STATISTICAL ANALYSIS PLAN	
Study Code	D967RC00001
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A Phase 3 Open-label Trial of Neoadjuvant Trastuzumab Deruxtecan (T-DXd) Monotherapy or T-DXd followed by THP Compared to ddAC-THP in Participants with High-risk HER2-positive Early-stage Breast Cancer (DESTINY-Breast11)

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
ALND	axillary lymph node dissection
ATC	Anatomical Therapeutic Chemical
CCI	
BICR	Blinded independent central review
BMI	Body mass index
BSA	Body surface area
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CR	Complete response
CRF	Case Report Form
CRO	Contract Research Organisation
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed topography
CTCAE	Common Terminology Criteria for AEs
ctDNA	Circulating tumour DNA
CV	Coefficient of variation
DCO	Data cut-off
ddAC-THP	doxorubicin + cyclophosphamide followed by paclitaxel + trastuzumab + pertuzumab
DLCO	Diffusion capacity of the lungs for carbon monoxide
CCI	
d.p.	decimal place
EBC	Early breast cancer
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form

Abbreviation or Specialized Term	Definition
EFS	Event-free survival
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
CCI	[redacted]
ER	Oestrogen receptor
FAS	Full analysis set
FEV1	Forced expiratory volume - 1 second
FVC	Forced vital capacity
HcRU	Healthcare resource use
HER2	human epidermal growth factor receptor 2
HR	Hormone receptor
HRCT	High resolution computed tomography
HRQoL	Health-related quality of life
H&E	Haematoxylin & eosin
ICU	Intensive care unit
IDFS	Invasive disease-free survival
IDMC	Independent data monitoring committee
IHC	Immunohistochemistry
IL123	Item Library 123
IL124	Item Library 124
IL125	Item Library 125
IL19	Item Library 19
ILD	Interstitial lung disease
IP	Investigational product
IPD	Important Protocol Deviation
IRR	Infusion-related reaction
IRT	Interactive Response Technology
ISH	in situ hybridisation
ITT	Intent-to-Treat
IV	intravenous
LD	Longest diameter
LLOQ	Lower limit of quantification
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or Specialized Term	Definition
MMRM	Mixed model for repeated measures
MRI	Magnetic resonance imaging
MTP	Multiple testing procedure
MUGA	Multigated acquisition
NA	Not applicable
nAb	Neutralising antibodies
NCI	National Cancer Institute
NE	Not evaluable
NED	No evidence of disease
NQ	Not quantifiable
NTL	Non-target lesions
CCI	
OS	Overall survival
pCR	Pathological complete response
PD	Progressive disease
PK	Pharmacokinetics
PGI-TT	Patient Global Impression of Treatment Tolerability
PgR	Progesterone receptor
PI	Principal investigator
PR	Partial response
PRO	Patient reported outcome
QW	Once a week
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QLQ-C30	30-item core quality of life questionnaire
QoL	Quality of life
RCB	Residual cancer burden
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SD	Stable disease

Abbreviation or Specialized Term	Definition
SLNB	sentinel lymph node biopsy
SoA	Schedule of assessments
T-DXd	Trastuzumab deruxtecan
TEAE	Treatment emergent adverse event
THP	paclitaxel + trastuzumab + pertuzumab
TL	Target lesions
VAS	Visual analogue scale
WHO	World Health Organisation

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	26-Oct-2021	Initial approved SAP	N/A	N/A
First amendment				
Statistical analysis method for primary endpoint(s)	13-June-2023	Clarified that strata weighting in Miettinen and Nurminen's method would be done using Mantel-Haenszel weights (Section 4.2.2).	No	To provide more clarification
Statistical analysis method for primary endpoint(s)	13-June-2023	Removed efficacy analysis set (EAS) (Section 2.1) and all related supplementary analyses (Section 4.2.2.1).	No	EAS is not applicable in this trial
Statistical analysis method for primary endpoint(s)	13-June-2023	Removed pooling strategy from EFS and added to own section as applicable to all stratified analyses (Section 4.2.20).	Yes	To provide more clarification and improve readability
Statistical analysis method for primary endpoint(s)	13-June-2023	Supplementary and complementary futility analyses described in full (Section 5.1).	Yes	To provide more details on Futility analysis
Statistical analysis method for secondary endpoint(s)	13-June-2023	Removed subgroup analyses from pCR secondary endpoint (Section 4.2).	No	The analysis is redundant as primary pCR subgroup analysis will provide necessary information
Derivation of primary endpoint(s)	13-June-2023	Added Modified FAS analysis set to be used in futility analysis (Section 2.1.5).	No	To provide more details on the futility set
Derivation of primary endpoint(s)	13-June-2023	Updated critical values of Arm A and B in multiplicity adjustment (Section 4.2.1).	No	To correct error relating to critical values in CSP
Derivation of primary endpoint(s)	13-June-2023	Subgroups updated for age (Section 4.2.2.1)	Yes	To align with the indication specific requirement

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Derivation of primary endpoint(s)	13-June-2023	Updated stratification factors in supplementary analyses to come from eCRF as per newer SAP template (Section 4.2.2.1).	No	To align with AZ standard
Derivation of secondary endpoint(s)	13-June-2023	Simplification and further details given on events and censoring of EFS endpoint (Section 3.1.3).	No	To provide more clarification
Derivation of secondary endpoint(s)	13-June-2023	IDFS patients updated to be censored at date of surgery if no progression or assessments post-surgery (Section 3.1.4).	NA	To provide more clarification
Derivation of safety endpoint(s)	13-June-2023	Added Modified SAF analysis set to be used in futility analysis (Section 2.1.6).	No	To clearly define analysis set to be used for futility
Derivation of safety endpoint(s)	13-June-2023	Updated intervals between dosing doxorubicin and cyclophosphamide in the calculation of intended exposure (Section 3.6.1).	Yes	To align with dosing schedules
Derivation of safety endpoint(s)	13-June-2023	Added the 10% weight change allowance in dose calculation for T-DXd (Section 3.6.2).	Yes	Clarification of analysis method
Derivation of safety endpoint(s)	13-June-2023	SAEs 48 days or more post-treatment are no longer considered treatment emergent (Section 3.6.3.1).	No	To align with new SAP template and to be consistent with the Enhertu project level
Derivation of safety endpoint(s)	13-June-2023	Imputation dates of missing AE start and end dates for prior anti-cancer therapies updated (Section 4.1.2).	NA	To provide more clarification and align with new SAP template
CCI [redacted]				

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
CCI [redacted]				
Data presentation	13-June-2023	Removed deviation numbers to reflect that deviation codes in PD plan may change (Section 2.2).	NA	To improve previous intent
Data presentation	13-June-2023	Updated LVEF decrease wording to Left ventricular dysfunction (Section 3.6.3.2).	NA	To align with EMA guideline
Data presentation	13-June-2023	Updated vital sign collections post infusion to relate to a 30- or 90-minute schedule as applicable (Section 3.6.5).	Yes	To align with protocol CSP v3.0
Data presentation	13-June-2023	Added negative sign to equation of corrected calcium (Section 3.6.8).	NA	To improve previous intent
Data presentation	13-June-2023	Updated Hy's Law total bilirubin criteria to be >=2xULN in line with CSP v3.0 (Section 3.6.8).	Yes	To align with CSP v3.0
Data presentation	13-June-2023	Removed tumour grade subgroups not present in updated CRF (Section 4.2.2.1).	NA	To align with the actual grades collected in the trial
Data presentation	13-June-2023	Remove unknown/missing reason from deaths summary (Section 4.2.12.3).	NA	Category not relevant

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Data presentation	13-June-2023	Updated whether high/low versions of lab parameters required to be analysed (Section 4.2.12.8).	NA	To provide relevant direction for a lab-abnormality
Data presentation	13-June-2023	BMI added to baseline characteristics summary (Section 4.2.13).	NA	BMI is an important baseline characteristic
Data presentation	13-June-2023	Removed 'disease-related' from medical history (Section 4.2.13).	NA	Disease related is not relevant
Second amendment				
Data presentation	14-Nov-23	Removed glucose from clinical chemistry parameters to be presented in shift table (Section 4.2.12.8).	NA	To align with CRF data collection
Data presentation	14-Nov-23	Update AE outputs to include grade 3 or higher rather than grade 3 or 4 (Section 4.2.12.3).	NA	To better characterise safety reporting
Data presentation	14-Nov-23	Removal of OAEs and AESIs from overall AE summary output (Section 4.2.12.3).	NA	To better characterise safety reporting
Derivation of secondary endpoint(s)	14-Nov-23	Inclusion of additional dates (AE grade change, adjudicated ILD dates, baseline disease assessment, disease recurrence assessment, breast cancer surgery assessment, concomitant procedures, radiotherapy, subsequent anti-cancer therapy) from CRF in derivation of last known alive date (Section 3.1.5).	NA	To include all available data
CCI [redacted]				
Study details	22-Nov-23	Language regarding accounting for a 5% dropout rate was removed (Section 1.3).	Yes, v4	To align with CSP v4.0 and is irrelevant
CCI [redacted]				

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
CCI [redacted]				
Study details	22-Nov-23	Adjust the maximum duration of follow-up for heart failure from 5 to 6 years (Sections 1.1.3, 3.6.3, 4.2.12.9.3).	Yes, v4	To align with CSP v4.0
Statistical analysis method for exploratory endpoint(s)	22-Nov-23	Update the items collected from the PRO-CTCAE instrument (Section 3.4.1.2).	Yes, v4	To align with CSP v4
Statistical analysis method for safety endpoint(s)	22-Nov-23	Added language for additional clinical laboratory tests (Section 3.6.3.2)	Yes, v4	To align with CSP v4
Derivation of endpoint(s)	23-Nov-23	Amend imputation of partial death dates (Section 4.1.2).	NA	To align with new TA SAP template

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Statistical analysis method for secondary endpoint(s)	23-Nov-23	Removal of pCR status and treatment administered post-surgery from subgroup analyses to remove use of post-baseline factors as subgroups (Section 4.2.4.1).	Yes, v4	To align with CSP v4
Statistical analysis method for exploratory endpoint(s)	23-Nov-23	Added a summary of residual cancer burden (Sections 3.2.4, 4.2.18, Table 4, Table 5)	Yes, v4	To align with CSP v4
Data presentation	27-Nov-23	Removed disease-related treatment modalities summary and nicotine use summary (Section 4.2.13).	NA	Not required
CCI				
Data presentation	27-Nov-23	Remove episode level adverse event summary; remove subject listing of AEs possibly related to treatment (Section 4.2.12.3)	NA	Not required
Data presentation	27-Nov-23	Remove healthcare resource use summaries (Section 4.2.11).	No, v4	Not required
Data presentation	27-Nov-23	Remove summary tables for urinalysis (Section 4.2.12.8).	No, v4	Not required
Data presentation	27-Nov-23	Remove box plots of haematology and clinical chemistry parameters (Section 4.2.12.8).	NA	Not required
Data presentation	27-Nov-23	Remove plots of maximum ALT/AST versus bilirubin and replace with a summary table (Section 4.2.12.8).	NA	Not required
Data presentation	27-Nov-23	Amended LVEF decrease summary (Section 4.2.12.9.1).	No, v4	Add further summaries into the output
Data presentation	27-Nov-23	Added a shift table for troponin (Section 4.2.12.8).	NA	To include further information
Data presentation	27-Nov-23	Removal of COVID-19 summaries (Section 4.2.19).	No, v4	Not required
Data presentation	27-Nov-23	Removal of listing of ophthalmologic assessments.	NA	Not required

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Data presentation	27-Nov-23	Replace ECOG listing with a summary (Section 4.2.12.9.4).	NA	Not required
Data presentation	27-Nov-23	Clarify that ILD/pneumonitis events are included in the summaries both pre-treatment and beyond safety follow-up (Section 4.2.12.4).	NA	To provide more clarification
Data presentation	27-Nov-23	Added several AESI summaries (Section 4.2.12.4).	NA	To include further summaries
Data presentation	27-Nov-23	Inclusion of new AE summaries: AEs leading to dose reduction, possibly related to study treatment, AEs leading to dose interruption, possibly related to study treatment, most common AEs with maximum CTCAE grade 3 or higher, deaths listing (Section 4.2.12.3).	NA	To provide more safety information
Data presentation	27-Nov-23	Inclusion of ECG shift table (Section 4.2.12.7).	NA	To include further summaries
Statistical analysis method for secondary endpoint(s)	27-Nov-23	Update to method of analysis for PROs: some summary tables swapped for figures, MMRM analysis added, compliance section re-worded (Table 15, Section 4.2.10).	Yes, v4	To align with study requirements
Statistical analysis method for primary endpoint(s)	30-Nov-23	Added a supplementary analysis for pCR which does not exclude patients who have taken subsequent neo-adjuvant therapy (Section 4.2.2.1).	NA	To include additional supplementary analysis.
Derivation of safety endpoint(s)	30-Nov-23	Added additional details on calculations of intended dose including BSA, removed windowing allowance (Section 3.6.2).	NA	To provide further clarity.
Data presentation	11-Dec-23	Added that PK listing will only cover PK analysis set (Section 4.2.15)	Yes, v4	To provide further clarity.
Data presentation	09-Jan-24	Added additional details around presentation of post-treatment AEs / AEs occurring after initiating subsequent anti-cancer therapy (Section 4.2.12.3).	NA	To provide further clarity.

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
CCI [redacted]				
Data presentation	15-Jan-24	Inclusion of new AE summary: SAEs leading to discontinuation of study treatment (Section 4.2.12.3).	NA	To provide more safety information
Statistical analysis method for secondary endpoint(s)	15-Jan-24	Added ADA evaluable set as an additional analysis set to be used for summaries and listings of ADA data rather than SAF (Table 5, Section 2.1.9, 4.2.16).	Yes, v4	To include relevant data
Data presentation	15-Jan-24	Added a summary of pulmonary function test at baseline (Section 4.2.13) and pulmonary medical history (Section 4.2.12.9.2).	NA	To provide more safety information
Statistical analysis method for safety endpoint(s)	15-Jan-24	Only include laboratory data up to the initiation of subsequent therapy, or date of last dose, whichever occurs first (Section 4.2.12.8).	NA	To include relevant data
Statistical analysis method for safety endpoint(s)	15-Jan-24	Added in definition of overall patient compliance (Section 3.4.5)	NA	To provide further clarity on definitions
Statistical analysis method for secondary endpoint(s)	15-Jan-24	Amend text to state that laboratory values will be converted to AZ preferred units rather than standard units (Section 4.2.12.8).	NA	To align with most recent TA SAP.
Definition of analysis sets	25-Jan-24	Amended the safety analysis set to be summarised using randomised treatment rather than treatment actually received (Section 2.1.3).	No, v4	To provide a summary of the underlying safety profile that patients should expect when initially prescribed treatment

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Definition of analysis sets	26-Jan-24	Remove statement that "Patients who violate or deviate from the protocol in ways that would significantly affect the PK analysis should not be included in the PK analysis set." (Section 2.1.4)	Yes, v4	To include all data in summaries.
Derivation of secondary endpoint(s)	26-Jan-24	Remove new lesion as an event for IDFS (Table 7).	Yes, v4	To correct definition of IDFS and align with CSP v4.0.
Derivation of secondary endpoint(s)	26-Jan-24	Add the definition of clinically meaningful change for EORTC QLQ-C30 (Section 3.4.1.2).	NA	To include further detail on PRO analyses
Derivation of secondary endpoint(s)	26-Jan-24	Amend the definition of time to deterioration to require confirmation at a subsequent assessment, and to censor deterioration after 2 missing visits and to censor deaths. Include all patients in the FAS and censor those where deterioration is not possible. Include a table to clarify definitions of events/censoring (Section 3.4.3).	NA	To update derivation per study requirements
Derivation of secondary endpoint(s)	26-Jan-24	Include definitions of ADA outcomes (Section 3.8)	NA	To provide additional clarity
Derivation of secondary endpoint(s)	26-Jan-24	Amend summary of symptomatic AE responses to say graphical representation rather than a stacked bar chart (Section 4.2.10.1).	NA	To allow alternative summaries
Derivation of secondary endpoint(s)	30-Jan-24	Include analysis windows for PROs (8).	NA	To provide additional clarity
Derivation of secondary endpoint(s)	07-Feb-24	Amend wording of PRO compliance summaries (Section 4.2.10)	NA	To provide additional clarity
Study details	04-Jun-24	Recruitment to Arm A is closed from 13 March 2024 onwards (Sections 1.2, 4.2.1).	Yes, v5	Following IDMC recommendation
Study details	04-Jun-24	Clarification that the planned statistical analyses are not changed due to the closure of Arm A (Section 1.3, 4.2.1).	Yes, v5	No change in statistical analyses.

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
CCI				
Definition of analysis sets	02-Jul-24	Clarified that ADA evaluable set includes patients who have received at least one dose of T-DXd rather than any study treatment (Section 2.1.9).	NA	To provide additional clarity
CCI				
Structural change	03-Jul-24	Swap order of Sections 3.4.1.1 and 3.4.1.2.	NA	Ease of reading
CCI				
Presentation of safety endpoint(s)	03-Jul-24	Add in a possible summary of surgical delays using the modified SAF – sensitivity analysis due to Arm A closure (Table 5, Section 3.6.1).	Yes, v5	Update analyses per study requirements
Statistical analysis method for primary endpoint(s)	03-Jul-24	Amend grouping of geographical regions for subgroup analysis to separate South America and combine Europe and Rest of the World (Section 4.2.2.1).	NA	Update analyses per study requirements
CCI				

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Data presentation	03-Jul-24	Clarify that immunogenicity summaries are of the maximum post-baseline titre (Section 4.2.16).	NA	To provide further clarity
Statistical analysis method of primary endpoint(s)	03-Jul-24	Pooling strategy also applied for logistic regression models (Section 4.2.20).	NA	To correct previous language
Derivation of safety endpoint(s)	03-Jul-24	Further details added on derivation of actual and intended cumulative dose (Section 3.6.2).	NA	To provide further clarity
Statistical analysis method of primary endpoint(s)	03-Jul-24	Added interaction test for consistency of treatment effect between subgroups for pCR (Section 4.2.2.1).	NA	Update analyses per study requirements
Statistical analysis method of secondary endpoint(s)	03-Jul-24	Removed interaction test for EFS (Section 4.2.4.14.2.2.1).	NA	Not required
Statistical analysis method of primary endpoint	03-Jul-24	Adjusted confidence intervals will also be presented for primary pCR (Section 4.2.2).	NA	To suit requirements of study
Data presentation	03-Jul-24	Add details for PK data below the lower limit of quantification (Section 3.7).	NA	To present relevant data
Data presentation	03-Jul-24	Add details for ADA data recorded as '<x' (Section 4.2.16).	NA	To present relevant data
Data presentation	03-Jul-24	Amend listing of ALT/AST/bilirubin to only include patients where ALT/AST elevation is prior to or on date of bilirubin elevation (Section 4.2.12.8).	NA	To present relevant data
CCI [redacted]				
Derivation of secondary endpoint(s)	04-Jul-24	Inclusion of additional dates (visit dates) from CRF in derivation of last known alive date and removal of sample dates CCI [redacted] (Section 3.1.5).	NA	To include all available data
CCI [redacted]				

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Definition of analysis sets	17-Jul-24	Amended ADA evaluable set to be patients with a non-missing result at any time (rather that one at baseline and one post-baseline) (Section 2.1.9).	NA	To suit needs of study
Protocol Deviations	17-Jul-24	Amend method of identifying IPDs and update to align with most recent protocol deviations plan (Section 2.2).	NA	To suit needs of study
Presentation of safety variable(s)	17-Jul-24	In the case of laboratory assessments, 5 decimal places will be kept (Section 4.1).	NA	To suit needs of study
Statistical analysis method of secondary endpoint(s)	17-Jul-24	Add sentence that a patient or particular data for a patient may be excluded from the PK analysis set if it affects the results (Section 4.2.15).	NA	To include relevant data
General	17-Jul-24	Update Section 6 to be in line with CSP v5.	Yes, v5	To align with CSP v5.0
Third amendment				
General	8-Jan-25	Add AJCC and EMA to list of abbreviations.	NA	To include relevant information
Statistical analysis method for secondary endpoint(s)	8-Jan-25	Add total exposure of whole treatment regimen (Section 3.6.1).	NA	To provide more relevant information on exposure
Statistical analysis method for secondary endpoint(s)	8-Jan-25	Amend summary of subjects undergoing breast surgery and lymph node surgery to use FAS (Section 3.6.1).	NA	To suit needs of study
Statistical analysis method for primary endpoint(s)	8-Jan-25	Amend subgroups for age and geographical regions and add race, nodal status and AJCC clinical stage to subgroup analysis (Section 4.2.2.1).	NA	To assess robustness of efficacy within important subgroups. To follow the principles from ICH E17 guidance
Statistical analysis method for primary endpoint(s)	8-Jan-25	Remove reference to significance level (Section 4.2.2.1).	NA	To correct previous language

