on file). These data suggest a possible trend for poorer clinical outcomes in NSCLC patients with activating HER2 mutations treated with currently available therapies compared to patients with HER2 wild-type NSCLC.

The IMMUNOTARGET registry included 29 cases of HER2 exon 20 mutated NSCLC treated with anti-PD-1/anti-PD-L1 monotherapy across first- and later-line settings. Median PFS from start of anti-PD-1/anti-PD-L1 therapy for patients with HER2 mutations was 2.5 months (95% CI: 1.8, 3.5), compared to 3.2 months (95% CI: 2.7, 4.5) for patients with KRAS mutations, and 2.1 months (95% CI: 1.8, 2.7) for patients with EGFR mutations. PD-L1 expression has generally been reported to be low in patients with HER2-mutant NSCLC, with over 80% of patients having PD-L1 < 10% (Lai et al 2018, Mazieres et al 2019), although tumour mutational burden has been reported to be similar to unselected NSCLC, ie, not selected per any criteria (Lai et al 2018). Some studies of patients with HER2-mutant mNSCLC have suggested lack of immunotherapy benefit in patients treated across various lines of therapy (Fang et al 2019, Mazieres et al 2019), but more definitive conclusions are limited owing to the rarity of this disease subgroup (Guisier et al 2020, Lai et al 2018).

Retrospectively collected data from a web-based patient registry and hospital chart review in

China included 75 patients with advanced or recurrent NSCLC with de novo HER2 mutations. Between October 2012 and December 2018, 65 patients with in-frame insertion mutations, 8 with point mutations and 2 with gene amplification were found. The most common subtypes of insertion mutations were A775_G776insYVMA, G776delinsVC, and V777_G778insGSP. HER2 mutated patients were mostly young-aged, females, never or light smokers, with adenocarcinoma. Chemotherapy achieved better outcomes than HER2-TKIs (median PFS: 5.5 versus 3.7 months in the first-line setting and 4.2 versus 2.0 months in the second-line setting, $p = 0.001$ and 0.031, respectively). In particular for the most common subtype, YVMA insertions, PFS was significantly longer in chemotherapy than HER2-TKIs both in the first-line (6.0 versus 2.6 months, $p = 0.008$) and the second-line (4.2 versus 2.6 months $p < 0.001$) (Xu et al 2020).

Patients who were diagnosed with advanced lung cancer and had undergone molecular testing from April 2016 to December 2018 at Zhongshan Hospital in China were reviewed. Forty-four patients that had HER2-mutant advanced lung cancer, were analysed for clinical and molecular features and clinical outcomes. Their median age was 56 years, with the majority being women (n = 24), never-smokers (n = 32), and having the adenocarcinoma genotype (n = 42). A 12-base pair in-frame insertion in exon 20 with p.771insAYVM was the most common subtype in patients with known detail variants of HER2 mutation (9/27). The median OS from the date of advanced disease diagnosis was 9.9 months with 24 deaths, and a median follow-up of 12.7 months for survivors. For patients with a known HER2 exon 20 insertion mutation, OS tended to be superior (though not statistically) in the first-line HER2 TKI group to that in the group receiving chemotherapy (10.8 versus 9.8 months, $p = 0.40$). However, patients that received first-line chemotherapy had a median PFS of 5.9 months, numerically longer than that of the HER2-TKI group (4.6 months, $p = 0.63$). Patients who received HER2 targeted therapy as first-line therapy had an improved OS (10.8 versus 10.1 months, $p = 0.30$) and PFS (4.6 versus 2.8 months, $p = 0.36$) relative to those who received HER2 targeted therapy as subsequent-line therapy, although they did not meet the threshold for statistical significance (Zhou et al 2020b).

TKIs, including those traditionally used for EGFR-mutated NSCLC (eg, dacomitinib, afatinib), have demonstrated at best modest activity against HER2 mutations in small clinical studies, including patients with exon 20 mutations. In a Phase 2 study of 26 mostly pre-treated patients with NSCLC harbouring HER2 exon 20 mutations, dacomitinib therapy resulted in an ORR of 12%, median PFS of 3 months, and median OS of 9 months (Kris et al 2015). Afatinib has shown more limited activity in a Phase 2 study of 13 pre-treated patients with mNSCLC and HER2 exon 20 mutations where only 1 PR was observed (Dziadziuszko et al 2019). Pyrotinib, a pan-ErbB TKI, in a Phase 2 study of 60 pre-treated NSCLC patients demonstrated an ORR of 30%, median DoR of 6.9 months (95% CI: 4.9, 11.1), and median PFS of 6.9 months (95% CI: 5.5, 8.3). Notably, SD or response was seen in patients with non-exon 20 insertion mutations such as exon 20 single nucleotide variants (eg, G776X) or

exon 19 mutations (eg, L755P, V777L) (Zhou et al 2020a).

HER2-targeted therapy such as TKIs or trastuzumab has shown limited efficacy in HER2-mutant NSCLC amongst small cohorts of patients treated in either the first-line or later setting. Chemotherapy has shown higher median PFS compared to TKIs with anti-HER2 activity in both first-line (5.5 months versus 3.7 months) and second-line (4.2 months versus 2.0 months) HER2-mutant NSCLC (Xu et al 2020). Use of trastuzumab-based therapy typically in combination with chemotherapy has also been described in these patients, although limited conclusions can be made regarding its comparative efficacy to other systemic options owing to limited data (Li et al 2020, Mazieres et al 2013, Patil et al 2020).

Amongst NSCLC patients treated with pemetrexed-based chemotherapy, patients with NSCLC harbouring HER2 mutations demonstrated a median PFS of 5.1 months, which was similar to the median PFS for KRAS mutations (5.0 months, p = 0.971), numerically shorter than the median PFS for EGFR mutations (6.5 months, p = 0.247) and statistically shorter than the median PFS for ALK and ROS1 mutations (9.2 months, p = 0.004) (Wang et al 2018). When evaluated retrospectively using propensity score matching, NSCLC patients with HER2 mutations had a worse prognosis than wild-type NSCLC patients (median OS 28.4 months versus 62.8 months, p = 0.005) (Wei et al 2020).

Considering the current treatment options available for mNSCLC patients with HER2 mutation, a clear need for more effective therapies exists.

HER2 ADCs are recognised as a promising therapeutic option (NCCN 2020). Activity of HER2-directed ADCs in HER2-mutant tumours has been demonstrated in cell line experiments, and a proposed mechanism of action for targeted apoptotic cell death is increased receptor and ADC internalisation for HER2-mutant tumours compared to wild-type tumours. Furthermore, studies have shown that radionuclide-tagged trastuzumab accumulates in HER2-mutant and -amplified lung cancer patients on PET imaging, suggesting that HER2-mutant tumours selectively accumulate HER2 targeting agents (Li et al 2020.

In a Phase 2 clinical study, T-DM1 showed activity in patients with NSCLC and HER2 mutations. T-DM1 demonstrated an investigator-assessed ORR of 50% (14/28, 95% CI: 31, 69) amongst patients with HER2-mutant NSCLC and 50% (5/10, 95% CI: 19, 81) amongst patients with concurrent HER2 mutation and amplification. Amongst the HER2 mutation or amplification population, ORR was 51% (25/49, 95% CI: 36, 66), median DoR was 4.4 months (95% CI not reported), and median PFS was 5.0 months (95% CI: 3.5, 5.9) (Li et al 2020).

The activity of T-DXd has been reported in patient-derived xenograft models of S310F with ERBB2 amplification and exon 20 YVMA insertion mutated lung cancers that developed resistance to T-DM1 over time. In these nonclinical models, T-DXd induced responses

resulting in complete tumour regression in all mice. It was concluded that T-DXd showed deeper and more durable responses in the xenograft models when compared to T-DM1 (Li et al 2020). In addition, T-DXd has also demonstrated promising preliminary clinical efficacy in the setting of heavily pre-treated NSCLC patients with HER2 exon 19 and 20 mutations and T-DXd response durability appears improved over that of T DM1 from nonclinical and clinical data.

Study J101 included 18 patients with NSCLC that were treated with T-DXd of which 11 patients had a diagnosis of HER2-mutant NSCLC. T-DXd showed promising efficacy in these 11 patients and results were consistent with patients with HER2-positive breast cancer, representing the majority of patients enrolled in Study J101. In these 11 patients 72.7% (95% CI: 39.0, 94.0) had confirmed ORR, median DoR was 9.9 months (95% CI: 6.9, 11.5), and median PFS was 11.3 months (95% CI: 8.1, 14.3). Median OS had not been reached as of the date of DCO. T-DXd demonstrated an acceptable and generally manageable safety profile. A total of 289 patients received at least 1 dose of T-DXd of which the majority (99.7%) experienced at least 1 TEAE, with most of the common TEAEs being gastrointestinal or haematological in nature. TEAEs of ≥ Grade 3 were reported in 59.9% of patients and 49.5% had TEAEs of ≥ Grade 3 that the investigator considered to be related to the study drug. Across all tumour types, a numerically higher proportion of patients in the CCI dose group than in the CCI group experienced AEs of ≥ Grade 3.

Study U204 included 78 HER2-mutant NSCLC patients of which treatment (T-DXd) in 38 patients (48.7%) was ongoing at the time of DCO (31 May 2020). At the DCO, of 66 patients with HER2-mutant NSCLC, 1 (1.5%) patient had a confirmed BOR of CR, 32 (48.5%) patients had a confirmed BOR of PR, 24 (36.4%) patients had a confirmed BOR of SD, 3 (4.5%) patients had progressive disease (PD), and 6 (9.1%) patients were NE. Confirmed ORR was 50.0% (95% CI: 37.4, 62.6), median DoR was 12.0 months (95% CI: 5.6, 18.3) and estimated median PFS was 13.8 months (95% CI: 6.0, 19.5). A total of 125 patients have received T-DXd in this study to DCO of which the majority (98.4%) experienced at least 1 TEAE. A total of 62.4% of patients experienced ≥ Grade 3 TEAEs with the most commonly (≥ 10% of patients) reported ≥ Grade 3 events, by Preferred Term being neutrophil count decreased (20.0%) and anaemia (10.4%).

When taken together, considering the low response rate and short PFS of available treatment options, there is a clear unmet medical need for NSCLC patients harbouring HER2 mutation who are recurrent from prior anticancer therapy. The nonclinical and clinical findings suggest that T-DXd may have clinically meaningful benefit over SoC therapy in HER2-mutant NSCLC patients who are recurrent or relapsed from prior treatments. However, T-DXd has not been investigated in Chinese patients with HER2-mutant NSCLC and warrants further investigation in this population.

2.3 Benefit/Risk Assessment

Detailed information about the known and expected benefits and potential risks of T-DXd may be found in the IB.

2.3.1 Risk Assessment

2.3.1.1 Potential Risks of T-DXd

Based on cumulative review of safety data from nonclinical, clinical, epidemiologic information, scientific literature and taking into account biological plausibility, ILD/pneumonitis and neutropenia, including febrile neutropenia, are considered important identified risks associated with administration of T-DXd. Based on the available nonclinical data, review of the cumulative literature, reported toxicities for the same class of agents, the important potential risks for T-DXd are LVEF decrease (re labelled as 'Left ventricular dysfunction' as the undesirable clinical outcome of LVEF reductions, in accordance with the Revision 2 of the EMA guidelines on Good Pharmacovigilance Practice (EMA 2017). This re-labelling of the risk does not affect the nature or monitoring methods of the LVEF decrease as a potential risk associated with T-DXd), and embryofoetal toxicity.

In the T-DXd clinical development programme, specific inclusion/exclusion criteria and monitoring/management guidelines are currently in place to mitigate the important identified risks of ILD/pneumonitis and neutropenia, including febrile neutropenia, and important potential risks of LVEF decrease and embryofoetal toxicity.

ILD/pneumonitis and LVEF decrease are considered as AESIs and are closely monitored in the T-DXd clinical development programme.

The potential risks of T-DXd are shown in Table 2. These identified and potential risks are generally manageable through dose modification and routine clinical practice.

Table 2 Risk Assessment

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: T-DXd		
ILD/pneumonitis and neutropenia, including febrile neutropenia are considered important identified risks associated with administration of T-DXd LVEF decrease and embryofoetal toxicity are considered important potential risks for T-DXd. Keratitis is considered a potential risk for T-DXd. Other identified risks for T-DXd are infusion-related reactions, haematological AEs (anaemia, leukopenia, lymphopenia, thrombocytopenia), pulmonary/respiratory AEs (cough, dyspnoea, upper respiratory tract infection, epistaxis), gastrointestinal AEs (abdominal pain, constipation, diarrhoea, dyspepsia, nausea, stomatitis, vomiting), hepatic AEs (hepatic function abnormality, ALT, AST and ALP increased), skin AEs (alopecia, rash, pruritis), blood bilirubin increased, pneumonia, dry eye, dehydration, hypokalaemia, decreased appetite, dizziness, fatigue, peripheral oedema, pyrexia and headache T-DXd has not been studied in participants with severe/moderate hepatic impairment or severe renal impairment.	Based on cumulative review of safety data from nonclinical, clinical, epidemiologic information, scientific literature and taking into account biological plausibility Based on the available nonclinical data, review of the cumulative literature, and reported toxicities for the same class of agents, the important potential risks for T-DXd are LVEF decrease (re-labelled as 'Left ventricular dysfunction' as the undesirable clinical outcome of LVEF reductions, in accordance with the Revision 2 of the EMA guidelines on Good Pharmacovigilance Practice (EMA 2017). This re-labelling of the risk does not affect the nature or monitoring methods of the LVEF decrease as a potential risk associated with T-DXd) and embryofoetal toxicity	Specific inclusion/exclusion criteria (Section 5) and monitoring/management guidelines (Appendix K) are currently in place to mitigate the important identified risks of ILD/pneumonitis and neutropenia, including febrile neutropenia, and important potential risks of LVEF decrease and embryofoetal toxicity. ILD/pneumonitis and LVEF decrease are considered as AESIs and are closely monitored in the T-DXd clinical development programme. These identified and potential risks are generally manageable through dose modification (Section 6.6) and routine clinical practice.

AE = adverse event; AESI = adverse event of special interest; ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; EMA = European Medicines Agency, ILD = interstitial lung disease; LVEF = left ventricular ejection fraction; T-DXd = trastuzumab deruxtecan.

2.3.1.2 Potential Risks of HER2-targeted Agents

Several agents that target HER2 and prevent its activation or heterodimerisation have been developed and marketed for the treatment of HER2-positive cancers. These include the mAbs trastuzumab (Herceptin®) and pertuzumab (Perjeta®), the ADC T-DM1 (Kadcyla®), and HER1- and 2-associated TKI, lapatinib (Tykerb®), and neratinib (Nerlynx®). The safety profile of these HER2-targeted agents has been well described. The main safety risks identified in participants receiving HER2-targeted products are described below; these could potentially be expected to occur in participants receiving T-DXd.

Cardiotoxicity: Participants treated with trastuzumab are at increased risk for developing CHF (NYHA Class II to IV) or asymptomatic cardiac dysfunction, including LVEF decrease. Cardiac dysfunction, mainly asymptomatic LVEF decrease, has also been observed with pertuzumab in combination with trastuzumab. Similarly, cardiac dysfunction has been observed in participants receiving T-DM1, at a lower incidence than in participants receiving trastuzumab. Most cases have been asymptomatic decreases in LVEF. Cardiac dysfunction with lapatinib has occurred mainly in participants receiving the combination of trastuzumab and lapatinib and has consisted of predominantly asymptomatic LVEF decrease.

Pulmonary toxicity: Cases of pulmonary toxicity, including ILD/pneumonitis, have been observed in participants receiving trastuzumab, T-DM1, and lapatinib. Occasionally, these cases have been severe in nature and have resulted in fatal outcomes. Risk factors associated with ILD/pneumonitis include prior or concomitant therapy with other antineoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine, and radiation therapy.

Hypersensitivity/infusion-related reactions: The administration of therapeutic proteins is associated with a risk of hypersensitivity and/or infusion reactions. Hypersensitivity/infusion-related reactions have been reported with trastuzumab, pertuzumab and T-DM1. These can range from mild reactions to severe anaphylactic shock with fatal outcome, as has been the case for trastuzumab.

Hepatic toxicity: Cases of hepatic toxicity have occurred with T-DM1, lapatinib, and trastuzumab. In participants receiving T-DM1, hepatic toxicity has manifested mainly as transient asymptomatic liver transaminase elevations, although serious cases of drug-induced liver failure and nodular regenerative hyperplasia have also been reported. Lapatinib has also been associated with serious cases of DILI.

Haematological toxicity: Haematological toxicity has been observed with all HER2-targeted therapies. Neutropenia, febrile neutropenia, leukopenia, and anaemia have occurred commonly with trastuzumab, pertuzumab, and T-DM1. Thrombocytopenia, including Grade 3 and 4, is a common occurrence in T-DM1-treated participants. Although rare, serious haemorrhagic events have been reported in the setting of thrombocytopenia. Lower rates of

thrombocytopenia have also occurred with trastuzumab and pertuzumab when used in combination with chemotherapy.

Refer to Appendix K for T-DXd TMGs.

2.3.1.3 Potential Risks of Topoisomerase I Inhibitors

DXd is a derivative of exatecan (DX-8951f), a topoisomerase I inhibitor. Other products of the same class include irinotecan and topotecan. Exatecan is a campothecin derivative, which has previously been developed by the former Daiichi Pharmaceuticals Co, Ltd. as an anticancer therapy.

The main risks associated with the use of topoisomerase I inhibitors include haematological and gastrointestinal toxicities. Haematological toxicities, manifesting as neutropenia, febrile neutropenia, anaemia, thrombocytopenia and pancytopenia are commonly observed. An increased risk of infections, including neutropenic colitis and neutropenic sepsis has been reported with these agents.

Acute and delayed onset diarrhoea, which can be severe and lead to dehydration, have been associated with topoisomerase I inhibitors. Other significant risks include ILD/pneumonitis, liver impairment, immune system disorders and alopecia. Acute cholinergic syndrome, manifesting as diarrhoea and other cholinergic symptoms has been reported with irinotecan.

The safety profile of exatecan is broadly similar to the safety profile of other topoisomerase I inhibitors, with haematological toxicities and gastrointestinal toxicities being the most significant groups of events.

2.3.2 Benefit Assessment

T-DXd is under development for the treatment of HER2-mutant tumours. Based on preliminary clinical observations in a Phase 1 study (Study J101 [Phase 1; NCT02564900]) and a Phase 2 U204 study (Study DESTINY-Lung01; [NCT03505710]) T-DXd demonstrated antitumour activity in HER2-mutant cancers and a generally acceptable safety profile in these populations.

A tabular summary of clinical studies using T-DXd is presented in the IB. Refer to Section 2.2.3 and Table 4 for a brief summary of Study J101 and Study U204.

2.3.3 Overall Benefit: Risk Conclusion

As of 08 Jun 2020, an estimated 2345 patients have been treated with T-DXd (alone or as a combination therapy), or with a comparator in 16 completed or ongoing clinical studies. The clinical development programme has investigated the use of T-DXd in breast cancer, gastric cancer, colorectal cancer, NSCLC, and multiple tumours.

Taking into account the measures taken to minimise risk to participants in this study, the potential risks identified in association with T-DXd are justified by the anticipated benefits that may be afforded to participants with HER2-mutant mNSCLC who have disease progression on or after at least one-line of treatment.