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
CCI				
Statistical analysis method for secondary endpoint(s)	8-Jan-25	Update wording of EFS section to use event-free survival (Section 4.2.4).	NA	To provide further clarity
Data presentation	8-Jan-25	Amend to only display HR and CI if sufficient events (Section 4.2.4).	NA	To align with SAP template 2022-09
Statistical analysis method for secondary endpoint(s)	8-Jan-25	Inclusion of Cox regression analysis adjusting for post-surgery treatment if statistically feasible (Section 4.2.4).	NA	Following EMA feedback
Statistical analysis method for secondary endpoint(s)	8-Jan-25	Add additional EFS landmark analyses at 12m, 18m, 24m and 30m (Section 4.2.4).	No, v5	To include relevant data
Statistical analysis method for secondary endpoint(s)	8-Jan-25	Update wording of duration of follow-up for OS section (Section 4.2.6).	NA	To correct previous language
Statistical analysis method for secondary endpoint(s)	8-Jan-25	Added duration of follow-up in all patients (Section 4.2.6).	NA	To provide further clarity
Statistical analysis method for secondary endpoint(s)	8-Jan-25	Removed average record from MMRM analysis (Section 4.2.10.4).	No	To suit requirements of the study due to arms following different cycles
Data presentation	8-Jan-25	Updated definition of most common AEs to be in any treatment arm instead of overall (Section 4.2.12.3).	NA	Update analyses per study requirements
Data presentation	8-Jan-25	Update age groups in demography section (Section 4.2.12.3).	NA	Update analyses per study requirements
Statistical analysis method for endpoint(s)	8-Jan-25	Updated pooling strategy (Section 4.2.20).	NA	Update analyses per study requirements
General	29-Jan-25	Updated list of abbreviations to remove best overall response and to add MMRM, IRR and Q6W	NA	To include relevant information
General	29-Jan-25	Updated the wording of table headers from "Endpoint/variable" to "Endpoint/estimand" (Section 1.1).	NA	To correct previous language

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
CCI				
Statistical analysis method for endpoint(s)	29-Jan-25	Removed reference to patients still on treatment and clarified list of CRF dates only used where SURVIVE is not completed (Section 3.1.5).	NA	To correct previous language and align with other Enhertu studies
Handling of missing data	29-Jan-25	Removed imputation section for partial/missing death dates (Section 3.1.5).	NA	To remove duplication of information
Demographics and baseline characteristics	29-Jan-25	Removed previous chemotherapy prior to this study (Section 4.2.13).	NA	Not applicable
Data presentation	29-Jan-25	Removed duplicate bullet point in definition of potential Hy's law (Section 4.2.12.8).	NA	To remove duplication of information
Data presentation	29-Jan-25	Removed OAE section (Section 3.6.3.2) and all references to OAEs (Section 4.2.12).	NA	No OAE is detected beside AESI
Statistical analysis methods	29-Jan-25	Changed all instances of alpha-adjustment to multiplicity-adjustment (Section 4.2.1 and Section 5.1)	NA	To correct previous language
Definition of analysis sets	29-Jan-25	Added that patients with margins that cannot be determined will be excluded from the resected analysis set (Section 2.1.2) and IDFS (Section 3.1.4).	No, v5	To include relevant information
Protocol deviations	29-Jan-25	Updated protocol deviation list to update failure to perform mandatory safety assessments rules and to remove patients randomised but who did not receive study treatment from first point (Section 2.2).	NA	To include relevant information
Analysis of endpoints	29-Jan-25	Updated "no change" to "maintained" for EORTC QLQ-C30 scales (Section 3.4.1).	NA	To align with endpoint and to correct previous language
Analysis of endpoints	29-Jan-25	Removed visit level summary of EORTC QLQ-C30 scales (Section 3.4.1).	NA	To suit needs of study

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Statistical analysis method for secondary endpoint(s)	29-Jan-25	Added actual exposure for whole treatment regimen (Section 3.6.1).	NA	To suit needs of study provide more relevant information on exposure
Analysis of safety endpoints	29-Jan-25	Added HRCT also measured after baseline Q6W (Section 3.6.3.2).	Yes, v5	To add relevant information
Handling of missing data	29-Jan-25	Added imputation rule for completely missing subsequent anti-cancer therapy date (Section 4.1.2).	NA	To handle missing date
Analysis of endpoints	29-Jan-25	Updated endpoints analysed and notes for EORTC QLQ-C30 Physical Function Scale in Table 15 (Section 4.2).	NA	For further clarity
Study objectives	29-Jan-25	Updated language regarding superiority assessed by pCR rate and removed reference to dual primary endpoints (Section 1.3).	NA	To correct previous language
Definition of analysis sets	29-Jan-25	Updated wording of analyses that use FAS (Section 2.1.1).	NA	For further clarity
Analysis of endpoints	29-Jan-25	Removed references to neoadjuvant baseline (Section 3.1.3) and neoadjuvant safety follow-up (Section 3.6.1).	NA	To correct previous language
Derivation of endpoint	29-Jan-25	Removed reference to patients still on treatment for OS analysis (Section 3.1.5).	NA	Redundant information
CCI [redacted]				
Analysis method for endpoint(s)	29-Jan-25	Updated that patients will perform PRO assessments using an electronic device (Section 3.4).	NA	To correct previous language

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Analysis method for endpoint(s)	29-Jan-25	Amend definition of an evaluable form to use scale instead of subscale (Section 3.4.5).	NA	To correct previous language
General	29-Jan-25	Replaced surgery delay section with surgery summary (Section 3.6.2).	NA	To provide further clarity
Definition of safety variables	29-Jan-25	Amend heart failure information collection such that it will be collected throughout the post-surgery period until end of study up to 6 years (not necessarily 6 years for all patients) (Section 3.6.3).	Yes, v5	To align with CSP
Statistical analysis method for endpoint(s)	29-Jan-25	Updated baseline definition for PRO assessments (Section 4.1.1).	NA	To suit needs of study
Handling of missing data	29-Jan-25	Updated imputation of completely missing AE/concomitant medications start dates (Section 4.1.2).	NA	To align with other Enhertu studies
Derivation of secondary endpoint(s)	29-Jan-25	Amend wording for visit based summaries to prevent very large tables (Section 4.1.3).	NA	To provide further clarity
Statistical analysis method for endpoint(s)	29-Jan-25	Added additional sensitivity analysis and supplementary analysis to Table 15 (Section 4.2).	NA	To add relevant information
Statistical analysis method for endpoint(s)	29-Jan-25	Amended grouping of tumour grade (Section 4.2.2.1)	NA	Update analyses per study requirements
Statistical analysis method for endpoint(s)	29-Jan-25	Added that the unstratified MN method will be used for complementary analysis (Section 4.2.2) and subgroup analysis (Section 4.2.2.1).	NA	To provide further clarity
Statistical analysis method for endpoint(s)	29-Jan-25	Added that Mantel-Haenszel weights are to be used to analyses secondary definition of pCR (Section 4.2.3).	NA	To provide further clarity
Statistical analysis method for endpoint(s)	29-Jan-25	Wording update for proportional hazards assumption (Section 4.2.4).	NA	To provide further clarity

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Data presentation	29-Jan-25	Amend wording of immunogenicity section to say effects may be evaluated rather than will (Section 4.2.16)	NA	To correct previous language as this is an exploratory endpoint
Data presentation	29-Jan-25	Added row to RCB summary table for patients with either RCB 0 or 1 (Section 4.2.18).	NA	To add relevant information
Changes of analysis from protocol	29-Jan-25	Removed Section 4.2.12.8.1 from changes of analysis from protocol section – information will now be summarised (Section 6).	NA	To suit needs of study
General	29-Jan-25	Restructured PRO section to be per endpoint (Section 4.2.10).	NA	To provide further clarity
Data presentation	29-Jan-25	Removed survival status CRF from bullet point list for last date for each individual patient (Section 3.1.5).	NA	To suit needs of study
General	29-Jan-25	Updated all occurrences of "anticancer" to "anti-cancer" (Section 2.1, Section 3.1.5).	NA	For consistency
Protocol deviations	7-Feb-2025	Update so patients not excluded from the PK analysis set due to protocol deviations (Section 2.2).	NA	To suit needs of study
CCI				
Statistical analysis method for endpoint(s)	7-Feb-2025	Added stratification details to Table 15 for all endpoints (Section 4.2).	NA	To add relevant information and to provide further clarity
CCI				

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Statistical analysis method for endpoint(s)	7-Feb-2025	Replaced "descriptive summaries" with "number and percentage of patients" (Section 4.2.2.1, Section 4.2.4.1, Section 4.2.5).	NA	To provide further clarity
Statistical analysis method for endpoint(s)	7-Feb-2025	Added stratification details for pCR (ypT0 ypN0) rate (Section 4.2.3).	NA	To provide further clarity
Pooling strategy	7-Feb-2025	Updated pooling strategy (Section 4.2.20).	NA	To provide further clarity
Analysis methods for safety analyses	7-Feb-2025	Added IRR definition (Section 3.6.5).	NA	To suit needs of study
Analysis methods for safety analyses	7-Feb-2025	IRR section created (Section 4.2.12.5).	NA	To suit needs of study
Data presentation	7-Feb-2025	Removed summary of total durations of AESI (Section 4.2.12.4).	NA	To align with other Enhertu studies
Data presentation	7-Feb-2025	Added summary table of patients who had potential ILD/pneumonitis sent for adjudication (Section 4.2.12.4)	NA	To suit needs of study
CCI [redacted]				
Statistical analysis method for endpoint(s)	7-Feb-2025	Added reference to pooling strategy for pCR (ypt0/Tis ypN0) (Section 4.2.2), pCR (ypT0 ypN0) (Section 4.2.3), EFS (Section 4.2.4), IDFS (Section 4.2.5), OS (Section 4.2.6), CCI (Section 4.2.8), CCI (Section 4.2.9), change from baseline in EORTC QLQ-C30 scale scores (Section 4.2.10.4).	NA	To provide further clarity
Statistical analysis method for endpoint(s)	7-Feb-2025	Removed survival rate difference from EFS landmark analyses (Section 4.2.4) and paper from references section (Section 7).	NA	To suit needs of study

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Data presentation	7-Feb-2025	Specified which countries are included in each geographical region (Section 4.2.2.1).	NA	To include relevant information
General	7-Feb-2025	Removed "but not limited to" as all subgroup analyses are listed (Section 4.2.2.1).	NA	To correct previous language
Statistical analysis method for endpoint(s)	7-Feb-2025	Added that symptomatic AEs will be summarised during neoadjuvant period (Section 4.2.10.1).	NA	To provide further clarity
Baseline definitions	7-Feb-2025	Added baseline derivation logic for non-numeric laboratory assessments (Section 4.1.1)	NA	To provide relevant information
CCI				
Statistical analysis method for endpoint(s)	18-Feb-2025	Amend method used to analyse time to deterioration using EORTC QLQ-C330 Physical Function Scale in Table 15 (Section 4.2)	NA	To correct previous language
Analysis method for endpoint(s)	03-Mar-2025	Amend expected forms to not exclude patients with no available translation (Section 3.4.5).	NA	To correct previous language
Fourth amendment				
Data presentation	24-Mar-2025	Corrected which countries are included in each geographical region in subgroup analysis (Section 4.2.2.1).	NA	To correct previous information

1 STUDY DETAILS

This statistical analysis plan (SAP) contains a more detailed description of the analyses in the clinical study protocol (CSP). This SAP is based on version 5.0 of the CSP.

1.1 Study Objectives

1.1.1 Primary Objective

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

Table 1 Primary objective and corresponding endpoint/estimand

Primary objective:	Endpoint/estimand:
pCR (ypT0/Tis ypN0): To demonstrate superiority of neoadjuvant T-DXd alone or in sequence with THP relative to ddAC-THP by assessment of pCR (ypT0/Tis ypN0) using central evaluation in participants with HER2-positive EBC	Rate of pCR is defined as the proportion of participants who have no evidence by H&E staining of residual invasive disease in the complete resected breast specimen and all sampled regional lymph nodes (ypT0/Tis ypN0) by central evaluation following completion of neoadjuvant therapy

ddAC-THP = doxorubicin + cyclophosphamide followed by paclitaxel + trastuzumab + pertuzumab; EBC = early breast cancer; HER2 = human epidermal growth factor receptor 2; H&E = haematoxylin & eosin; pCR = pathological complete response; T-DXd = trastuzumab deruxtecan; THP = paclitaxel + trastuzumab + pertuzumab; ypT0/Tis ypN0 = absence of invasive cancer in the breast and axillary nodes.

1.1.2 Secondary Objectives

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

Table 2 Secondary objectives and corresponding endpoints/estimands

Secondary objectives:	Endpoints/estimands:
pCR (ypT0 ypN0): To assess the effectiveness of neoadjuvant T-DXd alone or in sequence with THP relative to ddAC-THP by assessment of a secondary definition of pCR (ypT0 ypN0) using central evaluation	Rate of pCR is defined as the proportion of participants who have no evidence by H&E staining of residual invasive disease and in situ cancer in the complete resected breast specimen and all sampled regional lymph nodes (ypT0 ypN0) by central evaluation following completion of neoadjuvant therapy

Secondary objectives:	Endpoints/estimands:
EFS, IDFS, OS: To assess the effectiveness of neoadjuvant T-DXd, alone or in sequence with THP, relative to neoadjuvant ddAC-THP by assessment of 3-year EFS, 3-year IDFS, and OS	• EFS: Time from date of randomisation until disease progression precluding initial surgery, invasive disease recurrence (local, regional, distant, or contralateral), or death from any cause. • IDFS: Time from surgery until invasive disease recurrence (local, regional, distant, or contralateral), or death from any cause. • OS: Time from randomisation to death from any cause.
To assess patient-reported tolerability of T-DXd alone or in sequence with THP as compared with ddAC-THP during neoadjuvant treatment, including symptomatic AEs and overall side-effect bother	• Symptomatic AEs assessed by the PRO-CTCAE and items from the EORTC Item Library • Overall side-effect bother measured by PGI-TT at each time point in each treatment arm
To assess differences in physical function among participants treated with T-DXd alone or in sequence with THP relative to ddAC-THP	Physical function assessed by the EORTC QLQ-C30 Physical Function Scale. The measure of interest will be the proportion of participants who have maintained or improved physical functioning while on neoadjuvant treatment, as measured by EORTC QLQ-C30 at each time point in each treatment arm
To investigate the immunogenicity of T-DXd	Number and percentage of participants who develop ADAs for T-DXd
To assess the PK of T-DXd	Serum concentration of T-DXd, anti-HER2 antibody, and DXd

ADA = anti-drug antibody; AE = adverse event; ddAC-THP = doxorubicin + cyclophosphamide followed by paclitaxel + trastuzumab + pertuzumab; EFS = event-free survival; EORTC = European Organisation for the Research and Treatment of Cancer; HER2 = human epidermal growth factor receptor 2; H&E = haematoxylin & eosin; IDFS = invasive disease-free survival; OS = overall survival; pCR = pathological complete response; PGI-TT = Patient Global Impression of Treatment Tolerability; PK = pharmacokinetics; PRO = patient-reported outcome; PRO-CTCAE = patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-C30 = 30 item core quality of life questionnaire; T-DXd = trastuzumab deruxtecan; THP = paclitaxel + trastuzumab + pertuzumab; ypT0 ypN0 = absence of invasive and in situ cancer in the breast and axillary node.

1.1.3 Safety Objectives

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

Table 3 Safety objective and corresponding endpoints/estimands

Safety objective:	Endpoints/estimands:
To assess the safety and tolerability profile of T-DXd alone or in sequence with THP as compared with ddAC-THP	• Safety and tolerability will be evaluated in terms of occurrence of AEs, SAEs and changes from baseline in vital signs, clinical laboratory results, ECGs, and ECHO/MUGA. • Heart failure will be evaluated by determining the percentage of participants with NYHA Class III and IV heart failure during the neoadjuvant treatment period (pre- and post-surgery) and at end of study (maximum 6 years' follow-up). • Decreases in LVEF (requires at least 2 consecutive readings of decline) will be evaluated by determining the percentage of participants with decreases in LVEF of at least 10 points from baseline and to below 50% during neoadjuvant treatment period (pre- and post-surgery)

AE = adverse event; ddAC-THP = doxorubicin + cyclophosphamide followed by paclitaxel + trastuzumab + pertuzumab; ECG = electrocardiogram; ECHO = echocardiogram; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition; NYHA = New York Heart Association; SAE = serious adverse event; T-DXd = trastuzumab deruxtecan; THP = paclitaxel + trastuzumab + pertuzumab.

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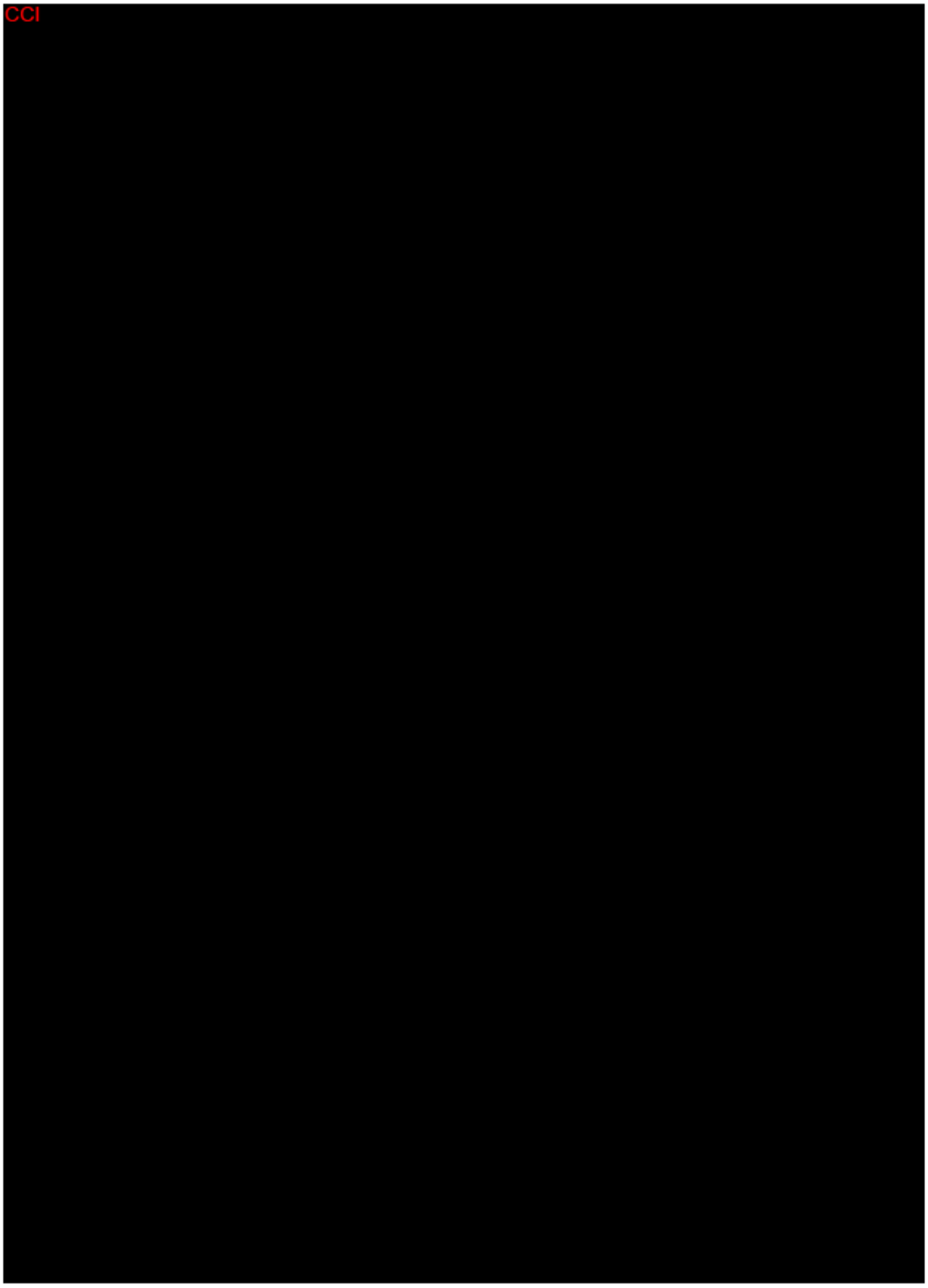

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1.2 Study Design

This is a Phase III open-label, multi-centre, randomised 3-arm study to determine the efficacy and safety of trastuzumab deruxtecan (T-DXd) monotherapy or T-DXd followed by paclitaxel + trastuzumab + pertuzumab (THP) as neoadjuvant treatment compared to doxorubicin + cyclophosphamide followed by paclitaxel + trastuzumab + pertuzumab (ddAC-THP) in patients with locally advanced or inflammatory human epidermal growth factor receptor 2-positive (HER2-positive), high-risk early breast cancer (EBC).

Approximately 900 patients will be randomised 1:1:1 to receive one of the following treatments, all with intravenous (IV) infusion:

Arm A: T-DXd (5.4 mg/kg every 3 weeks [Q3W]) for 8 cycles.

Arm B: T-DXd (5.4 mg/kg Q3W) for 4 cycles followed by paclitaxel (80 mg/m2 QW on Days 1, 8, and 15) concurrent with trastuzumab (6 mg/kg Q3W on Day 1) and pertuzumab (840 mg loading dose followed by 420 mg Q3W on Day 1) × 4 cycles.

Arm C: Doxorubicin (60 mg/m2 Q2W) and cyclophosphamide (600 mg/m2 Q2W) × 4 cycles followed by paclitaxel (80 mg/m2 QW on Days 1, 8, and 15) concurrent with trastuzumab (8 mg/kg loading dose followed by 6 mg/kg Q3W on Day 1) and pertuzumab (840 mg loading dose followed by 420 mg Q3W on Day 1) × 4 cycles.

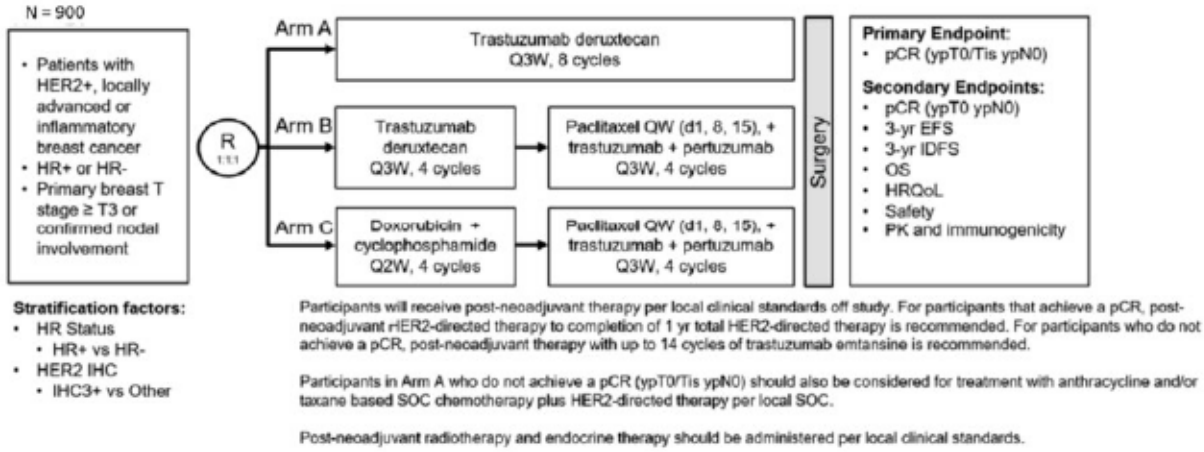
Note: For doxorubicin and cyclophosphamide, 1 cycle equates to 2 weeks. For all other treatments a cycle is 3 weeks.

Patients will be stratified according to hormone receptor (HR) status (oestrogen receptor [ER] and/or progesterone receptor [PgR] positive vs ER and PgR negative) by local assessment and central assessment of HER2-positive status (immunohistochemistry [IHC] 3+ vs other, where 'other' is defined as in situ hybridisation [ISH]+ in the absence of IHC3+ status). Patients will need to provide a tumour tissue sample at screening (newly acquired or archived sample < 6 weeks old) which will be sent to a central laboratory for HER2 status confirmation.

Eight cycles of neoadjuvant therapy will be administered for a total of 24 weeks (Arm A and Arm B) or 20 weeks (Arm C). In the event of disease progression, unacceptable toxicity, withdrawal of consent or study termination by the Sponsor, neoadjuvant therapy will be discontinued.

For an overview of the study design, see Figure 1.

Figure 1 Study design



d = day; EFS = event-free survival; HER2 = human epidermal growth factor receptor 2; HRQoL = health-related quality of life; HR = hormone receptor; IDFS = invasive disease-free survival; IHC = immunohistochemistry; OS = overall survival; pCR = pathological complete response; PK = pharmacokinetics; QW = once a week; Q2W = every 2 weeks; Q3W = every 3 weeks; R, randomisation; SOC = standard of care; ypT0/Tis ypN0 = absence of invasive cancer in the breast and axillary nodes; ypT0 ypN0 = absence of invasive and in situ cancer in the breast and axillary nodes.

From 13 March 2024 onwards, patients will be randomised in a 1:1 ratio to Arm B and Arm C. Patients already randomised to Arm A and still ongoing study treatment can continue on assigned study treatment (provided the investigator agrees it is in the best interest of the participant) and continue scheduled trial procedures until trial completion or any discontinuation criterion is met. Alternatively, patients can discontinue study treatment and receive investigator's choice of local standard of care. Patients randomised to Arm A who have not initiated treatment by 13 March 2024 will receive investigator's choice of local standard of care.

1.3 Number of Subjects

Approximately CCI patients will be screened to achieve 900 randomised patients with HER2-positive EBC for the assessments of pathological complete response (pCR). Eligible patients will be randomised 1:1:1 to either T-DXd monotherapy (Arm A), T-DXd followed by THP (Arm B), or ddAC-THP (Arm C). The randomisation will be stratified by HR status (ER and/or PgR positive vs ER and PgR negative) and central assessment of HER2-positive status (IHC 3+ vs other; where other is defined as ISH+ in the absence of IHC 3+ status).

The study is powered to demonstrate superiority of T-DXd monotherapy (Arm A) or T-DXd followed by THP (Arm B) versus ddAC-THP (Arm C), as assessed by pCR rate, in patients with locally advanced or inflammatory HER2-positive, high-risk EBC. If the true pCR rate in Arm C is CC %, the primary analysis will provide at least CCI % power to

demonstrate statistical significance regarding a CCI % improvement in pCR rates with either active treatment, at an overall CCI % alpha level (2-sided) for the primary endpoints. The data cut-off for the primary analysis for the primary pCR endpoint is expected approximately 39 months after the first participant is randomised, assuming a CCI -month recruitment period.

CCI [redacted]

Sample size estimates and the power of the study for the analysis of pCR have been calculated using EAST 6.5. The probability of observing a positive/negative trend in terms of EFS hazard ratio was calculated using R-4.1.0. For the multiple testing procedure refer to Section 4.2.1.

Note: From 13 March 2024 onwards, patients will be randomised in a 1:1 ratio to Arm B and Arm C. After this date no patient will be randomised to Arm A. The main analyses of primary and secondary efficacy endpoints will still follow the intention to treat principle i.e. all the efficacy analyses will be conducted for the full analysis set (FAS) (see Section 2.1.1 for the definition of FAS). Similarly, all safety endpoints will be analysed based on the safety analysis set (SAF).

2 ANALYSIS SETS

2.1 Definition of Analysis Sets

There are 9 analysis sets defined for this study. A summary of analysis sets that will be used to summarise various study data is provided in Table 5.

Table 5 Summary of outcome variables and analysis populations

Outcome variable	Analysis set
Efficacy Data	
pCR (ypT0/Tis ypN0)	Full analysis set
pCR (ypT0 ypN0), EFS, OS, , CCI	Full analysis set
CCI [redacted]	

Outcome variable	Analysis set
IDFS	Resected analysis set
HRQoL: EORTC QLQ-C30	Full analysis set
CCI	CCI
Futility analysis pCR (ypT0/Tis ypN0) and EFS.	Modified FAS - futility analysis set
CCI	
RCB	Full analysis set
Study Population/Demography Data	
Demography	Full analysis set
Baseline and disease characteristics	Full analysis set
Important deviations	Full analysis set
Medical/surgical history	Full analysis set
Previous anti-cancer therapy	Full analysis set
Concomitant medications/procedures	Full analysis set
Subsequent anti-cancer therapy	Full analysis set
Futility analysis demography and baseline characteristics	Modified FAS - futility analysis set
PK/Immunogenicity Data	
PK data	PK analysis set
ADA data	ADA evaluable set
Safety Data	
Exposure	Safety analysis set
CCI	
PRO-CTCAE, PGI-TT, EORTC Item Library items, and the EORTC QLQ-C30 Physical Function subscale	Safety analysis set
HcRU	Safety analysis set
AEs	Safety analysis set

Outcome variable	Analysis set
Vital signs	Safety analysis set
Laboratory measurements	Safety analysis set
ECGs	Safety analysis set
Futility analysis exposure and AEs	Modified SAF - futility analysis set

ADA = anti-drug antibody; AE = adverse event; CCI ; CCI CCI ECG = electrocardiogram; EFS = event-free survival; EORTC = European Organisation for the Research and Treatment of Cancer; CCI HcRU = healthcare resource use; HRQoL = health-related quality of life; IDFS = invasive disease-free survival; MRI = magnetic resonance imaging; CCI ; OS = overall survival; pCR = pathological complete response; PGI-TT = Patient Global Impression of Treatment Tolerability; PK = pharmacokinetics; PRO-CTCAE = patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-C30 = 30 item core quality of life questionnaire; RCB = residual cancer burden; CCI ; ypT0/Tis ypN0 = absence of invasive cancer in the breast and axillary nodes; ypT0 ypN0 = absence of invasive and in situ cancer in the breast and axillary node.

2.1.1 Full analysis set (FAS)

The FAS will include all randomised patients. Treatment groups will be compared on the basis of randomised study intervention, regardless of the treatment actually received. Patients who were randomised but did not subsequently receive study treatment are included in the FAS in the treatment group to which they were randomised. The analysis of data using the FAS therefore follows the principles of intention to treat (ITT).

The FAS will be used for all primary and secondary efficacy analyses except the invasive disease-free survival (IDFS) analysis.

2.1.2 Resected analysis set

The resected analysis set will include all randomised patients in the FAS who had surgical resection following neoadjuvant treatment and who do not have positive margins. Patients with margins that cannot be determined will also not be included.

The resected analysis set will be used for the IDFS endpoint.

2.1.3 Safety analysis set (SAF)

The SAF will consist of all randomised patients who receive any amount of study treatment (at least 1 of T-DXd, paclitaxel, trastuzumab, pertuzumab, doxorubicin, or cyclophosphamide). Safety data will not be formally analysed but summarised using the safety analysis set.

Patients who initially received a dose of study treatment will be summarised according to the arm to which they were randomised. This is in order to provide a summary of the underlying safety profile that patients should expect when initially prescribed treatment (i.e., T-DXd, T-DXd followed by THP, ddAC followed by THP).

2.1.4 PK analysis set

The pharmacokinetic (PK) analysis set will consist of all patients randomly assigned to study intervention who take at least 1 dose of T-DXd therapy per protocol and have any post-dose PK data available.

2.1.5 Modified full analysis set - Futility analysis set

The modified full analysis set for futility analyses comprises of the subset of patients included in the FAS who were randomised at least 296 days prior to FA data cut-off (DCO) and had the opportunity to be assessed for pCR or were unable to undergo surgery for any reason. The 296 days accounts for treatment duration, time to surgery and approximately 2 months for central pCR assessment.

2.1.6 Modified safety analysis set - Futility analysis set

The modified safety analysis set for futility analyses will consist of the modified FAS - Futility analysis set with the additional criterion that a patient needs to satisfy the criterion for safety analysis set i.e. patients must have received at least one dose of any of the study treatment (T-DXd, paclitaxel, trastuzumab, pertuzumab, doxorubicin or cyclophosphamide). Please refer to section 2.1.3 for more details on safety analysis set.

2.1.9 ADA evaluable set

The ADA evaluable set will consist of all patients who receive at least one dose of T-DXd who have a non-missing ADA result at any time. All major ADA analyses will be based on the ADA evaluable set.

2.2 Protocol Deviations

The following general categories will be considered important protocol deviations (IPDs) and will be programmatically identified within the clinical database, and/or identified by Source Data Review, and confirmed by medical review. These will be listed and discussed in the clinical study report (CSR) as appropriate:

- Patients who deviate from key entry criteria per the CSP. These are: inclusion criteria 1, 2(a), 2(c), 2(d), 2(e), 2(f), 3, 4, 5, 6 and exclusion criteria 1-7, 9-16, 19, 21-24, 27.
    - Discontinuation criteria for study product met but patient not withdrawn from study treatment.
    - Investigational Product (IP) deviation:
        - Patients randomised who received their randomised study treatment at an incorrect dose or received an alternative study treatment to that which they were randomised or received expired study treatment.
    - IP non-compliance
        - Received prohibited concomitant medications (including other anti-cancer agents). Please refer to the CSP Appendix I 2 for those medications that are detailed as being 'excluded' from permitted use during the study. This will be used as a guiding principle for the physician review of all medications prior to database lock.
- Failure to perform the following mandatory safety assessments in >=2 consecutive scheduled visit windows where assessment is expected: pulmonary assessments, haematology and/or clinical chemistry panel, electrocardiogram (ECG), echocardiogram (ECHO) or multigated acquisition scan (MUGA) or high resolution computed tomography (HRCT).
    - Other important deviations:
        - Any deviation that, in view of the Study Team, significantly compromises patient safety, study integrity, regulatory compliance or clinical trial compliance and were not prespecified in the protocol deviation plan.

  - Failure to collect samples for central pCR assessment. This includes if incomplete samples were sent to central lab, resulting in inability to appropriately conduct the pCR assessment.

  - Missing principal investigator (PI) or delegated signatures in eCRF for interim and/or final Clinical Data Lock

- Patients who receive the wrong treatment at any time will be included in the safety analysis set as described in Section 2.1. During the study, decisions on how to handle errors in treatment dispensing (with regard to continuation/discontinuation of study treatment or, if applicable, analytically) will be made on an individual basis with written instruction from the study team leader and/or statistician.

The IPDs will be listed and summarised by randomised treatment group. None of the deviations will lead to patients being excluded from the analysis sets described in Section 2.1.

A per-protocol analysis excluding patients with specific important protocol deviations is not planned; however, a 'deviation bias' sensitivity analysis may be performed on the pCR rate (ypT0/Tis ypN0) endpoint excluding patients with deviations that may affect the efficacy of the trial therapy if >10% of patients, which include the following deviations: inclusion criteria 2(a), 2(c), 2(d), 2(e), 2(f) and exclusion criteria 1, 2, 3, 14, 15, 16, 19, 23, 24.

The need for such a sensitivity analysis will be determined following review of the protocol deviations ahead of database lock and will be documented prior to the primary analysis being conducted.

In addition to the programmatic determination of the deviations above, other study deviations captured from the CRF module for inclusion/exclusion criteria will be tabulated and listed. Any other deviations from monitoring notes or reports will be reported in an appendix to the CSR.

3 PRIMARY, SECONDARY AND EXPLORATORY VARIABLES

3.1 Primary and Secondary Efficacy Variables

3.1.1 Pathological complete response (pCR): ypT0/Tis ypN0

Pathological complete response (pCR) (ypT0/Tis ypN0) is defined as having no evidence by haematoxylin and eosin (H&E) staining of residual invasive disease in the complete resected breast specimen and all sampled regional lymph nodes as assessed by central

evaluation on completion of neoadjuvant treatment. pCR rate is the proportion of patients who achieve pCR. Surgical specimens will be assessed by central pathology laboratory in accordance with a pathology review manual.

The following cases would be classified as no pCR in the primary analysis:

- Patients who discontinue study treatment, receive a subsequent neoadjuvant cancer treatment, and then achieve pCR
- Patients who have disease progression or die from any cause prior to surgery
- Patients with no valid records regarding pCR status due to any reason (including but not limited to withdrawal from the study, progressive disease or death before surgery, lack of surgical specimen or defined as not evaluable by the central pathologist)
- Any other randomised patients without evidence of pCR.

3.1.2 Pathological complete response (pCR): ypT0 ypN0

pCR (ypT0 ypN0) is defined having no evidence by H&E staining of residual invasive disease and in situ cancer in the complete resected breast specimen and all sampled regional lymph nodes as assessed by central evaluation on completion of neoadjuvant treatment. Surgical specimens will be assessed by central pathology laboratory in accordance with a pathology review manual in the same way as for the primary definition of pCR.

Definitions for responders and non-responders are the same as for the primary definition of pCR (see Section 3.1.1).

3.1.3 Event-free survival

Event-free survival (EFS) is defined as the time from date of randomisation until an event occurs (i.e., date of event or censoring – date of randomisation + 1). An event is defined as the earliest of:

- First documented disease progression that precludes initial surgery
- First evidence of documented invasive disease recurrence (local, regional, distant, or contralateral) post-surgery based on local assessments (Note: ductal carcinoma in situ, lobular carcinoma in situ and second primary non-breast cancers are not counted as events). See Table 6 of the CSP for events which qualify as disease recurrence

- Death due to any cause (event date is the date of death)

The EFS time will always be derived based on assessment dates (i.e. date of imaging scans or local pathology samples) and not on visit dates.

Positive margins in the surgical sample do not count as an event for EFS. Patients will be followed until an event regardless of whether the patient withdraws from therapy or receives a subsequent anti-cancer therapy.

Any patient without an event at the time of analysis will be censored at the last assessment date on which they were known to be alive and event-free. If the patient has surgery they will be censored at the date of surgery unless the patient dies, progresses or experiences recurrent disease following the date of surgery. If the patient has no evaluable disease assessments at baseline or post baseline, they will be censored at randomisation date unless they die in the period prior to surgery, in which case they will be treated as having an event at the death date.

Table 6 Events and censoring for EFS

Situation	Event or censored	Event date/censored date
No baseline or no post-baseline assessments, did not progress and did not die prior to surgery	Censored	Randomisation date (Study Day 1)
Disease progression that precludes surgery	Event	Date of progression*
Recurrence (local, regional, distant or contralateral) after surgery	Event	Date of recurrence**
No documented disease progression that precludes surgery nor recurrence, death due to any cause	Event	Date of death
No documented disease progression that precludes surgery nor recurrence nor death due to any cause	Censored	Last assessment date on which the patient was known to be alive and without an event

* Date of progression (BCSURG module) is the earliest date when a patient is unable to undergo surgery due to investigators' assessed progression.
** Date of recurrence (DISREC module) is the earliest date with an assessment of invasive disease recurrence (local, regional, distant or contralateral breast cancer).

The proportion of patients alive and event-free at 36 months (EFS36) will be defined as the Kaplan-Meier (KM) estimate of EFS at 36 months after randomisation.

3.1.4 Invasive disease-free survival

IDFS is defined as the time from surgery until the earliest of invasive disease recurrence (local, regional, distant, or contralateral) based on local assessments, or death from any cause (i.e., date of event or censoring – date of surgery + 1). The primary analysis of IDFS will be based on the resected analysis set. Patients with positive margins in the surgical sample will not count as disease-free after surgery, and therefore will be excluded from IDFS analysis. Patients with margins which cannot be determined will also be excluded from IDFS analysis.

Patients will be followed until an event regardless of whether the patient withdraws from therapy or receives a subsequent anti-cancer therapy. Any patient without an event will be censored at the last recorded date on which they were known to be alive and invasive disease-free after the surgical resection date.

Table 7 Events and censoring for IDFS

Situation	Event or censored	Event date/censored date
Invasive disease recurrence (local, regional, distant or contralateral) after surgery	Event	Date of recurrence
No documented disease progression, death due to any cause	Event	Date of death
No documented disease progression or death	Censored	Last assessment date after surgery on which the patient was known to be alive and without an event
No documented disease progression or death and no evaluable assessment after surgery	Censored	Date of surgery

The proportion of patients alive and invasive disease-free at 36 months (IDFS36) will be defined as the KM estimate of IDFS at 36 months post-surgery.

3.1.5 Overall survival

Overall survival (OS) is defined as the time from randomisation until death due to any cause (i.e., date of death or censoring – date of randomisation + 1), regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive (SUR_DAT, recorded within the SURVIVE module of the eCRF).

The proportion of patients alive at 36 months (OS36) will be defined as the KM estimate of OS at 36 months after randomisation.

Survival calls will be made following the date of DCO for each analysis timepoint where OS will be assessed. These should generally occur within 7 days of DCO. If patients are confirmed to be alive, or if the death date is after the DCO date, these patients will be censored at the date of the DCO. The status of ongoing, withdrawn (from the study), and "lost to follow-up" patients at the time of the final OS analysis should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patient's general practitioner, and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources, where it is possible to do so, as applicable by local laws.