The important identified risks associated with administration of T-DXd are ILD/pneumonitis and neutropenia, including febrile neutropenia; LVEF decrease and embryofoetal toxicity are considered important potential risks. To specifically mitigate the incidence of pulmonary toxicities, strict inclusion/exclusion criteria have been included in this CSP, prohibiting most patients with pre-existing pulmonary co-morbidities from entering the study. In addition, baseline pulmonary function tests will be performed for all patients. For haematological toxicities, the use of growth factors is allowed at the discretion of the investigator. Participants will be monitored closely throughout the study and clinical and laboratory assessments will be performed before every cycle. TMGs are added to assist with the management of the most commonly seen AEs (Appendix K).

The emergence of COVID-19 presents a potential safety risk for participants, therefore, several risk mitigation factors have been implemented in this study. Details regarding instructions related to COVID-19 and a more detailed description of benefit/risk considerations relevant to COVID-19 are provided in Appendix H.

T-DXd has the potential to provide meaningful clinical benefit. Considering the measures to minimise risks to participants, the benefit/risk assessment supports the proposed study.

There are no approved anti-HER2 targeted therapies for patients with HER2 mutations and unresectable or mNSCLC, so there is a significant unmet medical need for providing more treatment options and outcome in this patient population.

To date, the overall safety and tolerability profile of T-DXd monotherapy across the programme has been acceptable and the data available on the efficacy of T-DXd suggest that the overall benefit-risk assessment supports further clinical development.

3 OBJECTIVES AND ENDPOINTS

Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate confirmed ORR by ICR of T-DXd in participants with HER2-mutant NSCLC.	Confirmed ORR, defined as the proportion of participants with confirmed CR or PR, as assessed by ICR based on RECIST 1.1. The analysis will be performed on the population of participants with HER2 exon 19 or 20 mutation assessed by central laboratory.
Secondary	
To evaluate confirmed ORR by investigator assessment.	Confirmed ORR, by investigator assessment based on RECIST 1.1. The analysis will be performed on the population of participants with HER2 exon 19 or 20 mutation assessed by central laboratory.
To evaluate DoR, DCR, BOR, PFS, and OS.	• DoR, defined as time from the initial confirmed response (CR or PR) until documented tumour progression or death from any cause. DoR will be assessed by ICR and by the investigator based on RECIST 1.1. • DCR, defined as the proportion of participants who achieved confirmed CR, PR, or SD during study intervention. DCR will be assessed by ICR and by the investigator based on RECIST 1.1. • BOR, is a 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 progression or the last evaluable assessment in the absence of RECIST 1.1-defined progression. BOR will be assessed by ICR and by the investigator based on RECIST 1.1. • PFS, defined as the time from date of enrolment until first objective radiographic tumour progression or death from any cause. PFS will be assessed by ICR and by the investigator based on RECIST 1.1. • OS, defined as the time from date of enrolment until death from any cause.
To evaluate CNS-PFS.	CNS-PFS, defined as the time from date of enrolment until CNS tumour progression per RECIST 1.1 as assessed by ICR or death due to any cause in the absence of CNS progression.
To evaluate the PK and immunogenicity of T-DXd.	• Serum concentrations of intact T-DXd, total anti-HER2 antibody, and DXd, and evaluation of

Objectives	Endpoints
	appropriate PK parameters. T-DXd PK data will also be analysed via a PopPK approach if data allows. • Presence of ADAs against T-DXd in serum. Neutralising ADAs will also be assessed.
Safety	
To evaluate the safety and tolerability of T-DXd.	Occurrence of TEAEs, SAEs and AESIs, physical examination findings, ECOG PS, vital sign measurements, standard clinical laboratory parameters, ECG parameters, ECHO/MUGA findings, and ophthalmologic findings.
Tertiary/Exploratory	
CCI	CCI
CCI	CCI

ADA = anti-drug antibody; AESI = adverse event of special interest; BOR = best observed response; CNS-PFS = central nervous system progression-free survival; CR = complete response; DCR = disease control rate; DoR = duration of response; DXd = MAAA-1181a; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; HER2 = human epidermal growth factor receptor 2; ICR = independent central review; MUGA = multiple gated acquisition; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); PopPK = population pharmacokinetic(s); PR = partial response; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours, Version 1.1; SAE = serious adverse event; SD = stable disease; T-DXd = trastuzumab deruxtecan; TEAE = treatment emergent adverse event; CCI

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2, open-label, single-arm multicentre study in China assessing the efficacy and safety of T-DXd in participants with metastatic non-squamous NSCLC whose tumours have a HER2 exon 19 or 20 mutation, with disease progression on or after at least one-line of treatment.

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[redacted]

4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with COVID-19 or similar pandemic infection), which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The investigator or designee should contact the AstraZeneca to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with GCP, and minimise risks to study integrity. Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining reconsent for the mitigation procedures (note, in the case of verbal [consent/reconsent], the ICF should be signed at the participant's next contact with the study site).
- Rescreening: Additional (one) rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated study physician.
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix I.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Design

The second-line therapy of NSCLC without actionable mutation as recommended by the CSCO 2020 NSCLC Guideline, ie, docetaxel, other chemotherapy or immunotherapy, only provides an ORR of no more than 20% and a relatively short PFS as shown in Table 4 (Li et al 2012, Wu et al 2019). According to Study J101 and interim Study U204 data, T-DXd showed a compelling ORR of 72.7% and 50% respectively in patients with metastatic HER2-mutant NSCLC as a later-line treatment (Table 4). Considering the limited efficacy of current therapies, the high response rate observed for T-DXd, and the small number of patients with HER2-mutant NSCLC, DESTINY-Lung05 will be a single-arm design. This will enable all participants to be treated with T-DXd, and hence potentially obtain a more efficacious treatment compared to conventional therapy.

4.2.2 Rationale for T-DXd in HER2-mutant Metastatic NSCLC

HER2 mutations have been identified in approximately 2% to 4% of NSCLC globally including China (Arcila et al 2012, Mazieres et al 2013, Tomizawa et al 2011, Wei et al 2020). Currently, there are no therapies specifically approved for patients with HER2-mutant NSCLC as described in Section 2.2.3. In the absence of an approved anti-HER2 therapy, treatment of patients with metastatic HER2-mutant NSCLC generally follows the treatment paradigm for those patients without an actionable mutation. Patients with HER2 mutations have a poor prognosis when compared to patients with other mutations (Section 2.2.2).

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Table 4 T-DXd Efficacy and Safety Outcomes in HER2-mutant NSCLC per RECIST 1.1 (Study J101 and Study U204) Compared to China Studies

	Checkmate 078 Study (Wu et al 2019)		Pemetrexed vs Docetaxel (Li et al 2012)		Study J101 (DCO 01 Feb 2019)	Study U204 (Interim Analysis DCO 31 May 2020)
Population	Patients from China, Russia, and Singapore with NSCLC		Patients from China, Stage IIIB or IV NSCLC		Patients from global, HER2-mutation NSCLC cohort	
Arm	Nivolumab	Docetaxel	Pemetrexed	Docetaxel	T-DXd	T-DXd
Number	338	166	132	128	11	66
Age, median (range), years	60 (27 to 78)	60 (38 to 78)	58.2 (38 to 75)	55.6 (33 to 75)	-	60.0 (PPD)
Male, n (%)	263 (78)	134 (81)	67 (63.2)	74 (72.5)	-	20 (30.3)
Received line of therapy	1		1		-	2 (median)
Efficacy						
ORR (95% CI), %	16.6 (12.8, 21.0)	4.2 (1.7, 8.5)	9.4	4.9	72.7 (39.0, 94.0)	50.0 (PPD)
DoR, months	NR (range: 2.3, 19.2+)	5.3 (range: 2.2+ to 8.6+)	not stated	not stated	9.9 (95% CI: 6.9, 11.5)	12.0 (95% CI: PPD)
mPFS (95% CI), months	2.8 (2.4, 3.4)	2.8 (1.6, 2.9)	not stated	not stated	11.3 (8.1, 14.3)	13.8 (PPD)
mOS (95% CI), months	12.0 (10.4, 14.0)	9.6 (7.6, 11.2)	not stated	not stated	-	15.3 (PPD)
Safety						
≥ Grade 3, %	10	48	not stated	not stated	-	53.8
AE leading to discontinuation, %	4	8	not stated	not stated	-	26.9

AE = adverse event; CI = confidence interval; DCO = data cut-off; DoR = duration of response; HER2 = human epidermal growth factor receptor 2; mOS = median overall survival; mPFS = median progression-free survival; NR = not reached; NSCLC = non-small cell lung cancer, ORR = objective response rate; T-DXd = trastuzumab deruxtecan; vs = versus.

4.2.3 Rationale for Study Endpoints

The primary endpoint is confirmed ORR, defined as the proportion of participants with confirmed CR or PR, as assessed by ICR based on RECIST 1.1. Confirmed ORR by ICR represents the percentage of participants whose disease decreases in size or disappears and provides an early signal for clinical benefit. It is an appropriate and reasonable efficacy endpoint for single-arm studies considering the unmet medical needs and the encouraging efficacy data observed in J101 and U204. In accordance with the requirements of NMPA's Center for Drug Evaluation, efficacy response assessment is performed by independent review.

Additional secondary efficacy endpoints (ORR by investigator assessment; DoR, DCR, BOR, PFS by investigator assessment and ICR; CNS-PFS by ICR, and OS) will be used to further evaluate efficacy and to corroborate the benefits of antitumour effects demonstrated by confirmed ORR as assessed by ICR.

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

4.3 Justification for Dose

T-DXd will be administered at a dose of CCI

CCI

4.3.1 PK Comparability Between Metastatic Breast Cancer and Metastatic NSCLC

From a PK perspective, the systemic exposure parameters (C_{max}, $AUC_{0\text{-}21d}$, and C_{trough} in Cycle 1) of intact T-DXd and DXd were similar across patients with metastatic breast cancer and HER2-expressing or -mutant NSCLC at T-DXd CCI (Table 5).

Table 5 Cycle 1 PK Parameters (Mean ± Standard Deviation) of T-DXd at CCI Dose in HER2-positive or HER2-low Breast Cancer and HER2-expressing or -mutant NSCLC

Analyte PK Parameter (units)	T-DXd CCI		
	HER2-positive breast cancer	**HER2-low breast cancer**	**HER2-expressing or -mutant NSCLC**
	intact T-DXd		
C_{max} (µg/mL)	165.2 ± 51.0 [122]	171.7 ± 91.5 [79]	162.1 ± 36.1 [19]
$AUC_{0\text{-}21d}$ (µg·d/mL)	756.5 ± 205.1 [115]	680.9 ± 147.5 [79]	675 ± 212.2 [19]
C_{trough} (µg/mL)	9.25 ± 20.0 [116]	7.3 ± 10.4 [78]	6.5 ± 3.8 [18]
	DXd		
C_{max} (µg/mL)	10.5 ± 9.34 [122]	13.4 ± 4.35 [79]	11.5 ± 3.72 [19]
$AUC_{0\text{-}21d}$ (µg·d/mL)	43.6 ± 31.40 [103]	40.6 ± 11.94 [76]	40.4 ± 12.75 [19]
C_{trough} (µg/mL)	0.35 ± 0.244 [115]	0.33 ± 0.201 [78]	0.37 ± 0.210 [18]

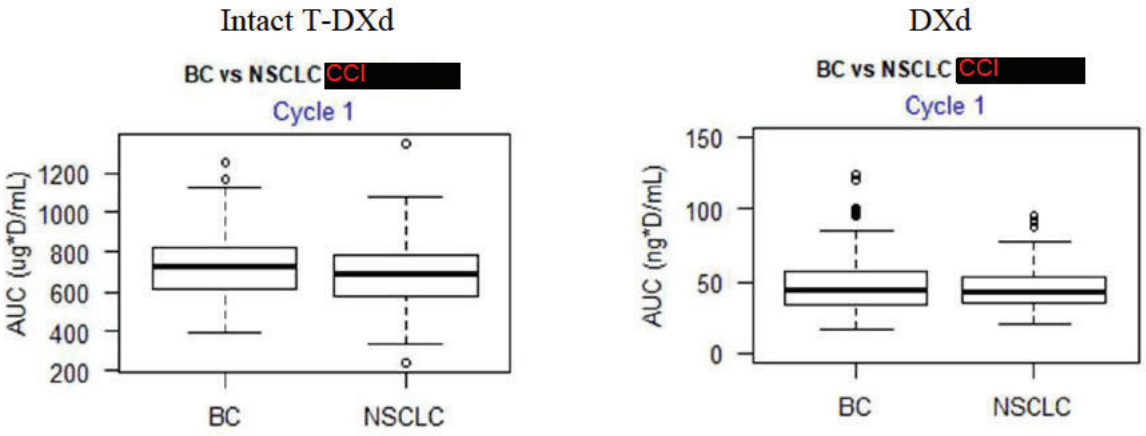
Values in the table are mean ± standard deviation [N].

HER2-positive breast cancer and HER2-low breast cancer data were combined across Studies DS8201-A J101, DS8201-A-J102, DS8201-A-A103, and DS8201-A-U201. NSCLC group includes 18 patients from Study DS8201-A-J101 and 1 patient from Study DS8201-A-A103. Data from NSCLC patients in Study DS8201-A-U204 were not included as PK sampling was sparse, compared to Study DS8201-A-J101, to provide robust non-compartmental analysis-based PK parameter estimates.

$AUC_{0\text{-}21d}$ = area under the concentration-time curve from time 0 to Day 21; C_{max} = maximum observed concentration; C_{trough} = trough serum concentration on Day 2; DXd = deruxtecan; HER2 = human epidermal growth factor receptor 2; NSCLC = non-small cell lung cancer; PK = pharmacokinetic(s); T-DXd = trastuzumab deruxtecan.

These data are reinforced by preliminary PopPK analysis, which showed similar systemic exposures for intact T-DXd and DXd (C_{max} and $AUC_{0\text{-}21d}$ in Cycle 1 or at steady state) in patients with breast cancer and NSCLC administered T-DXd CCI (Figure 2).

Figure 2 **Intact T-DXd and DXd Cycle 1 AUC Values for HER2-positive Patients with Breast Cancer or NSCLC Based on PopPK Analyses**



N = 209 for BC and N = 79 for NSCLC at T-DXd CCI 1 NSCLC patient received T-DXd CCI . Patients for NSCLC were combined across Studies J101 and U204.
AUC = area under the concentration-time curve from time 0 to Day 21; BC = breast cancer; DXd = deruxtecan; HER2 = human epidermal growth factor receptor 2; NSCLC = non-small cell lung cancer; PopPK = population pharmacokinetic(s); T-DXd = trastuzumab deruxtecan; vs = versus.

The systemic exposures of T-DXd CCI in patients with breast cancer and systematic exposure of T-DXd CCI in patients with breast cancer and NSCLC in Cycle 1 was observed to exceed the systemic efficacious exposure observed during the nonclinical pharmacology evaluation.

T-DXd exposure increases proportionally to dose in the range from CCI The systemic exposure of T-DXd should also be similar between patients with breast cancer and NSCLC receiving T-DXd CCI , given the similar exposure observed between the 2 tumour types at the dose level of CCI . The similarity of exposure between breast cancer and NSCLC is expected to extrapolate to Chinese patients, considering no clinically relevant ethnic difference in PK is expected between Chinese and non-Chinese patients.

4.3.2 Efficacy Comparison Between Metastatic Breast Cancer and Metastatic NSCLC

Metastatic Breast Cancer

In patients with metastatic breast cancer at T-DXd CCI , the confirmed ORR by ICR 58.3% (95% CI: 51.7, 64.7) in the pooled dataset (N = 235) across Study J101 (DCO 01 Feb 2019) and Study DS8201-A-U201 (hereinafter referred to as Study U201) (DCO 21 Mar 2019); ORR was 51.0% (95% CI: 36.6, 65.2) in Study J101 and 60.3% (95% CI: 52.9, 67.4) in Study U201. The confirmed ORR by ICR at T-DXd CCI was 53.7% (95% CI: 41.1, 66.0) in Study J101 and 68.8% (95% CI: 53.8, 81.3) in Study U201, which was modestly higher compared to the ORR observed with T-DXd CCI . Further details are provided in Section 4.3.4.

NSCLC

T-DXd CCI has shown promising preliminary efficacy in HER2-mutant NSCLC patients in Study J101. The confirmed ORR was 72.7% among HER2-mutant NSCLC patients (N =11).

Moreover, preliminary data from interim analyses of Study U204 have shown promising clinical efficacy of T-DXd CCI in HER2-mutant NSCLC patients. At the first interim analysis (DCO 25 Nov 2019), efficacy results were reported for 42 patients administered T-DXd CCI Q3W. Median follow-up duration was 8.0 months (range: 1.4, 14.2). The ICR-assessed confirmed ORR was 61.9% (95% CI: 45.6, 76.4) (Smit et al 2020). At the second interim analysis (DCO 31 May 2020), efficacy results were reported for 66 patients administered T-DXd CCI Q3W. Median follow-up duration was 8.2 months (range 0.7 to 19.5). The ICR-assessed confirmed ORR was 50.0% (95% CI: 37.4, 62.6).

Therefore, the ORR observed in HER2-mutant NSCLC patients in Study U204 are reasonably similar to the ORR reported in metastatic breast cancer patients in Study J101.

These preliminary data suggest that the ORR observed with T-DXd in HER2-mutant NSCLC is substantially higher than the ORR that has been reported for current SoC treatment for second-line or later NSCLC, namely nivolumab, docetaxel, or docetaxel and ramucirumab.

4.3.3 Safety Comparison Between Metastatic Breast Cancer and Metastatic NSCLC

The exposure-response analyses for safety in breast cancer patients estimated a numerically higher incidence (approximately 1% to 7%) for the safety endpoints analysed, AEs associated with discontinuation, dose reduction or drug interruption, AEs ≥ Grade 3, SAEs, anaemia, neutropenia or thrombocytopenia and ILD (any grade and ≥ Grade 3), and decreased LVEF (≥ Grade 2), at a dose of T-DXd CCI compared to a dose of T-DXd CCI .

A total of 48 patients with breast cancer received T-DXd CCI in Study U201. As of 31 May 2020, 78 patients with NSCLC had been administered T-DXd CCI in Study U204. The incidence of AEs associated with discontinuation, dose interruption, and dose reduction was 13%, 33%, and 40%, respectively, in Study U201, compared to 27%, 41%, and 28%, respectively, in Study U204. Grade ≥ 3 AEs were reported in 69% of patients in Study U201 and 54% of patients in Study U204. The most frequent ≥ Grade 3 AE was neutrophil count decreased in both Study U201 (21%) and Study U204 (19%). Adjudicated drug-related ILD was also reported at a similar incidence in Study U201 (8%) and Study U204 (9%).

Therefore, the safety profile of T-DXd CCI Q3W was similar in breast cancer patients and NSCLC patients.

4.3.4 Summary

In summary, T-DXd will be administered at a dose of CCI this study. CCI

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoA (Table 1) including follow-up for OS determination.

The study may be stopped if, in the judgement of AstraZeneca, study participants are placed at undue risk because of clinically significant findings.

The end of the study is defined as the time of the final DCO for the final analysis. Final analysis is planned to be performed approximately 15 months after the last participant has initiated study intervention. Based on data from Study U204, 15 months is sufficient time for participants to reach a response (median time to response is 1.4 months) and to allow DoR to be determined for responders (median confirmed DoR is 12 months). Participants may be withdrawn from the study at this time; however, participants may remain on study intervention beyond closure of the database if, in the opinion of the investigator, they continue to receive benefit from study intervention and have no evidence of disease progression (Section 6.7).