For any OS analysis performed prior to DCO, in the absence of survival calls being made, it may be necessary to use all relevant CRF fields to determine the last recorded date on which the patient was known to be alive for those patients . The last date for each individual patient where SURVIVE is not completed is defined as the latest among the following dates (Note: complete dates without imputation) recorded on the CRFs:

- AE start and stop dates, AE grade change dates
- Admission and discharge dates of hospitalisation
- Study treatment date
- End of treatment date
- Laboratory test dates
- Date of vital signs
- Tumour imaging assessment date
- Start and stop dates of alternative anti-cancer treatment
- PRO assessment date
- Overdose date
- ECG date

- Left ventricular ejection fraction (LVEF) date
- Date of pulmonary function test
- Date of ophthalmologic assessment
- Date of physical examination
- Date of examination for interstitial lung disease (ILD)/pneumonitis (ILDIS module of CRF) and AE start date and ILD onset dates (ADJAEILD from Adjudication Committee)
- Date of Eastern Cooperative Oncology Group (ECOG) performance status assessment
- Date of sampling for PK analysis
- Date of T-DXd anti-drug antibody (ADA) assessment
- Date of biopsy
- Baseline disease assessment dates
- Disease assessment dates on disease recurrence CRF
- Assessment dates and surgery dates on breast cancer surgery CRF
- Start and stop dates of concomitant medications, concomitant procedures, palliative and post-treatment radiotherapy and subsequent cancer therapies
- Visit dates
- Date of informed consent withdrawal
- End of study date

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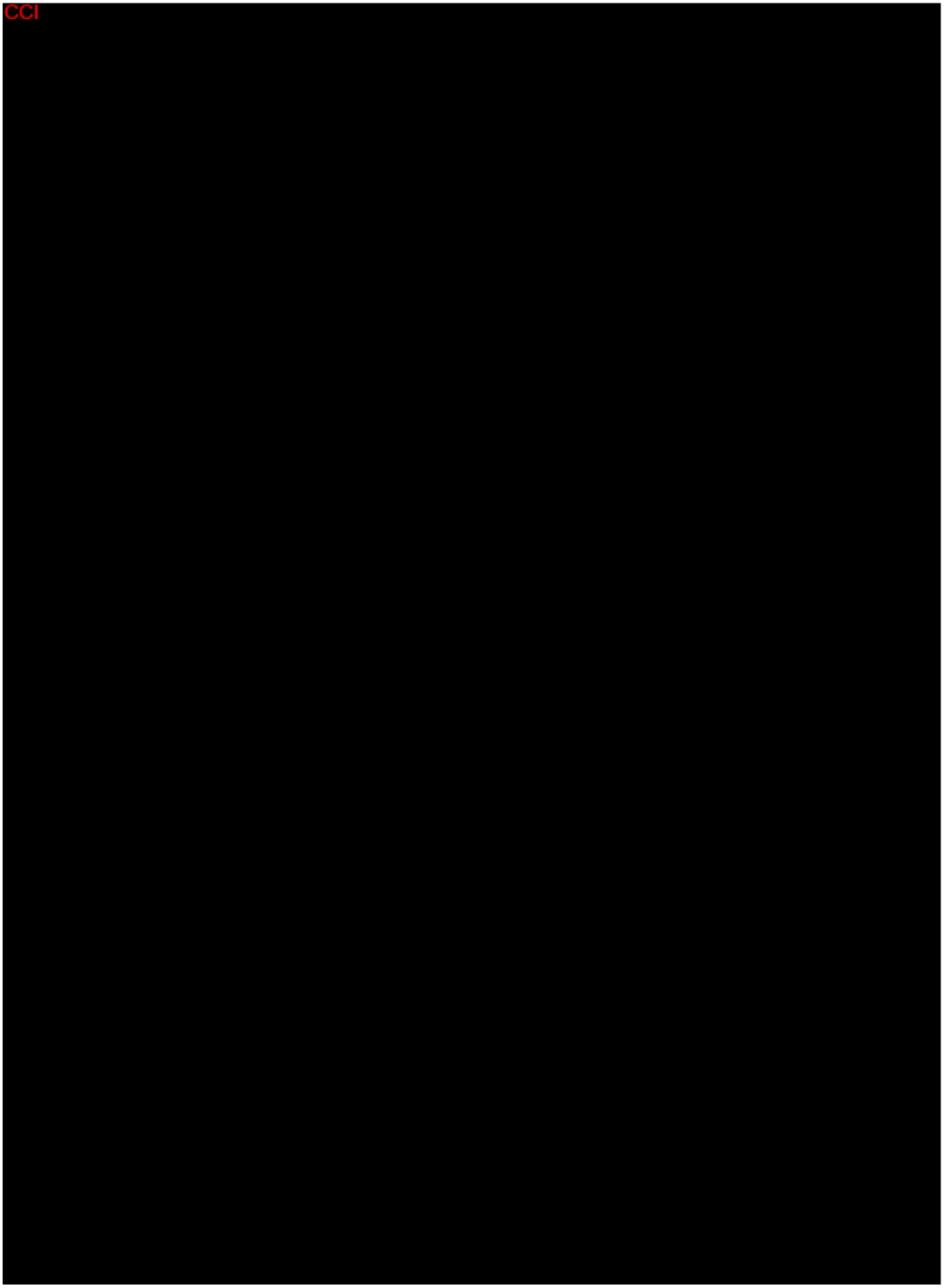
[redacted]

3.2.4 Residual Cancer Burden

The Residual Cancer Burden (RCB) is a categorised score based on the residual viable tumour identified on routine H&E staining after mapping of the surgical specimen (Symmans, et al., 2007). The categories are 0, I, II and III.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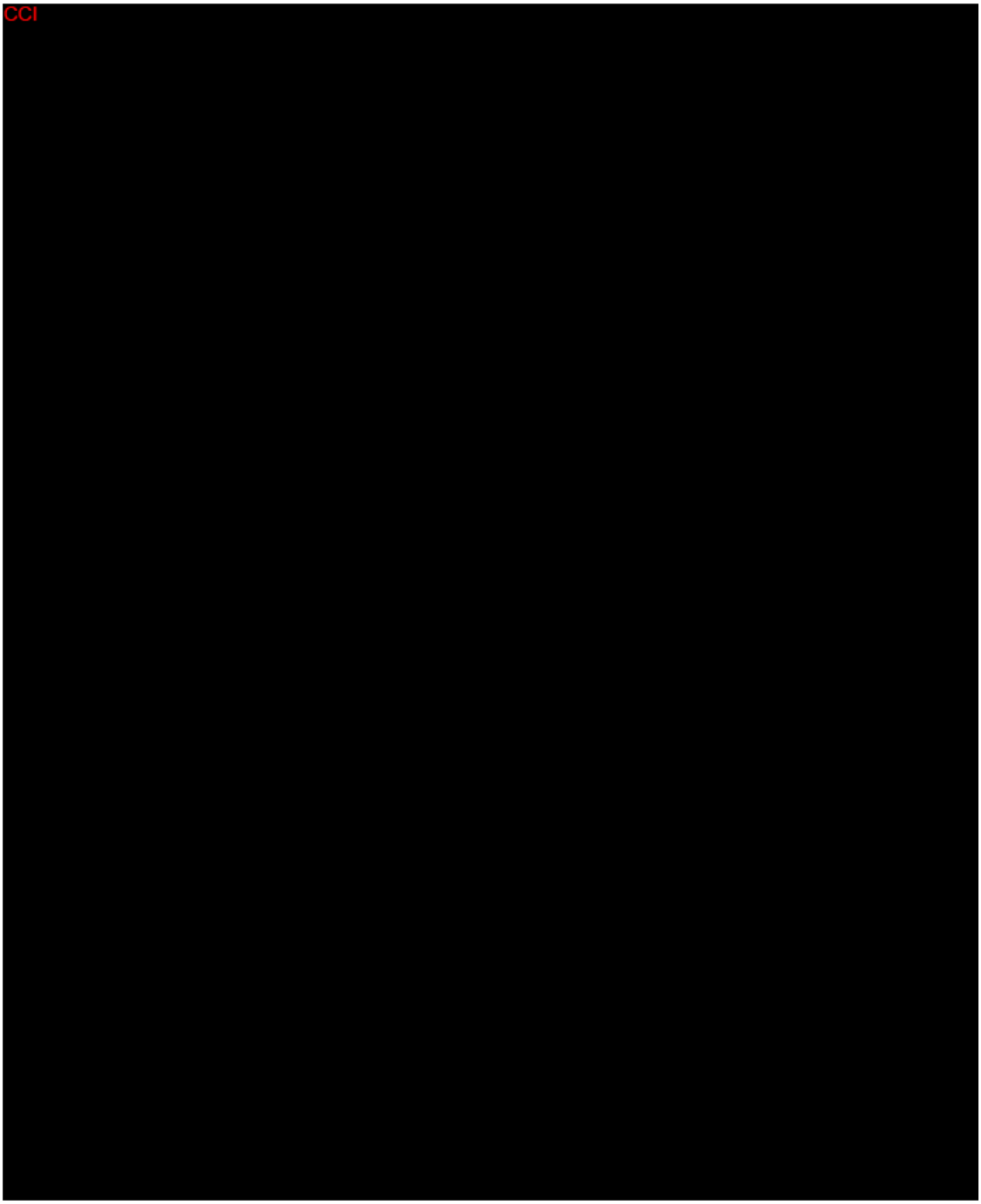
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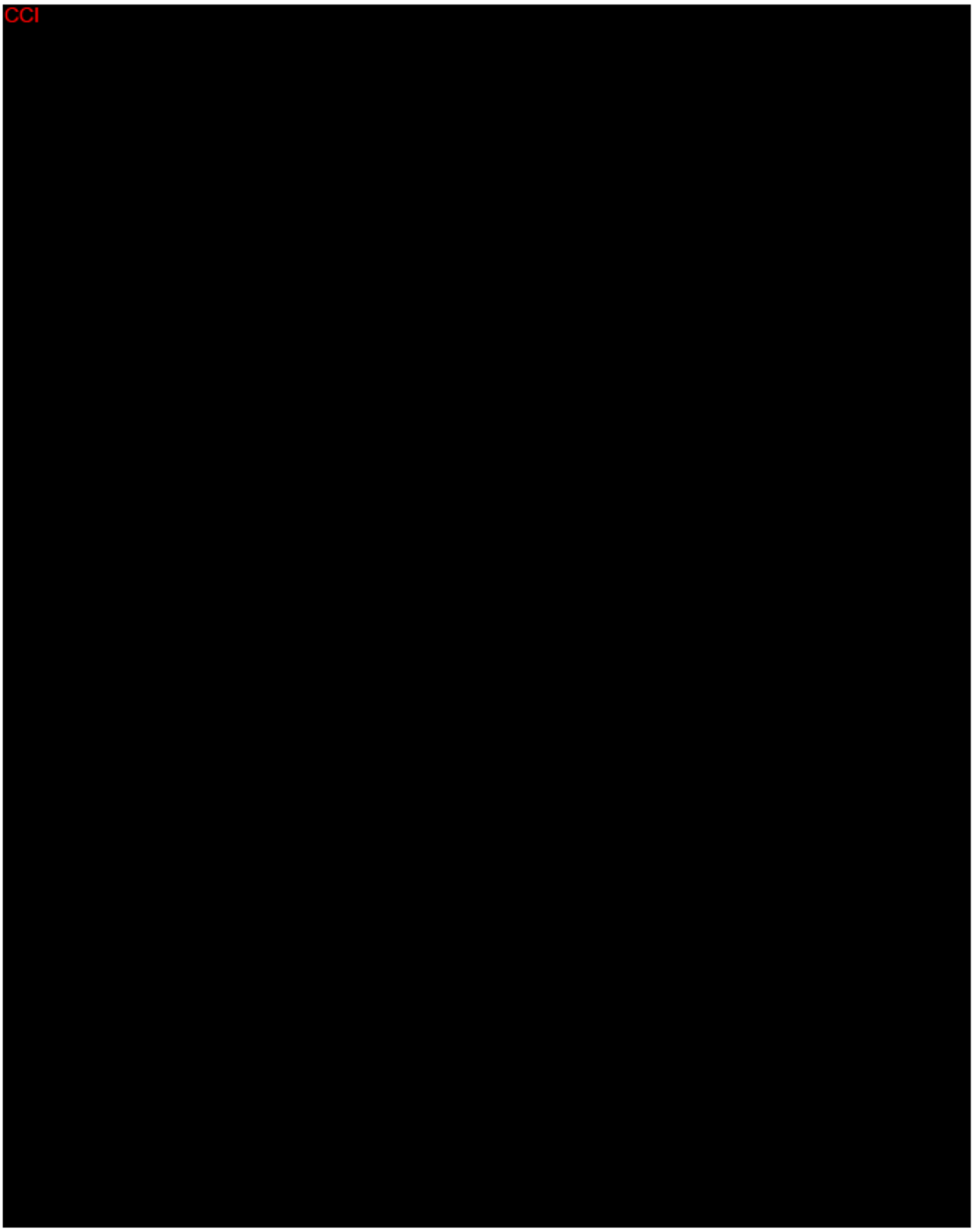
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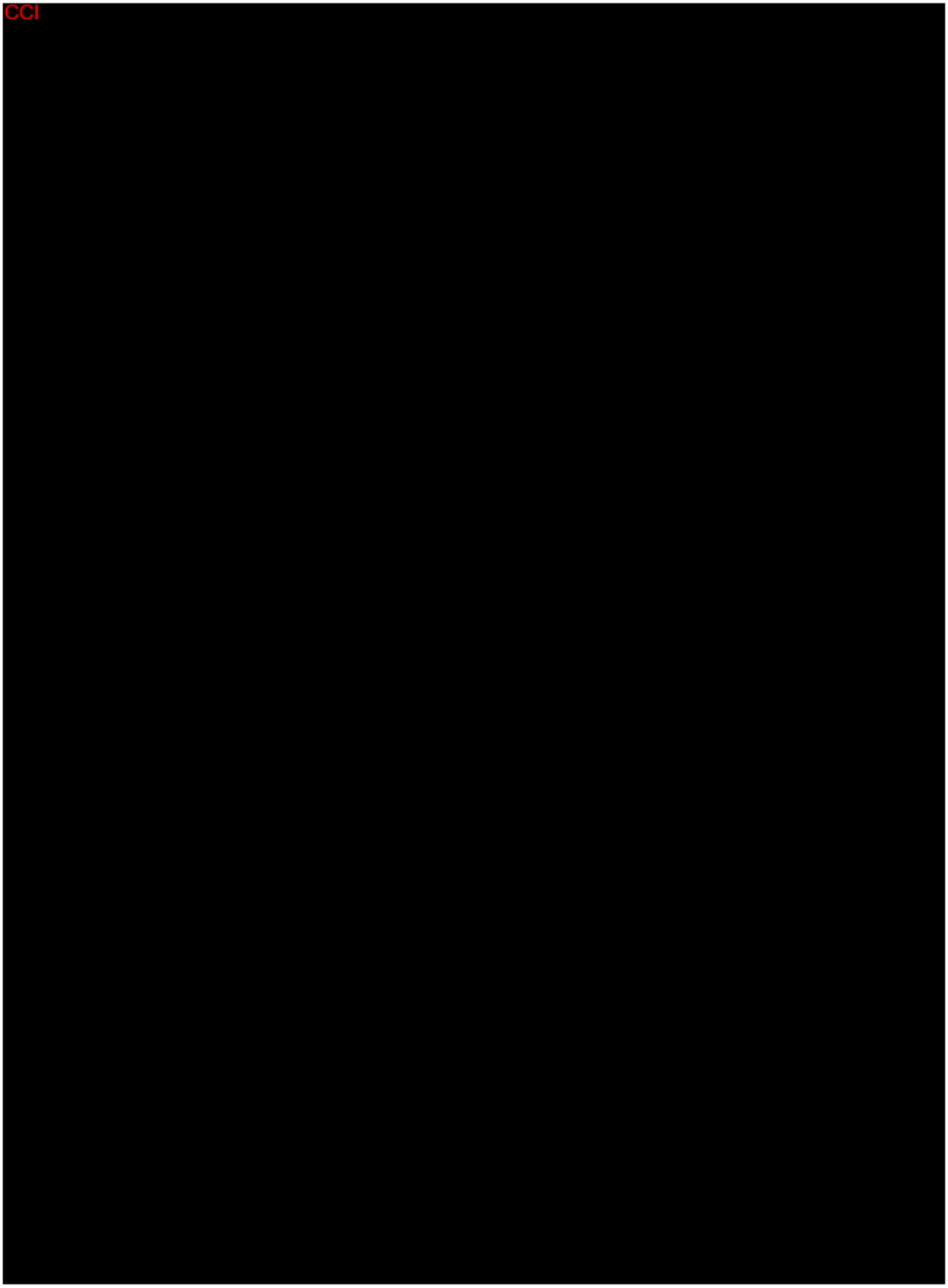

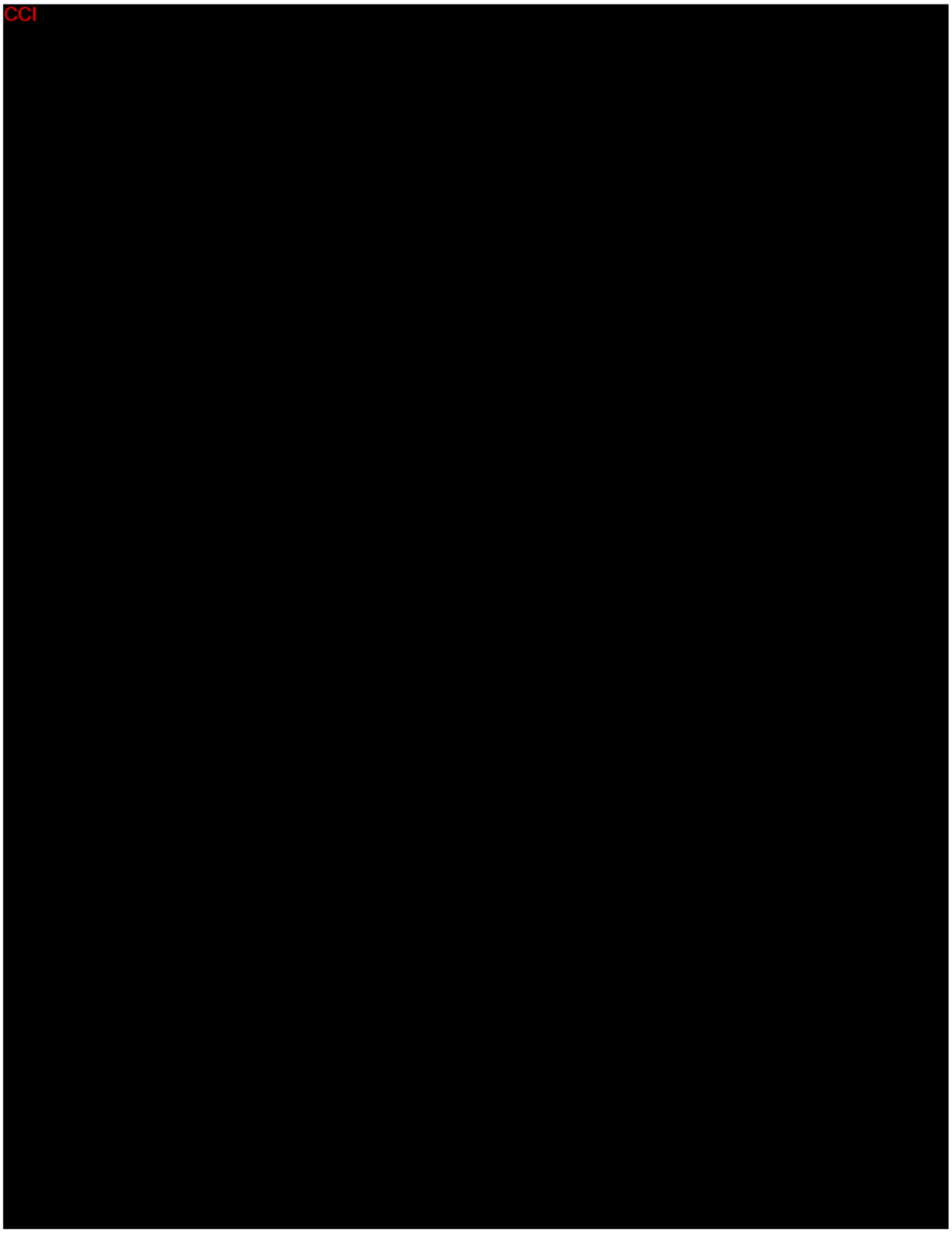
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3.3.4 Independent review

All radiological scans for all patients (including those at unscheduled visits, or outside visit windows) will be collected on an ongoing basis and sent to an AstraZeneca appointed Contract Research Organisation (CRO) for a potential central analysis. A blinded independent central review (BICR) of all radiological imaging data may be carried out using RECIST version 1.1.

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

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

3.4 Patient Reported Outcome (PRO) Variables

Patients will perform the Patient Reported Outcome (PRO) assessments using an electronic device (ePRO), administered in accordance with Table 7 and Table 8 of the CSP. The following PRO instruments will be administered in this study: the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), Patient Global Impression of Treatment Tolerability (PGI-TT), European Organisation for Research and Treatment of Cancer (EORTC) Item Library short forms

(123, 125, 124 and 19), EORTC 30-item core quality of life questionnaire (QLQ-C30), and CCI

PROs will be provided in the native language of the country in which it is administered. In the case that a linguistically validated version is not available, the PRO will not be administered.

All items/questionnaires will be scored according to developer-defined guidelines if available, otherwise raw item-level values will be used, as detailed below.

3.4.1 Patient-reported tolerability outcomes

3.4.1.1 Overall side effect bother

The patient's evaluation of treatment tolerability as measured by the PGI-TT will be described in graphical and/or tabular format. Counts and percentages for the response options of: "not at all", "a little bit", "somewhat", "quite a bit", and "very much" may be reported.

3.4.1.2 Symptomatic adverse events

Patient-reported symptomatic adverse events (AEs) will be described in graphical and/or tabular format using items from the PRO-CTCAE library, the EORTC Item-Library (EORTC-IL123 and EORTC-IL124), and select symptom items from the EORTC QLQ-C30 v3. These analyses will be performed on the same core set of symptom items over time, which includes instances where the same symptom item is administered within a different instrument/form at complementary timepoints. For example, the same EORTC nausea item ("Have you felt nauseated?") is administered within the full EORTC QLQ-C30 instrument and within EORTC IL124 at distinct timepoints. As a result, patient-reported nausea will be reported based on that single item over time irrespective of the instrument that was administered to patients.

The following symptomatic AEs will be reported:

		EORTC Form				PRO-CTCAE Form	
Symptom	**Item** *(or PRO-CTCAE Attribute*)*	QLQ-C30	IL123	IL124	IL125	PRO-CTCAE v1	PRO-CTCAE v2
Dyspnoea	Were you short of breath?	X		X	X		
Fatigue (Item 1)	Did you need to rest?	X		X	X		
Fatigue (Item 2)	Have you felt weak?	X		X	X		
Appetite Loss	Have you lacked appetite?	X		X			
Nausea	Have you felt nauseated?	X		X			

		EORTC Form				PRO-CTCAE Form	
Symptom	**Item** *(or PRO-CTCAE Attribute*)*	QLQ-C30	IL123	IL124	IL125	PRO-CTCAE v1	PRO-CTCAE v2
Vomiting	Have you vomited?	X		X			
Constipation	Have you been constipated?	X		X			
Diarrhoea	Have you had diarrhoea?	X		X			
Fatigue (Item 3)	Were you tired?	X		X	X		
Cough	Have you coughed?		X	X	X		
Chest Pain	Have you had pain in your chest?		X	X	X		
Mouth/throat sores	S, I					X	
Taste Changes	S					X	X
Rash	P					X	
Hair Loss	A					X	
Numbness or tingling	S, I					X	X
Headache	F, S, I					X	
Muscle Pain	F, S, I					X	X
Joint Pain	F, S, I					X	X
Insomnia	S, I					X	
Hot Flashes	F, S					X	
Nosebleed	F, S					X	

* PRO-CTCAE attribute refers to the specific items (aka questions) used to assess that symptom. The number of attributes also indicates the number of items for that symptom. *Example: Mouth sores is labelled S and I, meaning there is 1 question about the severity of the symptom, and a second question about the interference from that symptom. Thus, there are 2 total items for that symptom.*
A Amount; F Frequency; I Interference; P Presence; S Severity.
Note: Blue (IL124 and PRO-CTCAE v1) – Collected from C1D1 through to End of Treatment and Safety follow-up; Green (IL125 and PRO-CTCAE v2) – Collected during long-term follow-up; Purple (QLQ-C30/IL123) – collected both on treatment and during long-term follow-up.

Definition of Clinically Meaningful Change in EORTC QLQ-C30

Changes in score compared to baseline will be evaluated. A minimum clinically meaningful change is defined as a change in the score from baseline of ≥10 for scales/items from the EORTC QLQ-C30 (Osoba, Rodrigues, Myles, Zee, & Pater, 1998). For example, a clinically meaningful improvement in physical function (as assessed by EORTC QLQ-C30) is defined as an increase in the score from baseline of ≥10, whereas a clinically meaningful deterioration is defined as a decrease in the score from baseline of ≥10. At each post-baseline assessment, change in symptoms/functioning from baseline will be categorised as improvement, deterioration or maintained as shown in Table 12.

Table 12 Clinically Meaningful Changes in EORTC QLQ-C30 Scale Scores

Score	Change from Baseline	Visit Response
Symptom scales/items [a]	≥ +10	Deterioration
	≤ -10	Improvement
	Otherwise	Maintained
Functional scales and global health status/QoL	≥ +10	Improvement
	≤ -10	Deterioration
	Otherwise	Maintained

EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; QoL = quality of life.
[a] Including the item on the financial impact of the disease.

3.4.2 Maintained or improved physical function

Differences in physical function among participants treated with T-DXd alone (Arm A) or in sequence with THP (Arm B) relative to ddAC-THP (Arm C) will be summarised based on data collected from the Physical Functioning Score (items 1-5) of the EORTC QLQ-C30 or the EORTC IL19, where applicable. The scoring algorithm used to generate the physical function score for the EORTC QLQ-C30 will also be applied to the EORTC IL19.

The measure of interest will be the proportion of patients who have maintained or improved physical functioning, as defined with the thresholds in Table 12, while on neoadjuvant treatment, as measured by EORTC QLQ-C30/EORTC IL19 at each time point in each treatment arm.

3.4.3 Time to deterioration

Time to deterioration for each of the symptom, function and global health status/QoL scales in the EORTC QLQ-C30 will be defined as the time from randomisation until date of first clinically meaningful symptom deterioration (as defined in Table 12) that is confirmed at a subsequent assessment at least 14 days apart, regardless of whether a patient withdraws from study treatment or receives another anti-cancer therapy prior to symptom deterioration. Patients with a single deterioration and no further assessments will also be treated as deteriorated in the analysis.

Patients whose symptom, function or global health status/QoL have not shown a clinically meaningful deterioration and who are alive at the time of analysis will be censored at the time that their last symptom, function or global health status/QoL assessment could be evaluated. Also, in the case of first confirmed deterioration after 2 or more consecutive

missed PRO assessment visits (i.e., date from last PRO assessment prior to 2 or more consecutive missed PRO assessment visit minus date of first confirmed deterioration ≥62 days), the patient will be censored at the time of the last PRO assessment where the score could be evaluated prior to 2 or more consecutive missed visits. If the patient has no evaluable visits, does not have baseline data, does not have post-baseline data, or has a baseline score that will not allow for a 10-point deterioration (baseline score > 90 for pain symptom scale and < 10 for functional and global health status/QoL scales), they will be censored at Day 1 (randomisation date).

Time to deterioration = date of event or censoring – randomisation + 1

Table 13 Time to deterioration event or censoring

Situation	Event or censored	Event date/censored date
No evaluable visits or no baseline data or no post-baseline data or baseline score does not allow for a 10-point deterioration (baseline score > 90 for symptom scale and <10 for functional and global health status/QoL scales)	Censored	Randomisation date (Study Day 1)
Confirmed deterioration after 2 or more consecutive missed PRO assessments visits (i.e., more than or equal to 62 days)	Censored	Latest evaluable PRO assessment date prior to the two or more missed visits
Confirmed deterioration without 2 or more consecutive missed PRO assessment visits before (i.e., less than 62 days)	Event	Date of first deterioration
One single deterioration with 2 or more consecutive missed PRO assessment visits before (i.e., more than or equal to 62 days) and no further assessments	Censored	Latest evaluable PRO assessment date prior to the two or more missed visits
One single deterioration without 2 or more consecutive missed PRO assessment visits before (i.e., less than 62 days) and no further assessments	Event	Last PRO assessment date (the single deterioration date)
Death in the absence of clinically meaningful deterioration	Censored	Latest evaluable PRO assessment date

Situation	Event or censored	Event date/censored date
No clinically meaningful confirmed deterioration (either no deterioration, or one singular which is not the last assessment)	Censored	Latest evaluable PRO assessment date

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3.4.5 Compliance

Summary measures of compliance over time will be derived for all PRO questionnaires. The schedule of assessment for questionnaires is divided into patients receiving study

treatment i.e., neoadjuvant period, and post-surgery follow-up period. See Section 4.1.3 and 8 for PRO visit windows.

Summary measures of compliance will be based upon:

- An expected form = a questionnaire that is expected to be completed at a scheduled assessment time, i.e., a questionnaire from a patient who has not withdrawn from the study at the scheduled assessment time.
    - For patients that have progressed pre-surgery, had surgery or discontinued study treatment, the earliest of date of progression, date of surgery or date of study treatment discontinuation will be used to determine the last on-treatment neoadjuvant windowed visit, for each patient's expected forms, using the analysis windows as described in Section 4.1.3. If the date falls before the end of the visit window, then that visit will only be considered expected if they have a received form. If they have not received a form, then this visit is not considered expected as they have not had the full opportunity to complete the questionnaire within the window. For patients who have not progressed, had surgery or discontinued study treatment, the date of the DCO will be used to determine the last on-treatment visit for their last expected form following the same approach as above.
    - For the follow-up period, for patients who have had surgery, the date of surgery will be used along with the post-surgery SoA to determine the expected visits at which a form should have been completed, using the analysis windows described in Section 4.1.3. For patients who discontinue treatment but do not undergo surgery, the date of the end of treatment visit will be used rather than the date of surgery. For patients who discontinue the study during the follow-up period, the date of discontinuation will be used to determine the last expected form. For patients who have not discontinued the study during the follow-up period, the date of the DCO will be used to determine the last expected form.
- An evaluable form = a questionnaire with a completion date and at least 1scale that is non-missing.
- A received form = a questionnaire that has been received and has a completion date and at least 1 individual item completed.

Based on the above definitions, the following summary measures will be derived:

Overall patient compliance rate is defined as: total number of patients with an evaluable baseline and at least one evaluable follow-up questionnaire (as defined above), divided by the total number of patients expected to have completed at least a baseline questionnaire multiplied by 100.

Compliance over time will be calculated separately for each visit, including baseline, as the number of patients with an evaluable questionnaire at the time point, divided by number of patients still expected to complete questionnaires.

Similarly, the evaluability rate over time will be calculated separately for each visit, including baseline, as the number of evaluable questionnaires, divided by the number of received questionnaires.

3.5 Health Care Resource Use Variables

To investigate the impact of treatment and disease on health care resource use (HcRU), the following variables will be captured:

- Planned and unplanned hospital attendances beyond trial protocol mandated visits (including physician visits, emergency room visits, day cases and admissions)
- Primary sign or symptom the patient presents with
- Length of hospital stay
- Length of any time spent in an intensive care unit (ICU)

Where admitted overnight, the length of hospital stay will be calculated as the difference between the date of hospital discharge (or death date) and the start date of hospitalisation or start of study drug if the start of study drug is after start date of hospitalisation (length of hospital stay = end date of hospitalisation – start date of hospitalisation + 1). Patients with missing discharge dates will be calculated as the difference between the last day with available data and the start date of hospitalisation. The length of ICU stay will be calculated using the same method.

3.6 Safety Variables

3.6.1 Exposure and dose interruptions

Total (or intended) exposure of a specific study drug

The total (or intended) exposure of study treatment (i.e. duration of treatment) of a patient to a drug will be calculated using the start and stop dates of the drug, and the intended

dosing interval. For a dosing period of the drug, the total (or intended) exposure is calculated as the number of days from date A to date B (B-A+1) where

- A is the date of first dose of the study drug in the dosing period
- B is the earliest of:
    - The date of death,
    - The date of DCO, and
    - the date when the last non-zero dose of the study drug was received (e.g. > 0 mg) plus C, where C is equal to the scheduled number of days between doses minus one, as defined in Table 14.

Table 14 Values of C for total exposure calculation

Treatment	Dosing schedule	C
T-DXd	Q3W	20
Paclitaxel	QW	6
Trastuzumab	Q3W	20
Pertuzumab	Q3W	20
Doxorubicin	Q2W	13
Cyclophosphamide	Q2W	13

QW = every week; Q2W = every 2 weeks; Q3W = every 3 weeks; T-DXd = trastuzumab deruxtecan.

Total (or intended) exposure of whole treatment regimen

The total (or intended) exposure of the whole treatment regimen of a patient is calculated as the number of days from date A to date B (B-A+1) where

- A is the date of first dose of the study drug in the dosing period
- B is the earliest of:
    - The date of death,
    - The date of DCO, and
    - The maximum date of: last non-zero dose date of each study drug plus C, where C is equal to the scheduled number of days between doses minus one, as defined in Table 14.

Actual exposure

Actual exposure will be calculated separately for each study drug as the intended exposure (as described above) minus the total duration of dose delays. Intended exposure will be calculated as above, and a dose delay is defined as any length of time (days) where a patient has not taken any of the planned dose.

For example, for T-DXd, which patients receive via infusion q3w, the duration of dose delays will be calculated as follows:

- Sum of all positive values of (date of dose – date of previous dose – (21+ W) days), where W is 1 for all weekly taxane use, and 2 for all other treatments.

Thus, if no delays were encountered, the duration would sum up to 0.

If a patient permanently discontinues study treatment during a dose delay, then the date of last administration of study treatment recorded will be used for the calculation of exposure.

Actual exposure of whole treatment regimen will also be calculated. It will be the actual exposure of T-DXd + the maximum actual exposure of THP for patients in Arm B, and the maximum (actual exposure of doxorubicin and cyclophosphamide) + the maximum actual exposure of THP for patients in Arm C.

Number of treatment cycles received

Exposure will also be measured by the number of cycles received. A cycle corresponds to a period of 21 days except in Arm C where a cycle corresponds to 14 days for doxorubicin and cyclophosphamide. If a cycle if prolonged due to toxicity, this should still be counted as one cycle. A cycle will be counted if treatment is started even if the full dose is not delivered.

Safety follow-up

Safety follow-up is defined as up to 40 + 7 days after the last dose of study treatment.

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

Surgery summary

A summary of patients undergoing breast surgery and lymph node surgery will be presented including the type of surgery performed (breast lumpectomy, breast re-excision

of margins, bilateral mastectomy, mastectomy or radical mastectomy; axillary lymph node dissection or targeted axillary lymph node dissection). This summary will be based upon the FAS. Reasons for patients not undergoing surgery will also be presented.

A summary of patients with surgical delays will be presented. A surgical delay is defined as surgery not occurring within 3-6 weeks after the administration of the last cycle of neoadjuvant treatment. Surgical delays will be summarised based on the SAF. Also to assess the impact of surgery delays due to Arm A closure, it may be also summarised based on the modified SAF-sensitivity analysis due to Arm A closure for Arm A and Arm C.

3.6.2 Dose intensity

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

- RDI = 100% * d/D, where d is the actual cumulative dose delivered up to the actual last day of dosing and D is the intended cumulative dose up to the actual last day of dosing. D is the total dose that would be delivered if there were no modification to dose or schedule.

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

For the calculation of the intended dose of T-DXd, the >= +/- 10% weight adjustment will be applied, by which the latest weight measurement will be considered in the calculation if it differs by at least 10% from the previous weight used in the calculation. The patient's most recent weight prior to first administration is used to calculate the initial dose.

Body surface area (BSA), required for the paclitaxel, cyclophosphamide and doxorubicin RDI calculations, will be calculated using the Dubois formula:

BSA = 0.007184 x baseline height (cm) $^{0.725}$ x most recent weight (kg) $^{0.425}$.

3.6.3 Adverse events

AEs and serious AEs (SAEs) will be collected throughout the study, from date of the patient signing the main informed consent until the follow-up period is complete (40 + 7 days after the last dose of study treatment). ILD/pneumonitis events which are ongoing at the end of the safety follow-up will continue to be followed up until resolution, and heart failure information will be collected throughout the post-surgery period until end of study (up to 6 years follow-up). Additionally, if an event starts after the end of the defined safety

follow-up period but is considered to be due to a late onset toxicity to the study treatment, then it will also be reported as an AE or SAE as applicable.

3.6.3.1 Treatment emergent adverse events

A treatment emergent adverse event (TEAE) is defined as an AE which occurs, having been absent before the first dose of study treatment, or worsens in severity or seriousness (by investigator report of a change in intensity), after the first dose of study treatment, until 47 days after the last dose of study treatment.

The Medical Dictionary for Regulatory Activities (MedDRA) (using the latest or current MedDRA version) will be used to code the AEs. AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE) (using CTCAE v5.0).

3.6.3.2 AEs of special interest

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

An AESI is an event of scientific and medical interest specific to the further understanding of the study treatment safety profile. AESIs 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. AESIs will be identified based on MedDRA preferred terms. Preferred terms used to identify AESIs will be listed before database lock (DBL) and documented in the Trial Master File.

Based on the available pre-clinical and clinical data, review of the cumulative literature, reported toxicities for the same class of agents and biological plausibility, the AESIs for the study are ILD/pneumonitis and 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)).

Other categories may be added as necessary or existing terms may be merged. An AstraZeneca medically qualified expert after consultation with the Global Patient Safety Physician has reviewed the AEs of interest and identified which higher-level terms and which preferred terms contribute to each AESI. Further reviews may take place prior to

database lock (DBL) to ensure any further terms not already included are captured within the categories.

Interstitial lung disease (ILD)/pneumonitis

ILD is considered an important identified risk based on a comprehensive cumulative review of potential ILD/pneumonitis cases reviewed by the independent ILD Adjudication Committee. ILD event adjudication is a retrospective review and will not impact any safety decisions for patients.

HRCT of the chest and pulmonary function will be measured at baseline, Q6W (at least 35 days, but not more than 42 days from previous scan) until EoT and at the time of suspected ILD/pneumonitis events. If the AE is suspected to be ILD/pneumonitis during the study, study treatment should be interrupted pending further evaluations. Evaluations for ILD/pneumonitis should include HRCT, pulmonologist consultation, pulmonary function tests, including FVC and DLCO, and pulse oximetry (SpO2), arterial blood gases if clinically indicated, bronchoscopy and bronchoalveolar lavage as clinically indicated and feasible, and one blood sample collection for PK as soon as ILD/pneumonitis is suspected, if feasible.

An ILD Adjudication Committee and Charter will be established to review all cases of potential ILD/pneumonitis. More information is provided in Appendix L of the CSP regarding management of study treatment-induced ILD/pneumonitis.

LVEF decrease

LVEF decrease in association with T-DXd is considered to be an important potential risk based on the available pre-clinical data, literature, and available safety information for drugs of similar class. Refer to the current T-DXd IB for a summary of preliminary clinical trial data. For LVEF Decrease Management Guidance, please refer to Section 6.6.1 of the CSP.

3.6.4 Physical examinations

Physical examinations will be performed according to the Schedule of Assessments (SoA) in the CSP. A full physical examination will be performed at screening and will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, abdomen, skin, lymph nodes, thyroid, musculoskeletal, urogenital, dermatological, gastrointestinal, endocrine, hematologic/lymphatic, and neurological systems. At subsequent visits, targeted physical examinations are to be utilised by the Investigator on the basis of clinical observations and symptomatology.

3.6.5 Infusion-related reactions

The definition of infusion-related reaction (IRR) includes any AEs that occurred on the same day as infusion or the next day and are considered by the investigator to be related to study drug and with one of the following preferred terms: administration related reaction, anaphylactic reaction, hypersensitivity, infusion related hypersensitivity reaction, and infusion related reaction.

3.6.6 Vital signs

Vital signs (systolic and diastolic blood pressure [BP], pulse, body temperature, and respiration rate) will be evaluated according to the SoA in the CSP. Body weight is also recorded at each visit along with vital signs.

Standard infusion time for T-DXd is over 90 minutes for first infusion and over 30 minutes thereafter if the first infusion was well tolerated. On the day of infusion, BP and pulse will be collected before and after each infusion at the following times:

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the beginning of the infusion]).
- At the end of the infusion (approximately 90 minutes ±5 minutes for a 90-minute infusion or approximately 30 minutes ±5 minutes in the case of a 30-minute infusion).

Vital signs data obtained up to 47 days after the date of last dose of study treatment. The denominator in vital signs data should include only those patients with recorded data.

Change from baseline in vital sign variables will be calculated for each post baseline visit, for each timepoint (pre-dose, end of infusion). For the derivation of baseline and post-baseline visit values, the definitions and rules described in Section 4.1.3 for visit windows and how to handle multiple records will be used.

3.6.7 Electrocardiograms

Resting 12-lead ECGs will be performed locally and recorded as specified in the SoA of the CSP. The following ECG variables will be collected: ECG heart rate, PR duration, QRS duration, QT duration, and QTcF. In case of clinically significant ECG abnormalities, 2 additional 12-lead ECGs will be obtained to confirm the finding.

ECG data obtained up to 47 days after the date of last dose of study treatment will be used for reporting.

3.6.8 Laboratory safety variables

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (refer to the SoA of the CSP). The laboratory variables to be measured are presented in Table 9 of the CSP.

Change from baseline in haematology and clinical chemistry variables will be calculated for each post-dose visit on-treatment. For the derivation of baseline and post-baseline visit values, the definitions and rules described in Section 4.1.3 for visit windows and how to handle multiple records will be used.

Lymphocytes and neutrophils may be recorded as absolute counts or percentages, but will be converted to absolute counts for summaries.

CTCAE grades will be defined at each visit according to the CTCAE grading criteria using local or project ranges as required, after conversion of lab results to corresponding SI units.

The following parameters have CTCAE grades defined for both high and low values: potassium, sodium, magnesium, glucose and corrected calcium, so high and low grades will be calculated.

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

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

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

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

Project reference ranges will be used throughout for reporting purposes. The denominator used in laboratory summaries of CTCAE grades will only include evaluable patients i.e., those who had sufficient data to have the possibility of an abnormality.

For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value

- If a CTCAE criterion does not consider changes from baseline, to be evaluable, patients would need only have 1 post dose-value recorded

Laboratory data obtained from first dose up to 47 days after the date of last dose of study treatment will be used for reporting.

3.6.9 Other safety assessments

3.6.9.1 Echocardiogram/Multigated Acquisition Scan

An ECHO or MUGA scan to assess LVEF will be performed at the visits indicated in the SoA in the CSP. Note: in Germany, LVEF will be measured only by ECHO.