See Section 6.7 for details on participant management following the final DCO as well as following study completion.

5 STUDY POPULATION

The target population of interest in this study is participants with metastatic non-squamous NSCLC whose tumours have a study-qualifying HER2 exon 19 or 20 mutation, with disease progression on or after at least one-line of treatment.

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

Participants who do not meet the eligibility criteria requirements are screen failures; refer to Section 5.4.

5.1 Inclusion Criteria

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

Informed Consent

1 Capable of giving signed informed consent as described in 10, which includes compliance with the requirements and restrictions listed in the ICF and in this CSP.

Age

2 Male and female participants must be ≥18 years at the time of signing the ICF.

Type of Participant and Disease Characteristics

3 Pathologically documented metastatic non-squamous NSCLC. Participants with mixed histology are eligible if adenocarcinoma is the predominant histology.

4 Has relapsed from or is refractory to at least one-line of anticancer treatment in the metastatic setting.

5 Documented study-qualifying activating [redacted] either from a pre-existing tissue test result obtained from qualified local laboratory/assay or have the tissue HER2 mutation test result detected prospectively in a central laboratory.

6 Is willing and able to either:

- [redacted]
- [redacted]

7 WHO or ECOG performance status of 0 or 1.

8 Presence of at least one measurable lesion assessed by the investigator based on RECIST 1.1.

9 Has adequate organ and bone marrow function within 14 days before enrolment as defined in Table 6. All parameters must meet the inclusion criteria on the same day, and must be the most recent results available.

Table 6 Parameters for Adequate Organ and Bone Marrow Function

Adequate bone marrow function	
Platelet count	≥ 100×10^9/L. (Platelet transfusion is not allowed within 1 week prior to screening assessment)
Haemoglobin	≥ 9.0 g/dL **NOTE**: Participants requiring ongoing transfusions or growth factor support to maintain haemoglobin ≥9.0 g/dL are not eligible. (Red blood cell transfusion is not allowed within 1 week prior to screening assessment)
Absolute neutrophil count	≥ 1.5×10^9/L. (granulocyte-colony stimulating factor administration is not allowed within 1 week prior to screening assessment)
Adequate hepatic function	
ALT and AST	≤ 3 × ULN (< 5 × ULN in participants with liver metastases)
TBL	≤ 1.5 × ULN if no liver metastases or < 3 × ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline
Serum albumin	≥ 2.5 g/dL
Adequate renal function	
CrCL	≥ 30 mL/min as determined by Cockcroft Gault (using actual body weight). Males: CrCL (mL/min) = $\frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$ Females: CrCL (mL/min) = $\frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$
Adequate blood clotting function	
INR or PT and either PTT or aPTT	≤ 1.5 × ULN

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CrCL = calculated creatinine clearance; INR = international normalised ratio; PT = prothrombin time; PTT = partial thromboplastin time; TBL = total bilirubin; ULN = upper limit of normal.

10 LVEF ≥ 50% within 28 days before enrolment.

11 Minimum life expectancy of 12 weeks at screening.

12 Has adequate treatment washout period before enrolment, as defined in Table 7 below:

Table 7 Adequate Treatment Washout Periods

Treatment	Minimum Washout Period
Major surgery (as defined by the investigator) within 28 days prior to first dose or still recovering from prior surgery. Note: Local procedures (eg, placement of a systemic port, CNB, and prostate biopsy) are allowed if completed at least 24 hours prior to the administration of the first dose of study intervention	≥ 4 weeks
Radiation therapy including palliative stereotactic radiation therapy to chest	≥ 4 weeks
Palliative stereotactic radiation therapy to other anatomic areas including whole brain radiation (except as specified for CNS radiation, see exclusion criterion 2)	≥ 2 weeks
Anticancer chemotherapy (Immunotherapy [non-antibody-based therapy]), retinoid therapy, hormonal therapy	≥ 3 weeks
Antibody-based anticancer therapy	≥ 4 weeks
Targeted agents and small molecules	≥ 2 weeks or 5 half-lives, whichever is longer
Nitrosoureas or mitomycin C	≥ 6 weeks
TKIs approved for treatment of NSCLC	≥ 1 week [a]
Chloroquine/hydroxychloroquine	≥ 14 days
Cell-free and Concentrated Ascites Reinfusion Therapy (CART), peritoneal shunt or drainage of pleural effusion, ascites or pericardial effusion	≥ 2 weeks, prior to screening assessment

[a] Baseline CT scan must be completed after discontinuation of TKI.

CART = cell-free and concentrated ascites reinfusion therapy; CNB = core needle biopsy; CNS = central nervous system; NSCLC = non-small cell lung cancer; TKI = tyrosine kinase inhibitor.

Reproduction

13 Evidence of post-menopausal status or negative serum pregnancy test for females of childbearing potential who are sexually active with a non-sterilised male partner. For WOCBP, a negative result for serum pregnancy test (test must have a sensitivity of at least 25 mIU/mL) must be available at the screening visit and urine β-HCG pregnancy test prior to each administration of T-DXd.

WOCBP are defined as those who are not surgically sterile (ie, underwent bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal. Women will be considered post-menopausal if they have been amenorrhoeic for 12 months without an alternative medical cause.

14 Female participants of childbearing potential who are sexually active with a non-sterilised male partner must use at least one highly effective method of contraception. Not all methods of contraception are highly effective (see Table 19 for complete list of highly

effective birth control methods). They should have been stable on their chosen method of birth control for a minimum of 3 months before entering the study and continue to use it throughout the total duration of the drug treatment and the drug washout period (7 months after the last dose of T-DXd). Female participants must refrain from breastfeeding while on study and for 7 months after the last dose of T-DXd. Complete heterosexual abstinence for the duration of the study and drug washout period is an acceptable contraceptive method if it is line with the participant's usual lifestyle (consideration must be made to the duration of the clinical study); however, periodic or occasional abstinence, the rhythm method, and the withdrawal method are not acceptable.

15 Non-sterilised male participants who are sexually active with a female partner of childbearing potential must use a condom with spermicide from screening to 4 months after the final dose of T-DXd. Complete heterosexual abstinence for the duration of the study and drug washout period is an acceptable contraceptive method if it is in line with the participant's usual lifestyle (consideration must be made to the duration of the clinical study); however, periodic or occasional abstinence, the rhythm method, and the withdrawal method are not acceptable. It is strongly recommended for the female partners of a male participant to also use at least one highly effective method of contraception throughout this period. In addition, male participants should refrain from fathering a child, or freezing or donating sperm from the time of screening, during the study and for 4 months after the last dose of T-DXd. Preservation of sperm should be considered prior to entering the study.

16 Female participants must not donate, or retrieve for their own use, ova from the time of screening and throughout the study intervention period, and for at least 7 months after the final study drug administration. Preservation of ova may be considered prior to entering the study.

5.2 Exclusion Criteria

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

Medical Conditions

1 Mixed small cell lung cancer, squamous histology NSCLC, and sarcomatoid histology variant NSCLC.

2 Any spinal cord compression, leptomeningeal disease, or clinically active CNS metastases. Note: Clinically active CNS metastases are defined as untreated AND symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Participants with CNS metastases must have previously completed local therapy.

- Participants with previously treated CNS metastases are allowed if asymptomatic or neurologically stable and have recovered from the acute toxic effects of prior therapy.
- Participants with CNS metastases treated by radiation must be:

- ≥ 7 days since stereotactic radiosurgery or gamma knife prior to enrolment.
- ≥ 14 days since whole brain radiation therapy prior to enrolment.

3 Has a pleural effusion, ascites or pericardial effusion that requires drainage, peritoneal shunt, or cell-free and concentrated ascites reinfusion therapy (CART).

4 Has a concomitant medical condition that would increase the risk of toxicity, in the opinion of the investigator.

5 Multiple primary malignancies within 3 years with the exception of:

- adequately resected non-melanoma skin cancer.
- curatively treated in-situ disease.
- other solid tumours curatively treated.

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

7 Corrected QT interval (QTcF) prolongation to > 470 ms (females) or > 450 ms (males), based on average of the screening triplicate 12-lead ECG.

8 History of (non-infectious) ILD/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.

9 Lung criteria:

a) Lung specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disorder (eg, pulmonary emboli within 3 months of study enrolment, severe asthma, severe COPD, restrictive lung disease, pleural effusion etc).

b) Any autoimmune, connective tissue or inflammatory disorders (ie, rheumatoid arthritis, Sjogren's, sarcoidosis, etc) where there is documented, or a suspicion of pulmonary involvement at the time of screening. Full details of the disorder should be recorded in the eCRF for participants who are included in the study.

c) Prior complete pneumonectomy. Note: Prior lobar or segmental resection is permitted.

10 Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals or active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination, and radiographic findings, and tuberculosis testing in line with local practice).

11 Active primary immunodeficiency, known HIV infection, or active hepatitis B or C infection, such as those with serologic evidence of viral infection within 28 days of Cycle

1 Day 1. Note: Participants positive for HCV antibody are eligible only if PCR is negative for HCV RNA. Participants should be tested for HIV prior to enrolment if required by local regulations or IEC. Subjects with past or resolved hepatitis B virus (HBV) infection who are anti-HBc positive (+) are eligible only if they are HBsAg negative (-).

12 Receipt of live, attenuated vaccine (mRNA and replication deficient adenoviral vaccines are not considered attenuated live vaccines) within 30 days prior to the first dose of T-DXd. Note: Participants, if enrolled, should not receive live vaccine during the study and up to 30 days after the last dose of T-DXd.

13 Has substance abuse or any other medical conditions such as clinically significant cardiac or psychological conditions, that may, in the opinion of the investigator, interfere with the participant's participation in the clinical study or evaluation of the clinical study results.

Prior/Concomitant Therapy

14 Has unresolved toxicities from previous anticancer therapy, defined as toxicities (excluding alopecia) not yet resolved to Grade $\leq$1 or baseline. Note: participants may be enrolled with chronic, stable Grade 2 toxicity (defined as no worsening to >Grade 2 for at least 3 months prior to enrollment and managed with standard of care treatment) that the investigator deems related to previous anticancer therapy, such as:

- Chemotherapy-induced neuropathy
- Fatigue
- Residual toxicities from prior IO treatment: Grade 1 or Grade 2 endocrinopathies which may include:
  a) Hypothyroidism/hyperthyroidism
  b) Type 1 diabetes
  c) Hyperglycaemia
  d) Adrenal insufficiency
  e) Adrenalitis
  f) Skin hypopigmentation (vitiligo)

15 Has been previously treated with HER2-targeted therapies, except for pan-HER class TKIs, or has received prior treatment with an ADC which consists of an exatecan derivative that is a topoisomerase I inhibitor.

16 Any concurrent anticancer treatment (see Table 7 for adequate washout periods). Concurrent use of hormonal therapy for non-cancer-related conditions (eg, insulin for diabetes and HRT) is allowed.

Prior/Concurrent Clinical Study Experience

17 Known allergy or hypersensitivity to T-DXd or any of the study drug excipients.

18 History of severe hypersensitivity reactions to other mAbs.

Other Exclusions

19 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

20 Judgement by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions and requirements.

21 Pregnant (confirmed with positive pregnancy test) or breastfeeding female participants, or participants who are planning to become pregnant.

22 Has social, familial, or geographical factors that would interfere with study participation or follow-up.

23 Is a family member of the study site personnel or AstraZeneca personnel.

5.3 Lifestyle Considerations

The following restrictions apply while the participant is receiving study intervention and for the specified times before and after:

1 Participants must follow the contraception requirements outlined in Appendix F.

2 Participants should not donate blood or blood components while participating in this study and through 40 (+ 7) days after the last dose of T-DXd.

3 Male participants should consider to preservation of sperm prior to entering the study.

4 Female participants must not donate, or retrieve for their own use, ova from the time of screening and throughout the study treatment period, and for at least 7 months after the final study drug administration. They should refrain from breastfeeding throughout this time. Female patients may wish to consider preservation of ova prior to entering the study.

Restrictions relating to concomitant therapies are described in Appendix G 1.

5.3.1 Meals and Dietary Restrictions

In general, there are no dietary restrictions for the study assessments or treatment with T-DXd.

5.3.2 Tobacco

Use of tobacco products, e-cigarettes and vaping is strongly discouraged but not prohibited. Any prior or current use of these products should be recorded in the eCRF.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to

queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened a single time. Rescreened participants should be assigned the same participant number (ie, E-code) as for the initial screening. However, rescreening should be documented so that its effect on study results, if any, can be assessed.

Generally, all assessments should be repeated for rescreening unless they are within 28 days of enrolment (the date the participant is confirmed as eligible in the IRT). As of necessity of repeating central HER2 testing for defining eligibility, please contact AstraZeneca to discuss on a case-by-case basis.

These participants should have the reason for study withdrawal recorded in eCRF as "eligibility criteria not fulfilled" (ie, participant does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (ie, participants who are not entered in the study). Participant enrolment is described in Section 6.3.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the CSP.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

AstraZeneca will supply T-DXd.

The treatment schedule is described in Section 1.3

Dose modifications are described in Section 6.6.

Table 8 Study Intervention

ARM Name	T-DXd arm
Intervention Name	T-DXd
Type	Drug
Dose Presentation	Vial
Unit Dose Strength(s)	Powder for concentrate for solution for infusion CCI /vial
Dosage Level(s)/frequency	CCI
Route of Administration	IV infusion

Use	Experimental
IMP and NIMP	IMP
Sourcing	Provided centrally by AstraZeneca
Packaging and Labelling	Study intervention will be provided in CCI vials in carton. Each vial and carton will be labelled in accordance with GMP Annex 13 and per country requirements [a]
Current/Former Name(s) or Alias(es)	DS-8201a

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

GMP = Good Manufacturing Practice; IMP = investigational medicinal product; IV = intravenous; NIMP = non-investigational medicinal product; Q3W = every 3 weeks; T-DXd = trastuzumab deruxtecan.

6.1.1.1 Duration of Treatment

Participants will receive T-DXd CCI [redacted] Participants will continue to receive T-DXd until PD per RECIST 1.1 as assessed by the investigator, unless unacceptable toxicity, withdrawal of consent, or other criterion for withdrawal is met.

Participants with objective radiological CNS-only progression (based on RECIST 1.1), who in the investigator's opinion, continue to receive benefit from study intervention and meet the criteria for treatment in the setting of CNS-only progression may continue to receive study intervention on study for as long as they are gaining clinical benefit, as judged by the investigator, and are without any discontinuation criteria, until one of the criteria in Section 6.1.1.2 is met. Aside from within this context, study intervention treatment is not planned beyond progression with T-DXd. Participant level risk-to-benefit ratio favours discontinuing treatment as participants are highly unlikely to derive clinical benefit post-progression and remain at risk of ILD and other toxicities if treatment is continued.

6.1.1.2 Treatment Beyond Progression: CNS-only Progression

For participants with objective radiological CNS-only progression (based on RECIST 1.1), who in the investigator's opinion, continue to receive benefit from study intervention and meet the criteria for treatment in the setting of CNS-only progression may continue to receive study intervention on study for as long as they are gaining clinical benefit (see Section 7.1.3 for details) and are without any discontinuation criteria, until one of the following criteria is met:

1. Meets any of the discontinuation criteria.
2. Clinical symptoms or signs indicating clinically significant PD such that the benefit-risk ratio of continuing therapy is no longer justified based on investigator judgement.

3. Decline in WHO/ECOG performance status compared to baseline.
4. Rapid PD or threat to vital organs/critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention, and/or continuation of study treatment would prevent institution of such intervention.

CNS-directed radiotherapy (stereotactic radiosurgery, gamma knife, or whole brain radiation therapy) for CNS-only progression is permitted on study only after consultation with the AstraZeneca study physician. Participants who pursue local definitive radiotherapy for CNS-only progression must not receive study intervention ± 7 days within receiving stereotactic radiosurgery or gamma knife, or ± 14 days within receiving whole brain radiotherapy. Those who receive CNS-directed radiotherapy for CNS-only progression, providing there is no other systemic progression, may be allowed to continue study intervention until a second progression (CNS or body) is observed. Study intervention will be discontinued at the time of second progression.

Study intervention treatment is NOT permitted beyond progression when the site of PD is outside of the CNS. In the setting of PD outside of the CNS, participant level risk to-benefit ratio favours discontinuing treatment as participants are highly unlikely to derive clinical benefit post-progression and remain at risk of ILD and other toxicities if treatment is continued.

6.2 Preparation/Handling/Storage/Accountability of Interventions

1 The investigator or designee (eg, pharmacist) must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2 Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

3 The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4 Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual or other specified location.

6.2.1 T-DXd Preparation, Administration and Storage

The preparation, handling, storage, and administration instructions for T-DXd will follow the IP handling instructions.

T-DXd will be supplied by AstraZeneca as a CCI vial lyophilised powder for concentrate for solution for infusion. Following reconstitution with sterile water for injection, the solution contains CCI T-DXd in CCI mM histidine/histidine hydrochloric acid, CCI mg/mL sucrose, CCI polysorbate 80; it has a pH of CCI. The post-reconstitution label-claim volume is 5 mL.

The reconstituted product is a CCI

Preparation of T-DXd

The dose of T-DXd for administration must be prepared by the investigator's or site's designated study intervention manager using aseptic technique. Total time from needle puncture of the T-DXd vial to the start of administration must not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

If the final product is stored at both refrigerated and ambient temperature, the total time must not exceed 24 hrs.

Following preparation and during administration, the prepared IV bag must be covered by light protection cover.

Administration of T-DXd

It is recommended that participants receive prophylactic anti-emetic agents prior to infusion of T-DXd and on subsequent days. Antiemetics such as 5-HT3 antagonists or NK1 receptor antagonists and/or steroids (eg, dexamethasone) should be considered and administered in accordance with the prescribing information or institutional guidelines.

T-DXd will be administered using an IV bag containing 5% (w/v) Dextrose Injection infusion solution and delivered through an IV administration set with a 0.2- or 0.22-µm filter. The standard infusion time for T-DXd is approximately 90 minutes ± 10 minutes for the first infusion. If the first infusion is well tolerated and the participant does not experience an infusion-related reaction, then the minimum infusion time for subsequent cycles is 30 minutes ± 10 minutes. However, if there are interruptions during infusion, the total allowed time must not exceed 3 hours at room temperature.

The participant's weight at screening (baseline) will be used to calculate the initial dose. If, during the course of treatment, the participant's weight changes by ≥ ± 10% of the screening (baseline) weight, the dose will be recalculated based on the participant's updated weight.

Other drugs should not be co-administered with T-DXd through the same infusion line.

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

Monitoring of T-DXd Administration

Participants will be monitored during and after infusion of T-DXd. Vital signs will be measured according to the SoA (Table 1).

Management of study intervention-related toxicities are described in Appendix K. As with any biologic product, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognise and treat anaphylaxis.

Storage of T-DXd

The investigator, or an appropriate delegate, will ensure that all study intervention is stored in a secured area, at appropriate temperatures and as specified on the label, and in accordance with applicable regulatory requirements. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging are to be reported to the Study Monitor upon detection. Storage conditions stated in the respective IBs may be superseded by the label storage instructions.

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

6.3 Measures to Minimise Bias

Participant Enrolment

All participants will be centrally assigned to open-label study intervention using an IRT. Participants will begin treatment on the day of enrolment (confirmation of eligibility); every effort should be made to minimise the time between enrolment and first dose of study intervention (no later than 3 days). If it is anticipated that dosing cannot occur within 3 days, a discussion with the AstraZeneca study physician is required. Before the study is initiated, directions for the IRT will be provided to each site. The IRT will provide the kit identification number to be allocated to the participant at each dispensing visit.

If a participant withdraws from the study, then his/her enrolment code cannot be reused. Withdrawn participants will not be replaced.

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

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

- Obtain signed informed consent before any study-specific procedures are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the participant. However, all screening laboratory and imaging results must have been obtained within 28 days with exception that, if any case is out of this time window due to the central HER2 exon 19 and 20 mutation testing for defining eligibility or ophthalmologic assessments, the site should confirm with AstraZeneca on a case-by-case basis before moving to Cycle 1 Day 1.
- Participants will be identified to the IRT per country regulations. Obtain a unique 7-digit enrolment number (E-code), through the IRT in the following format (ECCNNXXX: CC being the country code, NN being the centre number, and XXX being the participant enrolment code at the centre). This number is the participant's unique identifier and is used to identify the participant on the eCRFs.
- Local results of EGFR, ALK, ROS 1, BRAF, NTRK, MET, KRAS, RET, or other driver mutation testing and PD-L1 expression status will be collected in the eCRF if available.
- Determine participant eligibility (see Sections 5.1 and 5.2).
- Following completion of all screening procedures and documentation of all baseline assessments, enrol eligible participant into the study and obtain a treatment assignment number. The treatment assignment number should be obtained from the IRT on the same day the participant's eligibility is confirmed and they are enrolled in the study. The date of enrolment is defined as the date the participant is confirmed as eligible in the IRT.

If the participant is ineligible for inclusion in the study for any reason, the IRT should be accessed to terminate the participant in the system. The date of screening failure is defined as the date the site determined that the participant was ineligible.

Refer to Section 5.4 for details of rescreening procedures, where applicable.

Participants will begin treatment on Day 1. Participants must not be enrolled and treated unless all eligibility criteria have been met.

Procedures for Handling Incorrectly Enrolled Participants

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

Where a participant does not meet all the eligibility criteria but is enrolled in error, or

incorrectly started on treatment, the investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the participant from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented and that the potential benefit/risk profile remains positive for the participant.

Methods for Assigning Treatment Groups

Not applicable; this is a single-group study.

Potential bias in data interpretation will be reduced through the following:

- Efficacy: The primary endpoint, confirmed ORR, will be based on ICR.
- Safety: An independent ILD Adjudication Committee will review and adjudicate on all cases of potential ILD/pneumonitis.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

The on-site study pharmacist is responsible for managing the study intervention from receipt by the study site until the destruction or return of all unused study intervention.

6.5 Concomitant Therapy

Any concomitant treatment, procedure, or other medication considered necessary by the investigator for the participant's safety and wellbeing, or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving from the time of screening or receives during the study including the 40-day (+7-day) follow-up period following the last dose of study intervention must be recorded in the eCRF along with:

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

The study physician should be contacted if there are any questions regarding concomitant or prior therapy.

If any concomitant therapy is administered due to new or unresolved AE, it should be recorded.

Participants must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

Restricted, prohibited, and permitted concomitant medications/therapies are described in more detail in Appendix G 1.

Guidance regarding potential interactions with concomitant medications is provided in Appendix G 1.

Drug-drug Interactions

There is no information to date on drug-drug interactions with T-DXd, either nonclinically or in participants. There may be a hypothetical interaction between T-DXd and hydroxychloroquine and/or chloroquine, therefore concomitant treatment with hydroxychloroquine or chloroquine is not allowed during the study intervention.

Guidance regarding potential interactions with concomitant medications is provided in Appendix G 1. Refer to Section 6.5.2 for details of required supportive treatments to be given with the study treatment interventions.

6.5.1 Prohibited Concomitant Medications

T-DXd safety-specific restrictions are listed below (refer also to Appendix G 1).

- Participants must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.
- Participants, if assigned treatment, should not receive live vaccine during the study and up to 30 days after the last dose of study intervention. Participants who have received live, attenuated vaccine within 30 days prior to the first dose of T-DXd will be excluded.
- The following medications are prohibited during the study. AstraZeneca must be notified if a participant receives any of these during the study:
  - Any concurrent chemotherapy, anticancer study intervention or biological, radiotherapy (except palliative radiotherapy to areas other than chest, after consultation with the study physician) or hormonal therapy for cancer treatment. including anticancer traditional Chinese medicines (ie, those with a label for cancer treatment). Concurrent use of hormones for noncancer-related conditions (eg, insulin for diabetes and HRT) is acceptable.

- T-DXd cannot be administered when the participant is taking immunosuppressive medications, including corticosteroids with the following exceptions:
  - Short-term courses (< 2 weeks) of low to moderate dose (< 10 mg prednisolone per day or equivalent) .
  - Long-term, alternate-day treatment with short-acting preparations.
  - Maintenance physiologic doses (replacement therapy).
  - Administered topically (skin or eyes), by aerosol, or by intra-articular, bursal, or tendon injection.
  - Treatment with corticosteroids to prevent or treat hypersensitivity reactions to radiographic contrast agents is allowed. A temporary period of steroid treatment will be allowed for different indications after discussion with the study physician (eg, COPD, radiation, nausea, etc). For steroid treatment of suspected ILD refer to TMGs.
  - Participants with bronchopulmonary disorders may use bronchodilators (such as albuterol) if only administered intermittently.
  - Use of immunosuppressive medications for the management of study intervention-related AEs or in participants with contrast allergies is acceptable.
  - Immunosuppressive medications also include drugs like methotrexate, azathioprine, and tumour necrosis factor-alpha blockers.

- Concomitant treatment with chloroquine or hydroxychloroquine is not allowed during the study intervention. If treatment with chloroquine or hydroxychloroquine is absolutely required for SARS-CoV-2 infection (ie COVID-19), study intervention must be interrupted. If chloroquine or hydroxychloroquine is administered, a washout period of at least 14 days is required before restarting study intervention.

6.5.2 Other Protocol Restrictions or Supportive Treatments

Other CSP-mandated restrictions or supportive treatments are listed below (see also Appendix G 1).

- Based on the currently available clinical safety data, it is recommended that participants receive prophylactic anti-emetic agents prior to infusion of T-DXd and on subsequent days. Antiemetics such as 5-HT3 antagonists or NK1 receptor antagonists and/or steroids (eg dexamethasone) should be considered and administered in accordance with the prescribing information or institutional guidelines.
- Haematopoietic growth factors may be used for prophylaxis or treatment based on the clinical judgement of the investigator.

- Concomitant use of dietary supplements, medications not prescribed by the investigator, and alternative/complementary treatments is discouraged, but not prohibited.
- Prophylactic or supportive treatment of study-drug induced AEs will be otherwise as per investigator's discretion and institutional guidelines.

6.6 Dose Modification

In case a dose reduction is necessary, the study intervention will be administered as follows:

Table 9 Dose Reduction Levels of T-DXd

CCI	CCI	CCI
CCI	CCI	CCI

T-DXd = trastuzumab deruxtecan.

CCI

CCI

[redacted]

ILD/Pneumonitis Management Guidance

Please refer to the Guidance for Management of Participants with Drug-induced ILD/Pneumonitis summary flow chart in Appendix J for the management of participants with drug-induced ILD/pneumonitis. All potential ILD/pneumonitis cases should be reported within 24 hours; including both serious and non-serious potential ILD/pneumonitis cases (potential ILD/pneumonitis is defined in the current Site Manual List of MedDRA Preferred Terms).

ILD/pneumonitis should be ruled out if a participant develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnoea, cough or fever. If the AE is confirmed to have an aetiology other than ILD/pneumonitis, follow the management guidance "Other non-laboratory adverse events" outlined in Appendix K.

If the AE is suspected to be ILD/pneumonitis, treatment with study intervention should be interrupted pending further evaluations. Evaluations should include those outlined in Section 8.2.5.3. As soon as ILD/pneumonitis is suspected, corticosteroid treatment should be started promptly as per clinical treatment guidelines.

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

All cases of potential ILD/pneumonitis will be reviewed internally by medical monitor and study safety physician. Safety Knowledge Group (SKG) members will also be consulted if needed. To ensure adequate and relevant evaluation, systematic additional data collection will be conducted for all cases that will be brought for evaluation. This additional data collection will cover a more in-depth relevant medical history (eg, smoking, radiation, COPD, and other chronic lung conditions), diagnostic evaluation, treatment and outcome of the event. This data collection will be triggered for AEs reported using selected MedDRA Preferred Terms.

LVEF Decrease Management Guidance

- LVEF will be measured by either ECHO or MUGA scan. All ECHOs/MUGAs will be evaluated by the investigator or delegated physician for monitoring cardiac function.
- Troponin-T (preferably high-sensitivity troponin-T) will be measured locally at screening, EoT, and if at any time a participant reports signs or symptoms suggesting CHF, myocardial infarction, or other causes of cardiac myocyte necrosis. If ECG is abnormal, follow institutional guidelines.
- ECGs will be performed at timelines as specified in the SoA (Table 1) and if an abnormality is detected or if there is a troponin increase. Triplicate ECGs will be performed at screening and before infusion on C1D1. Subsequent ECGs will be performed in triplicate only if abnormalities are noted. Twelve-lead ECGs will be performed, and standard ECG parameters will be measured, including RR, PR, QT intervals, and QRS duration. All ECGs must be evaluated by investigator or delegated physician for the presence of abnormalities prior to the injection of study intervention at every cycle. Whether or not measurement is performed, date performed, results, and findings for each parameter are to be recorded in the eCRF.
- Refer to Section 8.2.3 (ECG) and Section 8.2.5.1 (ECHO/MUGA) or details of investigations of cardiac function.
- Refer to Appendix K for information on the management of cardiac toxicities related to the study intervention.

Dose Modification Criteria for Suspected or Confirmed COVID-19

Refer to Appendix I for the dose modification and management plan for participants with confirmed or suspected COVID-19 who are being treated with T-DXd.

6.7 Intervention After the End of the Study

As described in Section 4.4, the study will remain open until all participants have discontinued study intervention and completed their last expected visit/contact.

After the final DCO for this study, AstraZeneca will continue to supply T-DXd to participants who received T-DXd until PD occurs as judged by the investigator or until meeting any other discontinuation criteria as defined in Section 7.1.

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, participants currently receiving treatment with T-DXd may be transitioned to such a study, and the current study would reach its end. The roll-over or extension study would ensure treatment continuation with visit assessments per its protocol, as applicable. Any participant who would be proposed to move to such a study would be given a new informed consent, as applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety and survival follow-up. The investigator should instruct the participant to contact the site before or at the time if study intervention is stopped. A participant that decides to discontinue study intervention will always be asked about the reason(s) and the presence of any AEs. The reason for discontinuation should be documented in the source document and the appropriate section of the eCRF.

Participants who have permanently discontinued from further receipt of study intervention will need to be discontinued from the IRT.

Participants may be discontinued from study intervention in the following situations:

- RECIST 1.1-defined radiological progression per investigator outside of CNS (refer to Section 8.1.1 and Appendix E). See Section 6.1.1.2 for details of treatment beyond CNS-only progression.
- The investigator determination that the participant is no longer benefiting from study intervention.

- 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 (see Section 6.6).
- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment. A participant who discontinues treatment is normally expected to continue to participate in the study (eg, for safety and survival follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.2).
- Severe non-compliance with the CSP as judged by the investigator or AstraZeneca.
- Pregnancy or intent to become pregnant. Refer to Section 8.3.14 for information on pregnancy and to Appendix F for contraceptive requirements.
- Initiation of subsequent anticancer therapy, including another investigational agent.
- Study terminated by AstraZeneca.
- Participant lost to follow-up.
- Subjective disease progression (global deterioration of health status) without objective evidence of PD according to RECIST 1.1.

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

Participants who are permanently discontinued from further receipt of study intervention, regardless of the reason, will be identified as having permanently discontinued treatment. End-of-Treatment is described as the date that the investigator makes the decision to discontinue the participant from all study intervention and not the last date that the participant received study intervention. The visit should occur within 7 days of the decision. Note: If EoT is > 40 days (+ 7 days) after last treatment, then EoT assessments can also function as the 40-day (+ 7 days) follow-up visit (See Section 1 for details). In this instance, all assessments for the EoT visit as well as the 40-Day (+ 7 days) follow-up visit must be performed as indicated in . If T-DXd is discontinued due to RECIST 1.1-defined progression by investigator, unacceptable toxicity, withdrawal of consent, or other discontinuation criteria, the EoT visit should be performed as soon as the participant is permanently discontinued from the last study intervention and will enter follow-up as Table 1.

7.1.1 Follow-up of Participants Post-discontinuation of Study Intervention

All participants who discontinue the study intervention will be followed up for safety assessments 40 days (+ 7 days) days after their last dose of study intervention. Additional assessments to be performed at the time of the 40-day safety follow-up are detailed in the SoA

(Table 1). For ILD/pneumonitis, safety follow-up will continue until the resolution of ILD/pneumonitis.

Participants who have discontinued study intervention prior to objective RECIST 1.1-defined radiological progression, regardless of whether or not they have commenced subsequent anticancer therapy, will be followed up with tumour assessments as indicated in the SoA (Table 1) until RECIST 1.1-defined PD (plus one additional follow-up scan (4 weeks later), if clinically feasible) or death regardless of whether or not the participant started a subsequent anticancer therapy, unless they have withdrawn all consent to study-related assessments.

7.1.2 Follow-up for Survival

Participants will be followed up for survival status as indicated in the SoA (Table 1) until death, withdrawal of consent, or the end of the study. Survival information may be obtained via telephone contact with the participant or the participant's family, or by contact with the participant's current physician, or local death registries as described in Section 7.2. Additional assessments to be performed at the time of survival follow-up are detailed in the SoA (Table 1).

Note: Survival calls will be made following the date of DCO for the analysis (these contacts should generally occur within 7 days of the DCO). If participants are confirmed to be alive or if the death date is after the DCO date, then these participants will be censored at the date of DCO.

7.1.3 Continuation on Study Intervention After CNS-only Progression

If a participant is found to have isolated progression in the CNS (including either parenchymal brain or dural metastases but not skull-based or leptomeningeal metastases) and does not have progression of disease outside the CNS, the participant may be eligible to continue on study interventions after completion of local treatment (radiotherapy) of the brain/dural metastases. Treatment with T-DXd must be temporarily stopped during local treatment of all participants with brain metastases (active or stable) and may continue until either systemic progression of disease or a second isolated CNS progression. The participant may continue on study provided the following criteria are met and the participant continues to demonstrate clinical benefit:

- The participant is not experiencing any worsening of cancer-related symptoms. Participants who are clinically deteriorating and unlikely to receive further benefit from continued treatment should discontinue study intervention.
- The participant is tolerating study intervention.
- Review and concurrence by the AstraZeneca Study Physician or delegate.

- Participant has no evidence of unequivocal systemic progression of disease.
- Participant has not had a previous isolated CNS progression while on study.

Study intervention may be withheld up to 126 days (from the date of last infusion) to allow local CNS therapy. Longer delays must be discussed and approved by the AstraZeneca Study Physician or delegate. All study interventions are to be withheld for a minimum of 1 week prior to planned CNS-directed therapy. Plans for holding and re-initiating study interventions before and after local therapy will require discussion with, and documented approval from, the AstraZeneca Study Physician or delegate. The durations of delays to study intervention that are required following radiation therapy are outlined in Section 6.1.1.2.

Following CNS-directed therapy for CNS-PD, the Investigators will continue to follow the participants and report CNS progression (worsening of current/new lesions) or systemic progression. Participants who undergo CNS-directed therapy while on study should maintain their regular assessment schedule, including monitoring of all AEs. All scans should continue as scheduled for brain, chest, abdomen, and pelvis (see Table 1).

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options to ensure the collection of endpoints and safety information including new AEs and follow-up on any ongoing AEs and concomitant medications (eg, telephone contact at 40 days [+ 7 days] after study intervention is discontinued, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an Early Study Intervention Discontinuation visit should be conducted, as shown in the SoA (Table 1). See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

  The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, AstraZeneca may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried in line with what was stated in the informed consent and local regulation. The

investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and no contact has been established by the time the study is completed (see Section 4.4), such that there is insufficient information to determine the participant's status at that time.

Participants who decline to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing participants throughout the study period. If contact with a missing participant is re-established, the participant should not be considered lost to follow-up and evaluations should resume according to the CSP.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

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

Discontinuation of specific sites or of the study as a whole are handled as part of 10.

In order to support key efficacy endpoints of PFS and OS analyses, the survival status of all

participants in the Full Analysis and the Safety Analysis Sets should be re-checked; this includes those participants who withdrew consent or are classified as "lost to follow-up."

- Lost to follow-up – Site personnel should check hospital records and a publicly available death registry (if available), as well as checking with the participants' current physician, to obtain a current survival status (the applicable eCRF modules will be updated).
- In the event that the participant has actively withdrawn consent to the processing of their personal data, the survival status of the participant can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Table 1). Data collection following study analysis until the end of the study is described below.

- Protocol waivers or exemptions are not allowed.
- The investigator is responsible for ensuring the accuracy, completeness, and timeliness of data recorded on the eCRFs and for the provision of responses to data queries. The investigator will sign the completed eCRFs and a copy of the completed eCRFs will be archived at site.
- Immediate safety concerns should be discussed with the AstraZeneca immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Table 1), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 1).
- If a participant has an unscheduled assessment or visit, eg, as a result of an AE, all relevant data must be collected on the eCRF.

- If a participant undergoes unscheduled imaging, eg, to investigate clinical signs/symptoms of progression and is found not to have progressed, every attempt should be made to perform the subsequent imaging at the next regularly scheduled visit.

Data Collection Following Study Analysis Until the End of the Study

Following the DCO for the final analysis, all participants who remain in the study will continue the scheduled "progression/survival follow-up" site visits indicated in the SoA (Table 1). Refer to Section 6.7 for further details. In addition, any AEs of ILD/pneumonitis will be followed up until resolution. For other safety reporting requirements after final analysis, see Section 8.3.12.

8.1 Efficacy Assessments

8.1.1 Imaging Tumour Assessments

Tumour evaluation scans will be performed at screening (as baseline) with follow-ups at Week 6 (±1)-week intervals from the date of enrolment for 48 weeks, and then every 9 (±1) weeks thereafter, starting at Week 57 until RECIST 1.1-defined radiological PD per investigator assessment (plus one additional follow-up scan [4 weeks later], if clinically feasible). In the case of CNS-only progression, participants continuing to receive study intervention should follow the on-treatment data collection schedule, including RECIST 1.1 tumour assessments, until a second progression (CNS or body; plus one additional follow-up scan [4 weeks later], if clinically feasible).