The modality of the cardiac function assessments must be consistent within a patient; i.e., if an ECHO scan is used for the screening assessment, then ECHO should also be used for subsequent scans. The patients should also be examined using the same machine and operator whenever possible, and quantitative measurements should be taken.

3.6.9.2 Pulmonary Assessments

Pulse oximetry is assessed at the scheduled visits indicated in the SoA in the CSP. Pulmonary function testing will be performed at screening, including FVC (L), FVC % predicted, FEV1 (L), FEV1 % predicted and FEV1/FVC % as a minimum.

3.6.9.3 ECOG performance status

ECOG performance status will be assessed at the scheduled visits indicated in the SoA in the CSP according to World Health Organisation (WHO) criteria as follows:

0 = Fully active, able to carry out all pre-disease activities without restrictions.

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, 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, cannot carry on self-care, totally confined to bed or chair.

3.6.9.4 Ophthalmologic assessments

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

3.7 Pharmacokinetic (PK) Variables

Pharmacokinetic concentration data will be collected according to Section 8.5.1 of the CSP. The schedule of assessment is as per the SoA of the CSP. Blood samples for determination of concentration in serum of T-DXd, anti-HER2 antibody, and DXd, for patients receiving T-DXd, will be obtained from all patients.

3.8 Immunogenicity Variables

The presence of ADAs will be assessed in serum samples taken according to the SoA in the CSP.

ADA samples may be further tested for characterisation of the ADA response. In addition, the presence of neutralising antibodies (nAb) may be tested for all ADA-positive samples using a validated assay. The nAb results will be reported as positive or negative.

The following ADA outcomes will be determined:

- ADA positive at baseline or post-baseline
- ADA positive post-baseline and positive at baseline
- ADA not detected (negative or missing) post-baseline and positive at baseline
- Treatment-induced ADA positive, defined as ADA not detected (negative or missing) at baseline and became ADA positive post-baseline
- Treatment-boosted ADA, defined as ADA positive at both baseline and post-baseline, but had a meaningful increase in ADA titre by at least 4-fold or higher from baseline to post-baseline
- Treatment-emergent ADA positive, defined as either treatment-boosted ADA positive or treatment-induced ADA positive
- Treatment-emergent persistently ADA positive, defined as being treatment-emergent ADA positive and having at least 2 post-baseline ADA positive measurements with $\geq$ 16 weeks between first and last positive measurement.
- Treatment-emergent transiently ADA positive, defined as having at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive
- nAb positive at baseline or post-baseline

- Treatment-emergent nAb positive, defined as being treatment-emergent ADA positive with any positive nAb assessment post-baseline.

3.9 Biomarker Variables

Patients will provide a tumour tissue sample at screening (newly acquired or archived sample < 6 weeks old) to determine HER2-positive status. CCI

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4 ANALYSIS METHODS

The primary objective of this study is to confirm the efficacy of T-DXd alone (Arm A) or in sequence with THP (Arm B) relative to ddAC-THP (Arm C) in terms of the rate of pCR.

The formal statistical analysis will be performed to test the following main hypotheses:

- One primary hypothesis of interest:
  - H0: No difference between Arm A and Arm C
  - H1: Difference between Arm A and Arm C
- The other primary hypothesis of interest:
  - H0: No difference between Arm B and Arm C
  - H1: Difference between Arm B and Arm C

There will be 3 DCOs for this study consisting of a futility analysis, the primary analysis regarding pCR (ypT0/Tis ypN0) and 1 final analysis. This study will have met its primary objective if either Arm A or Arm B is statistically significantly superior to Arm C in terms of pCR (ypT0/Tis ypN0) at the primary analysis.

1. Futility Analysis: The objective of the futility analysis is to assess whether to terminate Arm A or Arm B due to futility. pCR rates observed from Arm A and Arm B will be compared to that from Arm C respectively. An active treatment arm (Arm A or Arm B) will be terminated if its pCR rate is lower than the pCR rate of Arm C by more than CCI %. The planned DCO will take place after approximately CCI patients are treated and have had the opportunity to be assessed for pCR.

2. Primary Analysis: The objective of the primary analysis will be to test the main study hypotheses, as detailed above and will take place when all patients have had the opportunity to be assessed for pCR. The planned DCO will take place when all randomised patients have had the opportunity to receive a definitive surgery and be assessed for pCR or have discontinued or withdrawn from treatment.

3. Final Analysis: The objective of the final analysis is to look at long-term benefit data and will take place when all patients have had the opportunity to be followed for 3 years after randomisation. The rate of EFS, IDFS, OS and CCI at 3 years will be summarised.

4.1 General Principles

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

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

- Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment arm. Overall totals will be calculated for baseline summaries only.

- For continuous data, the mean and median will be rounded to 1 additional decimal place compared to the original data. The standard deviation will be rounded to 2 additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data. Note for laboratory assessments 5 decimal places will be kept after conversion.

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

- Results of all statistical analyses will be presented using a 95% CI and 2-sided p-value, unless otherwise stated.
- Confidence intervals and ratios (including hazard ratios) will be rounded to 2 decimal places. p-values will be presented to 3 decimal places.
- For PK data the arithmetic mean, standard deviation, median, geometric mean and CV will be presented to 4 significant figures, minimum and maximum will be presented to 3 significant figures and n will be presented as an integer.
- SAS® version 9.4 (or higher) will be used for all analyses.

A month is operationally defined to be 30.4375 days. Six months is operationally defined to be 183 days. One year is defined to be 365.25 days.

Data will be presented in data listings by patient identifier and treatment arm.

Where analysis models are stratified by the randomisation stratification factors, the strata obtained at randomisation will be used, not the values recorded in the electronic case report form (eCRF).

In all summaries change from baseline variables will be calculated as the post-treatment value minus the value at baseline. The percentage change from baseline will be calculated as (post-baseline value - baseline value) / baseline value x 100. For any variable subjected to log transformation, the change from baseline calculated and summarised on the log scale will be back-transformed and presented as a 'baseline scaled ratio' (BSR). Percentage change will then be calculated as (BSR - 1) x 100.

Efficacy and health-related quality of life (HRQoL) data will be summarised and analysed based upon the FAS. Safety and treatment exposure data, and patient-reported tolerability data, will be summarised based upon the SAF. Study population and demography data will be summarised based upon the FAS.

4.1.1 Baseline definition

For efficacy variables, except for IDFS and PRO, baseline is defined as the last observed measurement prior to randomisation. However, if an evaluable assessment is only available after randomisation but before the first dose of randomised treatment then this assessment will be used as baseline.

For PRO assessments, the baseline assessment will be the last assessment before the first dose.

For safety data including vital signs, laboratory data, ECGs, physical examinations, WHO/ECOG, PK and immunogenicity, the last evaluable assessment of the variable under consideration prior to the intake of the first dose of study treatment is considered the baseline measurement. For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose. Assessments on the day of the first dose where neither time nor a nominal pre-dose indicator are captured will be considered prior to the first dose if such procedures are required by the protocol to be conducted before the first dose.

If two measurements are equally eligible to be considered as the baseline with no time point indication to separate them, then if it's a numeric assessment, the average will be used. For non-numeric laboratory tests (i.e., some of the urinalysis parameters) where taking the average is not possible, the best value (value closest to none/normal/negative) will be used as baseline as this is most conservative.

4.1.2 Handling of missing data

Missing safety data will generally not be imputed. However, safety assessment values of the form of "< x" (i.e. below the lower limit of quantification) or > x (i.e. above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or "> x" in the listings. Additionally, AEs that have missing causality (after data querying) will be assumed to be related to study drug.

Furthermore:

- Patients with a partial date of birth (i.e., for those countries where year of birth only is given), the 1st of the month should be imputed if only day is missing, and 1st January imputed if the day and month are missing.
- For missing diagnostic dates, if day and/or month are missing use 1st and/or January. If year is missing, put the complete date to missing.
- For missing start dates for AEs and concomitant medications/procedures, the following will be applied:
    a. Missing day: Impute the 1st of the month unless month is the same as month of the first dose of study drug and the end date is on or after the first dose of study drug or ongoing then impute first dose date

b. Missing day and month: Impute 1st January unless year is the same as first dose date and the end date is on or after the first dose of study drug or ongoing then impute first dose date

c. Completely missing date: Impute first dose date unless the end date suggests it could have started prior to this in which case impute the date of consent

When imputing a start date, ensure that the new imputed date is sensible e.g., prior to the end date of the AE.

- For missing end dates for AEs and concomitant medications/procedures, the following will be applied:

  a. Missing day: Impute the last day of the month unless month is the same as month of study discontinuation, then impute as study discontinuation date. For prior anti-cancer medications impute date of informed consent if month is same as the month when informed consent was provided.

  b. Missing day and month: Impute 31st December unless year is the same as the year of study discontinuation then impute study discontinuation date. For prior anti-cancer medications impute date of informed consent if year is the same as the year informed consent was provided.

  c. Completely missing date: If an end date is completely missing then it will be treated as ongoing, unless this is a prior anti-cancer medication then impute the date of informed consent.

When imputing an end date, ensure that the new imputed date is sensible e.g., after the start date of the AE.

If a patient is known to have died where only a partial death date is available then the date of death will be imputed according to the rules for imputing AE start dates unless this date is before the last date the patient is known to be alive then the date of death will be imputed as the date the patient was last known to be alive +1. If death has been recorded but the date is entirely missing, then date of death will be imputed as the date the patient was last known to be alive + 1.

For partial subsequent anti-cancer therapy dates, the following will be applied:

a) Missing day only – if the month is the same as the study treatment end date then impute to the day after the end of treatment, otherwise use the 1st of the month

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

c) If subsequent anti-cancer therapy has been recorded but the date is entirely missing, then date of subsequent anti-cancer therapy will be imputed as the day after treatment.

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

4.1.3 Time windows for PRO assessments and safety data

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

- The time windows will be exhaustive so that data recorded at any time point has the potential to be summarised. Inclusion within the time window will be based on the actual date and not the intended date of the visit.
- All unscheduled visit data have the potential to be included in the summaries.
- The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls halfway between the two visits (the lower limit of the first post-baseline visit will be Day 2). If an even number of days exists between two consecutive visits then the upper limit will be taken as the midpoint value minus 1 day. For example, the visit windows for vital signs data (with 3 weeks between scheduled assessments) are:
    - Cycle 1 Day 1: Day 1, visit window NA
    - Cycle 2 Day 1: Day 22, visit window 2 – 32
    - Cycle 3 Day 1: Day 43, visit window 33 – 53
    - Cycle 4 Day 1: Day 64, visit window 54 – 74
    - Cycle 5 Day 1: Day 85, visit window 75 – 95
- The visit windows for the PROs can be found in 8.
- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval).

- Listings should display all values contributing to a time point for a patient.
- For visit based summaries
    - If there is more than one value per patient within a time window then the closest value to the scheduled visit date will be summarised, or the earlier, in the event the values are equidistant from the nominal visit date. The listings will highlight the value for the patient that contributed to the summary table, wherever feasible. Note: in summaries of extreme values all post baseline values collected are used including those collected at unscheduled visits regardless of whether or not the value is closest to the scheduled visit date
    - To prevent very large tables or plots being produced that contain many cells with meaningless data, for each treatment group, visit data will only be summarised if the number of observations is greater than the minimum of 20 and > 1/3 of patients dosed unless otherwise stated
- For summaries at a patient level, all values will be included, regardless of whether they appear in a corresponding visit-based summary, when deriving a patient level statistic such as a maximum.

4.2 Analysis Methods

Efficacy analysis (including PRO) will be performed to compare T-DXd as monotherapy versus ddAC-THP (Arm A versus Arm C), and to compare T-DXd in sequence with THP versus ddAC-THP (Arm B versus Arm C). CCI [redacted] CCI [redacted]

The primary objective of this study is to confirm the superiority of T-DXd (Arm A) or T-DXd in sequence with THP (Arm B) compared to ddAC-THP (Arm C) in terms of pCR (ypT0/Tis ypN0) using central evaluation in patients with HER2-positive EBC.

Table 15 details which endpoints are to be subjected to formal statistical analysis, together with pre-specified sensitivity analyses. If one of two treatment arms (Arm A & Arm B) is dropped at pCR interim analysis, other efficacy endpoints will not be analysed for the comparison between that treatment arm with Arm C. Unless otherwise stated, formal statistical analyses described below will be conducted on the FAS.

Table 15 Formal Statistical Analyses to be Conducted and Pre-planned Sensitivity Analyses

Endpoints Analysed	Notes
pCR rate (ypT0/Tis ypN0)	Primary analysis Stratified Miettinen and Nurminen's method with stratification factors in line with the pooling strategy Sensitivity and supplementary analyses Stratified logistic regression model with the same stratification factors used in the primary analysis Stratified Miettinen and Nurminen's method with the same stratification factors used in the primary analysis: • Analysis considering stratification factors based on values entered into the eCRF or from the third-party vendor data, • Analysis for pCR regardless of receiving a new subsequent anti-cancer treatment before surgery
pCR rate (ypT0 ypN0)	Stratified Miettinen and Nurminen's method with stratification factors in line with the pooling strategy
EFS	Stratified log rank test, point estimate and CI of hazard ratio by stratified Cox proportional hazards model with stratification factors in line with the pooling strategy
IDFS	Stratified log rank test (Resected analysis set), point estimate and CI of hazard ratio by stratified Cox proportional hazards model with stratification factors in line with the pooling strategy
OS	Stratified log rank test, point estimate and CI of hazard ratio by stratified Cox proportional hazards model with stratification factors in line with the pooling strategy
CCI [redacted]	
Patient-reported tolerability using PRO-CTCAE, EORTC Item Library short forms and PGI-TT	Summary and descriptive statistics
Proportion of patients with maintained/improved physical function in EORTC QLQ-C30 Physical Function Scale	Summary and descriptive statistics

Endpoints Analysed	Notes
Time to deterioration using EORTC QLQ-C30 Physical Function Scale	Stratified log-rank test, with stratification factors in line with the pooling strategy
Each scale/item of EORTC QLQ-C30	MMRM, time to deterioration

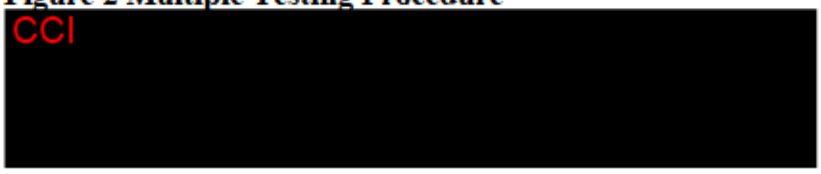
CCI BICR = blinded independent central review; CI = confidence interval; CCI CCI EFS = event-free survival; EORTC = European Organisation for the Research and Treatment of Cancer; IDFS = invasive disease-free survival; KM = Kaplan-Meier; CCI ; MMRM = mixed model for repeated measures; OS = overall survival; pCR = pathological complete response; PGI-TT = Patient Global Impression of Treatment Tolerability; PRO = patient-reported outcome; PRO-CTCAE = patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-C30 = 30 item core quality of life questionnaire; CCI ; ypT0/Tis ypN0 = absence of invasive cancer in the breast and axillary nodes; ypT0 ypN0 = absence of invasive and in situ cancer in the breast and axillary node.

4.2.1 Multiplicity

At the primary pCR analysis, hypotheses will be tested using a multiple testing procedure (MTP) with an alpha-exhaustive recycling strategy (Burman, Sonesson, & Guilbaud, 2009). The primary endpoints of improved pCR rate in either Arm A or Arm B will be tested simultaneously with split alpha values. A significance level of CCI will be used for the comparison between Arm B and Arm C, and a significance level of CCI will be used for the comparison between Arm A and Arm C. Assuming a CCI pCR rate in Arm C, the critical values in terms of the differences of pCR rates are CCI respectively, at the initial alpha levels for Arm A and Arm B. The spent alpha values can be recycled between successfully rejected tests of pCR. Implementation of this pre-defined ordered testing procedure, including recycling, will strongly control type I error at 5% (2-sided), among all key hypotheses.

Figure 2 presents an overview of the MTP and defines the initial overall type I error allocation.

Figure 2 Multiple Testing Procedure



α = alpha; pCR = pathological complete response.

No multiplicity-adjustment is required to account for the futility analysis because there will not be an opportunity to claim an early success.

Note: From 13 March 2024 onwards, as per IDMC's recommendation, patients will be randomised in a 1:1 ratio to Arm B and Arm C. After this date no patient will be randomised to Arm A. The main analyses of primary and secondary efficacy endpoints will

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[redacted]

4.2.2 Pathological complete response (pCR): ypT0/Tis ypN0

The pCR rate based on central assessment will be compared between Arm A and Arm C and Arm B and Arm C using a stratified Miettinen and Nurminen's method based on the FAS. The stratification variables include HR status (positive vs negative) and HER2 status (IHC3+ vs other). If there are insufficient number of patients per treatment arm per stratum, the strata will be pooled according to the pooling strategy in Section 4.2.20. The effect of treatment will be estimated by the difference in pCR rates together with its corresponding 95% confidence interval (CI) and the p-value from the stratified Miettinen and Nurminen's method with strata weighting by sample size (i.e. Mantel-Haenszel weights). Adjusted confidence intervals will also be presented for the relevant alpha level. The stratification variables will be based on values entered into the Interactive Response Technology (IRT) at randomisation, even if it is subsequently discovered that these values were incorrect. The active treatments will be considered superior to the control if the difference in the pCR rates is significantly bigger than zero.

A complementary analysis will be performed providing the observed pCR rates of each treatment arm. The 95% CI of the pCR rates will be provided using the Clopper-Pearson exact method. The differences in the observed pCR rates between the active treatment arms (Arms A and B) and the control arm (Arm C) will be reported using point estimates and their two-sided 95% CIs by the unstratified Miettinen-Nurminen method (Miettinen & Nurminen, 1985).

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[redacted]

CCI [redacted]

4.2.2.1 Sensitivity and supplementary analyses

A sensitivity analysis will be performed for pCR rates using stratified logistic regression models with treatment group and the same stratification factors used in the pCR primary analysis as covariates. The odds ratios and their 2-sided 95% CIs, and the p-value for the test against the null hypothesis of unity odds ratio will be reported.

As an additional sensitivity analysis, the primary analysis for pCR will be repeated, but the stratification variables will be based on HR status entered into the eCRF and HER2 status from the third-party vendor data.

As a supplementary analysis, the primary analysis for pCR will be repeated, but the analysis will include pCR regardless of receiving a new subsequent anti-cancer treatment before surgery.

The sensitivity and supplementary analyses described above will use the same stratification factors as used in the primary analysis. If there are less than 10 patients in each arm, the analysis will not be formally analysed. In this case, only number and percentage of patients will be provided.

Subgroup analyses will be conducted for pCR comparing the efficacy between Arm A and Arm C and Arm B and Arm C in the following subgroups of the FAS:

- HR status (ER and/or PgR positive vs ER and PgR negative)
- Central assessment of HER2 status (IHC 3+ vs other, where 'other' is defined as ISH+ in the absence of IHC 3+ status)
- Key baseline demographics, including:
    - Age (<65 years vs >=65 years)
    - Geographical region (Asia vs West Europe vs North America vs Rest of the World)
        - Asia: China, India, Japan, Korea, Philippines, Taiwan, Thailand
        - West Europe: Germany, Italy, Spain
        - North America: United States of America, Canada

- Rest of the World: Brazil, Bulgaria, Peru, Poland, Russia, Saudi Arabia

- Baseline ECOG (0 vs 1)
- Menopausal status (Post-menopausal vs Pre-menopausal)
- Race (Black or African American vs Native Hawaiian or other Pacific Islander vs American Indian or Alaska Native vs Asian vs White vs Other)
- Clinical tumour stage (T0-2 vs T3-4)
- Nodal status (N0 vs N+)
- AJCC clinical stage (II-IIIA vs IIIB-IIIC)
- Tumour grade (G1-G2 vs G3-G4)

Other baseline variables may also be assessed if there is clinical justification, or an imbalance is observed between the treatment groups. The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic and/or predictive factors.

All factors including stratification factors will be based on values recorded on the eCRF (HR status) or from the third-party vendor data (HER2 status).

For each subgroup, the difference in rates and 95% CI will be calculated from the unstratified Miettinen and Nurminen's method. These will be presented on a forest plot including the difference in rates and 95% CI from the overall primary analysis. If there are too few patients available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 10 patients in each arm in a subgroup), the subgroup in pCR will not be formally analysed. In this case, only number and percentage of patients will be provided.

Test for Consistency of Treatment Effect Between Subgroups

Interactions between treatment and stratification factors included in the analysis of the primary endpoint will be tested to rule out the presence of a quantitative interaction based on the means of an overall global interaction test. If the global interaction test is found to be statistically significant ($p<0.1$), an attempt to determine the cause and type of interaction may be made. Any quantitative interaction identified will then be tested to rule out any qualitative interaction using the approach of Gail and Simon (Gail & Simon, 1985).

Additional supportive analyses

To assess the impact of Arm A closure from 13 March 2024 onwards as described in Section 1.2, the primary analysis for pCR to compare the efficacy between Arm A and Arm C may be repeated based on the modified full analysis set – sensitivity analysis due to Arm A closure.

4.2.3 Pathological complete response (pCR): ypT0 ypN0

A secondary definition of pCR (ypT0 ypN0) will be analysed using the same stratified Miettinen-Nurminen method as described for the primary endpoint in Section 4.2.2. The effect of treatment will be estimated by the difference in pCR rates together with its corresponding 95% CI from the stratified Miettinen and Nurminen's method with strata weighting by sample size (i.e. Mantel-Haenszel weights).

CCI [redacted]

The two analyses for pCR (ypT0 ypN0) rate will use stratification factors in accordance with the pooling strategy as described in Section 4.2.20 for the secondary and exploratory efficacy endpoints. If there are less than 10 patients in each treatment arm, only the number and percentage of patients will be provided.

4.2.4 Event-free survival

EFS will be analysed using a stratified log rank test and following the pooling strategy regarding the secondary and exploratory efficacy endpoints as described in Section 4.2.20 for a meaningful analysis. Please refer to section 4.2.20 for a detailed pooling strategy. The hazard ratio together with its 95% CI and p-value will be presented provided there are sufficient number of events (at least 20 events across both treatment arms) for a meaningful analysis (a hazard ratio less than 1 will favour the active treatment arm). The hazard ratio and CI will be estimated from a stratified Cox proportional hazards model (with ties = Efron), and the CI will be calculated using a profile likelihood approach. If there are not sufficient number of events, only number and percentage of patients with events within each treatment group will be provided.

Kaplan-Meier (KM) plots of EFS will be presented by treatment arm. Summaries of the number and percentage of patients experiencing an EFS event and the type of event (e.g. progression or death), those still in survival follow-up, those lost to follow-up, and those who have withdrawn consent will be provided along with the median EFS for each treatment arm.

EFS36 (i.e., 3-year landmark rate of EFS) will be summarised (using the Kaplan-Meier curve) and presented by treatment arm. EFS landmark analysis will also be summarised at 12 months, 18 months, 24 months and 30 months.

CCI [redacted]

Cox regression analysis adjusting for post-surgery treatments (e.g. multivariate stratified Cox model with post-surgery treatments as time varying covariates) may be done if there are sufficient number of events within each combination of covariates. The same stratification factors will be used as for the EFS primary analysis.

Proportional hazards assumption

The assumption of proportionality in the Cox model will be assessed. Proportional hazards will be tested firstly by examining plots of complementary log-log (event times) versus log (time) and, if these raise concerns, by fitting a time dependent covariate to assess the extent to which this represents random variation.

If a lack of proportionality is evident, the variation in treatment effect may be described by presenting piecewise hazard ratio calculated over distinct time periods. In such circumstances, the hazard ratio from the primary analysis can still be meaningfully interpreted as an average hazard ratio over time unless there is extensive crossing of the KM survival curves.

4.2.4.1 Sensitivity and supplementary analyses

Subgroup analyses

Subgroup analyses will be repeated for the same subgroups as described in Section 4.2.2.1, using a Cox proportional hazards model with treatment as the only covariate. The hazard ratios and their 95% CIs will be presented on a forest plot including the hazard ratio and 95% CI from the overall primary analysis. If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 20 events across both treatment groups in a subgroup), the hazard ratio will not be reported. In this case, only number and percentage of patients with events within each treatment group will be provided.

4.2.5 Invasive disease-free survival

IDFS will be analysed based on the resected analysis set using the same methodology as described for EFS (see Section 4.2.4), and following the pooling strategy regarding the secondary and exploratory efficacy endpoints as described in Section 4.2.20 for a

meaningful analysis. If there are not sufficient events (less than 20 events across both treatment groups), only number and percentage of patients with events within each treatment group will be provided.

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4.2.6 Overall survival

OS will be analysed using the same methodology as described for EFS (see Section 4.2.4), and following the pooling strategy regarding the secondary and exploratory efficacy endpoints as described in Section 4.2.20 for a meaningful analysis. If there are not sufficient events, (less than 20 events across both treatment groups), only the number and percentage of patients with events within each treatment group will be provided.

The number of patients prematurely censored will be summarised by treatment arm. A patient would be defined as prematurely censored if their survival status was not defined at the DCO.

In addition, duration of follow-up will be summarised using medians:

- In all patients: Time from randomisation to the date of death (i.e. overall survival) or to the date of censoring (date last known to be alive).
- In all censored patients: Time from randomisation to the date of censoring (date last known to be alive).

4.2.6.1 Sensitivity and supplementary analyses

A sensitivity analysis for OS will examine the censoring patterns to rule out attrition bias with regard to the primary treatment comparisons, achieved by a KM plot of time to censoring where the censoring indicator of OS is reversed.

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4.2.10 Patient Reported Outcomes (PROs)

Physical functioning will be evaluated using the EORTC QLO-C30 Physical Function scale (obtained from either the EORTC QLQ-C30 scale or the EORTC-IL19). Symptomatic AEs will be evaluated using the PRO-CTCAE, EORTC-IL123, EORTC-IL124 and selected tolerability items from the EORTC QLQ-C30. Overall side-effect bother will be evaluated using the PGI-TT. Overall HRQoL will be evaluated using the EORTC QLQ-C30 assessment.

Compliance

Summaries of compliance over time by timepoint and overall will be reported for each PRO questionnaire where applicable (EORTC QLQ-C30, EORTC Item Library short forms, PRO-CTCAE, PGI-TT and CCI).

4.2.10.1 Symptomatic adverse events

PRO-CTCAE analyses will be based upon the SAF. In order to assess reversibility of select symptomatic AEs, change from the End of Treatment visit will be summarised by timepoint in the post-surgery period.

Symptomatic AEs during neoadjuvant period will be summarised using raw (non-transformed) item-level values, except where otherwise noted. These analyses may include, but are not limited to:

- Graphical representation of symptomatic AE responses will be provided, presenting the proportion of patients reporting each response option of each symptomatic AE at each time point according to treatment arm.

- Proportion of the worst response option reported by patients for each symptomatic AE across all available time points.

EORTC Item Library short forms contain items that are intended to describe symptomatic AEs and will be based on the SAF and analysed similarly to the PRO-CTCAE.

4.2.10.2 Overall side effect bother

PGI-TT analyses will be based on the SAF. The proportion of patients reporting each level of overall side effect bother from the PGI-TT during neoadjuvant treatment and at the End of Treatment visit, as well as following neoadjuvant treatment, will be reported in graphical and/or tabular format at each timepoint by treatment arm.

The number and percentage of patients for each response at each timepoint will be summarised in a figure. The exploratory evaluation of proportion of patient weeks with/without high side-effect bother will be summarised and described by treatment arm, where high side effect bother is defined as a score of 3 or 4 on the PGI-TT, and the proportion is calculated as the number of weeks scoring a 3 or 4 divided by the number of total weeks on treatment with available data, calculated across all patients.

4.2.10.3 Physical functioning

Study endpoints that evaluate physical function independently, as assessed by the EORTC QLQ-C30 Physical Function scale, will be analysed based on the SAF.

Number and percentage of patients with deterioration/maintained/improved physical function will be summarised by treatment arm over time during neoadjuvant period and then following neoadjuvant period in table and figure. Descriptive summary statistics will also be provided for each timepoint including absolute scores and change from baseline.

4.2.10.4 Overall HRQoL

Analyses that evaluate the overall HRQoL using the full EORTC QLQ-C30 assessment, which includes the Physical Function scale, will be analysed using the FAS.

Change from baseline in EORTC QLQ-C30 scale scores will be analysed using a mixed model for repeated measures (MMRM). The analysis will make use of all data from the neoadjuvant treatment period. The analysis will be to compare the average treatment effect over the analysed period, excluding timepoints with excessive missing data (defined as > 75% missing data). The model will include treatment, visit, treatment-by-visit interaction,

the same stratification factors used in the pCR primary analysis as fixed effects, baseline score as a covariate and the baseline-by-visit interaction. Restricted maximum likelihood estimation will be used. Adjusted treatment arm means will be calculated assuming coefficients for classification effects (i.e., the effects of categorical covariates) proportional to the margins observed in the group of subjects analysed (e.g., using the OM option in SAS® PROC MIXED).

An unstructured covariance matrix will be used to model the within-subject error and the Kenward-Roger approximation will be used to estimate the degrees of freedom. If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in order until convergence is reached: unstructured correlations, Toeplitz with heterogeneity, autoregressive with heterogeneity, Toeplitz, autoregressive and compound symmetry.

Time to deterioration will also be analysed using a stratified log rank test following the pooling strategy described for the secondary or exploratory endpoint in Section 4.2.20. Separate analyses will be conducted for the symptom (including single-item scales) and functioning scales and the global health status/QoL score. The effect of treatment arm (Arm A/Arm B) versus control arm (Arm C) will be estimated by the hazard ratio together with its corresponding 95% CI and p-value. Kaplan-Meier plots will be presented by treatment arm. Summaries of the number and percentage of patients who have an event, as well as who were censored, will be provided along with the medians for each treatment.

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4.2.11 Healthcare resource use

Information on hospital admissions will be listed, including the type of attendance, the primary sign or symptom the patient presents with, the dates of hospital admission and the dates of ICU stays.

To support submissions to payers, additional analyses may be undertaken, and these will be outlined in a separate Payer Analysis Plan.

4.2.12 Safety analyses

4.2.12.1 General considerations for safety assessments

Safety and tolerability data from all cycles of treatment will be combined and will be presented by treatment arm using the SAF. Safety summaries will be descriptive only. No formal statistical analyses will be performed on the safety variables.

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

4.2.12.2 Exposure

The following summaries for exposure will be produced:

- Total exposure
- Actual exposure
- Number of treatment cycles
- RDI
- Summary of delays and interruptions of study treatment
- Summary of patients undergoing surgery, type of surgery and surgical delays

4.2.12.3 Adverse events

AEs occurring before start of treatment and which did not worsen during the study will be included in the AE listings but will not be included in the summary tables. These will be referred to as 'pre-treatment'.

TEAEs, as defined in Section 3.6.3, occurring up to 47 days after the last dose of study treatment and prior to the initiation of the first subsequent anti-cancer therapy (in this definition, palliative radiotherapy is not considered a subsequent cancer therapy) will be used for reporting in the AE summary tables, unless otherwise specified. This will more accurately depict safety findings attributable to study treatment only as opposed to presenting all TEAEs, as they may include AEs likely to be attributable to subsequent cancer therapy.

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

However, to assess the longer-term toxicity profile, some of the AE summaries may also be produced including AEs observed up until 47 days after following last dose of study treatment, irrespective of initiation of subsequent cancer therapies.

Adverse events will be coded using the latest or current version of the MedDRA dictionary, and any missing coding terms should be listed and summarised as "Not coded".

All AEs, both in terms of current MedDRA system organ class (SOC) and preferred term (PT) will be summarised descriptively by count (n) and percentage (%) of patients reporting at least one event for each treatment arm.

Summary information (the number and percentage of patients by treatment) will be tabulated by SOC and PT for:

- all AEs
- all AEs possibly related to study treatment
- AEs with CTCAE grade 3 or higher
- AEs with CTCAE grade 3 or higher, possibly related to study treatment
- AEs with outcome of death
- AEs with outcome of death possibly related to study treatment
- AEs leading to dose reduction and interruption (separately)
- AEs leading to dose reduction, possibly related to study treatment
- AEs leading to dose interruption, possibly related to study treatment
- All SAEs
- All SAEs possibly related to study treatment
- AEs leading to discontinuation of study treatment
- AEs leading to discontinuation of study treatment, possibly related to study treatment
- SAEs leading to discontinuation of study treatment
- AEs leading to surgical delay
- AEs leading to surgical delay, possibly related to study treatment
- AESIs*

Additionally, an overall TEAE summary of the number and percentage of patients in each category (excluding those marked with an asterisk above) will be presented.

In addition, a truncated table of most common AEs, showing all events that occur in at least 5% of patients in any treatment group will be summarised by preferred term, by decreasing frequency in Arm A. This cut-off may be modified after review of the data. When applying a cut-off (e.g., 5%), the raw percentage should be compared to the cut-off, no rounding should be applied first (i.e., an AE with frequency 4.9% will not appear if the cut-off is 5%). This truncated table will be repeated for most common AEs with maximum CTCAE grade 3 or higher.

A summary of the number and percentage of patients will also be provided by maximum reported CTCAE grade, SOC, PT and actual treatment arm.

All AEs will be listed along with the date of onset, date of resolution (if AE is resolved), investigator's assessment of CTCAE grade and relationship to study drug. Frequencies and percentages of patients reporting each preferred term will be presented (i.e. multiple events per patient will not be accounted for apart from on the episode level summaries).

In addition, AEs with outcome of death, SAEs, AEs leading to discontinuation of treatment and AESIs will be listed.

Deaths

A summary of deaths will be provided with number and percentage of patients by treatment group, categorised as:

- Total number of deaths (regardless of date of death)
- Deaths related to disease under investigation only (as determined by the investigator)
- AE with outcome of death only
    - Sub-category: AE with outcome of death only (AE start date > 47 days after last treatment dose) (*)
- Death related to disease under investigation (as determined by the investigator) and AE with outcome death

- Sub-category: Death related to disease under investigation (as determined by the investigator) and AE with outcome death (AE start date > 47 days after last treatment dose) (*)

- Other deaths (not captured in above categories)

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

A corresponding listing will also be produced.

4.2.12.4 Adverse events of special interest

ILD/pneumonitis and left ventricular dysfunction are considered to be AESIs (see Section 3.6.3.2 for further details).

Summaries of ILD/pneumonitis events will be primarily based on adjudicated drug-related ILD/pneumonitis events from the ILD adjudication committee.

ILD/pneumonitis events collected both prior to first dose and after the safety follow-up will also be included in the summaries.

Summaries of adjudicated ILD/pneumonitis and left ventricular dysfunction events will include number (%) of patients who have:

- At least one AESI
- At least one AESI by group term, preferred term and maximum reported CTCAE grade (*)
- At least one AESI by outcome (*)
- At least one AESI leading to interruption of study treatment (*)
- At least one AESI leading to dose reduction of study treatment (*)
- At least one AESI possibly related to study treatment (as determined by the investigator for left ventricular dysfunction and by the ILD adjudication committee for adjudicated ILD/pneumonitis events)
- At least one AESI leading to discontinuation of study treatment (*)
- At least one AESI with outcome recovered/resolved by time of resolution (*)

In addition, an overall AESI summary will be presented, including the number and percentage of patients. When summarising adjudicated ILD/pneumonitis events, the categories marked (*) will only be presented for adjudicated drug-related events.

A summary table presenting number (%) of patients who had potential ILD/pneumonitis sent for adjudication will be presented. This will include summaries by outcome and maximum reported CTCAE grade.

Preferred terms used to identify AESI will be listed before DBL and documented in the Trial Master File. Grouped summary tables of certain MedDRA preferred terms will be produced and may also show the individual preferred terms which constitute each AESI grouping. Groupings will be based on preferred terms provided by the medical team prior to DBL, and a listing of the preferred terms in each grouping will be provided.

Time to the first treatment-emergent AESI will be summarised for patients with at least one AESI using descriptive statistics (mean, standard deviation, median, minimum, maximum).

When summarising time to and duration of the first treatment-emergent AESI for adjudicated ILD/pneumonitis events, only adjudicated drug-related events will be considered.

4.2.12.5 Infusion-Related Reactions

A listing of infusion-related reactions will be provided.

4.2.12.6 Vital signs

Vital sign parameters (systolic and diastolic BP, pulse, body temperature, respiration rate) and body weight will be presented for each treatment group.

For each scheduled post-baseline visit (including timepoint i.e., pre-dose, end of infusion), descriptive statistics for all vital sign parameters will be presented for absolute values and change from baseline.

4.2.12.7 Electrocardiograms

ECG abnormalities will be listed. A summary of baseline to worst ECG value on treatment will be provided.

4.2.12.8 Laboratory safety variables

Summaries of laboratory parameters will be based on data collected from date/time of the first dose of study treatment up to 47 days following last dose of study treatment and before the initiation of the first subsequent cancer therapy (palliative radiotherapy is not considered a subsequent cancer therapy), whichever occurs first.

Laboratory parameters will be presented by treatment group and by visit according to the visit windows defined in Section 4.1.3. All laboratory data recorded in the eCRF will be listed, including observed values and change from baseline, and abnormalities.

All values will be classified as low (below range), normal (within range) and high (above range) based on project-specific reference ranges. As applicable, values will be converted to AZ preferred units and will be graded using the CTCAE v5.

For each scheduled post-baseline visit, descriptive statistics for all clinical chemistry and haematology parameters will be presented for absolute values and absolute change from baseline. Shift tables will present movements from baseline to worst CTCAE grade (maximum or minimum as applicable).

The laboratory parameters for which CTCAE grade shift outputs will include (but are not limited to) are:

Haematology:

- Neutrophils (absolute count) - low
- Haemoglobin - low
- Leukocytes (white cell count) - low
- Lymphocytes (absolute count) - low
- Platelet count - low

Clinical chemistry:

- Albumin - low
- ALP - high
- ALT - high
- AST - high
- Corrected calcium – low and high
- Creatinine - high
- Gamma-glutamyl transferase - high

- Magnesium – low and high
- Potassium – low and high
- Sodium – low and high
- Total bilirubin - high

A shift table will present laboratory status including change in abnormality (e.g., low, normal, high) from baseline to maximum and minimum on-treatment value.

A summary of the shift from baseline to maximum on-treatment value will be provided for troponin.

Hy's Law

A summary of the patients with potential Hy's Law will be presented including the number (%) of patients who have:

- ALT ≥3x – ≤5x, >5x – ≤8x, >8x – ≤10x, >10x – ≤20x, and >20x ULN during the study.
- AST ≥3x – ≤5x, >5x – ≤8x, >8x – ≤10x, >10x – ≤20x, and >20x ULN during the study.
- Total bilirubin ≥2x – ≤3x, >3x – ≤5x, >5x ULN during the study.
- ALT or AST ≥3x – ≤5x, >5x – ≤8x, >8x – ≤10x, >10x – ≤20x, >20x ULN during the study.
- ALT or AST ≥3x ULN and total bilirubin ≥2x ULN during the study (potential Hy's law): the onset date of ALT or AST elevation should be prior to or on the date of total bilirubin elevation irrespective of an increase in Alkaline Phosphatase (ALP)

Liver biochemistry tests (ALT, AST, TBIL, ALP, GGT) results over time will also be presented graphically for patients with potential Hy's Law.

Individual patient data where ALT or AST plus total bilirubin are elevated and where the onset date of ALT or AST elevation is prior to or on the date of total bilirubin elevation will be listed also.

A summary table of the maximum on-treatment ALT and AST versus maximum on-treatment total bilirubin will be presented.

4.2.12.9 Other safety assessments

4.2.12.9.1 Echocardiogram/Multigated Acquisition Scan

A summary of LVEF will be presented, including the worst LVEF CTCAE grade post-baseline, the baseline LVEF, the end of treatment LVEF and maximum and minimum, as well as change from baseline.

4.2.12.9.2 Pulmonary Assessments

Peripheral oxygen saturation over time will be summarised. In addition, pulmonary medical history will also be summarised and listed.

4.2.12.9.3 Heart failure

The percentage of participants with NYHA Class III and IV heart failure during the neoadjuvant treatment period and at the end of the study (up to 6 years' follow-up) will be summarised by treatment arm using descriptive statistics.

4.2.12.9.4 ECOG performance status

ECOG performance status will be summarised over time.

4.2.13 Demographics and baseline characteristics

The following will be summarised for all patients in the FAS (unless otherwise specified) by treatment arm:

- Patient disposition (including screening failures and reason for screening failure)
- Important protocol deviations
- Inclusion in analysis sets
- Demographics (age, age group [<65 and ≥65 years], sex, race and ethnicity)
- Patient characteristics at baseline (height, weight, BMI)
    - BMI will be calculated as: weight (kg)/height $(m)^2$.
- Patient recruitment by region, country and centre
- Stratification factors recorded at randomisation on the IRT/RTSM and eCRF
- Disease characteristics at baseline (ECOG performance status, primary tumour location, histology type, tumour grade and overall disease classification)
- TNM classification at baseline

- Medical history (past and current)
- Relevant surgical history
- Disallowed concomitant medications
- Allowed concomitant medications
- Post-discontinuation cancer therapy
- Pulmonary function test at baseline

4.2.14 Concomitant medications and other treatments

Information on any treatment from screening to 47 days after the last dose of study treatment, with reasons for the treatment, will be recorded in the eCRF. Thereafter, only subsequent regimens of anti-cancer therapy will be recorded in eCRF.

Medications received prior to, concomitantly, or post-treatment will be coded using the AstraZeneca Drug Dictionary Anatomical Therapeutic Chemical (ATC) Classification codes. Concomitant medications will be summarised for the FAS by ATC classification codes.

For the purpose of inclusion in prior and/or concomitant mediation or therapy summaries, incomplete medication or radiotherapy start and stop dates will be imputed as detailed in Section 4.1.2.

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

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

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

The following summaries will be produced:

- Summary of prior medications
- Summary of concomitant medications
- Summary of post study treatment anti-cancer therapies

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

4.2.15 Pharmacokinetic (PK) Data

All serum concentrations will be listed for each patient in the PK analysis set, for each sampling time and each dosing day, regardless of whether they are excluded from summary statistics due to deviation (e.g. as a result of dose interruption, reduction or missing the dose before PK sample collection, or sampling time deviation, etc).