Tumour assessments use images from CT (preferred) or MRI, with IV contrast, of the chest, abdomen (including the entire liver and both adrenal glands), and pelvis, collected during screening/baseline and at regular (follow-up) intervals (at timelines as specified in the SoA, Table 1) during study intervention. Any other areas of disease involvement should be additionally imaged at screening based on known metastasis sites or by the signs and symptoms of individual participants. Scans (CT or MRI) of the chest, abdomen, and pelvis are mandatory. Brain CT or MRI is mandatory for all participants at screening and EoT (participants with brain metastases are not required to undergo an additional brain scan at EoT if the latest brain assessment was within 4 weeks of EoT or if they discontinue study intervention prior to RECIST 1.1-defined radiological progression per investigator). Participants who are enrolled with baseline stable brain metastases will have mandatory brain scans at regular (follow-up) intervals during study intervention as per SoA (Table 1). Additional scans can be performed as clinically indicated (including for cases where the investigator suspects a participant develops new brain metastases). The imaging modality used for baseline tumour assessment, CT/MRI for chest and abdomen and MRI for brain, should be kept the same consistently at each subsequent follow-up assessment throughout the study if possible. It is important to follow the tumour assessment schedule as closely as possible (refer

to the SoA, Table 1) relative to the date of enrolment. Screening/baseline imaging should be performed no more than 28 days prior to enrolment starting (the date the participant is confirmed as eligible in the IRT) and ideally should be performed as close as possible to and prior to the start of study intervention. Treatment continues until RECIST 1.1-defined radiological progression (refer to Appendix E) unless unacceptable toxicity, withdrawal of consent, or other criterion for withdrawal is met (with the exception of CNS-only progression). If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the participant has not progressed, every attempt should be made to perform the subsequent assessments at the next scheduled visit. Scanning will continue if participants discontinue study intervention due to toxicity without progression until PD is detected.

The RECIST 1.1 assessments of baseline images identify TLs (defined as measurable) and NTLs. On-study images are evaluated for TLs and NTLs chosen at baseline, and for NLs when they appear. This allows determination of follow-up TL response, NTL lesion response, the presence of unequivocal NLs, and overall time point responses (CR, PR, SD, PD, or NE).

8.1.2 Central Reading of Scans

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed iCRO for quality control, storage, and for ICR. Digital copies of all original scans should be stored at the investigator site as source documents. Electronic image transfer from the sites to the iCRO is strongly encouraged. An ICR of images will be performed at the discretion of AstraZeneca. Results of these independent reviews will not be communicated to investigators, and results of investigator tumour assessments will not be shared with the central reviewers.

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

8.1.3 Mandatory Tumour Tissue Sample

HER2 mutation for eligibility will be based on study qualifying activating HER2 exon 19 or 20 mutation either from a pre-existing tissue test result obtained from qualified local laboratory/assay or have the tissue HER2 mutation test result detected prospectively in a central laboratory. Retrospective central confirmation will be performed for those enrolled based on existing local HER2 mutation(s) results during study. Note: In addition, mandatory archival (preferred) or newly collected tissue samples are required for central testing. Should discordance between local and central test be higher than anticipated, enrolment by local test may be closed. If a modification to not allow further enrolment of participants on the basis of a pre-existing HER2 mutation result is made, this change will be communicated to participating sites in a timely manner. Prospective analysis of HER2 mutation status of tumor tissue using central laboratory testing is encouraged.

A mandatory tissue sample will be required from all participants at screening. For participants entering the study based upon a pre-existing local tumor tissue result, the pre-existing local HER2 mutation laboratory report and detailed information on the test method should be collected, maintained as a source document and captured in the eCRF. Participants entering the study based upon a pre-existing local tumor tissue result are still mandated to provide a FFPE tumor tissue for retrospective central confirmation testing. Central confirmation will not be mandated before enrolment for participants with a positive tissue HER2 mutation test result obtained from local laboratory. Discordance between pre-existing local HER2 results and confirmed central laboratory HER2 testing results has no impact on enrolment and study treatment of participants with study qualifying activating HER2 exon 19 or 20 mutation detected by local laboratory.

Archived FFPE surgical samples are preferred, however if participants do not have an adequate archival FFPE tumour tissue sample (surgical, CNB or FNA), for assessment of study-qualifying activating HER2 exon 19 and exon 20 mutation status (Section 8.6.1), then a CNB or FNA tumour tissue samples will be taken/biopsied to generate FFPE samples. These will be analyzed for study-qualifying activating HER2 exon 19 and exon 20 mutation status by a central laboratory designated by AstraZeneca. Samples collected will be used for eligibility check (for participants enrolled based on central lab assessment) or respective central confirmation (for participants enrolled based on existing local HER2 mutation results), and potential companion diagnostic filing if required by NMPA. See Section 8.6.1.1 for details of tumour sample collection.

8.1.4 Mandatory Blood Sample for Plasma-based ctDNA HER2 Mutation Testing

All participants must provide blood samples during screening period. The collected blood samples are to be tested to determine HER2 exon 19 and exon 20 mutation status retrospectively by a central laboratory designated by AstraZeneca for potential companion diagnostic development and filing in China. See Section 8.6.1.2 for details of blood sample collection.

8.1.5 Overall Survival

Assessments for survival will be conducted every 3 months ± 14 days following objective PD or treatment discontinuation from the date of the safety follow-up. Survival information may be obtained via telephone contact with the participant, participant's family, by contact with the participant's current physician, or local death registries as described in Section 7.2.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1).

Whenever ECGs, vital signs, and blood draws are scheduled for the same nominal time, the suggested order is: ECG assessments first, then vital signs assessments, and then blood draws; the timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the time points indicated in the SoA (Table 1).

8.2.1 Physical Examinations

- A complete physical examination will be performed and include assessments of the following; general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), urogenital, dermatological, gastrointestinal, endocrine, haematologic/lymphatic, and neurological systems.
- Targeted physical examinations are to be used by the investigator on the basis of clinical observations and symptomatology.

Physical examination, as well as assessment of height and weight, will be performed at timelines as specified in the SoA (Table 1); investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as AEs, see Section 8.3.5 for details.

8.2.2 Vital Signs

Vital signs will be performed at timelines as specified in the SoA (Table 1). Vital signs should be evaluated by the investigator or the delegate physician prior to and at the end of infusion of study intervention on Day 1 of each cycle.

Body temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed with the participant in the seated or supine position using a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the eCRF.

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

For any AEs of infusion reactions, the vital signs values should be entered into the eCRF.

8.2.3 Electrocardiograms

Triplicate ECGs will be performed at screening and before infusion on C1D1. Subsequent ECGs will be performed in triplicate only if abnormalities are noted. Single 12-lead ECGs will be performed at timelines as specified in the SoA (Table 1) after the participant has been resting for at least 5 minutes and recorded while the participant is in a supine/semi-recumbent position using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Appendix K for management of prolonged average QTc > 500 ms or > 60 ms change from baseline.

All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal. 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. If ECG is abnormal follow institutional guidelines.

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

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the visits indicated in the SoA (Table 1).

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

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

Other safety laboratory tests include assessment for pregnancy (serum at screening or urine other time points), and hepatitis B and C serology and HIV antibody test. Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Pregnancy tests will be conducted within 72 hours before enrolment for all WOCBP; a positive urine pregnancy test result must immediately be confirmed using a serum test. Repeat pregnancy tests (urine or serum test per institutional guideline) should be performed 72 hours before infusion of each cycle and at EoT. A negative result for serum pregnancy test (test must have a sensitivity of at least 25 mIU/mL) must be available at the screening visit and urine β-HCG pregnancy test prior to each administration of study intervention.

The following laboratory variables included in Table 10 will be measured.

Table 10 Laboratory Safety Variables

Haematology/Haemostasis (Whole Blood)	**Clinical Chemistry (Serum or Plasma)** [a]
Haemoglobin	Creatinine
	TBL
Leukocyte differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)	ALP
Platelet count	AST
Absolute neutrophil count	ALT
Absolute lymphocyte count	Albumin
Total white blood cell count	Potassium
Total red blood cell count	Calcium, total/Calcium
Haematocrit	Sodium
	Gamma-glutamyl transferase
Urinalysis	Glucose (random)
Haemoglobin/erythrocytes/blood	Lactate dehydrogenase
Protein/albumin	Protein, total
Glucose	Urea nitrogen/blood urea nitrogen/Urea
pH	Troponin (high-sensitive troponin-T preferred) [b]
Specific gravity	Magnesium
	Chloride
Coagulation	
Coagulation variables [c] (INR or PT and either PTT or aPTT)	

[a] Other tests may be performed if the investigator suspects an AE.
[b] See Section 6.6 for details of requirements for troponin testing.
[c] Coagulation tests performed only at screening include INR and aPTT.
ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; INR = international normalised ratio; PT = prothrombin time; PTT = partial thromboplastin time; TBL = total bilirubin.

The investigator should assess the available results with regard to clinically relevant abnormalities in documentation. Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 8.3.5.

All participants with Grade 3 or 4 laboratory values at the time of completion or discontinuation from study intervention must be followed and have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

NB. In case a participant shows an AST **or** ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN please refer to Appendix D "Actions required in cases of increases in liver biochemistry and evaluation of HL", for further instructions.

8.2.5 Other Safety Assessments

8.2.5.1 Echocardiogram/Multiple Gated Acquisition Scan

An ECHO or MUGA scan to assess LVEF will be performed at the visits as shown in SoA (Table 1).

The modality of the cardiac function assessments must be consistent for a given participant (ie, if ECHO is used for the screening assessment for a given participant, then ECHO should also be used for subsequent scans for that participant). The participants should also be examined using the same machine and operator whenever possible, and quantitative measurements should be taken (ie, accurate to 1% and not estimated to 5%). All ECHOs/MUGAs will be evaluated by the investigator or delegated physician for monitoring cardiac function.

If a participant has had an ECHO or MUGA performed within 4 weeks prior to treatment discontinuation, the discontinuation visit ECHO or MUGA scan is not required unless clinically indicated. If a participant has any clinically significant decrease in LVEF (greater than 10 percentage points to below 50%), there should be follow-up within 4 weeks until resolution.

Situations in which ECHO or MUGA results should be reported as AEs are described in Section 8.3.5.

8.2.5.2 Pulmonary Assessments

SpO_2 should be evaluated by investigator or the delegate physician prior to and after the administration of study intervention at each visit.

Pulmonary function tests should include basic spirometry at a minimum with optional additional components as mentioned in Table 11.

Table 11 Spirometry Component

Required spirometry components	Optional spirometry components
FVC (L)	PEF
FVC % predicted	DLCO
FEV1 (L)	FEV6
FEV1 % predicted	TLC
FEV1/FVC %	RV

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

DLCO will be performed/encouraged if feasible, but for participants with prior severe and/or prior clinically significant pulmonary disorders, DLCO is strongly encouraged. In the event of suspected ILD/pneumonitis, refer to Section 8.2.5.3 additional pulmonary assessments.

HRCT of the chest will be preferred and recommended if feasible (otherwise CT is acceptable, CT Scan should be used only when HRCT is not available) at screening, and if ILD/pneumonitis is suspected. Chest CT and/or chest HRCT scans will be reviewed separately for safety for the presence of ILD/pneumonitis prior to administration of the next scheduled dose of T-DXd. If both a non-contrast chest HRCT scan for assessment of ILD/pneumonitis and a diagnostic IV contrast enhanced chest CT scan for tumour response assessment (as part of chest-abdomen-pelvis imaging) are to be acquired in the same imaging session, HRCT should be performed first.

8.2.5.3 ILD/Pneumonitis Investigation

If new or worsening pulmonary symptoms (eg, dyspnoea, cough or fever) or radiological abnormality suggestive of ILD/pneumonitis is observed, study intervention should be interrupted and a full investigation is required as described in the T-DXd TMGs (Appendix K). Refer to Appendix J for guidelines on management of study intervention-induced ILD/pneumonitis. Evaluations should include:

- Signs and symptoms (cough, shortness of breath, and pyrexia, etc).
- Detailed past medical history, including concomitant medications.
- Physical examination, including auscultation of lung field.
- Blood culture and complete blood count (CBC)
- Arterial blood gases, if clinically indicated.
- Pulmonary function tests (Section 8.2.5.2) and SpO_2.
- Bronchoscopy and bronchoalveolar lavage, as clinically indicated and feasible.
- HRCT.

- Pulmonologist consultation (infectious disease consultation, as clinically indicated).
- One blood sample collection for PK as soon as ILD/pneumonitis is suspected, if feasible.
- Other tests could be considered, as needed.

The results of the full diagnostic workup (including HRCT, blood and sputum culture, haematological parameters, etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic oedema, or pulmonary haemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of ILD/pneumonitis should be considered and the TMGs should be followed. Troponin measurements will be done to rule out cardiac aetiology.

The following assessments should be performed, if feasible, to enhance the investigation and diagnosis of potential cases of ILD/pneumonitis. The results of the assessment will be collected.

- Other items
  - When ILD/pneumonitis is suspected during study intervention, the following markers should be measured where possible:
    - ILD/pneumonitis markers (KL-6, SP-D) and β-D-glucan.
    - Tumour markers: particular tumour markers that are related to disease progression.

    * Additional clinical chemistry: C-reactive protein, lactate dehydrogenase.

8.2.5.4 WHO/ECOG Performance Status

WHO/ECOG performance status will be assessed at the times specified in the SoA (Table 1) based on the following:

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

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

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

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

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

5 Dead.

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

8.2.5.5 Ophthalmologic Assessments

Ophthalmologic assessments will be performed as specified in the SoA (Table 1) and will include visual acuity testing, slit lamp examination and fundoscopy.

8.3 Adverse Events and Serious Adverse Events

The principal investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

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

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

AEs and SAEs (other than ILD/pneumonitis) will be collected from the time of signature of the ICF, throughout the treatment period and including the safety follow-up period (which is 40 + 7 days after the discontinuation of study intervention). For ILD/pneumonitis, safety follow-up will be continued until resolution of ILD/pneumonitis. If an event that starts post the defined safety follow-up period noted above is considered to be due to a late onset toxicity to study intervention, then it should be reported as an AE or SAE as applicable. Collection and reporting of AEs and SAEs after the final DCO is described in Section 8.3.12.

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

A TEAE is defined as an AE that occurs, having been absent before the first dose of study intervention, or has worsened in severity or seriousness after initiating the study intervention until 47 days after last dose of the study intervention.

The following types of events should be reported by the investigator in the AE/SAE eCRF pages in the clinical study database within 24 hours of becoming aware for the purposes of reporting in the global safety database:

- SAEs
- All potential ILD cases should be reported within 24 hours; including both serious and non-serious potential ILD cases (potential ILD/pneumonitis is described by the Event Adjudication Site Manual).

- Hepatic events (both serious and non-serious) which meet the PHL. Criteria defined as an elevated (ALT or AST) ≥ 3 × ULN and an elevated TBL ≥ 2 × ULN that may occur either at different time points or simultaneously during the study. A targeted questionnaire is built within the eCRF to collect relevant additional information for these potential cases.
- Overdose, defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. An "excessive and medically important" overdose includes any overdose in which either a SAE, a non-serious AE, or no AE occurs and is considered by the investigator as clinically relevant, ie, poses an actual or potential risk to the participant.
- Overdose is always serious. By definition an overdose is medically important, which meets the seriousness criterion of important medical event. An overdose can occur with or without an AE. AEs can either be serious or non-serious. Details of the overdose including T-DXd dosage, clinical course, associated AEs, and outcome must be captured in the Narrative form of the eCRF within EDC.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse Event Variables

The following variables will be collected for each AE;

- AE (verbatim).
- The date when the AE started and stopped.
- Initial CTCAE grade, plus any changes in CTCAE grade.
- Whether the AE is serious or not (Appendix B).
- Investigator causality rating against the study intervention(s) (yes or no).
- Action taken with regard to study intervention(s).
- AE caused participant's withdrawal from study (yes or no).
- Administration of treatment for the AE.
- Outcome.

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

- Date AE met criteria for SAE.
- Date investigator became aware of SAE.
- Seriousness criteria.
- Date of hospitalisation.
- Date of discharge.
- Probable cause of death.
- Date of death.
- Autopsy performed.
- Causality assessment in relation to study procedure(s).
- Causality assessment to other medication.

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

8.3.3 Causality Collection

The investigator should assess causal relationship between study intervention and each AE, and answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?”

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

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

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: “Have you had any health problems since the previous visit you were last asked?”, or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the CSP-mandated laboratory tests, vital signs, physical examinations, ECGs, and ECHO/MUGA scans will be summarised in the CSR.

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

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). Any diagnosis of the undesirable clinical outcome of 'left ventricular dysfunction', a valid or qualifying reduction of LVEF (as measured by MUGA or ECHO) should be confirmed and included in the AE report. In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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

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

8.3.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times$ ULN together with TBL$\geq$ $2 \times$ ULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of HL.

8.3.7 Disease Progression

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

8.3.8 Disease Under Study

Disease under study commonly occur in studies of chronic diseases with a variable pattern, eg, asthma; COPD; rhinitis; neuropsychiatric conditions such as depression, seizure disorders or multiple sclerosis; and cardiac disorders such as angina or heart failure. Symptoms of disease under study are those which might be expected to occur as a direct result of NSCLC. Events which are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the study intervention.

8.3.9 New Cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New primary cancers are those that are not the primary reason for the administration of study intervention and are identified after the participant's inclusion in this study. They do not include metastases of the original cancer.

8.3.10 Deaths

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

- Death clearly resulting from PD should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to PD under study, the AE causing the death must be reported as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign the main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE and documented in the Statement of Death page in the eCRF, but every effort should be made to determine a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual time frames.

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

8.3.11 Adverse Events of Special Interest

AESIs are events of scientific and medical interest specific to the further understanding of

T-DXd safety profile and require close monitoring and rapid communication by the investigators to AstraZeneca. An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF using a recognised medical term or diagnosis that accurately reflects the event. Serious AESIs will be recorded and reported as per Section 8.3.13.

AESIs will be assessed by the investigator for severity, relationship to the study intervention, possible aetiologies, and whether the event meets criteria for an SAE and therefore requires immediate notification to AstraZeneca. If an AESI evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form.

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

ILD/pneumonitis

ILD/pneumonitis is considered an important identified risk-based on a comprehensive cumulative review of potential ILD/pneumonitis cases reviewed by the independent ILD Adjudication Committee, the available safety data from the clinical development programme available data from recent epidemiology/literature, biological plausibility, and safety information from drugs of similar class. ILD event adjudication is a retrospective review and will not impact any safety decisions for participants. Refer to the current T-DXd IB for a summary of preliminary clinical study data.

Refer to Section 8.2.5.3 for details of investigations of ILD/pneumonitis.

LVEF Decrease

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

Refer to Section 8.2.3 (ECGs) and Section 8.2.5.1 (ECHO/MUGA) for details of investigations of cardiac function.

Additional relevant information regarding the AESIs, ILD/pneumonitis and LVEF decrease, for the trastuzumab deruxtecan clinical program regardless of seriousness is to be collected through the specific section of the eCRF.

8.3.12 Safety Data to be Collected Following the Final DCO of the Study

For participants continuing to receive T-DXd after the final DCO, AEs and SAEs will be collected, but only SAEs will be reported. In addition, it is recommended that investigators monitor the participant's safety laboratory results periodically during treatment with T-DXd in

order to manage AEs, consistent with the dose modification guidelines for management of study intervention-related toxicities (see Section 6.6). All data after the final DCO and database closure will be recorded in the participant notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

All SAEs that occur in participants still receiving T-DXd (or within the 40 +7 days following the last dose of T-DXd) after the final DCO must be reported as detailed in Section 8.3.13.

8.3.13 Reporting of Serious Adverse Events

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

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

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

If the EDC system is not available, then the investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone followed by completion of a paper SAE form. The AstraZeneca representative will advise the investigator/study site staff how to proceed.

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

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

8.3.14 Pregnancy

All pregnancies and outcomes of pregnancy with conception dates following the first date of study intervention, including pregnancy in the partner of male participants, should be reported to AstraZeneca.