Serum concentrations of T-DXd, total anti-HER2 antibody, and DXd will be summarised by nominal sample time using standard summary statistics for PK concentrations (geometric mean, geometric coefficient of variation, geometric mean ± standard deviation, arithmetic mean, standard deviation, minimum, maximum and n) within each treatment arm.

If any deviation is considered to have impact upon PK, a patient or particular data for a patient may be excluded from the PK analysis set.

For data below the lower limit of quantification (LLOQ) the following rules will apply:

- If, at a given time point, 50% or less of the serum concentrations are not quantifiable (NQ), the geometric mean, geometric CV%, mean and standard deviation will be calculated treating the NQ as missing.
- If more than 50%, but not all, of the concentrations are NQ, the mean, median, minimum and geometric mean are presented as "< LLOQ" and the geometric CV% and standard deviation will be reported as NA.

Further population PK and exposure-response analyses may be carried out and will be reported separately from the main CSR.

4.2.16 Immunogenicity Data

Immunogenicity data will be summarised and listed for the ADA evaluable set.

If a patient is ADA+ and their titre measurement is "<x" or "≤x" then impute as x. If a patient is ADA- and their titre measurement is "<x" then set to missing. If a patient's titre result is 'NRR' (No result recorded) or 'NA' then set to missing.

Immunogenicity results will be listed by patient for all patients in the ADA evaluable set. A summary, inclusive of minimum, maximum, and median of maximum post-baseline titres, will be provided of the number and percentage of patients who develop detectable anti-T-DXd antibodies by ADA categories (see Section 3.8). ADA categories will be listed. Anti-drug antibody 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, efficacy, and safety may be evaluated, if the data allow.

4.2.17 Biomarker Data

The relationship of baseline HER2 expression, CCI [redacted] CCI [redacted] to clinical outcomes (including but not restricted to) of pCR, EFS and OS may be presented.

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

4.2.18 Residual Cancer Burden

A summary of the RCB will be provided on the FAS including the percentage of patients by RCB class after central pathological evaluation, and also in the same table the combined percentage of patients with either RCB 0 or 1.

4.2.19 COVID-19

Additional analyses may be performed to explore the impact of COVID-19 on key efficacy and safety endpoints, for example repeating the AE summaries separately for patients where events are attributed to COVID-19.

4.2.20 Pooling strategy

Stratified Miettinen and Nurminen's method, log rank tests, Cox proportional hazards models and logistic regression models will adjust for the following stratification factors (as defined according to data from the IRT at time of randomisation, even if it is subsequently discovered that these values were incorrect):

- HER2 status (IHC3+ vs other)

- HR status (positive vs negative).

To ensure results are robust, at least 5 patients (or 5 events for a time to event endpoint) per treatment arm in each stratum are required (Silcocks, 2012; Vittinghoff & McCulloch, 2007), where a stratum is defined as strata1*strata2. So with 2 stratification factors, each with 2 levels, there are 2*2=4 strata. Stratification factors will be removed from the model in the following order, until there are at least 5 patients per treatment arm in each stratum: HER2 status, HR status. The primary analysis of primary endpoint (pCR: ypT0/Tis ypN0) will be conducted in accordance with the pooling strategy defined above. All sensitivity and supplementary analyses of the primary endpoint will be adjusted for the same stratification factors used in the primary analysis of the primary endpoint. Analyses of all secondary and exploratory endpoints will be adjusted for the same stratification factors used in the primary analysis of the primary endpoint. However, if there are secondary or exploratory endpoints that still do not conform to the requirement on the minimum number of patients (or number of events for time to event endpoints) when using the same stratification factors as that in the primary analysis of the primary endpoint, an unstratified or unadjusted analysis will be conducted if there are sufficient number of patients or events (refer to section of each secondary or exploratory endpoints for the minimum number of patients or events required for conducting an analysis).

5 INTERIM ANALYSES

5.1 Futility analysis

A futility analysis for pCR (ypT0/Tis ypN0) based on central assessment will be performed when approximately CCI patients (CCI% of the intended population) are treated and have had the opportunity to be assessed for pCR or have discontinued or withdrawn from treatment. The DCO for this analysis is expected approximately CCI months after the first patient is randomised.

The objective of the futility analysis is to assess whether to terminate Arm A or Arm B due to futility. The proportion of pCR in Arm A and Arm B will each be compared to the proportion of pCR in Arm C. CCI
CCI
The suggestion to stop Arm A or Arm B will be considered if the rate of pCR in a T-DXd treatment arm is lower than the rate of pCR in Arm C by more than CCI%, i.e., CCI
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CCI [redacted] The analysis is based on the observed pCR rates of each treatment arm. The 95% CI of the pCR rates will be provided using the Clopper-Pearson exact method. The differences in the observed pCR rates between the active treatment arms (Arm A and Arm B) and the control arm (Arm C) will be reported using point estimates and their two-sided 95% CIs by the Miettinen and Nurminen method (Miettinen & Nurminen, 1985).

As supportive summaries, the following will be provided:

- An analysis, which is based on stratified Miettinen and Nurminen with HR status and HER2 status considered as stratification factors, will be performed to assess differences in pCR rates.
- Kaplan-Meier plots of event-free survival will be presented by treatment arm.

To ensure results are robust for the stratified pCR analysis for FA, at least 5 patients per treatment arm in each stratum are required, where a stratum is defined as strata1*strata2, so with 2 stratification factors, each with 2 levels, there are 2*2 = 4 strata. Stratification factors will be removed from the model in the following order, until there are at least 5 patients per treatment arm in each stratum: HER2 status, HR status. The stratification variables will be defined according to data from the IRT, even if it is subsequently discovered that these values were incorrect.

CCI [redacted]

5.2 Independent data monitoring committee

Interim safety monitoring will be conducted by an independent data monitoring committee (IDMC). An IDMC will be established to monitor data on an ongoing basis to ensure the continuing safety of patients enrolled in this study, to ensure the integrity of the study, and to oversee the planned pCR-based futility analyses. The initial safety review will take place after approximately 60 patients have been randomised or after 6 months, whichever occurs earlier. The IDMC will meet at least every 6 months thereafter until the last patient has completed neoadjuvant treatment. Following each meeting, the IDMC will report to the sponsor and may recommend changes in the conduct of the study.

The IDMC will also specifically monitor the following:

- Proportion of patients who did not have definitive surgery within the study-specified window.
- Discontinuation rates of study treatment due to ILD/pneumonitis.
- Overall rates of premature study treatment discontinuation.

For the pCR-based futility analysis, the IDMC will review unblinded study data and inform AstraZeneca as to whether the futility boundaries are met.

This committee will be composed of therapeutic area experts and biostatisticians, who are not employed by AstraZeneca and are free from conflict of interest.

Following the reviews, the IDMC will recommend whether the study should continue unchanged, be stopped, or be modified in any way. Once the IDMC has reached a recommendation, a report will be provided to AstraZeneca. The report will include the recommendation, any potential protocol amendments, and will not contain any unblinding information.

The final decision to modify or stop the study will sit with the sponsor. The sponsor or IDMC may call additional meetings if at any time there is concern about the safety of the study.

Full details of the IDMC procedures and processes can be found in the IDMC Charter.

6 CHANGES OF ANALYSIS FROM PROTOCOL

The following is a list of changes from the CSP, version 5.0 (15 April 2024).

CCI [redacted]

Section 2.1.3 Summaries using the safety analysis set will be presented using the treatment arms to which the patients were randomised, rather than treatment actually received.

Sections 4.2.3, 4.2.5, 4.2.6.1 and 4.2.8 Subgroup analyses will not be performed for the secondary pCR endpoint, IDFS, DMFS or OS.

Section 4.2.12.8 The frequency table for urinalysis with number of patients reporting at least one treatment emergent increase in baseline category will not be presented. The shift table for urinalysis with baseline assessment against the maximum on treatment category will not be presented.

Section 4.2.19 Summaries of data relating to patients diagnosed with COVID-19, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued study intervention, and other protocol deviations) will not be generated.

Section 4.2.11 Descriptive statistics on hospital admissions will not be provided.

CCI [redacted]

Section 4.2.2.1 Added additional sensitivity analysis for pCR rates using eCRF/TPV stratification rather than IRT.

Section 4.2.4 Added additional EFS landmark analyses at 12m, 18m, 24m and 30m.

Section 2.1.2 and Section 3.1.4 Added extra sentence to state that patients who have margins which cannot be determined should also be excluded from the resected analysis set.

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8 APPENDIX

Appendix A Definition of visit windows for analysis of PROs

CCI

A 2 Visit windows for PGI-TT

Table 17 Visit windows for PGI-TT
PGI-TT will use the following visit window

Window period / Analysis visit	Minimum day	Target day	Maximum day
Baseline		1	
Study day 08	2	8	11
Study day 15	12	15	18
Study day 22	19	22	25
Study day 29	26	29	32
Study day 36	33	36	39
Study day 43	40	43	46
Study day 50	47	50	53
Study day 57	54	57	60
Study day 64	61	64	67
Study day 71	68	71	74
Study day 78	75	78	81
Study day 85	82	85	88
Study day 92	89	92	95
Study day 99	96	99	102
Study day 106	103	106	109
Study day 113	110	113	116
Study day 120	117	120	123
Study day 127	124	127	130

Window period / Analysis visit	Minimum day	Target day	Maximum day
Study day 134	131	134	137
Study day 141	138	141	144
Study day 148	145	148	151
Study day 155	152	155	158
Study day 162	159	162	End of treatment date - 8
End of treatment	End of treatment date -7	End of treatment date	End of treatment date + 7
Safety follow-up month 03	End of treatment date + 8	max(Date of surgery, Date of EOT visit) + 90	max(Date of surgery, Date of EOT visit) + 135
Safety follow-up month 06	max(Date of surgery, Date of EOT visit) + 136	max(Date of surgery, Date of EOT visit) + 180	max(Date of surgery, Date of EOT visit) + 225
Safety follow-up month 09	max(Date of surgery, Date of EOT visit) + 226	max(Date of surgery, Date of EOT visit) + 270	max(Date of surgery, Date of EOT visit) + 315
Safety follow-up month 12	max(Date of surgery, Date of EOT visit) + 316	max(Date of surgery, Date of EOT visit) + 360	max(Date of surgery, Date of EOT visit) + 405
Safety follow-up month 15	max(Date of surgery, Date of EOT visit) + 406	max(Date of surgery, Date of EOT visit) + 450	max(Date of surgery, Date of EOT visit) + 495
Safety follow-up month 18	max(Date of surgery, Date of EOT visit) + 496	max(Date of surgery, Date of EOT visit) + 540	max(Date of surgery, Date of EOT visit) + 585

Window period / Analysis visit	Minimum day	Target day	Maximum day
Safety follow-up month 21	max(Date of surgery, Date of EOT visit) + 586	max(Date of surgery, Date of EOT visit) + 630	max(Date of surgery, Date of EOT visit) + 675
Safety follow-up month 24	max(Date of surgery, Date of EOT visit) + 676	max(Date of surgery, Date of EOT visit) + 720	max(Date of surgery, Date of EOT visit) + 765
Safety follow-up month 27	max(Date of surgery, Date of EOT visit) + 766	max(Date of surgery, Date of EOT visit) + 810	max(Date of surgery, Date of EOT visit) + 855
Safety follow-up month 30	max(Date of surgery, Date of EOT visit) + 856	max(Date of surgery, Date of EOT visit) + 900	max(Date of surgery, Date of EOT visit) + 945
Safety follow-up month 33	max(Date of surgery, Date of EOT visit) + 946	max(Date of surgery, Date of EOT visit) + 990	max(Date of surgery, Date of EOT visit) + 1035
Safety follow-up month 36	max(Date of surgery, Date of EOT visit) + 1036	max(Date of surgery, Date of EOT visit) + 1080	

A 3 Visit windows for PRO-CTCAE

Table 18 Visit windows for PRO-CTCAE
PRO-CTCAE will use the following visit window

Window period / Analysis visit	Minimum day	Target day	Maximum day
Baseline		1	
Study day 08	2	8	11
Study day 15	12	15	18
Study day 22	19	22	25
Study day 29	26	29	32
Study day 36	33	36	39
Study day 43	40	43	46
Study day 50	47	50	53
Study day 57	54	57	60
Study day 64	61	64	67
Study day 71	68	71	74
Study day 78	75	78	81
Study day 85	82	85	88
Study day 92	89	92	95
Study day 99	96	99	102
Study day 106	103	106	109
Study day 113	110	113	116
Study day 120	117	120	123

Window period / Analysis visit	Minimum day	Target day	Maximum day
Study day 127	124	127	130
Study day 134	131	134	137
Study day 141	138	141	144
Study day 148	145	148	151
Study day 155	152	155	158
Study day 162	159	162	End of treatment date - 8
End of treatment	End of treatment date - 7	End of treatment date	End of treatment date + 7
Safety follow-up month 03	End of treatment date + 8	max(Date of surgery, Date of EOT visit) + 90	max(Date of surgery, Date of EOT visit) + 135
Safety follow-up month 06	max(Date of surgery, Date of EOT visit) + 136	max(Date of surgery, Date of EOT visit) + 180	max(Date of surgery, Date of EOT visit) + 225
Safety follow-up month 09	max(Date of surgery, Date of EOT visit) + 226	max(Date of surgery, Date of EOT visit) + 270	max(Date of surgery, Date of EOT visit) + 315
Safety follow-up month 12	max(Date of surgery, Date of EOT visit) + 316	max(Date of surgery, Date of EOT visit) + 360	

A 4 Visit windows for EORTC QLQ-C30

Table 19 Visit windows for EORTC QLQ-C30
The EORTC QLQ-C30 will use the following visit windows.

Window period	Minimum day	Target day	Maximum day
Baseline		1	
Study day 29	2	29	43
Study day 57	44	57	71
Study day 85	72	85	99
Study day 113	100	113	127
Study day 141	128	141	End of treatment date - 8
End of treatment	End of treatment date - 7	End of treatment date	End of treatment date + 7
Safety follow-up month 06	End of treatment date + 8	max(Date of surgery, Date of EOT visit) + 180	max(Date of surgery, Date of EOT visit) + 270
Safety follow-up month 12	max(Date of surgery, Date of EOT visit) + 271	max(Date of surgery, Date of EOT visit) + 360	max(Date of surgery, Date of EOT visit) + 405
Safety follow-up month 15	max(Date of surgery, Date of EOT visit) + 406	max(Date of surgery, Date of EOT visit) + 450	max(Date of surgery, Date of EOT visit) + 495
Safety follow-up month 18	max(Date of surgery, Date of EOT visit) + 496	max(Date of surgery, Date of EOT visit) + 540	max(Date of surgery, Date of EOT visit) + 585
Safety follow-up month 21	max(Date of surgery, Date of EOT visit) + 586	max(Date of surgery, Date of EOT visit) + 630	max(Date of surgery, Date of EOT visit) + 675

Window period	Minimum day	Target day	Maximum day
Safety follow-up month 24	max(Date of surgery, Date of EOT visit) + 676	max(Date of surgery, Date of EOT visit) + 720	max(Date of surgery, Date of EOT visit) + 765
Safety follow-up month 27	max(Date of surgery, Date of EOT visit) + 766	max(Date of surgery, Date of EOT visit) + 810	max(Date of surgery, Date of EOT visit) + 855
Safety follow-up month 30	max(Date of surgery, Date of EOT visit) + 856	max(Date of surgery, Date of EOT visit) + 900	max(Date of surgery, Date of EOT visit) + 945
Safety follow-up month 33	max(Date of surgery, Date of EOT visit) + 946	max(Date of surgery, Date of EOT visit) + 990	max(Date of surgery, Date of EOT visit) + 1035
Safety follow-up month 36	max(Date of surgery, Date of EOT visit) + 1036	max(Date of surgery, Date of EOT visit) + 1080	

A 5 Visit windows for EORTC IL123

Table 20 Visit windows for EORTC IL123
The EORTC IL123 will use the following visit windows.

Window period	Minimum day	Target day	Maximum day
Baseline		1	
Study day 29	2	29	43
Study day 57	44	57	71
Study day 85	72	85	99
Study day 113	100	113	127
Study day 141	128	141	End of treatment date - 8
End of treatment	End of treatment date -7	End of treatment date	End of treatment date + 7
Safety follow-up month 03	End of treatment date + 8	max(Date of surgery, Date of EOT visit) + 90	max(Date of surgery, Date of EOT visit) + 135
Safety follow-up month 06	max(Date of surgery, Date of EOT visit) + 136	max(Date of surgery, Date of EOT visit) + 180	max(Date of surgery, Date of EOT visit) + 225
Safety follow-up month 09	max(Date of surgery, Date of EOT visit) + 226	max(Date of surgery, Date of EOT visit) + 270	max(Date of surgery, Date of EOT visit) + 315
Safety follow-up month 12	max(Date of surgery, Date of EOT visit) + 316	max(Date of surgery, Date of EOT visit) + 360	

A 6 Visit windows for EORTC IL124

Table 21 Visit windows for EORTC IL124
The EORTC IL124 will use the following visit windows.

Window period / Analysis visit	Minimum day	Target day	Maximum day
Study day 08		8	11
Study day 15	12	15	18
Study day 22	19	22	29
Study day 36	30	36	39
Study day 43	40	43	46
Study day 50	47	50	57
Study day 64	58	64	67
Study day 71	68	71	74
Study day 78	75	78	85
Study day 92	86	92	95
Study day 99	96	99	102
Study day 106	103	106	113
Study day 120	114	120	123
Study day 127	124	127	130
Study day 134	131	134	140
Study day 148	141	148	151
Study day 155	152	155	158
Study day 162	159	162	

A 7 Visit windows for EORTC IL125

Table 22 Visit windows for EORTC IL125
The EORTC IL125 will use the following visit windows.

Window period / Analysis visit	Minimum day	Target day	Maximum day
Safety follow-up month 03		max(Date of surgery, End of treatment date) + 90	max(Date of surgery, End of treatment date) + 135
Safety follow-up month 06	max(Date of surgery, End of treatment date) + 136	max(Date of surgery, End of treatment date) + 180	max(Date of surgery, End of treatment date) + 225
Safety follow-up month 09	max(Date of surgery, End of treatment date) + 226	max(Date of surgery, End of treatment date) + 270	max(Date of surgery, End of treatment date) + 315
Safety follow-up month 12	max(Date of surgery, End of treatment date) + 316	max(Date of surgery, End of treatment date) + 360	

A 8 Visit windows for EORTC IL19

Table 23 Visit windows for EORTC IL19
The EORTC IL19 will use the following visit windows.

Window period / Analysis visit	Minimum day	Target day	Maximum day
Study day 08		8	11
Study day 15	12	15	18
Study day 22	19	22	29
Study day 36	33	36	39
Study day 43	40	43	46
Study day 50	47	50	57
Study day 64	58	64	67
Study day 71	68	71	74
Study day 78	75	78	85
Study day 92	86	92	95
Study day 99	96	99	102
Study day 106	103	106	113
Study day 120	114	120	123
Study day 127	124	127	130
Study day 134	131	134	140
Study day 148	141	148	151
Study day 155	152	155	158
Study day 162	159	162	End of treatment date

Window period / Analysis visit	Minimum day	Target day	Maximum day
Safety follow-up month 03	End of treatment date + 1	max(Date of surgery, End of treatment date) + 90	max(Date of surgery, End of treatment date) + 180
Safety follow-up month 09	max(Date of surgery, End of treatment date) + 181	max(Date of surgery, End of treatment date) + 270	

A 9 Visit windows for WHO/ECOG performance status

Table 24 Visit windows for WHO/ECOG performance status for Arms A & B – T-DXd monotherapy and T-DXd THP

The WHO/ECOG performance status questionnaire will follow the visit window below (Q3W for eight cycles):

Window period	Minimum day	Target day	Maximum day
Baseline		1	
Study day 22	2	22	32
Study day 43	33	43	53
Study day 64	54	64	74
Study day 85	75	85	95
Study day 106	96	106	116
Study day 127	117	127	137
Study day 148	138	148	End of treatment date - 8
End of treatment	End of treatment date -7	End of treatment date	For patients who complete treatment, use date of surgery. For patients who discontinue before completion, use date of discontinuation + 7.
Pre-surgery / definitive surgery	Date of surgery - 14		Date of surgery
Safety follow-up	Date of surgery + 1	End of treatment date + 47	

Table 25 Visit windows for WHO/ECOG performance status for Arm C – ddAC-THP
The WHO/ECOG performance status questionnaire will follow the visit window below (Q2W for four cycles then Q3W for four cycles):

Window period	Minimum day	Target day	Maximum day
Baseline		1	
Study day 15	2	15	22
Study day 29	23	29	36
Study day 43	37	43	50
Study day 57	51	57	67
Study day 78	68	78	88
Study day 99	89	99	109
Study day 120	110	120	
End of treatment	End of treatment date - 7	End of treatment date	
Pre-surgery / definitive surgery			
Safety follow-up		End of treatment date + 47	

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