8.3.14.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, study intervention should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the participant was discontinued from the study.

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.3.13) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

8.3.14.2 Paternal Exposure

Non-sterilised male participants who intend to be sexually active with a female partner of childbearing potential should refrain from fathering a child or donating or banking sperm for the duration of the study (from the time of screening) and for 4 months after the last dose of study intervention.

Pregnancy of the participant's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose of study intervention until 4 months after the last dose of study intervention should be followed up and documented in the medical record and provided to the AstraZeneca Patient Safety data entry site. Consent from the partner must be obtained before the information is collected and reported to AstraZeneca.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the investigator must obtain the consent of the participant's partner. The local study team should adopt the Master Pregnant Partner Form in line with local procedures/requirements and submit it to the relevant Regulatory Authority/IRBs/IECs prior to use.

8.3.15 Medication Error

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-threatening or follow-up Fatal/Life-threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (see Section 8.3.13) and within 30 days for all other medication errors.

The definition of a medication error can be found in Appendix B.

8.4 Overdose

Use of T-DXd in doses exceeding that specified in the CSP is considered to be an overdose. There is currently no specific treatment in the event of overdose of T-DXd, and possible symptoms of overdose are not established.

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

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for overdoses associated with an SAE (see Section 8.3.13) and within 30 days for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection, handling, storage and shipping of biological samples will be provided in the study-specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality.

Samples collected will be stored and disposed of according to local laws and regulations. PK and ADA samples will be destroyed after finalisation of Bioanalytical Report or completion of CSR.

For further details on Handling of Human Biological Samples, see Appendix C.

8.5.1 Pharmacokinetics

- Serum samples will be collected for measurement of serum concentrations of intact T-DXd, total anti-HER2 antibody, and DXd as specified in the SoA (Table 1).
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and AstraZeneca, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.
- Serum samples will be used to analyse the PK of intact T-DXd, total anti-HER2 antibody, and DXd. Samples collected for analyses of intact T-DXd, total anti-HER2 antibody, and DXd serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.5.1.1 Determination of Drug Concentration

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

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

8.5.2 Immunogenicity Assessments

Blood samples for determination of ADA and neutralising ADA in serum will be collected per the SoA (Table 1). Samples will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report.

ADA samples may also be further tested for characterisation of the ADA response and or other exploratory safety biomarker. Please also refer to Appendix H.

8.5.3 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

Participant consent to the study includes participation in the mandatory biomarker assessment components of the study.

Tumour tissue and blood samples for biomarker assessment are required and will be collected from all participants in this study as specified in the SoA (Table 1).

8.6.1.1 Mandatory Tumour Tissue Samples

Tumour tissue samples will be tested by a central laboratory for study-qualifying activating HER2 exon 19 and 20 mutations to define eligibility to be enrolled for the study or retrospective central confirmation, and evaluate their association with the observed clinical responses to T-DXd.

Archived surgical resection samples are most preferred, however CNB is second preference and FNA is acceptable if surgical resection or CNB samples are not available.

Unstained, archived FFPE tumour tissue slides with at least 20% tumour tissue remaining to allow for analysis (see the Laboratory Manual) must be made available.

If an archived tumour block is not available, then newly cut, unstained slides with tissue sections of CCI thick may be provided for analysis as described in the Laboratory Manual. Participants will only undergo tumour biopsy (CNB or FNA) if it is considered a medically acceptable risk by the investigator and archived surgical tissue samples are not available.

The mandatory tumour biopsy must not be taken from a previously irradiated lesion. In case of CNB or FNA, 2 cores should be placed in formalin and processed to a single paraffin-embedded block, as described in the Laboratory Manual. Tumour lesions used for newly acquired biopsies should not be the same lesions used as RECIST 1.1 TLs, unless there are no other lesions suitable for biopsy and in this instance only CNB or FNA is allowed.

Tumour tissue sample must be archived surgical resection, CNB or FNA FFPE samples or FFPE samples generated from CNB or FNA taken/biopsied following progression on the latest line of therapy.

Collection of tumour cells from fluid such as ascites or pleural effusion is not permitted.

8.6.1.2 Mandatory Blood Sample for Plasma-based ctDNA HER2 Mutation Testing

All participants must provide blood samples during screening period for retrospective central ctDNA testing to determine HER2 exon 19 and exon 20 mutation status.

8.6.1.3 Handling of Human Biological Samples

Tumour tissue and blood samples collected for HER2 exon 19 and exon 20 mutation testing from participants will be destroyed or repatriated maximally 5 years after study intervention is approved for marketing in China. To meet regulatory requirement, sections of the tumour and collected plasma may be retained that allow this for potential companion diagnostic filing in China, as requested by the NMPA.

For further details on Handling of Human Biological Samples, including storage, re-use and destruction, refer to Appendix C and the Laboratory Manual.

9 STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by AstraZeneca or its representatives.

A comprehensive SAP will be prepared prior to enrolment of the first participant in the study, with final amendments completed prior to database lock.

9.1 Statistical Hypotheses

This is a Phase 2, open-label, single-arm study in which all participants will receive the same study intervention at the same dose and schedule. The primary objective of the study is to evaluate the efficacy of T-DXd CCI by evaluating the confirmed ORR by ICR in participants with metastatic non-squamous NSCLC whose tumours have a HER2 exon 19 or 20 mutation, with disease progression on or after at least one-line of treatment.

The primary endpoint of the study is confirmed ORR by ICR, defined as the proportion of participants with CR or PR, as assessed by ICR based on RECIST 1.1. The analysis will include enrolled participants with study qualifying activating HER2 exon 19 or 20 mutation assessed by central laboratory.

In view of the open-label, single-arm study design, no formal statistical hypothesis will be tested and, unless otherwise specified, study data will be presented using descriptive statistics. However, confirmed ORR by ICR per RECIST 1.1 is considered an early signal for clinical benefit.

9.2 Sample Size Determination

CCI

9.3 Populations for Analyses

Analysis populations are defined in Table 12.

Table 12 Populations for Analysis

Population/Analysis Set	Description
ITT Analysis Set	All participants who signed an ICF and were enrolled in the study.
FAS	All enrolled participants with HER2 exon 19 or 20 mutation assessed by central laboratory.
Safety analysis set	All enrolled participants who have received at least 1 dose of study intervention.
RES	All enrolled participants with HER2 exon 19 or 20 mutation assessed by central laboratory who received at least 1 dose of study intervention and had measurable disease at baseline by ICR.
PK analysis set	All enrolled participants who have received at least 1 dose of study intervention and had at least 1 post-dose measurable serum concentration of T-DXd.
T-DXd ADA evaluable set	All participants in the Safety Analysis Set with a non-missing baseline T-DXd ADA result and at least one non-missing post-baseline T-DXd ADA result.

ADA = anti-drug antibody; FAS = full analysis set; ICF = informed consent form; ICR = independent central review; ITT = intent to treat; PK = pharmacokinetic(s); RES = response evaluable set; T-DXd = trastuzumab deruxtecan.

9.4 Statistical Analyses

The SAP will be finalised prior to enrolment of the first participant in the study and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints. Table 13 provides a summary of endpoints and corresponding analysis populations.

9.4.1 General Considerations

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

The DCO for the full final analysis of ORR by ICR will occur approximately CCI months after the last participant has initiated study intervention. Based on data from Study U204, CCI months is sufficient time for participants to reach a response (median time to response was 1.4 months) and to allow DoR to be determined for responders (median confirmed DoR was 12 months). The full final analysis will report the analyses of all primary and secondary endpoints, including updated ORR and DoR, DCR, BOR, PFS, OS, CNS-PFS, PK, immunogenicity and safety.

Table 13 provides a summary of endpoints and corresponding analysis populations.

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

Table 13 Summary of Outcome Variables and Analysis Populations

Outcome variable	Population(s)
Primary Efficacy Variable	
Confirmed ORR by ICR per RECIST 1.1	Primary analysis: FAS Supplementary analyses: ITT Analysis Set, RES
Secondary Efficacy Variables	
• Confirmed ORR by investigator assessment per RECIST 1.1 • DoR, DCR, BOR, and PFS, by ICR and by investigator assessment per RECIST 1.1 • OS • CNS-PFS	FAS [a] Supplementary analyses: ITT Analysis Set [a](only for ORR, DoR, PFS and OS)
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 Supplementary analyses: ITT Analysis Set (only for demography, disease characteristics and important deviations)
Pharmacokinetics	
• PK data	PK analysis set
Immunogenicity	
• ADAs	T-DXd ADA evaluable set
Safety	
• Exposure to study intervention • Safety data	Safety Analysis Set

[a] DoR analysis will be based on the subset of participants in the corresponding analysis population who achieved confirmed response.

ADA = anti-drug antibody; BOR = best observed response; CNS = central nervous system; DCR = disease control rate; DoR = duration of response; FAS = full analysis set; ICR = independent central review; ITT = intent to treat; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); RECIST 1.1 = Response Evaluation Criteria in Solid Tumours, Version 1.1; RES = response evaluable set; T-DXd = trastuzumab deruxtecan.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint(s)

9.4.2.1.1 Calculation or Derivation of Tumour Response Variables

Investigator RECIST 1.1-based Assessments

All RECIST 1.1 assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a participant discontinues study intervention or receives another anticancer therapy.

At each visit, participants will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, PD, or NE depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within the 28 days prior to enrolment. The tumour response endpoints (PFS, ORR, BOR, and DoR) will then be derived from the scan dates and overall visit responses.

Independent Central Review

An ICR of radiological scans will be performed on all participants.

All images will be collected centrally. The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and will be adjudicated, if required. For each participant, the ICR will define the overall visit response data (CR, PR, SD, PD, or NE) and the relevant scan dates for each time point (ie, for visits where response or progression is/is not identified). If a participant has had a tumour assessment that cannot be evaluated, then the participant will be assigned a visit response of NE (unless there is evidence of progression, in which case the response will be assigned as PD). Endpoints (ORR, DoR, DCR, BOR, and PFS) will then be derived from the scan dates and overall visit responses.

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

9.4.2.1.2 Primary Endpoint: Confirmed ORR by ICR

The primary endpoint of the study is confirmed ORR by ICR according to RECIST 1.1. Confirmed ORR (per RECIST 1.1 by ICR) is defined as the number (percentage) of participants with a confirmed response of CR or PR as assessed by ICR based on RECIST 1.1. Data obtained up until progression or the last evaluable assessment with the absence of progression will be included in the assessment of ORR. Participants who discontinue study intervention without progression, receive a subsequent anticancer therapy, and then respond will not be included as responders in the calculation of ORR.

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

Analyses of Primary Endpoint

The primary analysis of the primary endpoint will be based on the FAS. ORR will be estimated with 2-sided 95% exact CI. Summaries will be produced presenting the number and percentage of participants with a confirmed tumour response.

Supplementary Analysis

Supplementary analysis of the primary endpoint will be performed in the RES and in the ITT Analysis Set using the same methods as described above.

Sensitivity Analysis

Details of any sensitivity analyses to be conducted for the primary endpoint will be described in the SAP, as appropriate.

Subgroup Analysis

Details of any subgroup analyses to be conducted for the primary endpoint will be specified in the SAP.

9.4.2.2 Secondary Endpoint(s)

9.4.2.2.1 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.

Analysis Methods

Investigator assessed ORR will be estimated using the same methods as those specified for ORR by ICR for the FAS and ITT Analysis Set (see Section 9.4.2.1.2).

9.4.2.2.2 Duration of Response

Duration of Response by ICR

For participants who achieve a confirmed CR/PR per RECIST 1.1 by ICR, DoR is defined as the time from the date of first documented response until the date of documented progression (using RECIST 1.1 by ICR) or death in the absence of disease progression. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of CR or PR. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. If a participant does not progress following a response, then their DoR will be the PFS censoring time (ie, DoR = date of PFS event or censoring - date of first response + 1).

Duration of Response by Investigator Assessment

For participants who achieve a confirmed CR/PR per RECIST 1.1 by investigator assessment,

DoR is defined as the time from the date of first documented response until the date of documented progression (using RECIST 1.1 by investigator assessment) or death in the absence of disease progression.

Data will be handled as described above for DoR by ICR.

Analysis Methods

DoR will be analysed in the subset of participants in the FAS and ITT Analysis Set who achieved confirmed response.

A Kaplan-Meier plot of DoR will be presented. The estimate of median DoR and corresponding 95% CI using the Brookmeyer-Crowley method with log-log transformation will be reported (Brookmeyer and Crowley 1982).

9.4.2.2.3 Disease Control Rate

Disease Control Rate by ICR

The DCR by ICR at the time of each DCO is defined as the percentage of participants who have a confirmed CR/PR or SD for at least 5 weeks (ie, 6 weeks - 1 week to allow for an early assessment within the assessment window) after the date of enrolment (without subsequent anticancer therapy) per RECIST 1.1 by ICR.

Disease Control Rate by Investigator Assessment

The DCR by investigator assessment at the time of each DCO is defined as the percentage of participants who have a confirmed CR/PR or SD for at least 5 weeks (ie, 6 weeks - 1 week to allow for an early assessment within the assessment window) after the date of enrolment (without subsequent anticancer therapy) per RECIST 1.1 by investigator assessment.

Analysis Methods

DCR will be summarised descriptively with the number and percentage of participants with a confirmed CR/PR or SD for at least 5 weeks for the FAS.

9.4.2.2.4 Best Observed Response

Confirmed BOR by ICR

BOR is a participant's best response during their participation in the study, but prior to starting any subsequent anticancer therapy, up until RECIST 1.1-defined progression by ICR or the last evaluable assessment in the absence of RECIST 1.1-defined progression by ICR.

Categorisation of BOR will be based on RECIST 1.1 by ICR using the following response categories: (confirmed) CR, (confirmed) PR, SD, PD, and NE; unconfirmed CR/PR will be included in SD.

Confirmed BOR by Investigator Assessment

BOR is calculated based on the overall visit responses per RECIST 1.1 using investigator assessments. BOR is a participant's best response during their participation in the study, but prior to starting any subsequent anticancer therapy, up until RECIST 1.1 defined progression or the last evaluable assessment in the absence of RECIST 1.1 defined progression.

Categorisation of BOR will be based on RECIST 1.1 by investigator assessment using the following response categories: (confirmed) CR, (confirmed) PR, SD, PD, and NE; unconfirmed CR/PR will be included in SD.

Refer to Appendix E for guidance on the evaluation of tumour response per RECIST 1.1.

BOR will be determined programmatically based on RECIST 1.1 using all investigator assessments up until the first progression event per RECIST 1.1 as determined by the investigator. For participants whose first progression event is death, BOR will be calculated based on all evaluable RECIST 1.1 assessments prior to death.

For participants who die with no evaluable RECIST 1.1 assessments, if death occurs ≤ 91 days (ie, 2 × [6 weeks] + 1 week) after the date of enrolment, then BOR will be assigned to the PD category. For participants who die with no evaluable RECIST assessments, if the death occurs > 91 days (ie, 2 × [6 weeks] + 1 week) after the date of enrolment, BOR will be assigned to the NE category.

Analysis Methods

Confirmed BOR will be summarised descriptively by n (%) for each category (confirmed CR, confirmed PR, SD, PD, and NE) for the FAS.

9.4.2.2.5 Progression-Free Survival

Progression-free Survival by ICR

PFS by ICR will be defined as the time from the date of enrolment until the date of objective PD per RECIST 1.1 as assessed by ICR or death (by any cause in the absence of progression), (ie, date of event or censoring – date of enrolment + 1). The analysis will include all participants regardless of whether the participant withdraws from study intervention, receives another anticancer therapy or clinically progresses prior to RECIST 1.1 progression. The date of progression will be determined based on the earliest of the scan dates of the component that triggered the progression. Participants 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 1.1 assessment. However, if the participant progresses or dies after 2 or more consecutive missed visits, the participant will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits. (Note: NE visit is not considered as missed visit).

If the participant has no evaluable visits or does not have baseline data, they will be censored at Day 1, unless they die within 2 visits of baseline, ie, ≤ 91 days (2 × [6 weeks] plus 1 week allowing for a late assessment within the visit window).

Progression-free Survival by Investigator Assessment

PFS by investigator assessment is defined as the time from the date of enrolment until the date of PD per RECIST 1.1 as assessed by the investigator or death (by any cause in the absence of progression) (ie, date of event or censoring – date of the enrolment + 1).

Data will be handled as described above for the PFS and ITT Analysis Set by ICR.

Analysis Methods

PFS will be summarised for the FAS. A Kaplan-Meier plot of PFS will be presented. The estimate of median PFS and corresponding 95% CI using the Brookmeyer-Crowley method with log-log transformation will be reported (Brookmeyer and Crowley 1982). Summaries of the number and percentage of participants experiencing a PFS event and the type of event (RECIST 1.1 PD or death) will be provided. The proportion of participants alive and progression-free at 3-monthly intervals from the date of enrolment will be estimated.

9.4.2.2.6 Overall Survival

OS is defined as the time from the date of enrolment until death due to any cause. Any participant not known to have died at the time of analysis will be censored based on the last recorded date on which the participant was known to be alive.

Analysis Methods

OS will be analysed for the FAS and ITT Analysis Set.

A Kaplan-Meier plot of OS will be presented. Summaries of the number and percentage of participants with an OS event will be provided along with the estimate of median OS and corresponding 95% CI (if calculable) using the Brookmeyer-Crowley method with log-log transformation (Brookmeyer and Crowley 1982). The proportion of participants alive at 3-monthly intervals from the date of enrolment will be estimated.

9.4.2.2.7 CNS-PFS

CNS-PFS is defined as the time from the date of enrolment until the date of documented disease progression in the CNS as assessed by ICR using RECIST 1.1 or death by any cause in the absence of CNS progression. If CNS progression occurs, the date of CNS progression will be recorded as the date of the earliest RECIST 1.1 assessment where CNS progression was identified. Participants who have neither CNS progression nor death before the time of analysis will be censored at the latest date of their last evaluable RECIST 1.1 assessment. The analysis will include all enrolled participants defined in the FAS, regardless of whether the

participant withdraws from study intervention or receives another anticancer therapy.

A Kaplan-Meier plot of CNS-PFS will be presented. Summaries of the number and percentage of participants experiencing a CNS-PFS event and the type of event (RECIST 1.1 CNS-PD or death) will be provided along with appropriate descriptive statistics (based on Kaplan-Meier estimates).

9.4.2.3 Tertiary/Exploratory Endpoint(s)

CCI [redacted]

9.4.3 Safety

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

Baseline

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

Adverse Events

AEs will be coded using the most recent version of MedDRA that will be released for execution at AstraZeneca and NCI CTCAE v5.

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

An overview of TEAEs will be provided: the number and percentage of participants with any TEAE, TEAEs with outcome of death, serious TEAEs, and TEAEs leading to discontinuation of study intervention, as well as TEAEs leading to study intervention dose interruptions, and AEs leading to study intervention dose reduction.

TEAEs will be presented by System Organ Class and/or Preferred Term covering number and percentage of participants reporting at least one event and number of events where appropriate.

Separate TEAE tables will be provided taking into consideration the relationship to study

intervention as assessed by the investigator, the CTCAE grade, seriousness, death and events leading to discontinuation of study intervention as well as other action taken related to study intervention, AESIs and other significant TEAEs (if applicable).

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

A TEAE listing will cover details for each individual TEAE.

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

Vital Signs

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

Details of vital sign analyses will be provided in the SAP.

ECGs

For each scheduled post-baseline visit, descriptive statistics for all ECG parameters will be presented for observed values and change from baseline. QTcF will be derived during creation of the reporting database using reported ECG values (RR and QT) using the following formula, where RR is in seconds:

$$\text{QTcF} = \frac{\text{QT}}{3\sqrt{\text{RR}}}$$

Details of ECG analyses will be provided in the SAP.

Laboratory Parameters

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

Elevation in liver parameters for assessment of HL will be performed and reported appropriately if potential cases are identified during the course of the study.

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

$$\text{Corrected calcium (mmol/L)} = \text{total calcium (mmol/L)} + ([40 - \text{albumin (g/L)}] \times 0.02)$$

A shift table for urinalysis will be presented with baseline assessment against the maximum on study intervention category.

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

Details of laboratory summaries will be provided in the SAP.

Other Safety Analyses

All other safety endpoints, eg, physical examination findings including WHO/ECOG performance status, elevated troponin levels, ECHO/MUGA, and ophthalmologic findings, will be listed.

More detail will be described in the SAP.

9.4.4 Other Analyses

9.4.4.1 Pharmacokinetics

Serum PK concentration data for intact T-DXd, total anti-HER2 antibody and DXd will be listed for each sampling time for each participant, and a summary will be provided for all participants in the PK Analysis Set. Descriptive statistics may be calculated.

Details of PK, PopPK, and/or exposure-response analyses will be described in the SAP prior to enrolment of the first participant in the study. The PopPK and exposure-response analyses will be presented separately from the main CSR.

9.4.4.2 Biomarkers

Biomarker status will be assessed for all participants, more detailed information will be described in the SAP.

9.4.4.3 Immunogenicity Data

Anti-drug antibody data will be summarised using the T-DXd ADA Evaluable Set. Immunogenicity results will be listed by participant, and a summary will be provided by the number and percentage of ADA evaluable participants who develop detectable anti-T-DXd antibodies during the study. The immunogenicity titre and neutralising ADA data will be listed for samples confirmed positive for the presence of anti-T-DXd antibodies.

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

9.5 Interim Analyses

An interim analysis is not planned in this study.

9.6 Data Monitoring Committee

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the CSP and letters to investigators. An Independent Data Monitoring Committee is not considered necessary for this open-label, single-arm study.

9.6.1 ILD Adjudication Committee

An independent ILD Adjudication Committee and Charter will be established to review all cases of potential ILD/pneumonitis. To ensure adequate evaluation, relevant additional data from within the clinical database may be provided to the adjudication committee to fully characterise medical history (eg, smoking, radiation and pulmonary history), diagnostic evaluation, treatment, and outcome of the event. This data collection will be triggered for adverse events reported based on a set of pre-defined list of PTs eligible for adjudication as described by the Event Adjudication Site Manual. Further details can be found in the ILD Adjudication Charter.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the CSP and with the following:

  Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.

  Applicable ICH GCP Guidelines.

  Applicable laws and regulations.
- The CSP, CSP amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the CSP will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.

Regulatory Reporting Requirements for Serious Adverse Events

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

A 2 Financial Disclosure

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

financial certification or disclosure statements to the appropriate Regulatory Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

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

If a participant's partner becomes pregnant during or within 4 months after the last dose of study intervention, the partner is asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Participants" and provide information about the pregnancy accordingly.

A 4 Data Protection

- Participants will be assigned a unique identifier by AstraZeneca. Any participant records or datasets that are transferred to AstraZeneca will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by AstraZeneca in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by

AstraZeneca, by appropriate IRB/IEC members, and by inspectors from Regulatory Authorities.

Unless previously specified, the biomarker data will have unknown clinical significance and AstraZeneca will not provide biomarker assessment results to participants, their family members, any insurance company, any employer, a clinical study investigator, a general physician, or any other third party, unless required to do so by law; however, AstraZeneca may share data and biosamples with research partners, eg, Daiichi Sankyo.

The participant's samples will not be used for any purpose other than those described in the CSP.

A 5 Committees Structure

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the CSP and letters to investigators.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov, and https://www.clinicaltrialsregister.eu/ as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites (www.chinadrugtrials.org.cn) according to the regulations of the country (China) in which the study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on the eCRF unless transmitted to AstraZeneca or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and Regulatory Authority inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.
- AstraZeneca assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved CSP and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years from the end of the study (as defined in the CSP) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).
- A digital copy of all imaging scans should be stored as source documents.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

AstraZeneca designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of AstraZeneca. Study sites will be closed upon study

completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

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

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

- Failure of the investigator to comply with the CSP, the requirements of the IRB/IEC or local health authorities, AstraZeneca's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, AstraZeneca shall promptly inform the investigators, the IECs/IRBs, the Regulatory Authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to AstraZeneca before submission. This allows AstraZeneca to protect proprietary information and to provide comments.
- AstraZeneca will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, AstraZeneca will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a co-ordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence (other than progression of the malignancy under evaluation) in a participant or clinical study participant administered a study intervention and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the study intervention.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definitions of Serious Adverse Event

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

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

AEs for **malignant tumours** reported during a study should generally be assessed as **Serious** AEs. If no other seriousness criteria apply, the “Important Medical Event” criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **Non-Serious** AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour event in question is a new

malignant tumour (ie, it is *not* the tumour for which entry into the study is a criterion and that is being treated by the study intervention under study and is not the development of new or progression of existing metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B cell chronic lymphocytic leukaemia into diffuse large B cell lymphoma) should not be considered a new malignant tumour.

Life-threatening

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

Hospitalisation

Outpatient treatment in an emergency room is not in itself a SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment.
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation.
- Development of drug dependency or drug abuse.

Intensity Rating Scale

The grading scales found in the revised NCI CTCAE latest version 5.0 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

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

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a “reasonable possibility” that an AE may have been caused by the drug.

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

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

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

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

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

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

B 4 Medication Error

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

A medication error is not lack of efficacy of the drug, but rather a human- or process-related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred.
- Was identified and intercepted before the participant received the drug.
- Did not occur, but circumstances were recognised that could have led to an error.

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

- Drug name confusion.
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant.
- Drug not administered as indicated, eg, wrong route or wrong site of administration.
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet.
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature.

- Wrong participant received the medication (excluding IRT errors).
- Wrong drug administered to participant (excluding IRT errors).

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

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

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

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

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

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

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

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team for the remainder of the sample life cycle.

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

C 2 Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent specifically to the subsequent use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research. The participant will be presented with the option to opt out of the subsequent use of the donated samples during the withdrawal process. If the participant decides to opt out, then the donated samples will be disposed of. If the participant withdraws consent without opting out for the subsequent use of the donated samples, then the samples will be used as per CSP.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.

- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

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

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

IATA (https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx) classifies infectious substances into 3 categories: Category A, Category B, or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

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

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

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

Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

D 1 Introduction

CCI

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[redacted]

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

RNA = ribonucleic acid.

D 9 References

Aithal et al 2011
Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011;89(6):806-15.

FDA Guidance 2009
Food and Drug Administration. Guidance for industry: Drug-induced liver injury: premarketing clinical evaluation. July 2009. Available from: URL: https://www.fda.gov/downloads/guidances/UCM174090.pdf. Accessed on: 08 October 2019.

Appendix E Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

Introduction

This appendix details the implementation of RECIST 1.1 guidelines (Eisenhauer et al 2009). Investigator assessments will use the RECIST 1.1 guidelines described in this appendix.

Imaging Modalities and Acquisition Specifications for RECIST 1.1

A summary of the imaging modalities that can be used for tumour assessment of TLs, NTLs and NLs is provided in Table 15.

Table 15 Summary of Imaging Modalities for Tumour Assessment

Target Lesions	Non-Target Lesions	New Lesions
CT MRI	CT MRI Plain X-ray Chest X-ray	CT MRI Plain X-ray Chest X-ray Bone scan (Scintigraphy) ^{18}F-fluoro-deoxyglucose-PET/CT
CT = computed tomography; PET = positron emission tomography; MRI = magnetic resonance imaging.		

CT and MRI

CT with IV contrast is the preferred imaging modality (although MRI with IV contrast is acceptable if CT is contraindicated) to generate reproducible anatomical images for tumour assessments (ie, for measurement of TLs, assessment of NTLs, and identification of NLs). It is essential that the same correct imaging modality, image acquisition parameters (eg, anatomic coverage, imaging sequences, etc), imaging facility, tumour assessor (eg, radiologist), and method of tumour assessment (eg, RECIST 1.1) are used consistently for each participant throughout the study. The use of the same scanner for serial scans is recommended, if possible. It is important to follow the image collection/tumour assessment schedule as closely as possible (refer to Table 1), and this on-study imaging schedule MUST be followed regardless of any delays in dosing or missed imaging visits. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the participant has not progressed, every attempt should be made to perform the subsequent scan acquisitions at the next scheduled imaging visit.

Due to its inherent rapid acquisition (seconds), CT is the imaging modality of choice. Body scans should be performed with breath-hold scanning techniques, if possible. Therefore, CT of the chest is recommended over MRI due to significant motion artefacts (eg, heart, major blood

vessels, breathing) associated with MRI. MRI has excellent contrast and spatial and temporal resolutions; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. In general, local oncology diagnostic imaging parameters are applied for scan acquisition. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases.

The most critical CT and MRI image acquisition parameters for optimal tumour evaluation are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

a. Anatomic coverage: Optimal anatomic coverage for most solid tumours is the chest-abdomen (-pelvis). Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual participants. Because a lesion later identified in a body part not scanned at baseline would be considered as a NL representing PD, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

Required anatomical regions to be imaged for assessment of tumour burden (TLs and/or NTLs) at baseline and follow-up visits vary according to the study, and these time points are specified in the SoA (Table 1). Examples include the following:

- IV contrast-enhanced CT of chest-abdomen (including the entire liver and both adrenal glands) (-pelvis).
- Non-contrast CT of chest and IV contrast-enhanced abdomen (including the entire liver and both adrenal glands) (-pelvis).
- IV contrast-enhanced MRI (preferred) or CT of the brain.

For chest-abdomen (-pelvis) imaging, the following are scanning options in decreasing order of preference, with additional options (2 to 4) for consideration when participants have sensitivity to IV contrast or have compromised renal function:

1 Chest-abdomen (-pelvis) CT with IV CT contrast (most preferred).
2 Chest CT without IV contrast + abdomen (-pelvis) MRI with IV MRI contrast, if CT IV contrast (iodine based) is medically contraindicated at any time during the study.
3 Chest-abdomen (-pelvis) CT without IV contrast, if both IV CT and MRI contrast are medically contraindicated or the participant has compromised renal function.
4 Chest-abdomen (-pelvis) MRI with IV MRI contrast, if CT cannot be performed at any time during the study.

b. IV contrast administration: Optimal visualisation and measurement of metastases in solid tumours require consistent administration (dose and rate) of IV contrast as well as timing of scanning. An adequate volume of a suitable contrast agent should be given so that the tumour lesions are demonstrated to best effect and a consistent method is used on subsequent examinations for any given participant. Oral contrast is recommended to help visualise and differentiate structures in the abdomen and pelvis.

c. Slice thickness and reconstruction interval: It is recommended that CT or MRI scans be acquired/reconstructed as contiguous (no gap) slices with ≤5 mm thickness throughout the entire anatomic region of interest for optimal lesion measurements. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses >5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

For CT scans, all window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study.

Chest X-ray

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

Plain X-ray

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

Isotopic Bone Scan

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

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. NLs may be recorded in case positive hot-spots appear on a bone scan that were not present on a previous bone scan; however, a newly observed equivocal hot-spot on a bone scan that cannot be verified with correlative imaging (CT, MRI, or X-ray) of the same anatomical region shall not be the only trigger for a PD assessment at that time point.

^{18}F-Fluoro-deoxyglucose-PET/CT

^{18}F-fluoro-deoxyglucose-PET/CT scans may be used as a method for identifying new extrahepatic lesions (but not intrahepatic lesions) for RECIST 1.1 assessments according to the following algorithm: NLs will be recorded where there is positive ^{18}F-Fluoro-deoxyglucose uptake[1] not present on baseline or prior ^{18}F-fluoro-deoxyglucose-PET scan or in a location corresponding to a NL on a companion CT/MRI collected close in time to the ^{18}F-fluoro-deoxyglucose-PET scan. The PET portion of the PET/CT introduces additional data that may bias an investigator if it is not routinely or serially performed. Therefore, if there is no baseline or prior ^{18}F-fluoro-deoxyglucose-PET scan available for comparison, and no evidence of NLs on companion CT/MRI scans, then follow-up CT/MRI assessments should continue as per the regular imaging schedule to verify the unequivocal presence of NLs.

At present, low-dose or attenuation correction CT portions of a combined ^{18}F-fluoro-deoxyglucose-PET/CT scan are of limited use in anatomically based efficacy assessments, and it is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced CT scans for tumour measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed, as part of a PET/CT examination, is of identical diagnostic quality (with IV contrast) to a dedicated diagnostic CT scan, then the CT portion of the PET/CT can be used for RECIST 1.1 tumour assessments. Caution that this is not recommended because the PET portion of the CT introduces additional (PET) data that may bias an investigator if it is not routinely or serially performed.

Ultrasound

Ultrasound examination will not be used for RECIST 1.1 assessment of tumours as it is not a reproducible acquisition method (operator dependent), is subjective in interpretation, and may not provide an accurate assessment of the true tumour size. Tumours identified by ultrasound will need to be assessed by correlative CT or MRI anatomical scan.

Other Tumour Assessments

Clinical Examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will not be used for RECIST 1.1 assessments. Tumours identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

Endoscopy and Laparoscopy

Endoscopy and laparoscopy will not be used for tumour assessments as they are not validated

[1] A positive ^{18}F-fluoro-deoxyglucose-PET scan lesion should be reported only when an uptake (eg, standard uptake value) greater than twice that of the surrounding tissue or liver is observed.

in the context of tumour assessment.

Histology and Cytology

Histology or tumour markers on tumour biopsy samples will not be used as part of the tumour response assessment as per RECIST 1.1.

Results of cytological examination for the neoplastic origin of any effusion (eg, ascites, pericardial effusion, and pleural effusion) that appears or worsens during the study will not be used as part of the tumour response assessment as per RECIST 1.1.

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

Measurability of Tumour Lesions at Baseline

RECIST 1.1 Measurable Lesions at Baseline

A tumour lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter for non-nodal lesions or ≥15 mm in short axis[2] diameter for lymph node lesions with IV contrast-enhanced CT or MRI and that is suitable for accurate repeated measurements. Please see additional RECIST 1.1 guidance below on measurability of intrahepatic hepatocellular carcinoma lesions and porta hepatis lymph nodes.

Non-measurable Lesions at Baseline

- Truly non-measurable lesions include the following:

  Bone lesions (see exception below for soft tissue component).

  Leptomeningeal disease.

  Ascites, pleural effusion, or pericardial effusion.

  Inflammatory breast disease.

  Lymphangitic involvement of skin or lung.
- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis diameter at baseline).[3]
- Previously irradiated lesions.[4]

  A previously irradiated lesion that has shown objective progression and meets the other requirements for a measurable lesion may be considered as a TL if it is the only lesion available.

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

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

4 Localised post-radiation changes that affect lesion size may occur. Therefore, lesions that have been previously irradiated are typically considered non-measurable and as NTL at baseline and followed up as part of the NTL assessment.

- Brain metastasis.

Special Considerations Regarding Lesion Measurability at Baseline

- Bone lesions:

  Bone scan, PET scan, or plain X-ray are not considered adequate imaging techniques to measure bone lesions; however, these techniques can be used to confirm the presence or disappearance of bone lesions.

  Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability.

  Blastic lesions are considered non-measurable.

- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same participant, these should be selected over cystic lesions as TLs.

RECIST 1.1 TL Selection at Baseline

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

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

The site and location of each TL should be documented, as well as the longest axis diameter for non-nodal lesions (or short axis diameter for lymph nodes). All measurements should be recorded in millimetres. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits, the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special Cases for TL Assessment at Baseline

- For TLs measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis diameter.
- When lymph nodes are coalesced and no longer separable in a conglomerate mass, the vector of the longest diameter should be used to determine the perpendicular vector for the maximal short axis diameter of the coalesced mass. Non-nodal lesions that coalesce should similarly be assessed by the longest axis diameter.
- Tumour lesions selected for newly acquired screening biopsy should not be selected as TLs, unless imaging occurred at least approximately 2 weeks after biopsy, allowing time for healing.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as a NL.

RECIST 1.1 NTL Selection at Baseline

All other lesions, including non-measurable lesions and surplus measurable lesions, not recorded as TLs should be identified as NTLs at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Evaluation of Tumour Response and Progression

RECIST 1.1 TL Assessment at Follow-up

This section defines the criteria used to determine objective tumour visit response for RECIST 1.1-defined TLs. The imaging modality, location, and scan date of each TL identified previously at baseline should be documented at follow-up visits with the long axis diameter for non-nodal lesions or short axis diameter for lymph node lesions. All measurements should be recorded in millimetres. The sum of the diameters for all TLs at each follow-up visit will be compared with the baseline sum of diameters (for response or SD) or to the smallest prior (nadir) sum of diameters (for progression).

Special Cases for TL Assessment at Follow-up:

- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as an NL.
- If a TL splits into 2 or more parts, the sum of the diameters of those parts should be recorded.
- If 2 or more TLs merge, then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s). If the merged

TLs are non-nodal lesions, record the long axis diameter of the merged lesion. If pathologic lymph nodes coalesce and are no longer individually separable within a conglomerate mass, the vector of the longest diameter of the coalesced mass should be used to determine the perpendicular vector for the maximal short axis diameter.

- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention (eg, definitive radiotherapy, embolisation, surgery, transarterial chemoembolisation, etc) during the study, the size of the TL should still be provided where possible and the intervention recorded in the RECIST 1.1 eCRF for the current imaging visit and all subsequent visits. If a TL has been completely removed (surgery) or disappears, the longest diameter should be recorded as 0 mm.

Table 16 RECIST 1.1 Evaluation of Target Lesions

CR	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to <10 mm.
PR	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.
SD	Neither sufficient decrease in the sum of diameters to qualify for PR nor sufficient increase to qualify for PD.
PD	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of diameters (nadir). This includes the baseline sum if that is the smallest on study. In addition to the relative increase of 20%, the sum must demonstrate an absolute increase of at least 5 mm from nadir.
NE	Only relevant if any of the TLs at follow-up were not assessed or NE (eg, missing anatomy) or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides NE as a TL response.
Not applicable	Only relevant if no TLs present at baseline.

CR = complete response; NE = not evaluable; PD = progression of disease; PR = partial response; SD = stable disease; TL = target lesion.

RECIST 1.1 NTL Assessment at Follow-up

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the investigator.

To achieve “unequivocal progression” on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in TLs,

the overall tumour burden has increased sufficiently to merit unequivocal progression by NTLs. A modest "increase" in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PD of target disease will therefore be extremely rare.

Table 17 RECIST 1.1 Evaluation of Non-Target Lesions

CR	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/non-PD	Persistence of 1 or more NTLs.
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.
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 participants 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.
NA	Only relevant if no NTLs present at baseline.

CR = complete response; NA = not applicable; NE = not evaluable; NTL = non-target lesion; PD = progression of disease; TL = target lesion.

RECIST 1.1 NL Identification at Follow-up

Details, including the imaging modality, the date of scan, and the location of any NLs will also be recorded in the eCRF. The presence of one or more NLs is assessed as progression. The finding of a NL should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumour. If a NL is equivocal, eg, because of its small size, the treatment and tumour assessments should be continued until the previously (pre-existing) NL has been assessed as unequivocal at a follow-up visit, and then the progression date should be declared using the date of the initial scan when the NL first appeared.

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered a NL and will indicate PD.

RECIST 1.1 Evaluation of Overall Visit Response at Follow-up

Derivation of overall visit response as a result of the combined assessment of TLs, NTLs, and NLs uses the algorithm shown in Table 18.

Table 18 RECIST 1.1 Overall Visit Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Visit Response
CR	CR	No	CR
CR	NA	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE or NA	No	PR
SD	Non-PD or NE or NA	No	SD
NE	Non-PD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Non-CR/Non-PD for overall response if only NTL (no TLs) are present at baseline.
Note: An overall assessment of CR (all other disease disappears/reverts to normal) would be changed to PR if ascites remains present radiologically.
CR = complete response; NA = not applicable (only relevant if there were no TLs or NTLs at baseline), NE = not evaluable; NTL = non-target lesion; PD = progression of disease; PR = partial response; SD = stable disease; TL = target lesion.

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

- For participants with TLs (at baseline): CR, PR, SD, PD, or NE.
- For participants with NTLs only (at baseline): CR, Non-CR/Non-PD, PD, or NE.
- For participants with no disease at baseline: no evidence of disease (available as an option in the eCRF), PD, or NE.

Evaluation of Scans Subsequent to RECIST 1.1-defined Progression

A follow-up scan is requested at least 4 weeks after a RECIST 1.1-defined radiological progression and no longer than the next regularly scheduled imaging visit. The follow-up scans provide additional information to the investigator for participant management and further treatment decisions, and since the published RECIST 1.1 criteria (Eisenhauer et al 2009) do not provide guidance on how to assess scans acquired after RECIST 1.1-defined PD, supplemental instructions for investigators on how to evaluate these follow-up scans are provided below. An immediate prior RECIST 1.1-defined radiologic PD would be considered confirmed if *any* of the following criteria are met in the subsequent follow-up scan:

- ≥ 20% increase and at least a 5 mm increase in the sum of diameters of TLs compared with the nadir sum of diameters at 2 consecutive visits, and a further increase of ≥ 5 mm

in the sum of diameters at the follow-up scan time point compared with the immediate prior time point.

- Significant progression (worsening) of NTLs at the follow-up scan time point compared with the immediate prior time point.
- Significant progression (worsening) of previously NLs (pre-existing NLs) at the follow-up scan time point compared with the immediate prior time point.
- Additional brand-new unequivocal lesions at the follow-up scan time point.

Central Imaging

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed iCRO for quality control, storage, and for ICR. Digital copies of all original scans should be stored at the investigator site as source documents. Electronic image transfer from the sites to the iCRO is strongly encouraged. An ICR of images will be performed at the discretion of AstraZeneca. Results of these independent reviews will not be communicated to investigators, and results of investigator tumour assessments will not be shared with the central reviewers.

The management of participants will be based in part upon the results of the tumour assessments conducted by the investigator. Further details of the ICR will be documented in an Independent Review Charter.

References

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Appendix F Contraception Requirements

Contraception requirements for this study are as follows.

F 1 Female Participants

CCI

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CCI

F 2 Male Participants with a Female Partner of Childbearing Potential

CCI

[redacted]

F 3 Highly Effective Methods of Contraception

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly, are described in Table 19. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 19 Highly Effective Methods of Contraception (<1% Failure Rate)

Non-Hormonal Methods	Hormonal Methods
• Total sexual abstinence (evaluate in relation to the duration of the clinical study and the preferred and usual lifestyle choice of the participant) • Vasectomised sexual partner (with participant assurance that partner received post-vasectomy confirmation of azoospermia) • Bilateral tubal occlusion • Intrauterine device (provided coils are copper-banded)	• Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation - oral - intravaginal - transdermal • Progestogen-only hormonal contraception associated with inhibition of ovulation - oral - injectable - implantable • Intrauterine hormone-releasing system (IUS)

Appendix G Concomitant Medications

G 1 Restricted, Prohibited, and Permitted Concomitant Medications/Therapies

CCI

Table 20 Restricted Medications Therapies

CCI	

Table 21 Prohibited Medications/Therapies

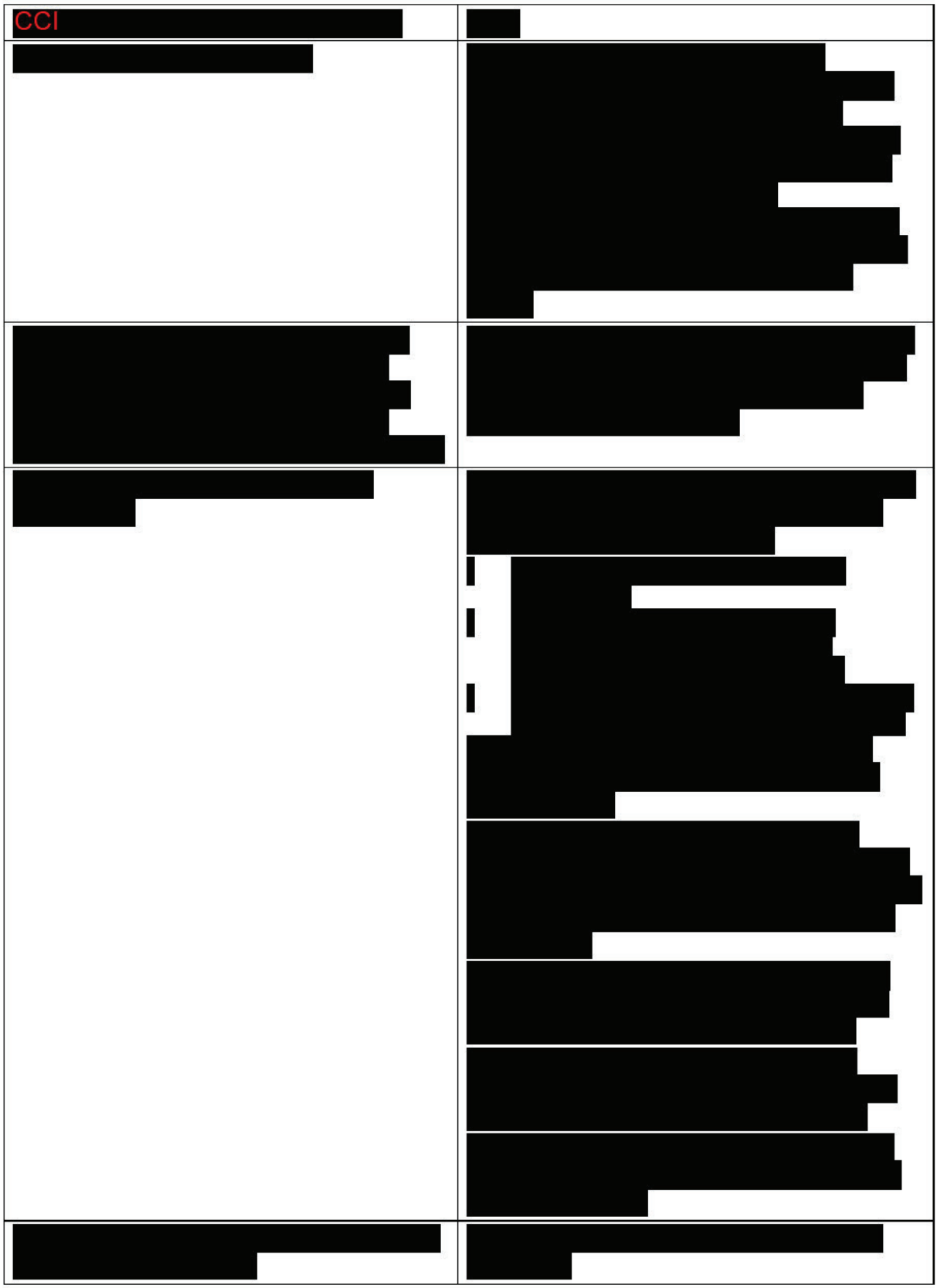

Table 21 Prohibited Medications/Therapies

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

Table 22 Supportive Medications/Therapies

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

Appendix H Instructions Related to COVID-19

The instruction below should only be implemented if allowable by local/regional guidelines and following agreement from AstraZeneca.

Benefit-Risk Considerations for COVID-19

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

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Inclusion Criteria

- CCI

Prior and Concomitant Medications

CCI

COVID-19 Assessment(s)

CCI [redacted]

Dose Modification Criteria

CCI [redacted]

Dose Modification Criteria for Suspected or Confirmed COVID-19

CCI [redacted]

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

Table 23 COVID-19 Dose Modification Criteria

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- CCI

Appendix I Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with COVID-19 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following agreement from AstraZeneca.

Refer to the Study Instruction Manual for Mitigation Due to Civil Crisis, Natural Disaster, or Public Health Crisis for step-by-step guidance.

Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Section 1.3. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

Rescreening of Participants to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The investigator should confirm this with the designated study physician.

In addition, during study disruption there may be a delay between confirming eligibility of a participant and either enrolment into the study or commencing of dosing with study intervention. If this delay is outside the screening window specified in Section 1.3 the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a participant in addition to that detailed in Section 5.4. The procedures detailed in Section 6.3 must be undertaken to confirm eligibility. Rescreened participants should retain the same participant number as for the initial screening.

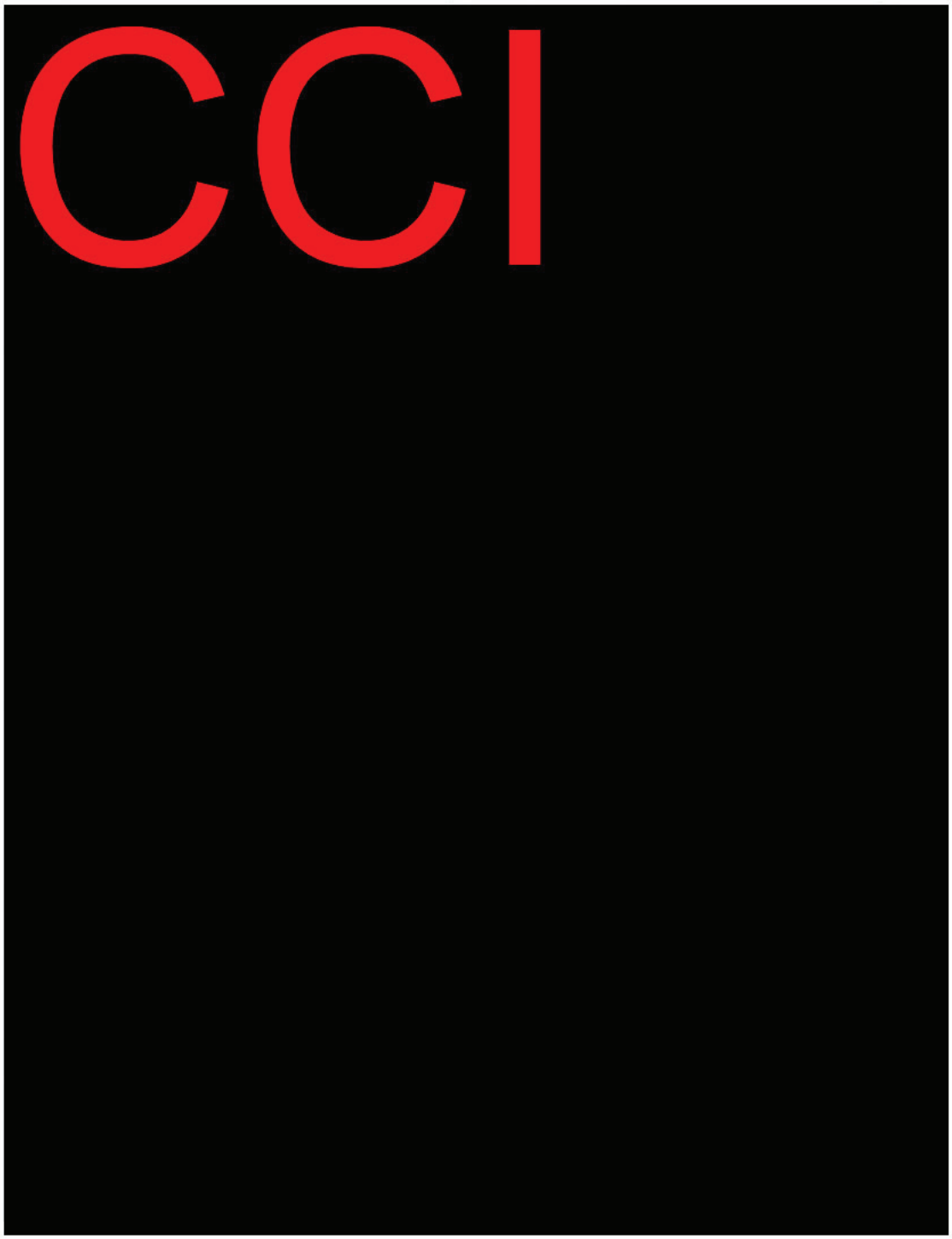
Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix and the associated Study Instruction Manual for Mitigation Due to Civil Crisis, Natural Disaster or Public Health Crisis, the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs and concomitant medication to be reported and documented.

Data collected during telemedicine will be captured by the participant themselves.

Appendix J Guidance for Management of Participants with Drug-induced ILD/Pneumonitis



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Appendix K Toxicity Management Guidelines

Table 24 Toxicity Management Guidelines for T-DXd

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

Table 24 Toxicity Management Guidelines for T-DXd

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Table 24 Toxicity Management Guidelines for T-DXd

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Table 24 Toxicity Management Guidelines for T-DXd

Table 24 Toxicity Management Guidelines for T-DXd

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

[redacted].

Appendix L CCI

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Table 25 Study-qualifying Activating HER2 Exon 19 and 20 Mutations

HER2 Mutation	Gene Location	SNV or InDel
p.D769H	TKD - Exon 19	SNV
p.D769N	TKD - Exon 19	SNV
p.D769Y	TKD - Exon 19	SNV
p.I767F	TKD - Exon 19	SNV
p.L755_E757delinsS	TKD - Exon 19	InDel
p.L755_T759delLRENT	TKD - Exon 19	InDel
p.L755A	TKD - Exon 19	SNV
p.L755M	TKD - Exon 19	SNV
p.L755P	TKD - Exon 19	SNV
p.L755S	TKD - Exon 19	SNV
p.L755W	TKD - Exon 19	SNV
p.I767M	TKD - Exon 19	SNV
p.A775_G776insV	TKD - Exon 20	InDel
p.A775_G776insYVMA (p.Y772_A775dup)	TKD - Exon 20	InDel
p.A775_G776insTVMA (p.Y772_V773insVMAT)	TKD - Exon 20	InDel
p.G776_V777insL	TKD - Exon 20	InDel
p.G776_V777insVC	TKD - Exon 20	InDel
p.G776_V777insVGC (p.G778_S779insCVG)	TKD - Exon 20	InDel
p.G776>LC	TKD - Exon 20	InDel
p.G776delinsVC (p.G776>VC)	TKD - Exon 20	InDel
p.G776C	TKD - Exon 20	SNV
p.G776S	TKD - Exon 20	SNV
p.G776V	TKD - Exon 20	SNV
p.G778dup (p.V777_G778insG)	TKD - Exon 20	InDel
p.G778_P780dup (p.P780_Y781GSP, V777_G778insGSP)	TKD - Exon 20	InDel
p.G778_S779insCPG (p.V777_G778insGCP)	TKD - Exon 20	InDel
p.G778_S779insLPS	TKD - Exon 20	InDel
p.S779_P780insVGS	TKD - Exon 20	InDel
p.V777_G778insCG	TKD - Exon 20	InDel
p.V777L	TKD - Exon 20	SNV
p.V777M	TKD - Exon 20	SNV
p.T798I	TKD - Exon 20	SNV

HER2 = human epidermal growth factor receptor 2.

Appendix M Abbreviations

Abbreviation or Special Term	Explanation
5-HT3	5-hydroxytryptamine 3
ADA	anti-drug antibody
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse event of special interest
Akt	PI3K/protein kinase b
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-}21d}$	area under the concentration-time curve from time 0 to Day 21
β-HCG	beta-human chorionic gonadotropin
BOR	best observed response
BRAF	v-raf murine sarcoma viral oncogene homolog B1
CHF	congestive heart failure
CI	confidence interval
C_{max}	maximum observed concentration
CNB	core needle biopsy
CNS	central nervous system
CNS-PFS	central nervous system progression-free survival
COPD	chronic obstructive pulmonary disorder
COVID-19	coronavirus disease
CR	complete response
CRO	Contract Research Organisation
CSCO	Chinese Society of Clinical Oncology
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
C_{trough}	trough serum concentration
DAR	drug-antibody ratio

Abbreviation or Special Term	Explanation
DCO	data cut-off
DCR	disease control rate
DILI	drug-induced liver injury
DLCO	diffusion capacity of the lungs for carbon monoxide
DoR	duration of response
DXd	MAAA-1181a (deruxtecan)
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EoT	end-of-treatment
FAS	full analysis set
FDA	Food and Drug Administration
FFPE	formalin-fixed and paraffin-embedded
FH-FMI CG	Flatiron Health-Foundation Medicine NSCLC clinico-genomic [database]
FNA	fine needle aspirate
GCP	Good Clinical Practice
GGFG	glycine–glycine–phenylalanine–glycine
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HL	Hy's Law
HRCT	high-resolution computed tomography
HRT	hormone replacement therapy
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICR	independent central review
iCRO	imaging Contract Research Organisation
IEC	Independent Ethics Committee
IHC	immunohistochemistry

Abbreviation or Special Term	Explanation
ILD	interstitial lung disease
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
KEAP1	kelch-like ECH-associated protein 1
KRAS	kirsten rat sarcoma 2 viral oncogene homolog
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
mNSCLC	metastatic non-small cell lung cancer
MET	MET proto-oncogene, receptor tyrosine kinase
MRI	magnetic resonance imaging
MUGA	multigated acquisition
NCI	National Cancer Institute
NE	not evaluable
NK1	Neurokinin 1
NL	new lesion
NMPA	National Medical Products Administration
NRG1	neuregulin 1
NSCLC	non-small cell lung cancer
NTL	non-target lesion
NTRK1	neurotrophic receptor tyrosine kinase
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progression of disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PHL	Potential Hy's Law
PK	pharmacokinetic(s)
PopPK	population pharmacokinetic(s)

Abbreviation or Special Term	Explanation
PR	partial response
Q3W	every 3 weeks
QTcF	QT interval corrected by Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumours, Version 1.1
RET	rearranged during transfection
RNA	ribonucleic acid
ROS	ROS proto-oncogene receptor tyrosine kinase
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SoA	Schedule of Activities
SoC	standard of care
SpO_2	pulse oximetry
STK11	serine/threonine kinase 11
TBL	total bilirubin
T-DM1	trastuzumab emtansine
T-DXd	trastuzumab deruxtecan
TEAE	treatment emergent adverse event
TKI	tyrosine kinase inhibitor
TL	target lesion
TMG	toxicity management guideline
ULN	upper limit of normal
US	United States
WHO	World Health Organisation
WOCBP	woman/women of childbearing potential
w/v	weight per volume

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